Fiscal Year:	FY 2011	**Task Last Updated:**	FY 02/27/2012
PI Name:	Hogan, Harry Ph.D.		
Project Title:	Contributors to Long-Term Recovery of Bone Strength following Exposure to Microgravity		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Bone Fracture**:Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (2) **Osteo**:Risk Of Early Onset Osteoporosis Due To Spaceflight		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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City:	College Station	**State:**	TX
Zip Code:	77843-3123	**Congressional District:**	17
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2007 Crew Health NNJ07ZSA002N
Start Date:	05/20/2008	**End Date:**	11/19/2012
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	2	**No. of Master' Degrees:**	1
No. of Master's Candidates:	3	**No. of Bachelor's Degrees:**	2
No. of Bachelor's Candidates:	4	**Monitoring Center:**	NASA JSC
Contact Monitor:	Baumann, David	**Contact Phone:**	
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Flight Program:			
Flight Assignment:	NOTE: New end date is 11/19/2012 per NSSC information (Ed., 6/01/2012) NOTE: New end date is 5/19/2012 per NSSC information (Ed., 5/31/2011)		
Key Personnel Changes/Previous PI:	Collaborator added: Dr. Stefan Judex, Stony Brook University		
COI Name (Institution):	Bloomfield, Susan (Texas A&M University) Martinez, Daniel (University of Houston)		
Grant/Contract No.:	NNX08AQ35G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

The project uses the adult male hindlimb unloaded (HU) animal model with three specific aims and associated experiments. The first aim addresses the observed "discordant recovery dynamic" reported for astronaut data (Lang et al., JBMR 21:1224, 2006) and will characterize bone mass, bone mineral density (BMD), and bone strength relationships after HU and during various periods of recovery. Additional outcome measures include bone biochemistry and gene expression. A major emphasis is to compare detailed dynamics between the animal model and astronaut data. The animal model also permits direct comparison of calculated/estimated bone strengths with measured strengths. The second aim examines multiple mission scenarios and will use HU, recovery for a period, and then a second HU exposure. The third aim will also follow the two-exposure protocol but with resistance exercise added during the recovery period.
The cross-cutting area, or element, of the Bioastronautics Critical Path Roadmap (CRP) that this research project addresses is Human Health & Countermeasures (HHC). The specific health risk is the Risk of Accelerated Osteoporosis as identified in the Bioastronautics Roadmap (Risk No. 1, Bone Loss, p. 19 of NASA/SP–2004–6113) and the Human Research Program (HRP) Integrated Research Plan (Risk 14.0). The Gaps addressed, as defined in the HRP-IRP, are:

B1 (Is bone strength completely recovered with recovery of BMD)

B10 (Time-course of bone degradation during missions)

The 2007 NASA Research Announcement (NNJ07ZSA002N) to which the proposal for this project responded included the following specific solicitation wording for Gap B1: "There are preliminary indications that overall bone quality/strength does not recover at the same rate that bone mineral density recovers after spaceflight. It is not known if there is a long term health effect related to this discordant recovery dynamic." {emphasis added} Research proposals are solicited that directly address this relationship. The specific topic solicited is: Novel research that defines the precise relationship between long term recovery of bone mineral density and bone strength/quality, including the effects of multiple spaceflights." {emphasis added} The research conducted as part of this project will provide unique data addressing these issues through well-controlled animal studies. The wide range of outcome variables will provide a comprehensive set of results that will give rise to new insights at the basic and applied levels.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

Results from this project will provide fundamental understanding of the way bone responds to mechanical unloading and how it recovers when mechanical loads are restored. Insights gained should be applicable to the clinically relevant case of aging adults with reduced activity levels, in addition to the effects of long term exposure to microgravity for crew members. Further, many of the same basic mechanisms overlap considerably with the broader health problem of osteoporosis and increased fracture risk in aging humans. It is widely known that bone mineral density (BMD) is not an accurate predictor of fracture incidence despite its wide use as a screening tool for osteoporosis. The findings of the research being conducted in this project will help to better define the relationships between BMD and other important factors, such as bone mineral content (BMC, i.e., bone mass), bone tissue quality, and most importantly bone strength. In addition, the project will identify which anatomic sites in the rat provide the closest correspondence to bone loss and recovery characteristics in humans (astronauts in this case). These results should bolster the utility and robustness of rodent animal models and linking their findings to clinical cases. Finally, the project will generate new and unique data on the effects of resistance exercise in restoring skeletal integrity during recovery from mechanical unloading. This information should be directly applicable to corresponding efforts aimed at using exercise to combat age-related losses from osteoporosis or related pathologies.

