

Influence of Space Environments in System Physiologic and Molecular Integrity: Redefining the Concept of Human Health beyond the Boundary Conditions of Earth

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ABSTRACT

Space travel since the 1960s has led to a number of physiological alterations to homeostasis in astronauts. Extensive variation in the pattern of responses observed has led a concerted effort to develop countermeasures to overcome such changes and restore homeostasis, and thus “health” is defined as more “Earth-like”. These adaptations to a space environment by a species which evolved and normally exists in the 1 g environment, the geomagnetic field, and background radiation of Earth are viewed as threats to health as defined by the conditions of Earth. Exposure to space can lead to alterations in genomic stability and epigenetic signatures, alterations which could redefine “health” and responses to risks for loss of health for those who will return to Earth. In contrast, in the future individuals born in non-Earth space environments will likely develop an integrated metabolic set point defined by those conditions. They will thus be shaped by both the local environments, and space-associated genomic/epigenomic alterations to their parents. Therefore, such an altered set point for those born and raised in non-Earth space environments will potentially have physiological and molecular consequences which may lead to either new evolutionary adaptation, or to compromise of long term health due to drastically altered set points for integrated physiologic function which is at odds with the evolutionary history of humans. The implications of the two options will be critical for defining “health” in altered environments encountered during space ventures, as well as providing insights into the regulation of human integrity at the physiological level. Therefore, the definition of “health” is dependent on the boundary conditions surrounding development and maturation, and is a dynamic concept.

1. INTRODUCTION

The current version of *Homo sapiens* evolved over eons, with multiple iterations that either contributed to the current version, or were branches that died out for various reasons. Some of these reasons may be related to failure to adapt to the dynamic nature of the Earth and its associated cycles of climate change, food availability, and reproductive advantage. Thus, the dynamic nature of the Earth likely contributed to migratory patterns and isolation of populations which evolved somewhat independently (e.g. Australian aboriginal populations). Such migration patterns and adaptations contributing to survival have led to a species which is very heterogeneous genetically, and one that can be influenced via epigenetic mechanisms to enhance survival over relatively short time frames. Such heterogeneity also likely contributes to survival from microbial threats as evidenced by survival of some individuals from plagues, HIV infection, and cholera, to name a few, that have ravaged populations in recorded history. Such heterogeneity also enhances reproductive success via histocompatibility antigens [1-3], where histoincompatibility of a fetus with the mother is important for being carried to term in the human mammal. Thus, the definition of health in such a heterogeneous species as *Homo sapiens* is based on a number of intrinsic (genetics and epigenetics) and extrinsic (nutrition and food security, climate and stochastic solar events) factors.

All of the above evolution of *Homo sapiens* has occurred within the boundary conditions imposed by the Earth, with its unique 1 g gravity, the magnetic field, the background radiation of the crust, and the dynamic nature of its tectonic plates and their influence on human adaptation (discussed in [4]). We do not usually think of these boundary conditions as “defining” us as humans, but these Earth condition variables are in the background of all of us. Thus, some of the genetic heterogeneity may be “silent” in the context of living on Earth, and therefore, health is defined within that context. For example, our bones, muscles, joints, and spine depend on functioning in a 1 g environment, and likely the neural control of such systems also depends on it. The human cardiovascular system is adapted to walking upright in the 1 g environment. The human neural system uses electrical elements and the brain emits biomagnetic signatures detectable using SQUID technologies (discussed in [4]), and thus, it has to function effectively in the context of the Earth’s magnetic field. Similarly, the Earth’s crust emits background radiation that is location dependent in intensity. Such low radiation levels may contribute to the mutation rate and effective evolution, but may also contribute to cancer rates (which are concentrated early in life and in the elderly—the latter of which was likely not a consideration as occurring past the reproductive age and likely not reached by many with short life spans until more recently).

Thus, the current version of *Homo sapiens* is heterogeneous, but is the product of the conditions of Earth, conditions which have been dynamic throughout evolution (magnetic pole reversals, solar influences, 1 g gravity, magnetic fields, and background radiation).

