NUTRITION, METABOLISM AND THE CRITICAL PATHS: A CRITICAL REVIEW
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ABSTRACT

A mission to Mars is estimated to take ~2.5 years. However there remain some problems which until they are resolved will limit how long humans can remain away from earth. The biomedical counter-measures part of the critical paths has evaluated these risks. They include, bone loss, cardiovascular effects, muscle loss, nutrition and radiation exposure. Three of the risks are related to metabolism, namely bone loss, muscle atrophy and nutrition. Probably the most encouraging aspect of these problems is that they are known, and because they are important for human health on the ground there are reasonably effective treatments available for the ground analogs. However it still remains to confirm that the actual proposed flight protocols are effective, first on the ground (with analogs of flight hardware) and then inflight.

INTRODUCTION

Forty years have elapsed since the first humans first ventured into space. By any standards the venture has been successful; humans survive well enough that manned missions to Mars are being planned. A mission to Mars is estimated to take ~2.5 years. However there remain some problems which until they are resolved will limit how long humans can remain away from earth. Probably the most encouraging aspect of these problems is that they are known, and because they are important for human health on the ground there are reasonably effective treatments available for the ground analogs.

During the last few years NASA has systematized its approach to developing a counter-measures program. The process is the bioastronautics critical paths road map. The road map lists 50 risks. The document is a living object, undergoing frequent updates. (For the latest update, see www.criticalpath.jsc.nasa.gov). The risks have been divided into three color coded categories; potential show stoppers (red, R), serious risk of mission impairment (yellow, Y), and probably controllable (green, G). The risks have been further sub-divided into 551 ‘critical questions’. As with the risks, some questions are more critical than others.

Risks in the biomedical counter-measures part of the critical paths include, bone loss, cardiovascular effects, muscle loss, nutrition and radiation exposure. Three of the risks are related to metabolism, namely bone loss, muscle atrophy and nutrition. They are the topic of this review. Table 1 shows an abbreviated version of the critical paths for the bone, muscle and nutrition disciplines.

Table 1: Critical paths with metabolic/nutritional aspects.

<table>
<thead>
<tr>
<th>DISCIPLINE</th>
<th>ISS RISK (1 yr)</th>
<th>ISS (1 yr)</th>
<th>MOON (30d)</th>
<th>MARS (2.5 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Bone loss and fracture risk</td>
<td>Y</td>
<td>G</td>
<td>Y</td>
</tr>
<tr>
<td>Bone</td>
<td>Impaired fracture healing</td>
<td>G</td>
<td>G</td>
<td>R</td>
</tr>
<tr>
<td>Bone</td>
<td>Injury to joints and intervertebral structures</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Bone</td>
<td>Renal stone formation</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Muscle</td>
<td>Skeletal muscle atrophy with reduced strength and endurance</td>
<td>G</td>
<td>G</td>
<td>Y</td>
</tr>
<tr>
<td>Muscle</td>
<td>Increased susceptibility to muscle damage</td>
<td>G</td>
<td>G</td>
<td>Y</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Inadequate nutritional requirements</td>
<td>G</td>
<td>G</td>
<td>Y</td>
</tr>
</tbody>
</table>

The objectives of the critical paths road map is to assess risks for human space exploration and to use this information for prioritizing research and technology programs. Defining the questions and targets provides a means assessing progress towards the reduction and deciding when the level of risk is low enough to be acceptable.

BONE

The losses are primarily from the weight bearing bones. Figure 1 shows a summary of some of the available bone data compiled by A.D. LeBlanc. Note the high degree of individual variation. There is also much variation in loss sites. Bone loss is unevenly distributed.

There are two counter measures for bone loss. Firstly the use of anti-resorptive drugs (e.g. bisphosphonates). Millions of people already take bisphosphonates as a treatment for osteoporosis. Bisphosphonates have also been found to be successful in long duration bed rest studies (Shackelford et al., 2004). A second treatment for bone loss is to place load on bone by resistance exercise. This too has been found to be effective in attenuating the bone loss during bed rest (Cavanagh, Licate and Rice, 2005; Shackelford et al., 2004). Thus two independent counter-measures for the bone loss have been found to be effective in the best ground based model for space flight (Alkner and Tesch, 2004; Iwase et al., 2004; Shackelford et al., 2004).

