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Potential Impact of Space Environments on Developmental and Maturational Programs Which Evolved to Meet the Boundary Conditions of Earth: Will Maturing Humans Be Able to Establish a Functional Biologic System Set Point under Non-Earth Conditions?

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ABSTRACT

Mammalian development and maturation, particularly processes for humans have evolved in the context of the boundary conditions of Earth (*i.e.* 1 g gravity, geomagnetic field, background radiation) to yield functional individuals, although the process is not perfect and "errors" do occur. With the advent of spaceflight to low Earth orbit (the International Space Station), humans are now exposed to microgravity and increased exposure to radiation. However, thus far, only adult humans have served as astronauts, but this will likely change with plans to explore deep space and colonize planets. Thus, conception, fetal development, post-birth maturation, puberty and skeletal maturity will occur in the context of boundary conditions that did not shape human evolution and influence physiological and biomechanical systems designed to function within the Earth's boundary conditions. Thus, processes utilizing the 1 g environment (*i.e.* walking upright) and the geomagnetic field (*i.e.* the electrical/biomagnetic basis of neural interactions) will have to adapt to new boundary conditions, providing opportunity for additional errors or alterations in processing during development which could impact functional outcomes at multiple levels. This review/perspective will discuss some of these issues and attempt to provide direction for addressing the potential issues to be encountered.

1. INTRODUCTION

According to evolutionary theory, cells likely developed in the oceans of the earth and over time became complex multicellular organisms, which subsequently evolved further into species that became larger, more complex, and ultimately moved from the buoyant ocean to the land where they likely encountered ground reaction forces associated with the 1 g environment. In order to accommodate such an environment, some species have likely adapted by developing appendages such as legs and arms and later hands/fingers/feet/toes, that allowed for enhanced functioning regarding mobility (e.g. survival, hunting and avoiding predators), and a rigid skeletal structure to resist ground reaction forces and atmospheric pressures.

However, the 1 g environment of earth is likely only one of the factors that have contributed, and shaped, complex organisms that have dominated this planet over the past perhaps billion years. Three of the other four are obviously ones localized to earth and include the geomagnetic field of earth, varying cycles of light and dark during the day and the year as the earth rotates and traverses around the sun, and the background radiation of the planet. The fourth is likely the cyclic impact of the sun itself on Earth conditions. The geomagnetic field is perhaps critical to the functioning of the neural system which is electrical in nature, and as such the higher order functioning of the brain likely relies in part on biomagnetic influences and must function in the context of the background geomagnetic field and its variations. Such biomagnetic patterns can be detected by SQUID technologies [1, 2], and they must have evolved to accommodate the background geomagnetic field and its fluctuations (e.g. as evidenced by variations at different locations on earth and the movement (*i.e.* flipping) of the location of the magnetic poles). Such SQUID technologies have also been adapted for assessing fetal bio-magnetic patterns [3], and as such can investigate the development of fetal bio-magnetic patterns in the context of the geomagnetic background of the Earth and potentially, the loss of such background in space environments on development (e.g. for example on Mars). Similarly, a system has also been developed to investigate brain development in neonates [4] which could also be useful to assess variation in brain development following birth in both Earth and non-Earth environments.

Certainly, many tissues including the brain are sensitive to exogenous magnetic and electromagnetic fields [discussed in [5, 6]]. It also appears that fetal or neonatal brains may be particularly sensitive to very low frequency magnetic fields, dependent in part, on which part of the brain is assessed [5], with the hippocampus being one in the rodent brain that exhibits sensitivity [5, 7]. However, the effects of prenatal exposure to such fields in somewhat inconsistent in mammals, and variability has been reported [reviewed in [8]]. Such inconsistency could be due to heterogeneity in the host exposed to the fields, and as humans are very heterogeneous, the impact on developmental aspects may reside in an underlying genetic susceptibility. Such findings could also be relevant to space environments due to the electromagnetic fields generated by equipment in the space vehicles or habitats on the surface.

Light and dark cycles also influenced evolution as humans and many other species use eyes (as well as other senses) to assess and navigate their environment for survival and hunting, and also use them for vestibular orientation. Given the pace of evolution, and the fact that we do not understand many aspects of sun-driven cycles, it is not clear how this influence could have shaped fundamental systems that humans still retain, except possibly as a varying source of radiation, but one that the geomagnetic field of Earth perhaps protects us from in large part. Likely of more importance to the evolution of complex organisms, including humans, is the background radiation of the planet which could have influenced both positively (enhanced mutation rates) and negatively (e.g. cancer rates) evolutionary processes.

