though such a preliminary evaluation would be of some interest to industry, it would appear content to first edge out onto the slope, as it is now doing, and evaluate the prospects of the rise from there.

That part of the oil industry has shown any interest at all in *Explorer* is indicative of other pressures felt by the oil companies. Although not of one mind on the question, many companies feel that it would be imprudent to refuse an offer to help evaluate the country's energy reserves, however costly and far-off their utilization may be. Although new drilling technology may be developed and new geologic data gathered, industry seems primarily interested in maintaining its public image as an enthusiastic developer of energy resources.

NSF is assuring everyone that enough oil companies have shown an interest for planning to proceed. In the next few months, a general drilling program must be hammered out that will satisfy all parties, including Congress. It will have to be strong enough to stifle the often-heard argument that *Explorer* is an expensive scientific tool looking for a job to do.

—RICHARD A. KERR

Osteoporosis: New Help for Thinning Bones

New evidence suggests that osteoporosis, once thought to be an unavoidable consequence of aging, may be preventable or at least treatable

No one knows why George Bernard Shaw climbed a tree when he was 93 years old, but the act had a most unfortunate consequence. He fell from the tree, broke his hip, and subsequently died.

This may be an extreme example, but the phenomenon is not all that unusual. Each year in the United States as many as 190,000 people, in late middle age or older, suffer broken hips. Perhaps one-sixth of these individuals die from the ensuing complications, and many of the survivors are incapacitated.

Most of the broken hip victims have an underlying condition, called osteoporosis, in which the bones lose abnormally large quantities of the calcium-containing mineral that helps to give them their strength. As a result, the bones become fragile and subject to fracture by stresses that would not break normal bones. Hip fractures, for example, often result from a relatively minor trauma such as falling from a standing position. Falling down stairs—or out of a tree—is not necessary. Says Robert Heaney of Creighton University, "Osteoporosis is a very significant problem. About 25 percent of all white women have had one or more fractures by age 65." These fractures include, in addition to the broken hips, about 100,000 broken wrists every year.

Vertebral fractures are another major feature of osteoporosis. They are usually the type called "crush fractures," in which the vertebrae collapse simply from carrying the weight of the body upright. There is no good estimate of the annual number of crush fractures, but they are a frequent complaint of patients who are seeing physicians for osteoporosis. The vertebral fractures, which cause the height loss and humped backs often seen in the elderly, can cause severe back pain.

Not only does osteoporosis cause a great deal of death and disability, but the dollar costs are also high. According to B. Lawrence Riggs of the Mayo Clinic, the cost of acute medical care for elderly patients with broken hips is more than $1 billion a year. This does not include such indirect or long-term costs as lost income and fees for nursing homes.

Many people, physicians included, consider osteoporosis to be an unavoidable consequence of aging. But as investigators learn more about what causes the abnormal loss of bone mineral in some people, they are beginning to think that the condition may be preventable. The research suggests that, contrary to popular opinion, dietary calcium requirements may increase with age, rather than decrease. Moreover, several experimental therapies for slowing bone loss and possibly decreasing the number of fractures experienced by individuals who have already developed osteoporosis are under investigation.

Although everyone begins losing bone mineral at around 40 years of age, women, especially white and Oriental women, are the most likely to suffer the fractures that are the major clinical feature of osteoporosis. Women usually have lighter bones than men, and there is general agreement that people with lighter bones run a higher risk of fractures than persons of the same age who have heavier bones. The heavier bones of black women may help to explain their decreased risk of osteoporosis.

Not only do women have lighter bones than men to start with, but women's bone losses accelerate at menopause. The high rate of loss continues for about 20 years, during which women lose 0.5 to 1.5 percent of their peak bone mass every year. The rate of loss eventually decreases, but before it does a woman's bones may be significantly weakened. Men do not show a comparable acceleration of bone loss during aging.

Over the years a picture has developed that shows bone to be in a constant state of change, undergoing alternate cycles of resorption (bone dissolution) and formation in a process known as remodeling. Because bone mineral consists primarily of a calcium phosphate salt called hydroxyapatite, remodeling helps to maintain the calcium and phosphate concentrations of blood and the other body fluids within normal bounds. Bone is resorbed, for example, when the blood calcium concentration drops and then replaced when the concentration returns to normal. Work in Heaney's laboratory has shown that in normal circumstances bone mineral dissolution is obligatorily coupled to a more or less equivalent amount of formation, with the result that the mineral content of adult bones remains roughly constant even though calcium is periodically withdrawn.