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The reduction of the bone loss may not be complete or equally effective for all bones, but judging by the published data, it is better than 80%. Reducing the bone loss by a minimum of 80% makes the problem manageable. Consider a worst case scenario. According to recent flight data from the ISS, the highest bone loss rate observed for an astronaut/cosmonaut was ~2% per month (Lang et al., 2004). Reducing this by 80% reduces the rate to 0.4% per month. For a 2.5 year round trip this translates into a maximum loss of 12%. For 6 months ISS stay the corresponding value is 2.4% which for a worst case is acceptable. NASA’s management seems to have bought into this argument. They have decided to give US astronauts a bisphosphonate (Alendronate) starting in 2007.

Since the number of future US astronauts is going to be somewhere between 20 and 40 before the shuttle is retired means there will be little further opportunities to evaluate any other in-flight measures for long duration missions between now and 2010. It is not likely that there will be other long duration opportunities between 2010 and the start of the Mars expeditions 30 years from now. Between shuttle and Mars there will be lunar missions. The lunar missions will be only about 30 days in duration. It would therefore seem that NASA has made the decision that the bone ‘counter-measure’ problem is well on the way to being solved. However it still remains to confirm that the actual proposed flight protocols are effective, first on the ground (with analogs of flight hardware) and then in-flight. If the studies are successful, it would be appropriate for NASA to descope ‘bone’ and its associated questions from the critical paths and redirect resources to other high priority risks.

**MUSCLE**

Skeletal muscle is plastic, responding to external workloads. Less work is required during space flight and bed rest from the anti-gravity muscles because there is no longer the need to support the body mass. The result is a reductive remodeling of the anti-gravity muscles to adapt to the reduced work-load (Grigoriev and Egorov, 1992; Thornton and Rummel, 1977). In addition to a net loss of protein, there is a shift in myosin isoforms from slow to fast isoforms (Fitts, Riley and Widrick, 2000). Fast twitch fibers are primarily glycolytic and prone to fatigue with endurance. This metabolic shift towards increased reliance on glycolysis is found with space flight (Baldwin, Herrick, and McCue, 1993), the rat hind limb suspension model (Fitts, Riley and Widrick, 2000; Henriksen and Tischler, 1988; Langfort et al., 1997) and bed rest (Acheson, et al., 1995). Glycolysis is very effective for high intensity short duration acute activities, but if sustained output is needed, an energy profile where fat use is favored is desirable. An inability to sustain work output is a major cause for concern. Astronauts need to maintain as much functional capacity as possible during space flight for extra-vehicular activities (space station construction and maintenance, emergency egress and eventually exploring Mars. These are all functions that require sustained work output. Less protein to do the work and increased fatigability in this context are counter-productive.

A recent Soyuz landing clearly illustrated the seriousness of this problem. After a 5½-month flight, the Soyuz landed somewhere in Kazakhstan. It took more than 5 h to recover the crew. For safety reasons the crew had to get out of the landing capsule unassisted. It took them five hours to accomplish what should have been a half hour task. The misadventure provides strong evidence for impaired muscle functionality after Mars-like transit, demonstrating serious weaknesses in crew performance. All three crew members exhibited reduced capability, up to voluntary immobility. More work is needed on the muscle atrophy problem. Because of the limitations of the space craft environment it may not be possible to totally prevent the reductive remodeling of skeletal muscle, but certain functional capacities must be retained. NASA has defined what these capabilities are for a successful Mars mission. They include the need for dexterity, essential for manipulating tools and performing complex actions; examples given by NASA are deploying solar arrays and erecting a habit; good hand eye coordination is needed for driving the mission exploration vehicle and for teleoperating robotic aides. There is of course a need for maintaining strength, flexibility, agility for such essential tasks as putting on and taking off the pressure suits and most importantly the ability to move away from danger should the situation merit. All of these functions are well met by maintaining a similar level of physical fitness as pre-flight.

