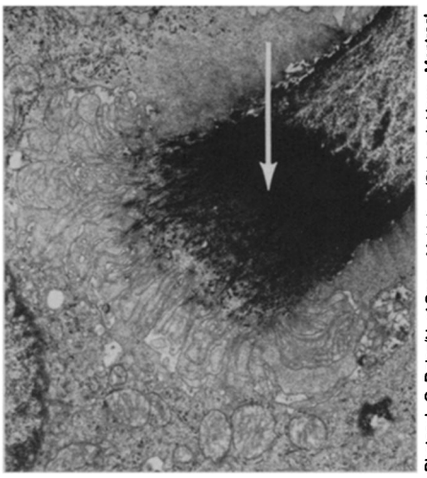
Boning Up on Osteoporosis

By JOAN AREHART-TREICHEL



Photos: L. G. Raisz/U. of Conn., M. Holtrop/Shriner's Hosp., Montreal.

"Business end" of an osteoclast secretes enzymes which dissolve a spicule of bone (see arrow).

Osteoporosis — fracturing of bone due to bone loss — afflicts millions of older Americans, especially women. It is responsible for spinal shrinkage and height loss, humped backs, hip fractures and considerable pain. In fact, many hip fracture victims die from shock, hemorrhage and other complications, making osteoporosis the 12th leading cause of death in the United States. The disease is estimated to cost a billion dollars annually in treatment, hospitalization and job loss.

Traditionally osteoporosis has been poorly understood, and prevention and treatment of it has been empirical. However, scientists are gaining important new insights and are coming closer to finding effective and safe preventives and treatments, a recent international bone disease symposium in Dearborn, Mich., revealed. The symposium was sponsored by the Henry Ford Hospital in Detroit, a leading bone disease research center.

Normally, human bone is made of a compact outer layer (cortical bone), an inner spongy layer (trabecular bone) and marrow. In contrast to marrow, both cortical bone and trabecular bone are routinely destroyed by cells called osteoclasts and routinely remade by cells called osteoblasts. The processes are called bone resorption and bone formation. Factors that may help bring about resorption, various scientists report, include calcium deficiency and the presence of parathyroid hormone or various other molecules, whereas factors that may help bring about bone formation include calcium, exercise, 1,25 dihydroxyvitamin D (the physiologically active form of vitamin D) and various skeletal growth molecules. There is also evidence that estrogen hormones inhibit bone resorption. However, the factors that influence bone resorption and formation are not well understood, says William A. Peck of Washington University School of Medicine in St. Louis, because "the field is in its infancy."

Nonetheless, advances in understanding healthy human bone have set the stage for better understanding of osteoporosis. And one of the most important insights into the disease is emerging from the lab of B. Lawrence Riggs of the Mayo Clinic in Rochester, Minn. It is that osteoporosis is not one disease, as formerly thought, but two. The first, postmenopausal osteoporosis, afflicts women 50 to 65 years old, involves loss of trabecular bone in the spine and forearm and fractures of the spine and forearm. The second, senile osteoporosis, afflicts both men and women aged 75 years and older, entails loss of both trabecular and cortical bone in the hip and leg and fractures of the hip and leg.

Scientists still aren't sure why postmenopausal osteoporosis occurs. But evidence from Borje E. C. Nordin of the Royal Adelaide Hospital in Adelaide, Australia, suggests that it is due to trabecular bone being destroyed at a faster rate than it is being made. And the reason it is being destroyed at an excessive speed may be because of the presence of one or more factors that encourages bone resorption or because of the absence of one or more factors that inhibit bone resorption.

For instance, because postmenopausal osteoporosis victims have impaired intestinal absorption of calcium and low levels of 1,25 dihydroxyvitamin D, researchers believe these factors may contribute to the condition, says John C. Gallagher of Creighton University School of Medicine in Omaha. Estrogen deficiency may likewise contribute to excess bone resorption and postmenopausal osteoporosis, scientists suspect, because women generally only succumb to it after the menopause, when their estrogen production falls off drastically. In fact, Nordin and colleagues have found that estrogen levels are lower in postmenopausal osteoporosis patients than in healthy postmenopausal women.

The putative role of estrogen deficiency in postmenopausal osteoporosis, in fact, has caused investigators to test estrogen replacement therapy as a preventive against the disease. Among dozens of studies that have now shown that it can prevent bone loss in healthy postmenopausal women, one has demonstrated that it can actually prevent spinal fractures in such women, says Robert Lindsay, a postmenopausal osteoporosis and estrogen authority at the Helen Hayes Hospital in West Haverstraw, N.Y.

