Breakthroughs in Bioscience

FASEB

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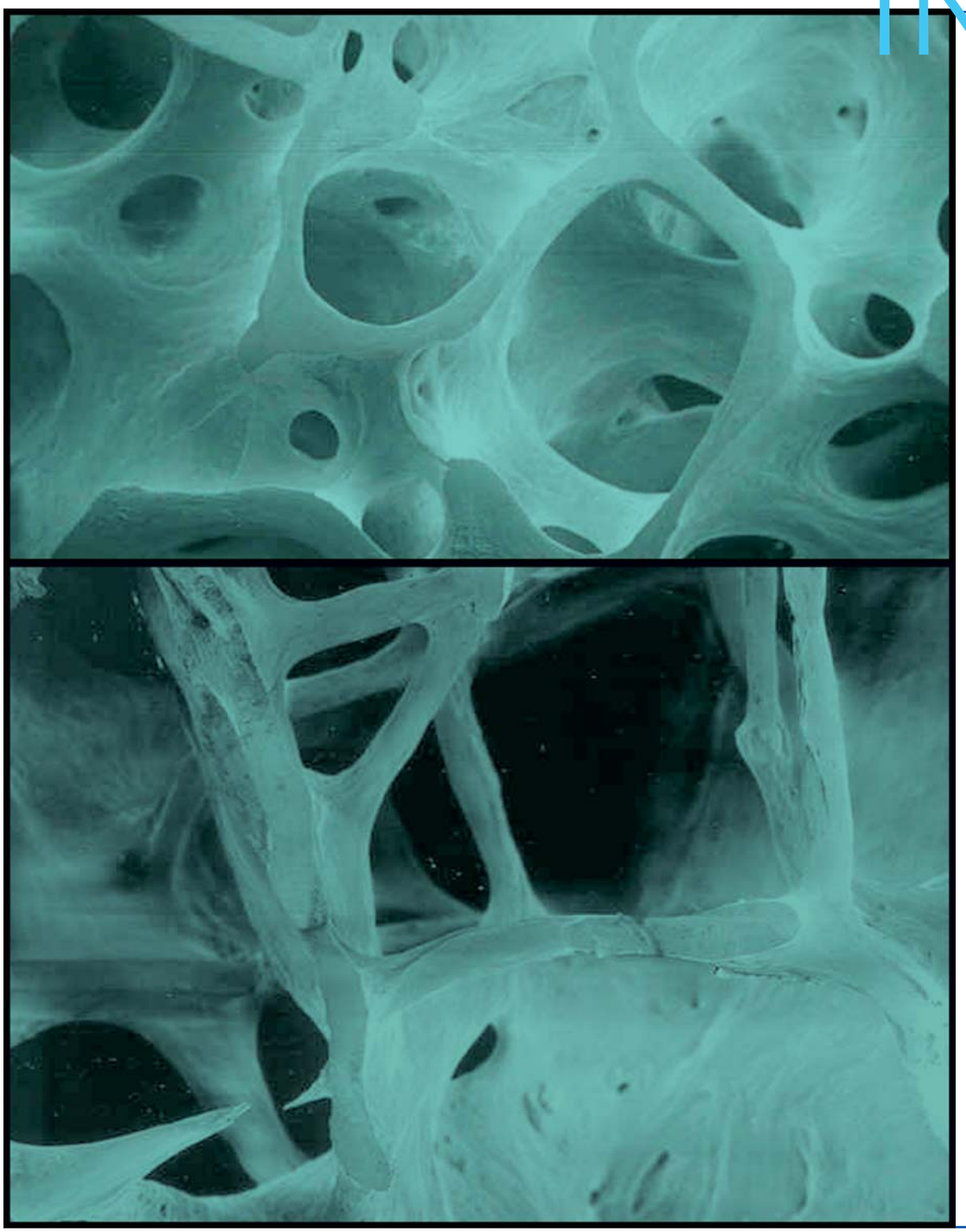