Most of the factors or variables discussed above were likely barriers to be overcome to enhance survival, with possibly the exception of the development of a neural system and an integrated brain to exert central regulatory mechanisms. While perhaps other options were explored in the distant past, the speed and efficiency of an electrical/biomagnetic neural system, and its integration with the musculoskeletal system and others, offered advantage for both survival and reproduction. From an evolutionary perspective, the influence of the background radiation of earth might be somewhat different from the others men-

tioned, in that was both a barrier to be overcome, as well as a potential driver of evolution and diversity in the past and currently.

Organisms on earth evolved using a fairly stable carbon-based system, but interestingly, chose molecules and processes for their information storage and strategy to pass on that information to the next generation that are readily influenced by radiation, including that sourced from the background radiation of the planet (e.g. radioactive molecules such as uranium, and others). That is, depending on a nucleic acid-based system for our information storage and passage to the next generations (e.g. DNA-coding, noncoding sequences; RNA-mRNA, miRNA, rRNA) opens the system to high mutation rates that can be advantageous, detrimental, or silent until one gets past the reproductive stage of life, and/or remains on Earth. The advantageous aspect could be related to the rate of mutations that offer advantage to the individual as it relates to ability to survive and adapt. For instance, humans are very diverse in systems such as the major and minor histocompatibility systems that regulate rejection of allografts (e.g. bone marrow, kidney, and heart organ transplants-obviously a recent development clinically and not one that could have contributed to development of the system, responsiveness to microbial/viral threats and diseases (e.g. a subset of people survived the plagues in the past, and HIV infections currently), and other immune-mediated events. Interestingly, this system also appears to play a role in the reproductive success of humans. That is, individuals of very similar major histocompatibility complex (HLA) antigens are more likely than those who are disparate at this genetic locus in failing to carry a fetus to term [9, 10]. As the fetus is an allograft, and one that has the potential of inducing a rejection response, this means that diversity has a positive influence on reproductive advantage. Thus, human breeding success would enhance this diversity. Interestingly, humans are thus extremely outbred as a consequence, and inbreeding leads to the elaboration of genetic defects due to what would have been otherwise silent or recessive mutations. This is also observed in pigs, where breeds are only 15% - 20% inbred, but not in rodents such mice which can be inbred to the point of near identity with maintenance of reproductive efficiency. While mice have a histocompatibility system analogous to the human HLA system [the H2 system; [11]], apparently it must function somewhat differently as they can be inbred. However, as a consequence, mice may not be representative of humans at multiple levels including this one.

While all of the above discussed variables (radiation, gravity, and geomagnetic fields) have influenced who humans are today, the two that are most likely interdependent are the electrical/biomagnetic based system and those focused on functioning in the 1 g environment of Earth. This is likely due to the central (brain) control of many of the systems involved in the 1 g adaptations such as muscle, bone, and cardiovascular systems. Adapting to the 1 g environment, predecessors of current humans learned to walk up-right, a feature that likely enhanced survival, and an alteration that likely required further adaptation to the spine (for stability), the lower extremities (muscles, tendons, ligaments, bones), the cardiovascular system (in order to pump blood to the extremities), and other systems that are wired into the brain such as neuromuscular control, vestibular orientation, pain, and ability to perform complex self-environment tasks. The fossil record is somewhat fragmented, but a number of variants of humanoid species have been reported, but it is not always clear what is directly in the path of current humans, and what were off-shoot "experiments" that did not offer functional advantage (e.g. current primates) or long term survival to continue the development to *Homo sapiens*! Obviously, current humans were able to adapt and exert functional mastery compared to potentially other species/lines who eventually disappeared or were partially assimilated, via enhanced hunting prowess, reproductive advantage, due to enlarged brain capacity and integrated functioning, or some other advantages.

Clearly, aspects of the primordial systems related to development in a fluid sac followed by subsequent direct exposure to the 1 g environment were retained, as were many of the systems required for functioning in this 1 g environment. Thus for humans, a long period of development in a fluid sac as an "allograft" in the mother led to protected development to a point where essential systems had matured to a stage that allowed birth and subsequent exposure to the 1-g environment, as well as more autonomy with regard to food intake, waste removal, and breathing.

The key adaptations that led to improved functioning in *Homo sapiens* were similarly, most likely re-

lated to the regulation of these systems, with their integration leading to a highly mobile species which walks up-right, and has the neuro-abilities to be a successful hunter and avoid predators, as well as the abilities to effectively transfer critical knowledge to subsequent generations.

While the basic process of development within a fluid sac is similar in some respects between many mammals, there is considerable variation between different species in the functionality of the off-spring immediately after birth. That is, a zebra is born and can then run with the herd within minutes. Thus, there is a survival advantage to having development proceed directly to a mobile and functional off-spring quickly after birth. As such, the developmental programing is sufficiently complete and incorporates the genetic needs to support independence at birth. In contrast, marsupials give birth to very "immature" off-spring after a short gestation which then requires a prolonged post-natal period to obtain the functional systems needed for independence.