That menopause accelerates bone loss and predisposes women to osteoporosis has been known since the pioneering work of the late Fuller Albright during the 1940's. The acceleration has been generally attributed to the deprivation of the hormone estrogen that occurs when the ovaries stop functioning. Direct proof that estrogen can slow bone loss did not begin to accumulate until about 10 years ago, however. And only within the past 5 years or so have investigators begun to understand how it affects bone.

Osteoporosis could be caused by increased bone resorption without a coun-

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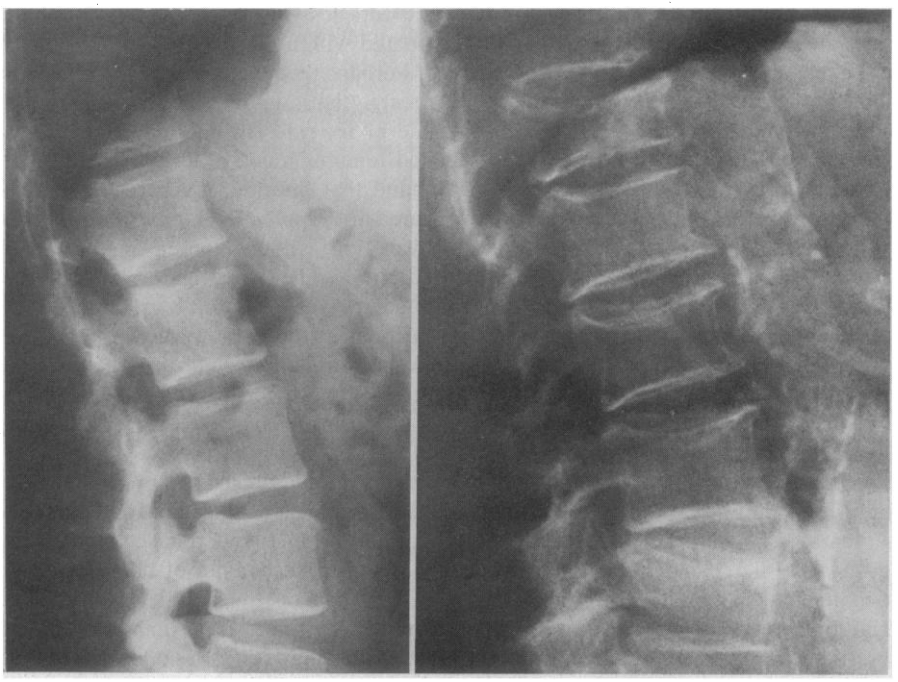
terbalancing increase in deposition, by impaired deposition, or by some combination of the two. Riggs, for one, thinks that the first alternative, increased resorption, is a major contributor to the accelerated calcium loss seen at menopause. He and his colleagues found that bone resorption in postmenopausal women with osteoporosis is abnormally high, whereas bone formation is normal. On treatment with estrogen, the resorption decreased.

Heaney proposed and the Mayo group has confirmed that estrogen produces this effect by making bone less sensitive to parathyroid hormone (PTH), which is secreted in response to decreased concentrations of calcium in the blood. The PTH is a major stimulator of bone dissolution and helps to restore calcium levels to normal. In the absence of estrogen, bone apparently becomes more susceptible to PTH, tilting the balance toward resorption.

Because bone dissolution is increased in postmenopausal women, their blood calcium levels are at the high end of the normal range. Consequently, the blood concentration of PTH is decreased, possibly contributing to the loss of calcium from the body, according to Riggs. The PTH is also known to increase calcium absorption from the intestine and decrease its excretion by the kidney. Riggs points out that decreased calcium absorption is consistently observed in osteoporosis patients.

This observation ties in neatly with the finding by Heaney and his colleagues that to avoid a net loss of bone mineral from their bodies, postmenopausal women need to consume more calcium than do premenopausal women. Before menopause, consumption of approximately 800 milligrams of calcium per day is adequate to maintain body calcium; afterwards, however, women need to ingest roughly 1500 milligrams—about the amount in $1^1/_3$ quarts of milk—every day. Postmenopausal women taking estrogens absorb calcium about as well as premenopausal women.