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Acknowledgments

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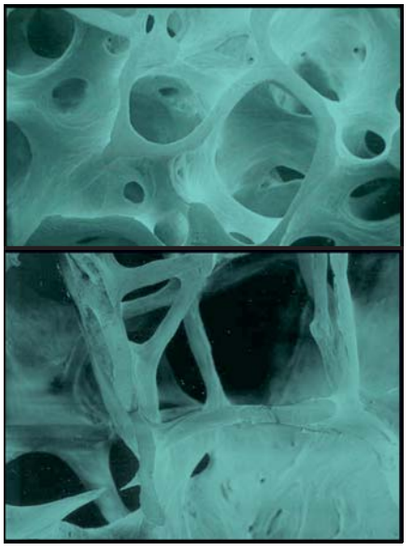

COVER IMAGE: Shown on the cover are reproductions of two scanning electron micrographs of osteporotic and normal human cancellous bone. (Colorization added for effect.)

Bone Builders:

The Discoveries Behind Preventing and Treating Osteoporosis

Ask an actress to portray an old woman and chances are she'll start by stooping over so she appears to have a curved spine, or "dowager's hump." Until recently, such a posture was thought to be a frequent and inevitable consequence of a woman's aging. This assumption is evident in literature and art, which often depict women bent over with age. "Her chest had dropped, so that she stooped," noted Charles Dickens in his description of the elderly Miss Havisham in his novel Great Expectations. A striking example of a dowager's hump also appears in a painting of an old woman by the fifteenth century artist Vittore Carpaccio (fig. 1). And everything from Greek myths to classic fairy tales are peopled with stooped older women.

Figure 1. A curved spine, or "dowager's hump," can be seen in the elderly woman depicted in this painting by fifteenth century artist Vittore Carpaccio. Such deformity is caused by osteoporosis.

More often than not, these depictions are probably of women with a bone-thinning disease known as osteoporosis. This disease will ultimately afflict about half of all women who reach the age of sixty-five, and frequently causes the bones in the spine to collapse. Such spinal collapses cause women to be perpetually hunched over and, in severe cases, cause them to lose as much as a foot in height (fig. 2). Osteoporosis also affects as many as two out of every ten men over the age of seventy.

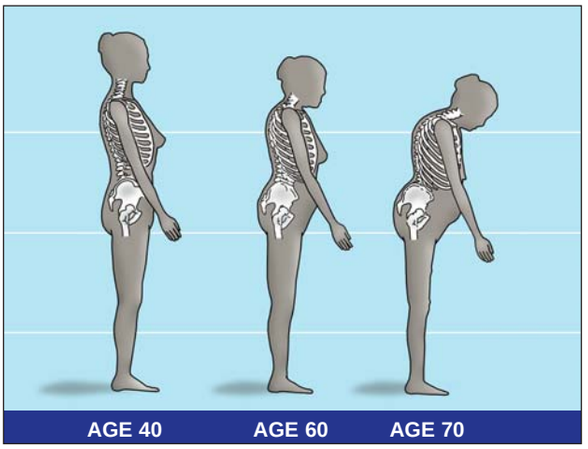

Figure 2. Women with postmenopausal osteoporosis tend to experience numerous fractures in the bones in their spine (vertebrae) as they age. Eventually these vertebrae can collapse, causing the spine to curve. Such curvature causes loss of height, a tilted rib cage, a dowager's hump, and a protruding abdomen. *Designed by Corporate*

Osteoporosis makes the bones so fragile that the simplest things can cause them to break: stepping off a curb, a sneeze, a hug. The disease often causes such pain and disability that people afflicted by it must spend their last days in a nursing home. Hip fractures due to osteoporosis are especially disabling and can even be deadly. One out of five elderly people who break a hip die within a year from complications of the fracture. The annual costs of osteoporosis exceed fourteen billion dollars in this country, according to the National Osteoporosis Foundation.