In contrast, humans are born after an ~9 month gestation, and even then are born without the ability to walk upright and be mobile in their 1 g environment. It is likely that after joint cavitation and movement is established, that there is some influence of gravity while in the womb, and as well, the geomagnetic field can be sensed by the fetus during brain development. However, it is only after an additional period of time (ranging from 8 - 15 months usually) have human infants developed the ability to walk upright and be mobile, are able to exert the neuromuscular control and visual acuity to navigate their environment, and develop the fine motor skills to exert eye-hand coordination. Interestingly, many primates exhibit the same progression at birth and during early development, although the timing may vary, but then they do not progress further. Thus, the early regulatory pathways and the systems involved may predate the separation of humans from other primates in the past.

In the context of the above discussion, what physiologic systems might be involved with regard to the 1g environment, and how might they be regulated? First of all, given the variation between individual humans in gaining the ability to function up-right and exert vestibular control, and be mobile in the 1g environment with regard to timing post-birth, the critical events are likely not "fixed" in time, but may be dependent on several maturational pathways converging (neuromuscular control; visual acuity distinguishing self from the environment; actual muscle, tendon, and bone strength and their neural integration; cardiovascular competence required for walking upright; others). Secondly, the variation in timing does not appear to be detrimental to survival, but microgravity or microgravity simulation may influence developmental programs which could impact later events [reviewed in [12]]. Thirdly, the variations may be due to otherwise "silent" mutations (as long as one stays within the 1 g environment) within the central systems involved, or in some peripheral ancillary systems. If this is true, they may only become evident when the environment is drastically altered such as in microgravity or space environments. The question of whether there is any correlation between some of these developmental factors and the responses of astronauts to microgravity has never been asked based on a search of the literature. Furthermore, in space or non-Earth environments, those with short times to independent mobility and navigation may be less able to adapt to such non-Earth conditions than are their counterparts who take a much longer time frame (*i.e.* 7 - 8 months vs 13+ months). However, it may depend on the specifics of the environment (*i.e.* 1/6 g and no geomagnetic field on the moon, 1/3 g and no geomagnetic field on Mars, microgravity and magnetic field of the habitat in space).

Insights into what the actual systems are and how they might be regulated may be gleaned from "accidents" occurring during fetal development in humans on Earth, exposure to microgravity and loss of the 1g environment restrictions and their subsequent recovery after a return to earth, and information from manipulation of other species or exposing them to microgravity environments (a less ideal scenario based on the above discussion, but such experiments may be informative none the less). Better understanding of the systems involved regarding their effective establishment to achieve optimal functioning in a 1 g environment, and thus the variation may also provide insights into their regulation during maturation to skeletal maturity, adulthood and potential contribution to senescence and aging-related conditions and diseases! That is the premise of this review.

2. FETAL AND POST-NATAL MATURATION TO PRE-PUBERTY "MATURITY"

As mentioned above, humans develop *in utero* in an aqueous environment, initially somewhat protected from the 1 g environment. Thus, for ~9 months, the fetus develops in an environment that mimics in part, the marine/aqueous environs of our primitive ancestors with its buoyant influences. During development, articulating joints are induced by cavitation, bone-tendon-muscle units become organized, coordinated and innervated, leading to the first vestiges of movement and mobility. Cardiovascular system development likely precedes some of these changes, while other aspects may develop coordinately. Whether all of this programed development *in utero* is based purely on the genome of the fetus, or is also indirectly influenced by the mother's constant mobility in a 1 g environment via transplacental information transfer remains to be defined. Thus, by 5 - 6 months of gestation, the fetus is capable of movement and is fairly well developed. Therefore, the third trimester of human gestation is focused on gaining weight, further development of some physiologic systems such as the respiratory system, as well as continued brain development, and system maturation and integration to better function in the post-natal world.

Thus, the basic/fundamental systems required for post-natal functioning in a 1 g environment may be in place following the first two trimesters of human gestation. This conclusion is further supported by the fact that preterm delivery of a human fetus does not have overt complications regarding subsequent maturation and functioning in the 1 g environment. Of course, there are limitations regarding how preterm the infant actually is and subsequent survival. Some of the survival is dependent on advances in neonatology for sure, and it remains to be determined whether all aspects of the fundamental systems are in place in a one pound infant, or some can continue to develop after birth in a protective and assisted environment.

