Osteoporosis Reexamined: Complexity of Bone Biology Is a Challenge

Researchers in osteoporosis endorse calcium and estrogen therapy but call routine bone screening of healthy people unwarranted

In 1984, the National Institutes of Health sponsored a consensus conference on osteoporosis that made this disease of brittle bones a household word. Millions of women went to the drug store to buy bone-strengthening calcium in response to the NIH recommendation that everyone should consume 1000 milligrams a day.

Four years ago, sales of calcium supplements totaled $47 million. Now, the figure is closer to $200 million a year and the industry is growing even larger as food companies move to cash in on the calcium craze by adding it to everything from whole wheat bread to diet colas. In fact, the public's response to the calcium doctors has been so great that some began to feel that things were getting out of hand. Last summer, B. Lawrence Riggs of the Mayo Clinic said that "The advertisers are out way ahead of the scientific evidence," and Richard Mazess of the University of Wisconsin in Madison called calcium the "laetrile of osteoporosis" (*Science*, 1 August, p. 519). And there are many doubts about the value of adding calcium to certain foods because it may not be biologically available.

And so, when NIH made plans to hold another osteoporosis meeting this month, there was speculation that researchers would pull back from previous recommendations. But it did not happen. Although speakers at last week's conference on "Research Directions in Osteoporosis"* clearly delineated calcium's role in bone formation and emphasized that osteoporosis is not a "simple calcium-deficiency disease," they reiterated that all adults should consume 1000 milligrams of calcium a day as part of a program to prevent debilitating bone fractures in old age. Postmenopausal women, particularly thin, white women, who are most at risk were urged to take 1500 milligrams a day.

Lawrence Shulman, director of the new National Institute of Arthritis and Musculoskeletal and Skin Diseases, noted at the outset that the meeting was meant to be a "scientific workshop" to lay out what is yet to be known about osteoporosis, not a consensus conference. Nevertheless, after two-and-a-half days of sometimes heated debate, there was substantial consensus on what is known and how much more has to be learned. Calcium was only part of it. There was considerable support for estrogen replacement therapy in high-risk postmenopausal women. And there was a consensus that it is a waste of time and money to measure bone mass in perfectly healthy younger women, even though many practitioners are making a fortune cashing in on this new fad in preventive medicine.

William A. Peck of the Jewish Hospital in St. Louis, who co-chaired the meeting with Riggs of Mayo, called osteoporosis a "major public health problem that will only get worse as the population ages." Medical and nursing home care for osteoporosis victims now costs an estimated $7 billion to $10 billion a year, Peck noted. It becomes a real threat to older women who lose bone mass rapidly in the first 8 to 10 years after menopause and among hip fracture patients there is a mortality as high as 12%. Men, who are endowed with greater bone mass than women, become vulnerable later—in their 70s and 80s. Shulman told *Science* that, at present, NIH spends a total of $14.5 million on osteoporosis-related research.

Even though data on calcium are incomplete at the level of cellular mechanisms and contradictory from epidemiological studies, the importance of calcium consumption is unquestioned and, meeting participants concluded, should be recommended as sound public health policy.

Riggs spoke for instance, about eight clinical trials of varying dosages of calcium supplementation in women during the first 8 to 10 years after menopause. "Half of these trials have shown a partial slowing of bone loss whereas the others have shown little or no effect." Nevertheless, Riggs pointed out, there "clearly is a threshold level of dietary calcium intake that must be achieved in order to maintain bone mass" and calcium in the recommended dosages is safe and relatively inexpensive. The best source of calcium seems to be dairy products where its "bioavailability" is certain. Whether calcium is as bioavailable from green vegetables, or from fortified foods is not clear. One new study demonstrated that, contrary to what is said in a plethora of pamphlets handed out by grocery chains and fitness groups, calcium is not readily available from spinach. In one of the few such studies anyone has done of calcium in nondairy foods, Robert R. Recker of Creighton University grew radioactively labeled hydroponic spinach, pureed it, and fed it to volunteers. The calcium, he reported, was not bioavailable.