Osteoporosis has haunted women since the dawn of history—Egyptian mummies from 4,000 years ago have been found with the telltale dowager's hump. But there is now hope that most young women today can expect to spend their old age standing as straight and tall as they ever were, thanks to recent dramatic improvements in the diagnosis, prevention, and treatment of osteoporosis. A better understanding of what puts people at risk of developing osteoporosis has armed women with strategies to help prevent the disorder (see "What Makes Women Prone to Postmenopausal Osteoporosis?" on page 4). New diagnostic tools

allow doctors to detect osteoporosis in its early stages, before it causes widespread harm to the skeleton. And a fuller picture of what causes osteoporosis has led to effective treatments that can stave off bone fractures. Many of these improvements stem not from targeted research on the disease but from more basic research aimed at answering such fundamental questions as, how do bones grow, why do female pigeons have more massive bones than males, and how does the body maintain the delicate balance of calcium it needs to run smoothly?

Mysteries of bone growth

An early medical pioneer, the eighteenth century English surgeon John Hunter, described himself as one who "pestered people with questions about what nobody knew or cared anything about." One of those questions was, how does bone grow and develop over time? Hunter's experiments on animals, along with observations of changes in the human jaw, led him to a surprising discovery: As new bone is laid down in the body, old bone is destroyed, or resorbed. This discovery that bone is constantly being remodeled predated widespread use of the microscope and the notion of cells as the workhorses of the body. So Hunter was unable to find out what caused such striking bone remodeling.

It took a hundred more years of observations and experiments by many basic scientists to discover that lodged in living bone are large ruffle-edged cells known as osteoclasts, which break down bone. Close on the heels of osteoclasts are bone-building cells known as osteoblasts (fig.

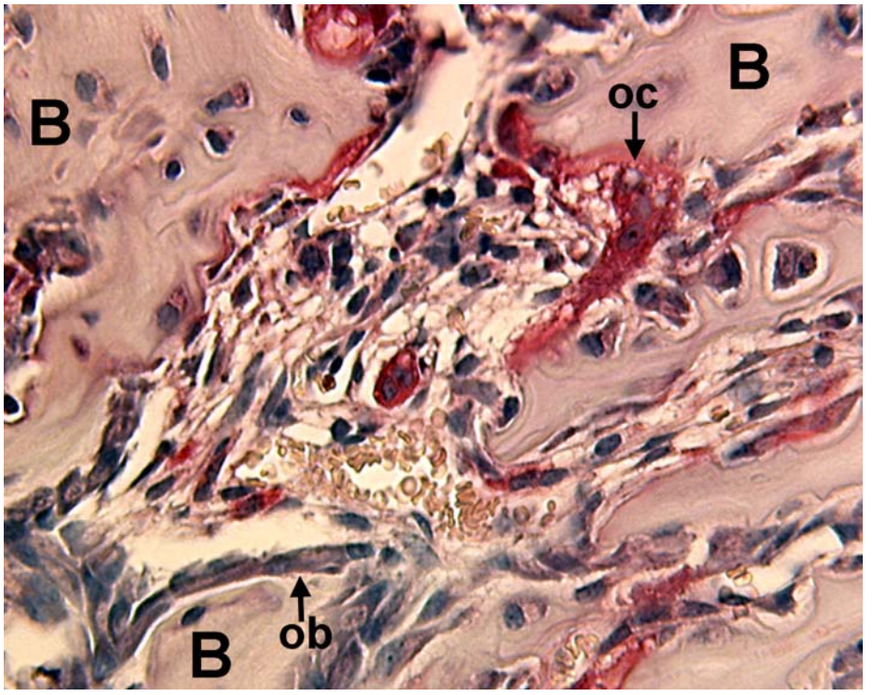

Figure 3. Osteoclasts (oc), which are stained red in this section of bone (B), are responsible for the degradation of bone and cartilage. Their multiple nuclei appear as darkly stained bodies within the cell. Osteoblasts (ob) are the rectangular-shaped cells, each with a single prominent nucleus, lining the surface of the bone. These cells appear dark in color due to the presence of numerous ribosomes, which are structures in cells that synthesize protein. The catabolic and anabolic activities of osteoclasts and osteoblasts, respectively, are coupled under physiological conditions to maintain bone homeostasis (the balance between bone growth and degradation). *Courtesy of Jonathan Lam, Washington University School of Medicine, St. Louis, MO.*

What Makes Women Prone to Postmenopausal Osteoporosis?