Surviving birth is the first step towards maturity leading to functionality in the 1 g environment of earth (as well as integration into its geomagnetic fields and endogenous radiation background) for humans. Once essential systems have matured to allow for upright walking, and some autonomy, other systems then mature, such as learning to communicate verbally (2 - 3 years of age), developing a fully functional immune system (up to 5 years), learning skill development, and then puberty (11 - 13 years of age) followed by skeletal maturity (16 - 18 years of age). These pathways can differ in timing in different individuals, as well as the final outcomes (intellectual capacity, musculature and neuromuscular control, growth rate, as well as sex-dependent differences). Likely all of these are related in part to patterns laid down regarding the boundary conditions of earth (*i.e.* 1 g, geomagnetic fields, background radiation), genetics and epigenetics, as well as access to nutrition and exposure to microbes and potential pathogens.

The above discussion describes the general sequence of events and outlines some of the issues involved for the fetal and post-fetal time frame. More specific discussions are addressed below with incorporation of relevant references to specific issues regarding how environment could impact seminal events.

3. DEVELOPMENTAL ERRORS OR "MISSTEPS"-ARE SOME OF THEM IN SYSTEMS RELATED TO OPTIMAL FUNCTIONING IN A 1 G ENVIRONMENT?

The above discussion regarding successful living in a 1 g environment was focused on elements regarding the relationship age and function. However, it is also possible that the implementation and establishment of the required physiologic systems is not perfect, and some developmental "missteps" could also provide some research direction to better understand the systems and their regulation.

As discussed above, development and maturation of a human are complex, with successful generation of a functional phenotype requiring the integration of a number of parallel and sequential steps over the course of establishment of the end result. In this context, considerable variation is accepted (e.g. height, neuromuscular abilities, intellectual integration) so the strength of the process for human survival is likely its flexibility and ability to accommodate variation.

In the context of its complexity, the opportunity for errors or missteps to occur increases, partly due to stochastic events, genetic recombination risks, epigenetic modifications or environmental factors. Op-

portunities for error risk can arise either centrally (e.g. in the brain) or in the periphery (e.g. un-responsive or hyper-responsiveness at the level of targets of central regulation). As the result of such errors would likely be manifested peripherally, integration of the research effort between, for example, neuroscientists and those focused on bone-tendon-muscle complexes would be required to decipher the mechanisms involved.

An example of a candidate condition or error in development that involves a system required for functioning upright in 1 g may be cerebral palsy (CP). CP is believed to be condition that arises in the brain, but is manifested in the periphery as compromised function of the bone-tendon-muscle complexes. Such compromises can be restricted to upper or lower extremities, or both. The spasticity associated with CP as associated with abnormal functioning of locations in the brain, but may not be restricted to one neural centre to impact outcomes [13-17]. This somewhat distributed approach to function is not restricted to CP, and can also be evident in vestibular disorders and eye-hand coordination in children as well. While clinician-scientists are focused on the how such errors occur, and what can be done to alleviate their impact, most do not associate the missteps with the issue of functioning in a 1 g environment, or ask why conditions such as CP are so prevalent. If these conditions were also prevalent in prehistory, likely the affected individuals would not have survived due to the effort required to sustain them and the fact that they may not have contributed to the survival of the family/clan/tribal unit.

In the case of CP, the extent of the development error is overt. However, it is also possible, and likely, that other less obvious or even subtle developmental "errors" occur on a regular basis and are undetected due to a lack of overt pathology or detectable abnormality with today's technology. Thus, such "errors" can occur on Earth with modest frequency, and the impact on outcomes of space environments may shift such subtle errors to become overt effects on function with the removal of both the 1 g and geomagnetic elements in deep space.

4. SEXUAL AND SKELETAL MATURATION-WILL IT STILL OCCUR NORMALLY IN A SPACE ENVIRONMENT?

In the above discussion, the focus was on the direct influence of space environments on development and early maturation, as well as the indirect effect of parents exposed to space environments on the development and early maturation of their offspring. The next transition point where space environments could influence outcomes for *Homo sapiens* is the onset of puberty and subsequent skeletal and physiologic maturation. For both males and females, puberty is associated with a growth phase and sexual maturation, but for females this is accompanied by a more complex set of physiologic elements. Thus, for females there are structural alterations (*i.e.* Q angle of the hips), as well as physiologic changes that are dynamic (*i.e.* menstrual cycles). Such hormonal changes are imposed on the "baseline" of the outcomes of the developmental and early maturational programing.