Overall, the work of the Heaney and Riggs groups suggests that estrogen deprivation leads to increased sensitivity of bone to PTH, causing increased dissolution of bone mineral and elevated blood calcium concentrations, which are followed by decreased secretion of PTH and decreased calcium absorption. The theory helps to explain why bone losses increase as people age and, especially, why women lose calcium faster than men. But it does not explain why some women develop the fractures of osteoporosis and others do not. Nor does it account for the lack of a compensating increase in bone deposition that would normally follow increased bone resorption, a deficiency that may be at the heart of the osteoporosis puzzle.



X-rays of normal (left) and osteoporotic spines. The vertebrae of the osteoporotic spine are compressed and much less dense than normal. [*Source: David Baylink*]

Research on the latter point has been handicapped by an incomplete understanding of how the two competing processes—bone resorption and formation—are coupled in the first place. As David Baylink of the Veterans Administration Medical Center in Tacoma, Washington, points out, investigators have had very little success in trying to correlate any of the major hormones, vitamins, or other factors that regulate bone mineralization with coupling. "Instead," he says, "we were forced to consider the possibility that coupling might be an inherent property of bone, not dependent on any systemic factor."

Because so many agents—20 or so—affect deposition and dissolution of bone mineral, coupling is very difficult to study in the living animal. With Guy Howard, who is also at Tacoma, Baylink has developed a bone culture system in which the bone displays many of the properties of the bone of living animals. Coupling is still observed in this system, even though the medium that bathes the bone is artificial and contains none of the systemic agents, with the exception of PTH, which is used to stimulate bone resorption. Since the culture medium does not contain any agent known to stimulate bone deposition, Baylink says, the observation of coupling in the cultured bone is evidence that it is an intrinsic property of bone.

Recently, he and Howard isolated a material from the fluid bathing the resorbing bone that stimulates bone formation. They think that the material, which is probably a protein with a molecular weight of around 75,000, might be the coupling agent.

Baylink cautions, however, that it is far too early to tell whether this substance has anything to do with human osteoporosis. The investigators use embryonic chick bone in the culture system, and what is true for it may not be true for aging human bone. Human bone may not produce a comparable material, and if it does, the agent may not be involved in osteoporosis. Nevertheless, it is tempting to hypothesize that a deficiency of such a coupling factor in aging humans may contribute to the development of osteoporosis by causing a decrease in bone formation. In a related observation, Anthony Parfitt of the Henry Ford Hospital in Detroit, Michigan, finds that bone formation is depressed with age. He observes fewer of the cells that build new bone in people over 40, and those he does find are less active than cells from younger people.

Although research into the causes of osteoporosis has not solved all the problems, it has provided clinicians with some new ideas for therapies for the disease. Estrogen replacement therapy has been one of the principal treatments for postmenopausal osteoporosis even though evidence showing that it slows bone calcium loss is a fairly recent development. The hormone cannot strengthen bones already weakened, however.

In addition, the long-term use of estrogens has been suspect ever since the drugs given to menopausal women were linked to an increased risk of uterine cancer in several studies. Consequently, prescriptions for the drugs, which are used primarily for such menopausal symptoms as hot flashes, have dropped substantially in the past few years. Physicians who treat osteoporosis patients think that estrogens still may be useful for women who are at high risk of developing the condition. These might be women who have a strong family history of osteoporosis. Riggs points out that the women need to be carefully watched for abnormal uterine changes and therapy should not be prolonged beyond 2 or 3 years, especially since research suggests that the drugs' effects on bone eventually wear off. Women who have had hysterectomies are not at risk of uterine cancer and for them estrogen replacement therapy is easier to justify.

Among the newer agents for which promising results have been reported are calcitonin, a hormone secreted by the thyroid gland that decreases bone resorption, and stanolozol, a derivative of a male sex hormone. According to Baylink and Charles Chesnut III of the University of Washington School of Medicine, both agents not only slow bone loss but even increase bone mass.

The effect of calcitonin lasted for 18 months but then appeared to fall off. The effect of stanolozol was more persistent and was still observable after 30 months of therapy, which was the duration of the trial. Chesnut said that the side effects of the drugs were generally mild. Stanolozol, for example, produced some masculinizing effects that disappeared when the dosage was reduced.

Another substance that has shown promise in clinical trials is a material formed from vitamin D that is called 1,25-dihydroxyvitamin D [1,25-$(OH)_2D$]. The increase in calcium absorption from the intestine that is stimulated by PTH is actually mediated by 1,25-$(OH)_2D$, according to Hector De Luca of the University of Wisconsin. The PTH stimulates the formation of the material from vitamin D, and the material in turn stimulates calcium absorption.