2. SPACE FLIGHT-THE NEW OPPORTUNITY FOR UNDERSTANDING *HOMO SAPIENS*

The advent of space flight to low Earth orbit (LEO) for short or extended time periods, as well as short flights to the moon and back have revealed that a number of human physiological and psychological systems are impacted by microgravity (discussed in [4]). While the number of humans who have experienced space flight is not large (~600 since the 1960s; mostly males and some multiple times) and the length of time in space variable (days to 1 year) (<https://www.worldspaceflight.com/bios/stats.php>) the other important feature of these alterations is that humans are quite variable in their responses, with some individuals and some systems affected more or less than others, and to varying extents in different individuals. The systems affected are similar in some regards to those affected during the aging process, leading to some to argue that exposure to microgravity conditions, as on the International Space Station, is a form of “accelerated aging” (reviewed in [4, 5]). As humans have had the opportunity to explore space via space flight for only ~60 years, this is all both new and somewhat foreign to a species that evolved under the influence of the boundary conditions of Earth. However, we can both learn about the regulation and genetic and epigenetic contributions to human systems by studying humans in space, and as well, learn how to impact the adaptive changes using countermeasures.

The changes occurring in astronauts living in microgravity are considered by many as threats to health, and thus, considerable effort and money has gone into developing countermeasures to prevent the changes from occurring. In part, this investment may be necessary as currently, astronauts are destined to return to Earth and resume their lives under its boundary conditions once again. The real issue with countermeasures is that “one size does not fit all”. That is, astronauts are genetically and epigenetically diverse, and thus, the systems affected and the extent of the changes vary on an individual basis. Thus, one may not expect that any given countermeasure would be equally effective in all astronauts.

Similarly, some countermeasures are effective in many astronauts (e.g. exercise to overcome muscle atrophy), while the same exercise as an artificial surrogate for ground reaction forces to overcome bone atrophy and accelerated bone turnover, particularly of the lower extremities is not as effective [6]. While it may be possible to overcome this resistance of bone to be positively influenced by physical means, it may also be possible to overcome this resistance with drug interventions such as the use of bisphosphonates that are effective on Earth in many patients with osteoporosis. Interestingly, the use of such drugs is not without risks (atypical femoral fractures, TMJ complications) [7], so it may not be a viable long term solution for extended spaceflight to deep space such as travel to Mars and beyond.

1) The example of bone and reduced gravity

The above discussion, using bone turnover in space/microgravity as an example of a system adapting to its new environment to achieve a new metabolic and functional set point, may indicate that a new definition for bone health is required, and one not determined by the rules which led to the establishment of the set point under the boundary conditions of Earth for a skeletally mature adult.

Continuing to use bone as an example of a tissue adapting to space conditions leading to a new set point for the definition of “Bone Health”, there are a number of potential outcomes from the prolonged exposure to microgravity and then spending time on the Moon or Mars, transiently or permanently.

a) In microgravity, bone loss continues past a threshold when frailty fractures start to occur before a new homeostatic equilibrium point is reached. This would imply that bone loss under such circumstances is not regulated independent of a minimal structure. However, no fractures have been reported in astronauts.

b) When exposed to microgravity, one loses a unique subset of bone that is very sensitive to mechanical loading, which then slows down or stops when that subset is lost. This would imply that not all bone is equal, and that frailty fractures on Earth pass this threshold quicker than in space due to the 1 g environment impacting the consequence of losing the bone. One could also assess the premise for this by studying bone loss in astronauts who go into space (ISS trips) more than once.

c) There is a threshold for a fraction of the 1 g Earth environment that is sufficient to suppress bone atrophy, so once microgravity is survived, landing on the moon (1/6 g) or Mars (1/3 g) is sufficient for inhibiting the mechanisms responsible for the bone loss. While bone appears to be regulated as a binary system (osteoblasts, osteoclasts) plus a regulatory cell (osteocytes), and menisci are not regulated in a similar manner, in some experiments with rabbit menisci *in vitro*, Natsu-ume *et al.* [8] showed that removal of menisci from the rabbit knee leads to a rapid de-repression of a subset of genes capable of inducing catabolism in the menisci. Exposure of the menisci to intermittent cyclic hydrostatic compression (1 MPa) completely blocked de-repression of these genes. Furthermore, exposure to cyclic 0.75 or 0.5 MPa also completely blocked de-repression, but 0.25 MPa did not (Natsu-ume and Hart, unpublished observations). Thus, there appeared to be a threshold for induction of catabolism/atrophy in menisci. Whether a similar threshold exists for bone with its unique multi-cellular regulatory system, remains to be investigated.