Based on the above discussed scenarios, the outcomes of the post-puberty and maturity programing may have multiple outcomes on a *Homo sapien* conceived and developed in a space environment. The first is that they may *not* different from a human going through the same sequence on Earth, with the same heterogeneity leading to variations, but within normal limits. Alternatively, the process in space leads to overt alterations that may compromise function relative to Earth, but may also lead to enhanced functioning in the space environment. Thus, the outcomes may lead to compromise in the long term of function, or to changes that could lead to adaptation to a space environment (adaptive evolution). In this regard, the series of events could be considered a set of "experiments" regarding the adaptability of humans to new environments, and the analysis of the consequences of altered environments on human functioning. Unfortunately, it may depend on the humans "selected" for the experiments, and that aspect may be difficult to define given our current understanding regarding response patterns of astronauts to space environments thus far (discussed below).

Some of these reproductive issues and other related issues have been addressed previously by Ronca and colleagues [18, 19]. Certainly such issues are central to the long term sustainability of colonies of hu-

mans in non-Earth environments.

5. INSIGHTS FROM SYSTEMS IN SKELETALLY MATURE ASTRONAUTS AFFECTED BY EXPOSURE TO MICROGRAVITY

Exposure of skeletally mature cosmonauts and astronauts to microgravity conditions (as well as altered geomagnetic fields and changes in exposure to radiation) in Low Earth Orbit (LEO) could not have been anticipated during human evolution. Prolonged exposure to microgravity has been a recent "opportunity" of the past 50+ years. Actually, this opportunity has provided insights into the regulation of physiological systems on earth exactly because it could not have been anticipated! More recently, the existence of the International Space Station (ISS) has permitted the study of humans in space in a somewhat controlled environment with equipment to both assess changes, and potential counter measures to evaluate their effectiveness.

The physiologic changes that have been focused on over the past several decades include muscle atrophy, accelerated bone turnover (particularly the lower extremities), alterations to cardiovascular tone, loss of vestibular perception and altered vision, as well as some cognitive influences [reviewed in [20]]. Whether the potential cognitive impact of microgravity is a direct effect on the brain, or an indirect effect via the cardiovascular changes is not yet defined. However, since exercise can diminish aspects of dementia onset and progression [21, 22], involvement of these responses to microgravity may be more related to cardiovascular tone than a direct effect on cognition. Disruption to vestibular control, a fundamental central neurosystem, occurs rapidly on exposure of adults to microgravity, but then re-orientation adaptations occur over ~2 weeks [personal communication; Dr. Guiseppe Laria, University of Calgary]. Therefore, this system which is important for functioning upright on Earth remains sufficiently plastic to accommodate the LEO microgravity. Thus, some of these brain functions must not be irreversibly fixed during the initial post-birth years.

Interestingly, there is considerable variation between individuals in their responses to microgravity. Some lose bone at ~2% a month, while others lose 0.2%. Astronauts also vary in the recovery of bone after returning to earth. The effectiveness of resistance training versus aerobic training in impacting bone loss has been noted [23]. Furthermore, disturbances to vestibular perceptions do not as yet appear to have lasting impact, and many astronauts recover very rapidly after returning to earth. Interestingly, the vision alterations induced during exposure to microgravity may not rapidly revert on returning to earth. While most of the astronauts have been males, it has been reported that vision changes affect male, but not female astronauts [20]. Whether such sex differences are evident if/when more female astronauts are assessed, it is an interesting preliminary finding. Why there should be sex-based differences in this response to microgravity is not currently clear. However, it is known that eye shape can change during pregnancy and surgical menopause in rabbits can lead to molecular alterations in tissues and fluids of the eye [discussed in [24, 25]; Hart, unpublished findings], therefore, the female eye may be regulated differently than those of males. This may also be relevant to the role of the eye in addressing vestibular disturbances in space, but these relationships have not yet been addressed based on a search of the literature.

It is also important to point out that all of the astronauts and cosmonauts that have been exposed to prolonged microgravity are skeletally mature, and usually between 35 - 50 years of age. Thus, the females are likely premenopausal (although a 56 year old female astronaut was on the ISS and likely post-menopausal), and nearly all of the men are young to middle age (except perhaps for John Glenn who made a return trip to space when he was 77). Thus, the impact of exposure to microgravity, an modestly altered magnetic field and different types and intensities of radiation on skeletally immature and sexually immature humans has not been investigated since they are likely variables not relevant to the current space programs.

While very young humans have not been in space, some experiments in space and space analogues have been carried out with rodents, and other experimental models (e.g. fruit flies, worms, and fish). Fish have mated and yielded live births in space and early maturation occurred without obvious defects [26]. These types of studies are encouraging, but fish are fish which live in a very different environment than

humans. They likely are also not as heterogeneous as humans (as discussed in an earlier section), so considerable validation and verification is needed. In addition, pregnantrats have been flown on the ISS and the offspring born normally and they were viable, but did exhibit some developmental deficits [27, 28]. These were vestibular in nature, and since the ISS is still under the influence of most of the geomagnetic field of Earth, attributed to microgravity influences. However, this does raise the point that abnormal gravity and a loss of the geomagnetic field in the future could lead to interactions that compound the impact of each variable individually on the developing human!