The problem with routinely prescribing estrogens for all postmenopausal women in order to protect them from postmenopausal osteoporosis, however, is that estrogens also increase the risk of uterine cancer (SN: 1/3/76, p. 9). On the other hand, two other preventives are emerging that may turn out to be safe as well as effective. A study by Peter Jacobson and co-workers at the University of North Carolina in Chapel Hill has shown that exercise that puts weight on bone, such as tennis, running or jogging, can prevent, or at least slow, bone loss among healthy postmenopausal women (SN: 6/4/83, p. 367). Exercise plus calcium can also prevent bone loss among healthy postmenopausal women, Robert P. Heaney and colleagues at Creighton University School of Medicine in Omaha have found.

Some treatments for postmenopausal osteoporosis also look promising. For example, estrogen replacement therapy can reduce bone loss and prevent 50 percent of expected further fractures in postmenopausal osteoporosis patients, and if estrogens are combined with calcium and sodium fluoride, they can reduce the subsequent fracture incidence in such patients by 90 percent, Riggs and his team have found. But here again is the question of estrogen's safety.

On the other hand, Pierre J. Meunier and colleagues at Faculty A. Carrel in Lyon, France, gave sodium fluoride, along with calcium and vitamin D supplements, to postmenopausal osteoporosis patients and found that the combination increased bone and reduced subsequent spinal fractures. Although the regimen produced gastrointestinal irritation and transient arthritis-like pain, these side effects were mild. Moreover, low doses of 1,25 dihydroxyvitamin D not only increase bone and reduce subsequent spinal fractures among postmenopausal osteoporosis patients, but seem to be essentially free of side effects, Gallagher reports.

However, scientists are not making as much progress against senile osteoporosis as against postmenopausal osteoporosis. One reason, A. Michael Parfitt of Henry Ford Hospital explains, is that it is difficult to study bone from elderly hip fracture patients because fracture complications can alter bone. Another reason, Gallagher says, is that it is difficult to study elderly, and especially sick elderly, populations over a period of a few years because so many of them die. Yet that is how long it would take to find out whether a drug might truly counter or prevent senile osteoporosis. Still, some advances are being made against this disease.

For instance, it is not known whether senile osteoporosis is due to increased bone resorption, decreased bone formation or both in trabecular and cortical bone. But evidence from Nordin, Samuel H. Doppelt and co-workers at Massachusetts General Hospital in Boston and

Paul Lips and colleagues at Vrije University in Amsterdam suggests that the disease may be triggered by a vitamin D deficiency, perhaps because of inadequate exposure to sunlight (SN: 6/4/83, p. 367).

Riggs and his team have evidence that excess parathyroid hormone may also be a contributing factor. Furthermore, Seizo Yoshikawa of the University of Tsukuba in Niihari-Gun, Ibraki, Japan, and colleagues have found in a six-month pilot study that when the thyroid hormone calcitonin, which is known to both suppress bone resorption and increase bone formation, is given with calcium supplements, it can increase bone in senile osteoporosis patients. In spite of the difficulties of studying elderly populations over an extended time period, Lips and his co-workers still hope to launch such a study to see whether vitamin D supplementation can prevent bone loss and hip fractures in healthy elderly people.

And still other questions about both kinds of osteoporosis press for answers. For example, Riggs and his team were not able to confirm the finding of Nordin and his colleagues that estrogen levels are lower in postmenopausal osteoporosis patients than in healthy postmenopausal women. So the extent to which estrogen deficiency after the menopause contributes to postmenopausal osteoporosis is unknown, Riggs says.

The mechanism by which estrogens inhibit bone resorption and prevent bone loss in postmenopausal women is also unclear, notes Lawrence G. Raisz of the University of Connecticut School of Medicine in Farmington. A third question is whether postmenopausal osteoporosis and senile osteoporosis involve not just trabecular bone and cortical bone but bone marrow. "It is an intriguing possibility, and a number of investigators are looking into it," says Peck.

Bone showing a row of osteoblasts (A), unmineralized bone deposited by the osteoblasts (B) and mineralized bone (C).

Yet a fourth question is whether the various skeletal growth molecules that influence bone resorption and formation play a role in osteoporosis. For instance, David J. Baylink of the Veterans Administration Hospital in Loma Linda, Calif., and colleagues have isolated a human skeletal growth factor that is probably a protein. They want to learn whether the factor is implicated in osteoporosis.