Riggs, De Luca, and J. C. Gallagher, who is now at Creighton University, have shown that the blood concentration of 1,25-$(OH)_2D$ falls off with increasing age, with the biggest decrease seen in osteoporosis patients, a finding consistent with their depressed PTH concentrations. When the investigators treated osteoporosis patients for 6 months with physiological doses of 1,25-$(OH)_2D$, the patients lost less calcium than patients treated with a placebo.

Perhaps the most controversial experimental therapy for osteoporosis is the use of fluoride. In an early trial, Riggs and Jennifer Jowsey, at the Mayo Clinic, found that fluoride, given together with calcium supplements, increases bone formation without increasing bone resorption. The investigators stress the need for the calcium supplementation. Without it, the bone formed in response to fluoride is abnormal in structure and may be more brittle and easily broken than normal bone, even though fluoride increases the bone mass.

This finding illustrates a problem with many of the clinical trials of osteoporosis therapies. Most have focused on calcium loss or measurements of bone changes, rather than on the number of fractures suffered by the trial participants. As yet no studies have shown conclusively that a therapy will prevent fractures, although the investigators think that a treatment that increases bone density will help. As Chesnut puts it, "We think that if we increase bone mass, we will strengthen bone and reduce fractures, but it is not yet proved." Fluoride therapy, which increases mass, does not necessarily produce greater strength.

Although Riggs himself has always considered treatment with fluoride and calcium to be experimental, the therapy has already come into widespread use, a circumstance that may not be justified, according to the results of a trial recently concluded at the Mayo Clinic. The trial showed that treatment with fluoride and calcium does increase bone mass. More than 40 percent of the women experienced side effects, however. Some of them, such as inflamed joints, recurrent vomiting, and anemia, were serious.

An encouraging finding was that, of the 28 women who were followed for at least 4 years (some patients dropped out because of the side effects), there were 12 who had increased bone density that was detectable on x-rays. These 12 had one-sixth as many fractures as the 16 who did not show increased density. Riggs thinks that further investigation of the fluoride plus calcium therapy is warranted because of this favorable trend, but that there are too many uncertainties about the effects of the agent to warrant its widespread use.

Except for the use of estrogen, which has been questioned because of its link to uterine cancer, most therapies for osteoporosis are still in the early investigational stages of development. Moreover, many researchers doubt that bones already weakened by the disease can ever be restored to normal strength. Certainly, the loss of height resulting from crush fractures of the vertebrae will not prove reversible.

For these reasons, there is a growing emphasis on efforts to prevent osteoporosis. Says Donald Whedon, director of the National Institute of Arthritis, Metabolism, and Digestive Disease, "We need a major effort to educate middle-aged people to manage their lives to prevent this thinning of bone tissue."

Among the measures Whedon recommends is maintenance of physical activity. Whedon is one of the investigators who showed that deprivation of physical activity, as in patients immobilized in bed, is associated with a dramatic loss of bone mineral. Astronauts living in the zero gravity of space show a similar loss, leading Whedon to conclude that the activity of the muscles working against gravity is needed to maintain strong bones. As yet there is little evidence on whether normally active persons on earth can prevent the bone mineral loss of osteoporosis by increasing their activity—jogging or performing other exercises—but it is clear that inactivity can hasten calcium loss.

Another measure that Whedon recommends is increasing one's calcium consumption. He thinks that 1000 to 1500 milligrams per day as suggested by Heaney's studies, should be adequate. Figures for the recommended daily intake of calcium for adults vary, but values of 600 to 800 milligrams per day are typical. Many people do not even consume that much. The National Health Survey reported in 1977 that postmenopausal women in this country typically consume less than 500 milligrams per day.

Good sources of calcium include sardines and green leafy vegetables, in addition to milk (skim milk has as much calcium as whole milk) and other dairy products. Some people, especially those who cannot digest milk properly or cannot stand the taste, may need calcium supplements.

Baylink sounds a note of caution, however. People who have kidney stones or who are at risk of getting the stones because they have high urinary calcium concentrations may not be able to take large amounts of calcium.

Nevertheless, unless osteoporosis can be prevented, it promises to be a growing problem as the number of people living to older ages increases. Women tend to develop the condition in greater numbers and at younger ages than men, but men are not immune to the condition. Heaney warns, "We can all get osteoporosis if we live long enough."—JEAN L. MARX