6. INFORMATION DERIVED FROM SPACE FLIGHT ANALOGUES

As mentioned above, the N for people who have gone into space and had prolonged exposure to microgravity is relatively small (approximately 600; https://www.worldspaceflight.com/bios/stats.php). However, the N has increased in recent years due to the crew capacity of ISS becoming 6. Given the cost, the risks, and the crew limitations to sending people into space, many have turned to analogues on earth that may mimic the changes observed in space. Likely the one that exhibits the most features of space flight and affects similar physiologic systems is 6˚ degree head down tilt with prolonged (days, weeks or months) bedrest [reviewed in [29, 30]]. Of interest, this approach mimics the microgravity environment of space, without modifying the geomagnetic field and background radiation parameters. Thus, the analogue is mainly of the microgravity component, likely in isolation. The bed rest component eliminates much of the 1 g element and the ground reaction forces used when an individual is upright and mobile, while the 6^0 head down tilt is believed to mimic the disruption of fluid distribution and many of the same cardiovascular and brain associated changes as are observed in microgravity [[31]; and others]. Similar to space flights, most bedrest studies have used young, healthy skeletally mature males and females. Also similar to space flight, this form of bedrest leads to alterations in cardiovascular tone [31], muscle atrophy, accelerated bone turnover, and altered metabolism in part due to muscle associated insulin resistance [31, 32], but whether it leads to an impact on vision or an acceleration of vestibular disruption or cognitive decline remains to be confirmed. However, if exercise inhibits cognitive decline in the elderly [21, 22], it would not be surprising if sedentary bedrest led to an acceleration of such decline (and an exercise-based countermeasure could prevent such associated declines).

Of interest, and again similar to actual microgravity exposure, the physiological responses to this form of prolonged bedrest are very individual, with considerable variation again noted between volunteers in these studies with regard to the time to onset, degree or extent of the changes, and recovery. Again, such variation appears to be silent while the individual is maintained in the 1 g environment that apparently "over rides" the impact of the mechanistic basis for the variation when the environment is altered to the bedrest situation or exposed to microgravity. Of note, the impact of such analogues on epigenetic alterations in specific systems has not been reported to the author's knowledge.

Aside from being a space flight analogue, prolonged bedrest also occurs in populations on earth, mostly the elderly but also some younger people and even a subset of pregnant females. Thus, the outcomes of bed rest studies could have relevance not only to space flight, but also better understanding of life on earth. In fact, some have advanced the concept that exposure to microgravity and space flight (and by extension, analogues) are forms of accelerated aging [33, 34], forms of aging that can be reversed in some of the individuals affected. This is an intriguing concept that may or may not utilize the exact same mechanisms, but sheds some potential light on possible lines of investigation to pursue regarding the validity of the concept. For instance, aging in some individuals may be associated with a decline in the regulatory integrity of the systems evolved to allow for living in a 1 g environment, and thus, there could be overlap with potential interventions/countermeasures. Such declines may be accelerated with an increasingly sedentary lifestyle with aging, and it is known that exercise can prevent/inhibit the rate of decline in age-associated systems (muscles, bones, cardiovascular, cognition). Therefore, it is curious that similar systems are affected by exposure to microgravity, the bedrest analogue, and aging, but it remains to be determined whether the same mechanisms are involved. In this regard, it would be interesting to determine

physiologic and genetic responses of astronauts during a shorter term (10 - 14 days) bed rest study and their recovery pathway, well in advance of their scheduled space flight. It should then be possible to compare those responses to the ones that occur in actual space flight and during time on ISS, and the effectiveness of that recovery phase after returning to earth. Certainly, investing in projects using the appropriate experimental designs may have considerable implications for the treatment of aging-associated conditions, as well as more complete understanding of human development, maturation, and decline during aging, in addition to the development of intervention strategies. Such studies may also reveal the spectrum of genetic mutations that are silent as long as humans remain in their earth-bound habitat, information that could potentially be used prior to aging to negate their influence and modify disease risks. It could lead to benefits on earth beyond the investment for space and its potential to explore and live in space-related environments with their altered gravity (e.g. the moon at 1/6 g and Mars at 1/3 g), and as well as their lack of a magnetic field plus radiation risks.

Of critical importance to those in future generations, another response to prolonged space flight (*i.e.* 1 year) is epigenetic variations that occur in some of the cells while in space [35]. Whether such changes are consistent between astronauts, occur in all of the tissues affected by the space environment, occur in some orderly fashion with time in space (*i.e.* short vs long term), occur as a direct or indirect of time in space, and whether cells of the reproductive system of males and females are affected, are questions that remain to be answered. The last possibility is of critical concern since some epigenetic alterations can be inherited from either parent [36, 37], and can influence the metabolism and outcomes in off-spring [38].