Louis Avioli of the Jewish Hospital presented figures on the range of bioavailability among calcium supplements—some health food versions are virtually indestructible he said—and urged the federal government to require drug houses and food companies to prove that their calcium is bioavailable.

For all of the sentiment in favor of calcium consumption, there was equal agreement that "calcium cannot substitute for estrogen" in preventing accelerated bone loss during the first years of menopause because estrogen deficiency is the primary cause of this phase of bone deterioration. Peck summarized current estrogen data by saying that "a relatively low dose of estrogen is effective," and that "Ideally, estrogen should be initiated as soon after menopause as possible." However, he said, "Because estrogen use is not uncomplicated, it is recommended only in women who are at high risk, have no contraindications, and will adhere to a program of careful follow-up," that includes annual mammography.

A reasonable body of evidence indicates that 0.625 milligram of estrogen is effective and that higher dosages, say 1.25 milligrams, confer no appreciable advantage while increasing the risk of endometrial hyperplasia or cancer. Recent data suggest that just 0.3 milligram of estrogen efficiently retards bone loss when it is given in conjunction with 1500 milligrams of calcium daily, but further work is needed to confirm that.

According to Howard L. Judd of the University of California at Los Angeles,

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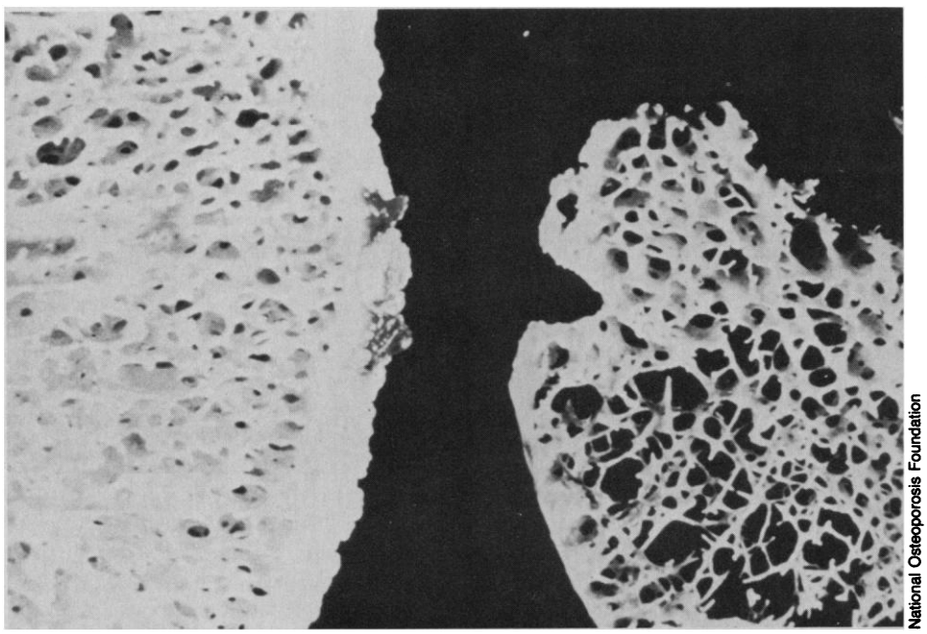

National Osteoporosis Foundation

Porous bone: *Normal bone (left) reaches its peak mass about age 35. Osteoporotic bone, which has lost calcium, is porous, fragile, and easily broken.*

there are many millions of women for whom estrogen therapy should be considered, but only an estimated 5 million are receiving treatment.

One of the more compelling reasons for postmenopausal estrogen replacement comes from data that pertain not to osteoporosis but to cardiovascular disease. Researchers cited studies showing that mortality from cardiovascular disease can be reduced as much as 40% among postmenopausal women on estrogen.