d) The fact that bones of the lower extremities appear to lose more bone and faster than bone of the upper extremities (discussed in [6]), also implies that not all bone is entrained to the 1 g conditions of Earth equally. This has implications for the setting of the “mechanostat” as defined by Frost (discussed in [9-11]) for bone, as well as the studies regarding Wolff’s Law (discussed in [12, 13]), and many of the models which attempt to regulate bone (combination of mechanical stimuli/stresses, and biological elements).

e) The finding that exercise-based countermeasures, even those with magnetic boots to impart a

loading element to mimic Earth's 1 g ground reaction forces, work for muscle but not so well for bone, also has raised concerns about regulation of bone in microgravity and attempts to re-establish a "healthy" set point. Either, we do not understand the integration of the unique regulatory features of the multi-cellular bone system, or we are ignoring some elements that are essential regulatory elements besides the "usual suspects". Regarding the former, perhaps investigators have been using the wrong loading protocols to transmit the mechanical signals. Thus, vibration-based stimuli and loading via exercise running in magnetic footwear does not mimic the forces necessary to impart an effective load to the cells of bone in the lower extremities, a load that has to overcome the dampening effect of crossing the "disconnects" of the ankle, knee, and hip joint.

Regarding the other option, perhaps we are currently ignoring an essential regulatory element in the bone that is not one of the major players based on direct cell involvement (e.g. osteoblasts, osteocytes, and osteoclasts). However, many who model bone to better understand its regulation appear to ignore the fact that bone is both innervated and vascularized [14, 15]. Such innervation is not necessarily to the same extent as in many organs (liver, spleen, brain, etc.), but it is significant, and not unlike other connective tissues (ligaments, tendons, menisci, etc.). Thus, if the nerve endings in bone, which likely both take away information as well as impart information to the bone, are compromised by loss of the 1 g environment of earth, and associated inputs both peripherally and centrally, then we may be asking the wrong cells to get involved in the microgravity environment. Most research focuses on the major cellular players in bone, and that may have led us to ignore some of the "minor" but important regulators [16].

Considerable research may be required to better understand the regulation of bone, and the evolutionary control mechanisms that have gone into effective regulation in the context of the boundary conditions of Earth. If "healthy" bones in the context of space/microgravity or an altered g-environment (moon, Mars, others) is to lead to functional outcomes, then such new information will be essential for long term survival and understanding of the rules for set point establishment.

2) The example of fluid redistribution under reduced gravity

As humans developed and evolved under the influence of Earth's gravity, particularly when we evolved to stand upright, our cardiovascular systems, as well as other systems with essential fluid compartments (e.g. the lymphatic system, cerebral spinal fluid, the brain, the vitreous humor of the eye) had to adapt to the 1 g environment to establish mechanisms to maintain volume and homeostasis with the fluid needs of associated cells (as we are mostly water). Thus, regulation of fluid homeostasis to the lower extremities, the brain, the eye, and other organs which are mostly water, as well as kidney function is dependent on functioning in a 1 g environment as is the integrity of vasculature function.

From the work of Hughson and colleagues [17, 18] and others (reviewed in [4, 19]), it is clear that astronauts undergo vascular changes that are significant and similar changes can be observed following prolonged bed rest (reviewed in [20, 21]). In fact some of the vascular changes can also be observed in aging populations. Whether the underlying molecular mechanisms responsible are also identical between the astronaut-associated changes and those observed in aging populations remain to be confirmed. Thus, the similarities in end results of impact on health risk may not relate to similarities in the mechanisms responsible. Therefore, better understanding of the mechanisms involved in the space-related changes will be required to improve predictions regarding what is defined as "health" which has developed and matured under boundary conditions different from those of Earth.

3) The influence of magnetic fields and their loss

The Earth has a magnetic core and the crust is also replete with ferrous ores that are also magnetic. These features contribute to the geomagnetic field that surrounds the planet, which is viewed as a protective "shield" against extra-terrestrial radiation. The north and south poles of the Earth reflect the orientation of such magnetic fields. The geomagnetic field on Earth is not uniform, with variation in different parts of continents. In addition, the Earth can undergo pole reversals of long duration, and the actual point of a pole can "drift", leading to issues in navigation fidelity when the geomagnetic poles can move.

It is within the context of the geomagnetic environment that life on Earth evolved. Likely, by many it is either ignored as irrelevant, or not considered in the context of human functioning. Such perspectives

are interesting considering we have a well-developed brain and nervous system that is electrical in nature, and can generate biomagnetic fields that can be measured by sensitive systems such as SQUID technologies [22].