7. WHAT MAY HAPPEN WHEN THE DEVELOPMENTAL AND MATURATIONAL PATHWAYS DEVELOPED FOR EARTH CONDITIONS ARE IMPLEMENTED IN SPACE AND OTHER NON-EARTH ENVIRONMENTS?

This question, and the answers to it, are critical if humans (*Homo sapiens*) are to become a spacefaring species in which future generations born on the moon, Mars, and beyond are to mature and function in non-Earth environments. Thus, development of mobility and integration into navigation in an environment requires sophisticated molecular coordination in a temporal sequence that is likely programed over eons during human evolution on Earth. Certainly, gravity is likely an important consideration for several processes in embryos and the fetus [discussed in [39, 40]]. If indeed the fetus can detect the 1 g of Earth during gestation [40], then it would potentially also be able to sense the "abnormal" lower gravity of the moon [1/6 g] or Mars [1/3 g] and adapt accordingly. Such adaptation may impact the post-birth set points which form the basis for subsequent maturational events and processes.

Similarly, regulation of fluid control via the cardiovascular system also requires fine tuning of basic mechanisms, again with neural control, and again likely based on programing derived from Earth boundary conditions. With these two examples, will humans be able to modify such programs to yield a functional human capable of survival in such environments, and in a reverse of that situation, will they be able to continue to function following reverse adaptation to the boundary conditions of Earth?

Developmental programs are designed and fashioned in an attempt to optimize the fetus to survive in the post-fetal environment. Thus, in the example of the zebra, the length of time in the fetal state and preparedness to survive, means the ability to be born and then up and running with the herd within minutes. Therefore, to be successful the program must be fairly hard wired to allow for a near immediate response to the external environment. In contrast, in some marsupials, the offspring are born very immature, and they survive in that environment to mature to a state of independence. Thus, in that situation the pre-birth programing must allow for the post-birth maturation and maybe is less hard wired. Humans appear to use the first two trimesters of fetal life gaining developmental integrity, and the last trimester gaining additional maturation to enhance survival in the post-birth environment, but are still born very dependent on the mother for an extended period of time before developing independent mobility and navigation abilities in the 1 g environment. Likely, cardiovascular system development and the basics of brain function occur *in utero*, and thus those aspects are hard wired. That likely means that the brain develops *in utero* in the

presence of the geomagnetic field in that location, along with the ambient background radiation. However, the post-birth maturation of the MSK system and its integration into the brain (or vice versa) may occur via a blue print outline rather than a hard wired program. The finding of rather large variations in this musculoskeletal maturational sequence to walking (8 - 15 months post-birth) may indicate this program has plasticity which follows a blue print rather than a hard wired response pattern. Thus, this aspect of maturation would then dependent on the external environment, including the 1 g gravity of Earth, or if in space, that particular environment. If this is true, then it opens the door for establishment of a biological set point dependent on the environment. As some upper extremity neuromuscular training (e.g. eye-brain-hand control) appears to occur in humans prior to walking, this may be a logical comparator to lower extremity variation in bone-tendon-muscle coordination under non-Earth conditions.

Thus, integration of functional systems biology at the developmental levels with the knowledge gained from studying responses on exposure to acute or chronic microgravity may reveal insights into the complexity of the system. One approach is would be to modify the "template" that humans have used and are using in other complex circumstances. One could approach this modification by gene editing or other molecular techniques, or use parents who have been epigenetically altered due to time in space conditions.

While still somewhat preliminary in nature (e.g. N = 1), the concept that spending time in a space environment leading to epigenetic alterations in blood cells has been reported [1]. As mentioned above, this finding leads to the potential for space-associated epigenetic alterations to be inherited [36-38] if cells other than blood cells are also altered either in some cell and tissue-specific manner or generally. Further, it would be important to determine whether genetically heterogeneous astronauts experience some of the same epigenetic alterations. Regarding the latter point, it has been shown that individuals from two very disparate populations (Dutch and Han Chinese) experience similar epigenetic alterations following prolonged starvation [41]. Other "natural experiments" also have been implicated in altering fetal development leading to risks later in life [42].

If further investigation indicates that fetuses conceived from parents epigenetically modified by space environments yield inheritable modifications, then likely the program evolved on Earth to embrace the boundary conditions of Earth will be changed in unpredictable manners. In part, the outcomes would be dependent on whether the epigenetic alterations were similar or common between adult individuals, or exhibited some astronaut-specific alterations. One approach to circumvent this dilemma would be to take frozen (and radiation protected) embryos generated on Earth prior to space flight to alleviate aspects of this complicating scenario.