Task Progress:

As the project neared the end of Year 3, we requested and were granted a one-year no-cost extension. The project was originally posed in terms of three animal experiments, corresponding to the three Specific Aims. The original Specific Aims and Hypotheses are summarized in the following section. The animal experiments for Specific Aim 1 were conducted from September 2008 to August 2009. The animal experiments for Specific Aim 2 were conducted from October 2009 to April 2010. The animal work for Specific Aim 2 took slightly longer than originally anticipated due to modifications in the experimental design as described below. The animal experiments for Specific Aim 3 started in March 2011 and ended in November 2011. Much of the effort during year 3 (May 20, 2010 to May 19, 2011) was devoted to data analysis and post-mortem testing, as well as refining the detailed protocols for exercising the animals in the context of hindlimb unloading exposures. It should also be pointed out that another project review meeting was held during this year (11/16/10) with NASA–JSC personnel, as was also done the previous year (11/16/09).
Numerous new results were generated for a variety of tests, variables, and scenarios. This includes additional results for the loss and recovery animal experiments conducted during year 1. Because of the sequential nature of the procedures for many of the analyses, assays, and tests, results must necessarily be spread over a protracted time period following the conclusion of the animal experiment portion for each phase. The following new results were generated for the year 1 (experiment 1) phase of the project:

• Mechanical testing of the femoral neck. This included testing using both axial and lateral loading configurations, and also permitted direct comparison of mechanical strength results with pQCT results. Results showed a much more dramatic affect upon strength than bone mineral density and very little difference between axial and lateral loading cases.

• Mechanical testing of the distal femur metaphysis. Reduced platen compression (RPC) testing was used for this, and the protocols required careful and meticulous procedures for specimen preparation as well as mechanical testing. Results showed dramatic losses in trabecular bone density and strength, with the greatest losses in strength.

• Collagen biochemistry for the tibia midshaft. Results showed that HU had a strong and consistent negative affect on collagen content as well as cross-links.

• Proximal tibia micro-CT. Results were generated from our newly established collaboration with Dr. Stefan Judex at Stony Brook University. The data provide much higher resolution results and greater insight into the details of the effects of HU and recovery upon the proximal tibia metaphysis, including both trabecular bone and the cortical shell.

Additionally, numerous new results were generated for experiment 2, which consisted of two HU exposures plus recovery periods following each. Specifically, results were generated for the following:

• Longitudinal (in vivo) pQCT scans of the proximal tibia. These measurements allowed tracking of various densitometric parameters at 28-day intervals over a total of 168 days. Results indicated that previous HU exposure had no additional negative affect on the second HU, and may have even had a protective effect for some variables.

• Mechanical testing of the distal femur metaphysis. Reduced platen compression (RPC) testing was also conducted for bones harvested at each 28-day endpoint for the double–HU protocol. Once again, mechanical properties were much more dramatically affected by HU. Also, trabecular bone properties never fully recovered to baseline values although many did recover to aging control values. : The lack of recovery to baseline is consistent with reported crewmember data.

• Analysis of posterior crural (calf) muscles. Results showed that muscles were affected similarly for all three HU cases. Muscle properties recovered rapidly after each HU exposure.

Another major accomplishment during this project year was refinement and establishment of resistance exercise protocols to be used in the final set of experiments. Although the exercise protocols have been used previously other studies, there were several details that needed to be explored and updated for the current study. In particular, our goal was to exercise the animals for 7 to 8 weeks during the recovery period following the end of the first HU and until the beginning of the second HU. This entire recovery period was 8 weeks total. Thus, the procedures for operant conditioning of the animals had to be streamlined and shortened in order to allow a few days of recovery of the animals after removal from the first HU and early enough initiation of exercising in order to gain 6 to 7 weeks of meaningful exercise. This effort was enhanced significantly by our having direct interaction with Dr. James Fluckey and his graduate students here at Texas A&M University. Several technical and procedural challenges were encountered during this process but all were eventually overcome. The animal procedures for the last phase of the project (experiment 3) were initiated near the end of year 3 (in March 2011).

Bibliography Type:	Description: (Last Updated: 01/11/2021)
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