It is well known that animals and birds that migrate can use magnetic field detection systems in their brains, as well as optic sensing to direct navigation during migration (reviewed in [23]). It has also been reported that exposure to weak magnetic fields can manipulate regeneration in worms either positively or negatively depending on the field strength [24]. Such fields are also reported to alter stem cell-mediated growth [24]. In addition, alterations in vestibular homeostasis have been reported to be influenced by exposure to exogenous static magnetic fields (reviewed in [25]). A number of possible mechanisms to explain the effects of such exogenous magnetic fields on vestibular stimulation have been discussed [25], but these magnetic fields are strong and several magnitudes higher than the endogenous geomagnetic field. Such studies have led to the possibility that humans can detect magnetic fields via brain elements [26].

While there is emerging evidence that humans and many other species can utilize the geomagnetic field, and by extension, detect fluctuations in the geomagnetic field of Earth in a functional manner (implying that detection can be used and thus, is integrated into an evolved response pattern. Which in turn implies the evolution of an overt neuro-based system), not as much evidence or thought has gone into what the effect of loss of the geomagnetic field would be on humans such as those traveling well beyond the Earth's field. Up to the present time, those in Low Earth Orbit (LEO) are still influenced by the Earth's geomagnetic field so this issue has not presented itself, particularly for long durations, thus far in space exploration. However, it could present some issues regarding brain development, maturation, and functioning for those involved in colonization efforts where the impact could exert significant impact regarding neurological aspects of health.

4) Summary

While the assessment of physiological adaptations of astronauts to space has covered up to 6 months in space quite thoroughly, and to 1 year in LEO for some, a number of questions still remain. Firstly, do the changes reach a new "equilibrium" for each astronaut for the systems affected? That is do the adaptations stabilize to the new conditions of the ISS, indicating a new metastable state has been reached, or so they continue to progress? This question may take longer than 1 year in space to answer given the heterogeneity of human responses to space flight. Secondly, what are primary adaptations, and what are secondary responses? Thus, prolonged changes to the cardiovascular system and fluid redistribution could lead to secondary effects on tissues of the lower extremities via alterations to the peripheral circulation. Similarly, the elevated serum calcium levels during bone loss could lead to secondary complications in other tissues over the long term. The answers to these and other related questions could be very relevant to those going to Mars or beyond, as well as to those investigating development of countermeasure approaches.

3. DEFINING HEALTH DEVELOPING OUTSIDE OF THE BOUNDARY CONDITIONS OF EARTH

As discussed above, current humans are very diverse genetically and epigenetically. For the most part, current understanding of how such diversity arose, how it contributes to health and disease on Earth, and what its implications are for defining health under conditions where the boundary conditions of Earth are not in play, is not clear at multiple levels. Furthermore, based on comparisons of epigenetic "signatures" of identical twins who were either on Earth or the ISS for a year [19], as well as comparisons of pre- during and post-flight assessments would indicate that spending time in space conditions/environments can lead to epigenetic alterations and some genomic instability, at least in the blood cells that were assessed. Some of the epigenetic changes detected were reversible once the astronaut returned to Earth. However, whether any tissue-specific epigenetic changes remained irreversible remains to be determined. In the future, it would be interesting to assess whether such changes also occurred in sperm, biopsies of various muscles, or other tissues. Furthermore, it is not known in any detail regarding the temporal relationships between the genomic and epigenomic alterations and the physiologic adaptations assessed (e.g. bone loss, cardio-

vascular changes, etc.). Thus, whether the genomic and epigenetic alterations were induced by the altered environment or were a consequence of the physiologic alterations remains to be clarified.

While still limited by the restricted breadth of tissue that was analyzed and the fact that $N =$ one twin pair, there are some potential implications of the findings that epigenetic changes and genomic instability occur during prolonged space flight. The first is that any changes occurring could influence the effectiveness of drugs used to treat illnesses that arise, and thus the health of the astronauts. This possible outcome would likely depend on the drugs involved, the genes affected, and the tissues affected (e.g. liver, lungs, kidney, etc.). A second possible consequence is an altered response pattern of immune cells to any infectious agents that arise. Thirdly, the genome and epigenetic changes could contribute to the elaboration of otherwise silent risks for loss of health (e.g. risk for autoimmune conditions, cancer, via loss of system integrity). These are examples of how “health” would be redefined in space that would potentially occur in the context of other physiologic sequelae of the space environment.

