Could Broken Hips and Other Fractures be Prevented?

An OREF-funded clinician scientist sought to answer these questions with metabolic bone research

William H. Harris, M.D.,
1960 and 1970 Research Grant recipient

Topic: Tetracycline labeling to study metabolic bone diseases

Result: Treatments for osteoporosis

Patient Care Application of Results:

Treatment of osteoporosis — a condition in which bones decrease in mass with increasing age, causing them to become fragile — which helps reduce risk of fractures or other injuries

Wrist fractures, broken hips, and sore backs are just part of growing older — or could they be potentially preventable injuries at any age?

This question prompted the Surgeon General to publish a report, *Bone Health and Osteoporosis: A Report of the Surgeon General*, in 2004. The report stresses the need for individuals to learn how they can prevent bone-loss diseases, such as osteoporosis. According to the report, although more research must be conducted on the subject, "great improvements in the bone health status of Americans can be made by applying what is already known about early prevention, assessment, diagnosis, and treatment."

Some of what is already known about metabolic bone diseases is the result of research that began with an OREF grant. **William H. Harris, M.D.**, director emeritus of the Orthopaedic Biomechanics and Biomaterials Laboratory at Massachusetts General Hospital, received research grants from OREF in 1960 and 1970 for his work involving tetracycline labeling. This led to research that covered several decades of studies of metabolic bone responses, spatial and temporal variation in cortical bone formation, skeletal reaction to internal fixation devices, and studies on skeletal balance and calcium and phosphorus metabolism.

"The orthopaedic surgeon sees patients with metabolic bone diseases not only in the form of osteoporosis, but, though more rarely, in terms of hyperparathyroidism or osteomalacia. The study of the rates of bone formation helps to understand these diseases," said Dr. Harris.

Tetracycline labeling was developed to help quantify rates of bone formation and to study the questions: Why do elderly women fall down and break their hips? Why do older patients suffer from spine fractures or break their wrists?

"The skeleton in everybody in the older age groups loses strength because it loses mass. It becomes weaker, and many hip fractures are not related so much to trauma but to the weakening of the bone. Many hip fractures, vertebral fractures, and wrist fractures are secondary to the weakening of the skeleton over time because of osteoporosis," Dr. Harris said.

According to Dr. Harris, the integrity of the skeleton is based on two processes which occur simultaneously: the formation of bone and the removal (or resorption) of bone. If bone removal exceeds bone formation, the skeleton weakens.

"It's like a brick wall in which you're removing some bricks all the time and replacing some bricks all the time. To maintain the strength of the wall, you must remove and replace bricks in balance."

Tetracyline labeling helped study this process by allowing measurement of rates of new bone formation. The tetracycline molecule, an antibiotic, is preferentially incorporated and retained at all sites where new bone is formed. Any new bone formed during the time the tetracycline was in the bloodstream fluoresces under ultraviolet light.

To learn whether too little bone formation or too much bone resorption is the culprit in cases of osteoporosis, new bone formation

Dr. William H. and Mrs. Johanna (Nan) Harris

can be measured by administering tetracycline markers at specific time points. For example, administering an intravenous dose of tetracycline one day and then another dose 10 days later would indicate where and how much bone was laid down in those 10 days. This method is valuable in answering the question of what causes osteoporosis.

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Tetracycline labeling also helps test potential treatments for the disease. To test a treatment, rates of bone formation must be measured to find out if the treatment slowed down the bone resorption, increased bone formation, or both.

"In addition there's a difference between whether the skeleton became stronger because of the treatment or just stopped getting weaker," Dr. Harris said. "One of the ways to find out if the skeleton has become stronger is to measure rates of new bone formation. There are ways other than tetracycline labeling to measure bone formation, and there are ways to measure bone resorption, but tetracycline labeling is one important method in measuring bone formation rate."

Tetracycline labeling can also be used to study other metabolic bone responses, which underlie many diseases other than osteoporosis, such as parathyroid diseases, osteomalasia, and the changes that occur in bone due to complications from cancer.

Throughout his research career, Dr. Harris continued to conduct research that involved bone formation.

"The skeleton doesn't uniformly respond. Some areas resorb a lot of bone, while others form a lot of bone, and yet other areas are quiet," he said. "If you performed a biopsy in a quiet area, it would look as if no bone was being formed, or conversely if the biopsy were performed in an active area, you would think bone was forming rapidly. So it's important to study over time which area is active and which is not."