The basic understanding of osteoporosis that emerged during the last half of the twentieth century not only led to new treatments but also set some investigators on a research path aimed at uncovering why some postmenopausal women suffer from osteoporosis while others are virtually untouched by the disease. These scientists, known as epidemiologists, searched for the risk factors that make women susceptible to postmenopausal osteoporosis, hoping that some of these factors could be modified.

Thanks to the basic research on bone biology that had been done over the past century or two, epidemiologists had a number of clues to follow. The most obvious clue was calcium in the diet. Basic research showed that calcium is the main component of bone, and that insufficient blood levels of calcium can trigger the erosion of this mineral from bones. Epidemiologists therefore hypothesized that low levels of calcium in the diet might boost a woman's risk of developing postmenopausal osteoporosis.

3). Because of the industry of both types of cell, the entire adult human skeleton is completely replaced about every ten years. Such bone remodeling, which Hunter first discovered in the 1770s , was later shown to play a critical role in osteoporosis.

For more than a hundred years after Hunter died, however, osteoporosis wasn't even a recognized disease. A step toward such recognition was made in the 1830s by the French pathologist Jean Georges Chretien Frederic Martin Lobstein. He noticed that some patients' bones were riddled with larger than normal holes, and he coined the term osteoporosis (porous bone) to describe such deteriorated human bone. But Lobstein didn't pursue the question of what might be causing these holes to form in bone, or even whether they might be a symptom of disease.

We now know that bone consists of a matrix of fibers of the tough protein collagen, hardened with calcium and other minerals. The outside portion of every bone is a tough dense rind called cortical bone. Inside is a honeycomb network made up of intersecting plates, or trabeculae. Osteoporosis eats away at both cortical and trabecular bone, resulting in large holes such as Lobstein saw (see cover picture). These holes weaken the skeleton. Like a building without support beams, bone without enough cortex and trabeculae easily cracks or collapses when it is knocked or compressed.

But what caused such bone deterioration? Early in the last century, doctors assumed it was a natural consequence of age or immobility, but one astute clinical researcher in the 1930s was puzzled by the fact that so many of his patients with osteoporosis were older women who had gone through menopause. A few of his patients were in their thirties or forties, but these women shared something with the older women with osteoporosis—they, too, were in effect postmenopausal, because their ovaries had been removed. Intrigued by this observation, and being an imaginative man who believed that every clinical problem has an explanation, Fuller Albright of Massachusetts General Hospital couldn't help but ponder what it was about being postmenopausal that made women particularly susceptible to having frail bones.

A piece that helped Albright solve this puzzle came from a pair of anatomists who noticed, in 1934, that the bones of ovulating female pigeons were much more massive than those of male pigeons. Could the hormone estrogen, which is produced chiefly by the ovaries, be causing the difference in bone mass? Researchers at Yale University explored this possibility. When they injected estrogen into male pigeons, the birds' bone mass increased dramatically, reaching levels found in female birds.

A revolutionary hypothesis

Prompted by the findings in pigeons, in 1940 Albright proposed his revolutionary hypothesis: Estrogen triggers the buildup of calcium reserves in bone, from which calcium can be released into the bloodstream during pregnancy and lactation to serve the needs of the fetus and newborn. The sharp reduction in estrogen that occurs with menopause causes a loss of bone, he suggested, by enabling more bone to be broken down than is subsequently built up. Women whose skeletons long outlive the functioning of their ovaries often reach the point of having too little bone, which makes them susceptible to bone

Studies have shown that women with osteoporosis tend to consume less calcium than women without the disorder, and that they absorb it less efficiently from the foods they eat. But there have been conflicting findings as to whether a greater calcium intake is linked to an increase in bone mass or bone density or a decrease in fractures. Because most studies show a positive relationship between increased calcium intake and bone health, the National Academy of Sciences in 1997 boosted the amount of daily calcium intake recommended for post-menopausal women.