The finding of epigenetic changes occurring in space potentially could also mean that the parents of any offspring conceived and born at a destination (e.g. Mars) or back on Earth could be influenced by such epigenetic changes since such alterations can be transmitted to the fetus by either the male or female parent (reviewed in [27-29]). Transmission of space-associated epigenetic alterations can thus complicate the definition of health in the offspring born under non-Earth boundary conditions, or born on Earth to parents exposed to space conditions and resultant irreversible epigenetic alterations. Thus far, $N = 1$ for showing that epigenetic alterations happen in LEO, so it is not known whether any changes occurring exhibit commonalities between individual response patterns, or whether the changes occurring are dependent, at least in part, on the genetic makeup of an individual. This issue should be addressed for ISS astronauts (e.g. DNA from biopsies from a number of tissues before, during and after their tenure on the ISS).

Based on the above, it is unlikely that extensive analysis of health in humans on Earth who are going to destinations in space will lead to productive outcomes regarding predicting success for defining health on a place like Mars or beyond. However, with more detailed analysis of those going into space, one may be able to minimize some parameters (e.g. selecting those who lose 0.1% of bone/month in space vs those that lose 2%/month). As we do not know how to predict risks for loss of health on Earth very well, it is unlikely that such analysis will have much impact on predicting health in LEO or space environments, although the former may provide some approaches and outputs that could be useful for enhancing predictions for the Earth-bound.

Of course, this perspective could be altered in the future by the clinical acceptability of technologies which could “correct” current *Homo sapien* limitations. For instance, if CRISPR and related gene therapy technologies became safe and reliable for humans (discussed in [30]), it may be possible to “correct” some of the current genetic limitations. Furthermore, if technologies to modify epigenetic signatures became specific, reliable and safe, one may be able to modify specific genes to impact the health of astronauts and their progeny.

4. SPACE ENVIRONMENTS AS DRIVERS FOR HUMAN EVOLUTION

Human evolution, culminating in the current version of *Homo sapiens* is the result of a number of evolutionary changes from what are reported to be previous iterations of hominids based on incomplete fossil records. Whether such evolution to *Homo sapiens* resulted from stochastic events or specific pressures is not clear, but certainly from other spheres evolutionary drift can result from pressures or result from drift in the genetic makeup of an isolated population of humans or animals (as for example, described by Darwin; [31]). In this regard, space environments can be regarded as drivers of human evolution, based in part by the genetic/epigenetic makeup of the starting population and the stressors presented by the environment. As in the past of human history, many of the attempts will likely lead to failure to thrive until a new set of parameters is reached which re-defines health for that set of circumstances. Furthermore, if the diversity of current humans is an example, it is likely that there may be multiple ways to achieve success as there are many gene variants on Earth that are silent within its boundary conditions.

Thus, space can be an effective driver for human evolution over time, and therefore, health has a dynamic quality that fits with specific conditional requirements. Interestingly, if one takes a generational perspective on this process, at what point are those evolutionarily adapted for a new environment still *Homo sapiens*?

5. CONCLUSIONS

The considerable effort on the part of the space medical community and technology industries to work to maintain the health of astronauts and prepare for extended exposure to space environments via time on the Moon, Mars and beyond has focused on using definitions of health based on Earth parameters. This approach may be short-sighted as we gain more information regarding adaptations of people who have matured and thrived under Earth-bound conditions when they are subsequently exposed to conditions where those boundary conditions no longer apply. Is this a valid approach, or one that is going to be limited when addressing the needs of astronauts away from Earth conditions for several years or longer? The answer may be that some astronauts are likely going to be better prepared genetically for maintaining their health under the impact of space environments than others, and there is a need to apply “precision health” approaches to identifying such individuals, and thus, health is a personal dynamic rather than a population determinant.

For those who are conceived, born and maturing under space conditions, a number of factors, mostly unknown presently, will contribute to their evolving definition of health which will be very different than those of us who remain on Earth. Over generations, such evolutionary drivers will lead to humans who are changed significantly to maintain “health” within new boundary conditions. Therefore, health is a dynamic parameter, with both individual and environmental considerations impacting the definition. Thus, considering health in space as an extension of health on Earth is likely not appropriate as humans go beyond LEO, and is being limited by the medical perception of the concept. However, that is not to say we should abandon efforts to better characterize astronaut responses to space environments in more detail as that information may help determine aspects of who might be more likely to better adapt to space environments than others, and still maintain long term functionality.

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CONFLICTS OF INTEREST

The author declares he has no conflicts of interest to disclose.

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