Whether it is beneficial to add progestin to estrogen replacement therapy remains a subject of debate, as does the potential role of various other agents in preventing osteoporosis, among them: calcitonin and fluoride, each of which is in clinical trial and has its advocates. Other agents on which more research is needed include vitamin D metabolites, low dose parathyroid hormone, diphosphonates, and anabolic steroids.

The value of exercise is another "therapeutic" strategy of uncertain value. Weight-bearing exercise adds to increased bone mass in teenagers and young adults, but its value beyond that has yet to be proved. Nevertheless, the best available evidence says that 3 to 4 hours of exercise per week may be beneficial.

Figuring out who is at risk of osteoporosis and then explaining the connection between the risk factor and disease is another area in need of better definition. Steven R. Cummings of the University of California at San Francisco showed a slide listing more than 50 items, ranging from antacids to stress, that have been suggested as risk factors by someone. Even though it is not yet possible to separate real from imagined risks in every case, the ones of major concern can be put into one of three categories. "Well-established" factors that increase one's risk are: older age, premenopausal oophorectomy, corticosteroid use, extreme immobility, and being a thin, white female. Well-established protective factors include obesity (though no one recommended it), and being black. For reasons that are not known, black men and women have greater bone mass than do Caucasians. Low calcium intake, cigarette smoking, and even moderate alcohol consumption are risk factors for which there is "moderate evidence." The category of "inconclusive or inadequate evidence" of risk or protection includes moderate physical activity, Asian ethnicity, parity, diabetes, and use of thiazide diuretics, which may confer some protection.

New public awareness of osteoporosis, along with the current American interest in physical fitness, has spawned a good sized new industry in the bone measurement business. Practitioners are offering to screen women of all ages, and health insurance companies are under pressure to pay for it. Some have already agreed to. But at the NIH conference, there was little sympathy for mass screening. C. Conrad Johnston, Jr., of Indiana School of Medicine argued against mass screening on grounds that it generally does not yield useful information. "If I screened a healthy 35-year-old woman and found low bone mass, I wouldn't tell her anything that I wouldn't advise her to do anyway," he said. "Consume calcium and get exercise." Furthermore, researchers noted that various methods of bone scanning yield different kinds of information that cannot be extrapolated from one to the other. For instance, single energy photon absorptiometry is good for measuring bones in the periphery. It can be done easily and accurately and does not require a large radiation dose. It is often offered now by general practitioners and bone screening clinics. However, it does not tell you anything about bone in the hip or spine which, clinically and economically, is more important. Quantitative computed tomography can be used to measure the spine, and dual energy photon absorptiometry is used for measuring hip, spine, and total body calcium. However, its use requires great skill and "is reserved for research use at this time," Johnston said.

The most reasonable candidates for bone measurements, researchers concluded, are patients who are on therapy that should be monitored to determine if bone loss is being slowed, or patients who are candidates for estrogen replacement.

For the future, research is needed to sort out the role of reduced bone mass versus bone quality in susceptibility to osteoporotic fracture, and better methods (easier, cheaper, with lower radiation exposure) for measuring bone are needed. Until there are better screening methods and improved therapies, there is no good reason for mass screening of asymptomatic people, the researchers concluded.

And, they agreed, there is a lot to learn about basic bone biology before one can hope to develop surefire therapies for preventing or reversing osteoporosis. It is now clear that the biology of bone is phenomenally complex, perhaps as complex as the biology of the immune system. New research suggests a connection between the two. Recently, a number of substances have been found to act on bone, including several lymphokines and cytokines. Speaking on immunological factors in bone metabolism, Gregory R. Mundy of the University of Texas Health Science Center in Dallas said new data on lymphokines and cytokines are coming along every couple of months. Other players in the biology of bone formation and resorption under study are interleukin-1, tumor necrosis factor alpha, and gamma interferon.

The list goes on. Said Shulman of the arthritis institute, the meeting sorted out a few things in the area of current measures for prevention and treatment and also produced a "new catalogue for our research agenda." But it will cost more than NIH's current budget of $14.5 million. ■

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