Research reveals that a woman's bone mass peaks at about age thirty, after which more bone is lost than formed. As with money in a retirement account, the more bone deposited in the "bone bank" before age thirty, the more that will remain later in life. Studies indicate that adolescent girls and young women often do not have adequate amounts of calcium in their diets, and thus may not build as much bone as possible. However, researchers have shown that if growing girls increase their calcium intake they are more likely to build denser bones. Such increased bone density should theoretically translate into less susceptibility to bone fractures in later years.

fractures. Albright named the resulting condition postmenopausal osteoporosis. He was the first to suggest that loss of bone was what caused the painful fractures and spinal collapse that were driving older women to the clinic in droves.

To support his hypothesis, Albright cited his laboratory findings, which showed that postmenopausal women excrete more calcium and phosphate—the major components of bone mineral—in their urine, blood, and stools than they consume in their diet. He also showed that regular injections of estrogen reversed this calcium imbalance, boosting the amount of calcium retained in the body, presumably in the bones.

Not only did Albright identify a new disease, postmenopausal osteoporosis, but he also offered the first treatment for the condition. Numerous studies have since shown the effectiveness of estrogen replacement therapy at staving off osteoporosis in women. Interestingly, researchers have recently shown that estrogen prevents osteoporosis in men too.

If given to women when they first enter menopause, estrogen can prevent height loss and slash the chances of breaking a bone by more than half. But estrogen therapy can only prevent damage to the skeleton by stemming bone loss. The hormone cannot replace lost bone. Consequently, to be effective, estrogen therapy needs to be started before serious bone loss occurs.

That was easier said than done in the 1940s. Osteoporosis is called a silent disease because by the time it causes symptoms it has already extensively damaged the skeleton. Standard X rays can't detect the minimal bone loss seen in the early stages of the disease. Albright solved this dilemma by giving estrogen therapy to all postmenopausal women who came to his clinic. But research shows that only one in four postmenopausal women is likely to develop severe osteoporosis. To avoid unnecessary treatment, doctors needed a way to identify those postmenopausal women most prone to severe consequences of the disorder.

Fortunately, starting in the 1960s, researchers developed more sensitive devices for detecting bone loss, including densitometers, which can determine bone density by measuring changes in the absorption of energy passing through bones in the hand, spine, hip, or other body part. This technique enables physicians to detect osteoporosis in its early stages, well before fractures occur. Densitometers can detect as little as a 1 percent change in bone density between successive measurements. Ultrasound, magnetic resonance imaging (MRI), and computerized tomography (CT scans) can also be used to assess bone density or bone strength. (See the MRI article in the Breakthroughs in Bioscience series.)

In addition, basic research has uncovered several specific compounds that are released into the bloodstream or urine when bone is broken down. Doctors can use blood or urine tests for these compounds to assess how rapidly bone is being lost and whether bone loss is due to osteoporosis or another disorder. The tests guide a doctor's choice of therapy and can help determine whether a treatment is effective.

The end result of these new tests and imaging tools is that now doctors can, as part of routine checkups, assess whether postmenopausal women are losing significant amounts of bone due to osteoporosis. If this is the case, doctors can begin treatment before the disease robs the bones of minerals and makes them prone to fractures.

Although estrogen is a highly effective treatment for postmenopausal osteoporosis, it is not right for every woman. It can cause side effects such as breast tenderness and vaginal bleeding that some women find intolerable. And because some studies have linked estrogen therapy to an increased risk of breast cancer, women with a family history of such cancers may not be ideal

Several studies have found that premenopausal women, particularly those younger than thirty, can also stem their risk of developing osteoporosis through regular weight-bearing exercise such as jogging, walking, or tennis. Such exercise builds more massive bones, and evidence suggests that even small increases in peak bone mass translate into a significantly reduced risk of fracture later in life.