Along with this study of spatial and temporal variation in cortical bone, Dr. Harris also studied the skeletal reaction to internal fixation devices to learn what happens to the bone underneath devices, such as plates, used to fix fractures. He also investigated how administering calcium or phosphorus can increase the formation of or decrease the resorption of bone to achieve skeletal balance. Work was also done on the effects of giving growth hormone.

In addition to being a clinician scientist himself, Dr. Harris supports others' research endeavors. Not only is he part of the Shands Circle, OREF's highest-level recognition society, but he has also contributed to the Annual Campaign at the Order of Merit level — $1,000 or more — for more than 20 years. Dr. Harris would like to see more young investigators receive support similar to the grants he received from OREF to further improve knowledge about bone diseases.

"Young investigators are somewhat like seedlings that begin to sprout in the spring. While their potential is enormous, so is their vulnerability," he said. **"It is at that stage**

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Why the Study of the Formation of and Resorption of Bone is Important:

From *Bone Health and Osteoporosis: A Report of the Surgeon General*

- Each year about 1.5 million individuals suffer an osteoporotic-related fracture.
- Four of every 10 Caucasian women age 50 or older in the United States will experience a hip, spine, or wrist fracture; 13% of men age 50 or older will also experience these injuries.
- As defined by the World Health Organization's bone density measurement, about 10 million Americans over the age of 50 have osteoporosis and 34 million have low bone mass of the hip, which puts them at risk for osteoporosis.
- By 2010, nearly 12 million Americans over 50 are expected to have osteoporosis and another 40 million to have low bone mass; By 2020 there could be about 14 million osteoporosis patients — one of every two Americans — and more than 47 million cases of low bone mass.
- Advances in scientific knowledge have led to an era in which bone diseases can be prevented in most individuals and identified early so that they can be treated in those patients who do suffer from them.

David Edelstein, M.D.

"As a small orthopaedic program with limited resources, the funding of our journal club truly enhances our educational experience. By funding our journal club, OREF gives the residents, including myself, the ability to set aside time and review journal articles in an organized fashion. The impact on my career lies in the critical thinking skills I've attained, as well as the ability to analyze literature now and in my future practice." — **David Edelstein, M.D.**, Maimonides Medical Center, Brooklyn, 2004-2005 *JBJS* Journal Club Grant recipient

Javad Parvizi, M.D.

In addition to the *JBJS* Journal Club grants, the *Journal of Bone and Joint Surgery* made a sizeable contribution to OREF to support a Clinician Scientist Award — OREF's highest award category — for three years.

The *Journal of Bone and Joint Surgery's* donation to OREF's 2003 fund made **Javad Parvizi, M.D.'s** Clinician Scientist Award possible. This award will provide Dr. Parvizi with a salary stipend of $100,000 per year until 2007.

With this funding, Dr. Parvizi is investigating Smart Implants with biological surfaces, which could possibly reduce the risk of periprosthetic infection, leading to improved longevity of the artificial joints and aversion of the psychological and economic costs to patients.

For information about making endowment gifts to OREF or funding a Clinician Scientist Award, please contact **Gene Wurth** at (847) 384-4362 or wurth@oref.org.

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that the stimulating and reinforcing support which comes from an OREF grant has its greatest impact and its greatest significance. The central role of OREF at that pivotal stage cannot be overemphasized."

William H. Harris, M.D.

While more research needs to be conducted to achieve a complete understanding of bone diseases, current knowledge, including that gained from Dr. Harris' tetracycline labeling studies, can help to treat or prevent the devastating effects of them, leading to a healthier, better quality of life for patients.

"The basic techniques learned in these studies were tools important in studying or beginning to understand bone diseases that the orthopaedic surgeon sees every single day," Dr. Harris said. "That problem has been successfully addressed by the introduction of medicines, such as the bisphosphonates and the intermittent use of parathyroid hormone injections, which inhibit or block the resorption of bone or increase formation. If bone formation continues but resorption of bone decreases, the skeleton is strengthened. And many of those basic studies hinged on the ability to measure bone formation. The OREF grant played an important role in establishing and maintaining this tetracycline labeling research."