8. AN OUTLINE OF POTENTIAL RESEARCH TO ADDRESS THE ISSUES DISCUSSED AND PROVIDE NEW RELEVANT UNDERSTANDING

In order to address some of the issues raised in the above discussion, several lines of research could be undertaken to provide further insight into aspects of the potential problems. Some of these would require the cooperation of astronauts as employees of their respective space agencies, while others would not. If not possible to use a sufficient number of astronauts, perhaps the lifespan of the ISS could be extended and turned into a laboratory populated in part by astronauts to maintain the facility, and others that would be contracted to be study subjects [43].

1) Better genetic analysis of those who will be exposed to space environments is needed. Human responses to living on the ISS are quite variable and the genetic basis for such variability is needed. Sequencing the genome of astronauts prior to first flight (and potential additional flights) could provide considerable information regarding correlations between genetic/epigenetic variables and responses to space flight.

2) Better understanding of the epigenetic alterations associated with exposure to space environments is needed. For males, this could be investigated by assessing blood, sperm and muscle biopsies with samples taken before, during (early and late), and then after return to Earth (to assess reversibility). For females, this could be assessed using blood samples and muscle biopsies taken at similar intervals. The re-

sults would indicate whether the changes are similar between genetically diverse individuals, whether there are tissue-specific changes occurring, and whether any possible sex-dependent alterations occur within a tissue or cell population.

3) Determine whether any epigenetic changes occur during the prolonged bedrest space analogue (males and females). As mentioned, some aspects of the changes occurring during such bedrest mimic the space environment. Therefore, are epigenetic changes occurring during bedrest, and if so, are they similar to those occurring in a space environment?

4) Assess the epigenetic changes associated with pre-clinical models. Some characterization has been done with fish and other models [12], but work with rodents is more limited. However, pregnant rats were sent to the ISS and the offspring born in space [27]. The offspring were born without overt problems, but post-flight assessment indicated some developmental/maturational deficits [27]. These were focused on vestibular alterations, and as the experiments were done on the ISS, were attributed to microgravity since the ISS is still under the influence of most of the Earth's geomagnetic field.

Thus, while acknowledging that rats are not humans and rodent data does not translate well to humans, data from parallel mouse or rat experiments performed on Earth and on the ISS regarding pregnancy, birth, and maturation with two or more genetically different mouse strains could yield some interesting results regarding species-specific epigenetic changes, strain-specific changes, sex-specific alterations, and whether some systems are affected more than others. However, some reports indicate that epigenetic mechanisms may not be operative regarding inheritance in inbred mice [44], but that might be related to their ability to be inbred and not reflective of humans. In spite of this potential limitation, mice may be a good starting point. This type of study may require returning frozen animals back to Earth for analysis, or the development of miniaturized technologies to assess live animals on the ISS. Furthermore, as the ISS is still under the influence of most of the Earth's geomagnetic field, the results would be a starting point to better design experiments to be performed in deep space beyond the geomagnetic field of Earth.

While other lines of investigation could also be entertained, based on the results of those outlined above, one could entertain others that may address specific issues (e.g. the influence of the geomagnetic fields of Earth on development and maturation) not feasible on the ISS, as well as the likely interactions between microgravity and loss of geomagnetic influences on development and maturation programs.

9. SUMMARY

Identifying and characterizing physiologic systems, and their molecular underpinnings, that have contributed to the success of humans to survive, adapt and dominate their earth environment with its various demands (e.g. 1 g gravity, geomagnetic field, background radiation) that imposed boundary conditions for evolution is an on-going process, and is an area in need of thoughtful and well thought out research, particularly as it related to development and maturation of humans. As with all things evolutionary, there is no endpoint, just processes leading to "optimal" configurations without backing a species into an evolutionary corner and compromising adaptation. Space flight and exposure to microgravity has now offered the opportunity to explore what systems humans have used to gain advantage in the context of the boundary conditions of earth, how such systems define human lifespan, and how the dynamics of fetal growth, post-natal growth and maturation, and age-related declines are framed by these systems. Without such knowledge, the impact of supporting space-related ventures will not realize their potential for impacting humans on earth, nor how they will need to adapt to continue to explore space off of earth. We were not designed for space, and therefore if we are seriously committed to space travel, humans will have to learn how to adapt to the new conditions in a planned manner and not be restricted to attempting to recapitulate earth conditions using "countermeasure" thinking to trick physiologic systems into pretending to be on Earth, particularly as they relate to reproduction and maturation in non-Earth conditions.

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CONFLICTS OF INTEREST

The author has no conflicts of interest or disclosures to make regarding this review.

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