The goal of this research program is to eliminate stress fracture in initial entry training in the military, a problem estimated to cost the DoD in excess of $10 million per year in medical costs and lost duty time. Bone physiology research which leads to improved bone health of men and women will enhance military readiness by reducing the incidence of stress fracture during physically intensive training and is also expected to reduce the risk of osteoporosis and other bone disorders later in life.

Supported by the National Coalition of Osteoporosis and Related Bone Diseases, a fiscal year 1997 special appropriation from Congress provided $10 million for bone research. This program augments current Army and Navy funded research on optimization of physical performance and fills a distinct gap in federal bone research, with investigations of biomechanical influences on normal bone remodeling and repair mechanisms in physically active young men and women.

**Background**

Stress fractures have a marked impact on the health of service personnel. They also impose a significant cost to the DoD in medical costs by delaying the training of new recruits (e.g., costs due to stress fractures just among the 2,000 female Marine recruits trained annually are estimated to be $1,850,000/year, with 4,120 lost training days and an extended training period). Current stress fracture incidence for Army recruits is 2.6% for men and 8.1% for women in similar training. Recent Navy research demonstrates that thoughtful modification of physical training programs can delay the time to stress fracture occurrence and reduce the overall incidence of stress fractures without compromising physical standards or training level. The present program is expected to provide information to further reduce training injuries through: better identification of at risk individuals, scientifically-based training and dietary and medical interventions.

**Current Studies**

**Mechanical Influences on Bone Cells:** One study explores how bone cells sense their mechanical environment through specific cell surface receptors (integrins); determines the role of mechanical stimuli; and explores the signaling systems responsible for regulating gene expression of various matrix proteins. Applications will include concepts for tests of bone quality and approaches to enhance adaptive responses of bone to mechanical stimulation. Another study examines the mechanisms of bone cell stimulation from the flow of surrounding fluids during compression (loading) of the bone. As the bone matrix is repeatedly compressed due to physical activity, fluid flows in a network of spaces: this oscillating fluid flow is a potent stimulator of bone cells. This study examines the nature of the flow-induced signal transmission between cells, and possible age-related changes in this intercellular communication.

**Functional Imaging Technology:** Better and more sensitive methods are needed for the noninvasive assessment of bone metabolism along with bone density to detect normal bone remodeling, impending risk of bone injury, and bone responses to interventions. The development of positron emission tomography to ob-
tain high resolution images of labeled bone growth markers is being pursued with a device for three dimensional bone measurements that will detect physiological changes in blood supply, metabolism and drug accumulation.

Physiology of Bone Remodeling: Recent studies from humans and race horses suggest that increased remodeling precedes the occurrence of bone microdamage and stress fractures. The role of intracortical remodeling in the pathogenesis of stress fracture is being tested in a project using a rabbit tibial model. Alendronate (a drug used to treat osteoporosis) will be used to inhibit both bone remodeling and increased bone porosity to determine if microdamage and severity of stress fracture is diminished.

Hormonal Factors: Even a weak androgen such as dehydroepiandrosterone (DHEA), the most important circulating androgen in women, may play an important role in attaining and maintaining high bone mineral content in women. One study will determine if DHEA and other steroids downregulate cytokine production and upregulate insulin-like growth factor (IGF1) production in human marrow cells, exploring mechanisms by which DHEA can provide both anabolic and antiosteolytic actions. A separate animal study will explore the role of androgenic steroids to determine if oral contraceptive steroids (OCS) can reduce androgen levels and produce decreased bone formation and lower peak bone mineral. Oral contraceptives that contain even low level estrogens may have important positive actions for women who are estrogen deficient, including those with menstrual abnormalities resulting from nutritional and other military operational stressors. A study of young female runners will assess the effects of oral contraceptive use on bone mineral density and incidence of stress fracture.

Nutritional Factors: A placebo-controlled study of U.S. Naval Academy midshipmen is testing the hypothesis (based on regional bone mineral density and biochemical studies) that two years of dietary protein supplementation will improve benefits to bone health of calcium supplementation. Another study will test the hypothesis that ethanol reduces the ability of the skeleton to adapt to increased mechanical stress through direct effects of ethanol on bone cell membranes and disruption of cell signaling pathways for factors that regulate bone remodeling.

Effects of Physical Training: A previous study of cadets at the U.S. Military Academy defined changes in lumbar bone density of young men and women based on biannual measurements during their four years at the Academy. These subjects will be re-tested now, nearly a decade later, with special emphasis on case comparisons to a group of 24 men and women in the original study who did not demonstrate high rates of bone density increase during the study. Another study will follow cadets at the Academy to describe factors associated with stress fractures and factors which might influence the incidence of fractures. Another study is consolidating existing knowledge, published and unpublished, of the effects of resistance and endurance exercise training on bone mineral density in men and women using meta-analytical and other novel statistical approaches.

Stress Fracture Diagnosis and Treatment: The prolonged healing time of stress fractures with the conservative but generally favored treatment of rest from weight bearing activity is well known and averages three months. A double-blinded study is comparing recovery times from tibial stress fracture in subjects treated with active or placebo-controlled electric field stimulation, including evaluation of male and female responses. Diagnostic imaging methods (radiographs, bone scan, MRI, and CT) will be compared and a stress fracture severity grading system for each imaging tool developed.

Additional Studies: Additional funding to this program received in FY99 and programmed for FY00 will support projects to better understand individual factors such as: gait and anthropometry in risk for stress fracture, practical biomarkers for field assessment of bone metabolic status and prediction of impending injury, and additional basic research on biomechanical influences on bone. A longitudinal military “Framingham” study (which defines age-, gender- and weight status-related changes in bone, other aspects of body composition, and injury risk) is planned.

For more information on stress fracture research in the military, consult the Institute of Medicine review, “Reducing Stress Fracture in Physically Active Military Women”, available from National Academy Press at the web site below.

http://www.nap.edu/html/stress