There is conflicting evidence on whether exercise by postmenopausal women significantly reduces their risk of developing osteoporosis. What is certain is that bed rest and other situations that strongly hamper a woman's mobility increase her risk of developing the disease.

Findings by both epidemiologists and basic scientists also suggest that a woman can stem her chances of developing

candidates for estrogen therapy.

But thanks to the striking findings of researchers conducting experiments on mice and rats in the 1960s, women can now lower their risk of developing both osteoporosis and breast cancer. The researchers were searching for an anti-estrogen drug that could be used to prevent or treat breast cancer, which may be fostered by exposure to estrogen. They tested a novel compound on rodents to assess how well it countered the effects of estrogen in the body, and found that the compound did indeed stem the growth of breast tumors but, surprisingly, it could also trigger cells in the uterus to divide. The discovery that a compound could have anti-estrogen effects in one part of the body (the breast) and simultaneously have estrogen-like effects in another part (the uterus) led other researchers to develop what are known as selective estrogen receptor modulator (SERM) drugs.

One of these drugs, raloxifene (Evista), has been on the market since 1998 to prevent postmenopausal osteoporosis. Although it does not preserve bone density as much as estrogen does, studies indicate that it can stem the risk of fractures in the spine by as much as 45 percent. Raloxifene does not cause vaginal bleeding and, most important, preliminary results indicate that it may also dramatically reduce women's risk of breast cancer, slashing the risk by as much as three-quarters.

The ins and outs of calcium

Four drugs other than estrogen and raloxifene have also proven effective for postmenopausal osteoporosis, and several others are on the horizon. The discoveries that led to the development of these drugs were not made by researchers searching for an osteoporosis cure, but rather by scientists curious about what controls muscle contractions, why abnormalities in certain glands affect the strength of bones and teeth, and why cows experience malnutrition on some diets.

In 1900, a Rockefeller University biologist wondered what would happen if he changed the composition of an animal's body fluids. He found that when he took a muscle from a living frog and put it in a solution of water and table salt, the muscle contracted rhythmically. But when he added calcium, the muscle stopped contracting. He concluded that calcium in the blood prevents our muscles from continuously twitching.

At about the same time, Albright's mentor, the Viennese pathologist Jacob Erdheim, noted that the parathyroid glands—pea-sized glands in the neck—were enlarged in three patients with a condition known as osteomalacia. In this condition, the bones are softened because they lack adequate calcium and phosphorus. Always trying to find the cause of the abnormalities he observed, Erdheim conducted a series of experiments and showed in 1906 that when he removed the parathyroid glands in rats, their teeth lost calcium. These findings suggested that the parathyroids might affect the amount of calcium lodged in the skeleton.

Building on those findings, in 1909 a pathologist and chemist research duo at Johns Hopkins University in Baltimore showed that when they removed the parathyroids from dogs the animals began to convulse. But if they gave these same animals calcium salts, the convulsions stopped.

These experiments strongly indicated that the parathyroid glands play a role in governing the flux of calcium in the body, and launched a quest by scientists to pinpoint the compound secreted by the parathyroids that has this action. One of these scientists was Adolph Hanson, a small-town doctor from Minnesota who conducted his experiments in a makeshift lab in the basement of his home. Hanson reported in 1923 that, using cattle parathyroid glands he had collected from a slaughterhouse, he had isolated the active compound from the

osteoporosis if she refrains from smoking or consuming large amounts of alcohol on a regular basis. Investigators have found evidence suggesting that cigarette smoking lowers levels of estrogen in the bloodstream, interferes with calcium absorption, and inhibits the growth of bone-building osteoblasts. They have also shown that alcohol inhibits the absorption of calcium in the intestines and the activation of vitamin D.