There is no longer any doubt that exercise is effective in ground based models for preventing disuse muscle atrophy (Bamman et al., 1998; Ferrando, et al., 1997; Shackelford et al., 2004). However the results have not been replicated in flight – beginning with Skylab and continuing through shuttle, MIR and the ISS. Indeed,
exercise has been part of US and Russian missions for more than 30 years; yet the problem persists (Cena, Sculati and Roggi, 2003; Smith, et al., 2005; Stein, 2001). In the first 10 ISS missions full functionality of the exercise equipment has been less than 50% and this together with the inadequate dietary intake accounts for the unsatisfactory results with the current in-flight exercise regimens (Smith, et al., 2005, Stein, 2001).

ENERGY BALANCE

Energy deficits have been found on most, but not all short duration shuttle missions and has been a consistent finding with long duration missions (Rambaut, Leach and Leonard, 1977; Rambaut, et al., 1977). The negative energy balance is a mission related effect on dietary intake and not a specific response to the absence of gravity. Dietary intake is mission dependent rather than subject dependent (figure 2, (Stein, 2001, Stein, 2000)) Astronauts on the same mission appear to eat about the same amount of food (figure 2).

Elsewhere, we have suggested that the inverse relationship between exercise and energy intake is due to problems in disposing of the metabolic by-products from exercise, namely heat and CO$_2$ (Stein, 2000). Thermoregulatory mechanisms are less efficient during space flight and this persists into the immediate post flight period (Acheson, et al., 1995; Fortney et al., 1998). Heat disposal has been shown to depress intake in both rats (Llamas-Lamas and Combs, 1990) and humans (Edholm, Fox, Goldsmith et al., 1964).

A negative energy balance is not an appropriate physiologic state when the need is to counter-act a net muscle catabolic state. Proteins are the 'machinery' of the body. All of the metabolic functions in the body, from cell division to obtaining energy from foodstuffs to host defense mechanisms to doing muscle work involve proteins. So it is important to prevent the breakdown of body protein for use as an energy source.

A similar degree of weight loss together with poor intake has been found with ISS astronauts. The same degree of poor intake and weight loss (4.4 ± 0.1 kg, n=6) that was found on MIR (Stein et al., 1999) is now being found with ISS crews (3.8 ± 0.1 kg, n=24, personal communication, S.M. Smith, NASA and (Smith, et al., 2005)).

There is great variation on the magnitude of the weight loss. It is not known whether the weight loss is continuous or whether an adaptation/accommodative state is achieved. Figure 3 shows data from the ISS (Smith, et al., 2005). The lines represent individual weight changes. The two heavy black lines represent least squares regression analysis of the data with either a linear or curvilinear fit. The curve fits suggests that a steady state is reached after about 100 days. The linear regression suggests that the weight loss is continuous. Both regressions are statistically significant. Which is correct? If the weight loss is continuous, then the problem is very serious, chronic weight loss is unsustainable over the 2.5 yr period it will take to go to Mars. On the other hand, establishment of an adapted state after ~100 days may be acceptable. This question needs to be addressed.

As yet there is no counter-measure being evaluated for the inadequate intake. We would like to suggest one. Weekly measurement of body mass with dietary consultation with the ground support team. In contrast to dietary records, measurement of body mass is a real measurement and can be directly related to energy balance status. Astronauts losing weight inflight should be encouraged to eat more. Body mass devices have been flown on many prior missions beginning with Skylab and including shuttle.

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Figure 2: Comparison of energy intake during the first two weeks of space flight for the 3 Skylab missions, shuttle SLS1/2 and shuttle LMS (Stein, 2001).

Figure 3: Weight change with flight on the ISS (Smith, 2005).
REFERENCES


