Bone Research and animal support of Human Space Exploration: Where do we go from here?

Emily R. Morey-Holton, Ph.D., NASA-Ames Research Center

NASA exploration goals include returning humans to the moon by 2015-2020 as a prelude for human exploration of Mars and beyond. The number of human flight subjects available during this very short time period is insufficient to solve high-risk problems without data from animals. This presentation will focus on three questions: What do we know? What do we need to know? Where do we go from here?: roles for animals in the exploration era. Answers to these questions are based on flight and ground-based models using humans and animals.

First, what do we know? Adult humans have spent less than 1% of their lifespan in space while juvenile rats have spent almost 2%. This information suggests that our data are rather meager for projecting to a 30-month mission to Mars. The space platforms for humans have included Skylab, STS/MIR, and STS/ISS and for animals have included the unmanned Bion series and shuttle. The ground-based models include head-down bedrest in humans (BR) and hindlimb unloading in rodents (HU).

We know that as gravity decreases, the impact forces generated by the body during locomotion decrease. For example, on Earth, your legs supports approximately 1 body weight (BW) when standing, 1.33BW when walking, and 3BW when jogging. On Mars, the same activity would generate 0.38BW standing, 0.5BW walking, and 1BW when jogging. In space, no impact load is generated, as gravity is minimal.

The well-known curves depicting physiological systems responses to spaceflight vs. time suggest that each physiological system acclimates to microgravity at a different rate. However, these curves were generated from assumptions based on techniques and timing of samples. For example, the gradual, continuously increasing, loss of bone and calcium is based on metabolic studies and pre/postflight measurements in humans. Current bone scanning procedures, while becoming more sensitive, are not sufficiently sensitive to detect early changes in adult bone that turns over very slowly. Rodent data suggest that bone changes begin very early in flight or during HU. Bone markers in BR and rats (both HU and space flown) indicate that bone formation slows quickly. Biochemical markers from BR and spaceflight in humans indicate an early increase in bone resorption . In adult HU rats, increased bone resorption has been reported. Whether the bone changes stabilize with time is not known.

The musculoskeletal system is composed of bones, muscles, joints, and minor components including connective tissues (ligaments, tendons, vertebral disks), blood vessels and nerves. The shape and size of the musculoskeletal system is determined by mechanical/gravity load, metabolic demand, and function over time. In other words, structural support is only one component of a complex system. Following spaceflight, both rodents and humans have postural problems as postural reflexes have slowed, muscles may be weak and damaged by reloading, and bones may be less supportive. The musculoskeletal system is an integrated system and fixing only one component may not improve the system. Strong muscles could break weak bones, strong bones will not go anywhere with weak muscles, and motion is not possible without appropriate neural input.

Bone is a very complex tissue. You cannot extrapolate from one site to another site in the same bone or from the exterior to the interior of a bone as the tissue remodels according to the loads (metabolic and structural) placed on specific bone sites. Those bone sites experiencing the highest muscle/mechanical loads on Earth are the sites most impacted by unloading. The Bion series of flights have provided multiple insights into flight changes in rodents. The masticatory muscles may change in space as the jaw will no longer be working against gravity. Evidence suggests that bone formation slows in the rat mandible at sites where muscle is not attached. Rat long bones decrease formation at the outer bone surface with increases in lipid droplets in the vessels and abnormal collagen patterns. These changes ultimately decrease the mechanical strength of the bones. In human crewmembers, trabecular bone appears to be lost faster than cortical bone and the usual mechanical compensation by periosteal expansion may not occur. Leg and spinal muscles lose mass faster and to a greater extent than bone, although recovery upon return to Earth is more rapid in muscle. Exercising may protect certain bone sites, e.g., heel bone and lumbar vertebra. Spinal scans from cosmonauts suggest that muscle atrophy may directly affect bone integrity. Many crewmembers report back pain that may be a function of less curvature and suggests that the disk function may be altered. Space flown rats have smaller lumbar annuli with altered collagen-to-proteoglycan ratios. These data suggest that the musculoskeletal system adapts to the space environment. This adaptation of the entire system makes the individual more susceptible to rips, tears, and fractures upon entering a higher gravity environment. Most data are pre/post flight, thus we do not know if/when bone stabilizes during flight and if there is a mineralization defect that might increase fracture risk or delay fracture repair. Only two flight studies on bone healing have been reported (in rats) and the fractures were initiated 3 or 5d before flight. Both studies suggest that bone healing is impaired. One study suggests that metabolic differences may play a role.

Given these data, we still need more information to mitigate risk of fracture and connective tissue problems for long duration missions. NASA has a limited budget and must maximize science return. This approach will require a new way of doing business. For example, NASA needs to determine the appropriate age, species, and genetic strain of rodents to quickly provide maximal insights into risks and fund only the use of these animals. Many investigators assume that a sexually mature (about 6 wks old) rat is an adult rat. Recent publications suggest that albino rats are not skeletally mature until the epiphyses close which occurs after the rat is 8 (male) or 10 (female) months old. Thus, rats at least one year of age should be considered for bone studies. Given that rats live approximately 3 years and humans 75 years, a one-year-old rat is comparable to a 25yr old human. The Wistar-Hanover outbred rat is a smaller genetic stain that is available across the world, is being used in a number of labs, and should be considered. Mice strains vary greatly in their response to unloading; mice strains with the highest bone mass show the least change while those with the lowest density appear to show the greatest change. The C57B6 mouse appears similar to the human in terms of ageing and unloading responses. In addition to selecting rodent age and genetic strain, NASA should institute an integrated test regime for rodent studies similar to the human countermeasures evaluation and validation program so that all major physiological systems all studied during each experiment. Measurements in animals should be similar to those in humans.

Rodents can make major contributions toward mitigating risks in the exploration era. Immediate studies in HU rodents can investigate bone repair. Animals should be adapted to HU prior to initiation of the fracture using a well-established fracture model. Such studies will determine if the fracture repair proceeds normally during unloading or if the bone changes with unloading impair the healing process. In addition, long duration HU studies should determine if bone alterations continue or stabilize over time and if these changes increase fracture risk or delay fracture repair. Once the process is defined, then exercise paradigms or drugs might be used to minimize critical musculoskeletal changes. Any countermeasure used for bone should maintain metabolic capacity, fluid distribution, muscle/ligament attachments points, disk integrity, and marrow components and not adversely impact any other physiological system. Data from these studies could lead to focused flight experiments. Once the centrifuge is on station, rodents can be used to obtain data suggesting whether moon gravity is sufficient to maintain fitness within acceptable levels.

The NASA vision is to improve life here, to extend life to there, to find life beyond. The exploration era has set impressive goals within a very short time frame. If we are to meet these goals, extensive animal experimentation, starting today, is required to meet the challenge of sending humans back to the Moon and eventually to Mars.