The end result of all this research on risk factors for postmenopausal osteoporosis is that women now have strategies for reducing their chances of developing the disorder, particularly if they implement those strategies early in life. Indeed, osteoporosis has been described as an adolescent disease with a geriatric onset, highlighting the importance of beginning to take steps early in life, through exercise and diet, to reduce its disabling impact in later years.

parathyroids that can prevent the convulsions that occur when these glands are removed from dogs. The renowned Canadian biochemist James B. Collip independently isolated the same active extract in 1925 and showed that it boosted the level of calcium in the blood. These extracts were then purified and the active compound was named parathyroid hormone. This work led to the hypothesis that when blood levels of calcium are low, parathyroid hormone stimulates bones to release calcium into the bloodstream. It is now known that calcium is a vital mineral in the body that not only plays a key role in muscle contraction, including heartbeat, but also is essential for nerve transmission, blood clotting, and other functions. To work properly, the body must keep the blood level of calcium within a narrow range. When the blood supply of this mineral drops too low, parathyroid hormone fosters its replenishment by triggering the bones to release calcium into the bloodstream (fig. 4). The skeleton is the storehouse for the body's calcium; of the two to four pounds of calcium in the body, more than 99 percent is in the teeth and bones.

The parathyroids also boost blood supplies of calcium by increasing the amount of this mineral that is absorbed from the intestines and decreasing the amount that is passed in the urine. Although regular large doses of parathyroid hormone foster bone resorption, researchers in the 1930s discovered that when they regularly gave rats small doses of this hormone, bone formation actually increased. Recent tests of this approach in postmenopausal women have shown that it prompts impressive gains in bone density and substantially lowers the risk of fractures. Although easier means of delivering the hormone (for example, via nose sprays or inhalants rather than injections) and additional safety tests are needed, parathyroid hormone holds substantial promise

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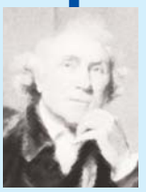

John Hunter

Elmer McCollum

Fuller Albright

1770s—John Hunter discovers that as new bone is formed, old bone is destroyed (resorbed).

1922—Elmer McCollum discovers vitamin D.

1923-1925—Parathyroid hormone is independently isolated by Adolph Hanson and James Collip and shown to boost levels of calcium in the blood.

1930s—Hans Selye shows that small doses of parathyroid hormone foster bone formation in rats.

1930s and 1940s—Fuller Albright defines postmenopausal osteoporosis and begins treating women with the condition with estrogen.

1960s—Herbert Fleisch discovers compounds known as bisphosphonates, which inhibit bone resorption.

1960s—Researchers discover that compounds known as selective estrogen receptor modulators (SERMs) can simul taneously block breast tumors and trigger the growth of uterine cells.

1970s—Researchers discover that osteoclasts and white blood cells come from the same parent cells in the bone marrow.

1970s—Researchers discover compounds called cytokines, which are generated by white blood cells and influence the cells' own development and activity.

1980s and 1990s—Researchers discover cytokines that influence the development and activity of osteoclasts.

1990s—The bisphosphonates alendronate and risedronate enter the market as anti-osteoporosis drugs.

1990s—Researchers discover some of the molecules that enable osteoclasts to break down bone.

1990s—Researchers uncover growth factors and other com pounds that stimulate the production and activity of osteoblasts.

1998—The selective estrogen receptor modulator drug raloxifene enters the market as a drug to treat and prevent postmenopausal osteoporosis.

Photos courtesy of the National Library of Medicine.