But whether these particular questions are answered or not, osteoporosis researchers are confident that they will make still more onslaughts against the disease during the next decade or so. For instance, C. Conrad Johnston, an osteoporosis authority with Indiana University School of Medicine in Indianapolis, anticipates that the disease will be better understood and that not just two but even more osteoporotic syndromes will become apparent.

Boy Frame, head of the Bone and Mineral Metabolism Division at Henry Ford Hospital, believes that it will also become possible to routinely identify persons at high risk of osteoporosis, something which is not now the case, thanks to revolutionary new diagnostic techniques like CT scanning and dual photon absorptiometry (SN: 5/12/83, p. 325). Those persons could then receive the best available preventive for their disease. Both Frame and Johnston likewise envision some effective and safe osteoporosis treatments becoming routinely available, at least to postmenopausal osteoporosis patients, as scientists learn how to use currently experimental therapies more appropriately. □

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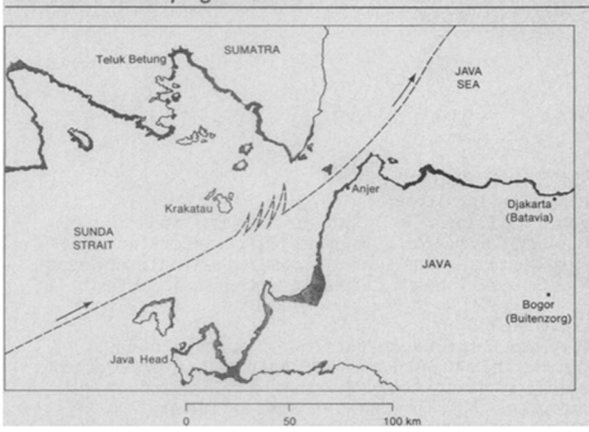
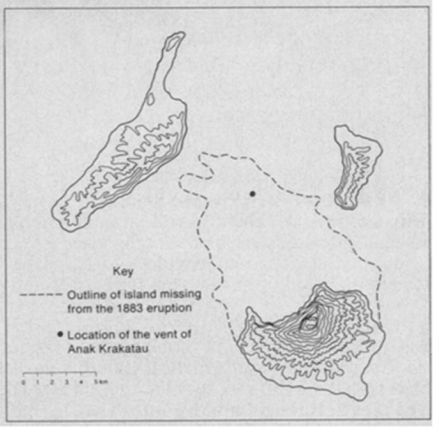


Left: Java and Sumatra took the brunt of the seawaves that shoved through the Sunda Strait after the main explosions at Krakatau. After the eruption, two-thirds of Krakatau was gone, replaced by an underwater crater formed as the volcano collapsed. Right: Lower end of drawing shows what remained of the island.



sist of old rock, rather than fresh melt and ash. His studies revealed that less than 5 percent of the material ejected by the volcano was composed of old rock.

"He reckoned that when the magma left the chamber, the volcano collapsed in upon itself," says Simkin. "That was certainly the first description of the collapse process as a historic event in the history of geology." Subsequent studies have verified Verbeek's conclusion. The volcano *had* collapsed, forming a cavernous basin, five miles wide and more than 700 feet deep, on the floor of the Sunda Strait.

Scientists still have much to learn from the eruption at Krakatau. For instance, controversy persists over the cause of the massive sea waves that were responsible for so much destruction and human suffering. Simkin, who with Richard Fiske, director of the Museum of Natural History, has written a forthcoming book commemorating the Krakatau centennial*, describes four possible stimuli for the waves. One is that as the caldera collapsed, successive landslides sent huge volumes of rock cascading into the sea, generating the waves. Another possible cause is that when the magma chamber caved in, submarine faulting and earthquakes set the waves in motion. Again, the waves might have resulted when the heavier material ejected into the sky quickly fell back to earth and sea, or when a submarine eruption blasted up a large dome of water that collapsed and moved out as a giant ripple. All four actions occurred at Krakatau. It is not known which one was primarily responsible for causing the deadly waves.

A century has passed, and Krakatau remains a classic geophysical event. As Fiske and Simkin note, the eruption's coincidence with growing sophistication and interest in science, and with improved communications, taught the world that impacts from such an event are global, and that the powerful forces of earth, sea and air are complexly, and inextricably, intertwined. □

*"Krakatau 1883—The Volcanic Eruption and Its Effects," by Tom Simkin and Richard S. Fiske, Washington, D.C., Smithsonian Institution Press, 1983.