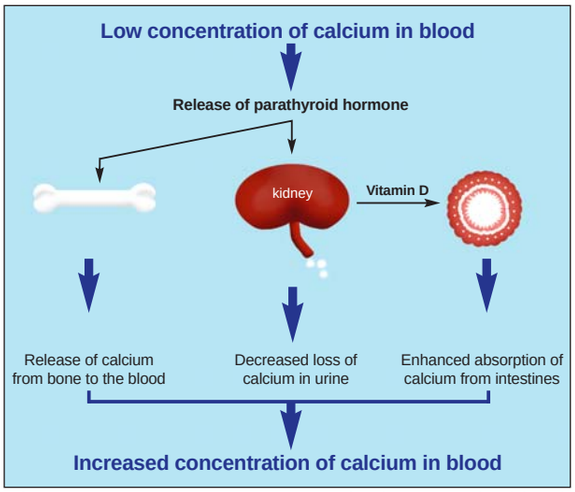

Figure 4. Low concentrations of calcium in the bloodstream trigger the release of parathyroid hormone. This hormone boosts calcium levels in blood by prompting bones to release some of their calcium stores into the blood and by inducing the kidneys to stem the loss of calcium in urine. Parathyroid hormone, in conjunction with vitamin D activated by bodily exposure to sunlight, also enhances the absorption of calcium from the intestines. *Designed by Corporate Press.*

as a drug that can prompt bone formation in women suffering from postmenopausal osteoporosis.

New drugs for osteoporosis accidentally discovered

In the 1960s, a Swiss physiologist by the name of Herbert Fleisch wanted to know exactly what causes calcium to be deposited in or removed from bone. Through his experiments, he identified a new compound in human blood and urine that prevented the formation of calcium salts in laboratory experiments. The compound, a pyrophosphate, was remarkably similar to compounds that have been used for over a century to prevent the buildup of scale (calcium deposits) in water boilers. Curious as to how this compound operated, Fleisch conducted a series of experiments that led him to discover that the pyrophosphate avidly latches onto calcium (one of the principal components in bone). This finding suggested that the compound could affect the flow of calcium into and out of the skeleton.

Fleisch was quick to see the potential usefulness of pyrophosphates in treating various bone disorders, including osteoporosis. But pyrophosphates are quickly broken down in the body, so Fleisch worked with pharmaceutical companies to develop longer-lasting synthetic versions of the compound he had discovered. Some of these pyrophosphate-mimicking drugs, known as bisphosphonates, were shown to suppress bone resorption, apparently by inhibiting the capacity of osteoclasts to break down bone. Two of these drugs, alendronate (Fosamax) and risedronate (Actonel), have been on the market since 1996 and 2000, respectively, as treatments for postmenopausal osteoporosis. Studies show that these drugs can cut the risk of bone fracture nearly in half in women with the disorder.

ABCs and Ds of nutrition

Another compound used to prevent and treat postmenopausal osteoporosis was discovered by a researcher bent on uncovering why cows were failing to thrive when fed certain diets. In 1907, biochemist Elmer McCollum came to the University of Wisconsin to study what causes the malnutrition seen in cows fed single- grain diets—only corn, only wheat, or only oats. Something vital was missing from these animals' diets, and McCollum set out to find out what it was by conducting a series of experiments in rats.

McCollum reasoned that rats would be easier to work with than cows because they had a shorter life span. The small animals also ate little, so they required less resources during an experiment. But because of the vigorous objections of his superiors, who thought rats were farm pests not worthy of experimentation, McCollum was unable to get funding for his research. He had to use his own resources to support a series of experiments in which he systematically supplemented the rats' single-grain diets with various foods to see which foods could counter the malnutrition these animals experienced. From these experiments he discovered vitamin A. His success also established the much-maligned rat as a useful animal model for nutrition studies.

At the time, children often suffered from a bone-deforming disease known as rickets, and researchers had shown that cod liver oil could prevent the disease. To determine whether vitamin A in cod liver oil was responsible for this effect, McCollum destroyed the vitamin A in a sample of the oil and then fed the oil to rats. The animals did not develop rickets, suggesting that another vitamin besides vitamin A lurked in cod liver oil. McCollum called this essential nutrient vitamin D.

McCollum's findings, which he reported in 1922, triggered a flurry of basic research aimed at pinpointing the chemical structure of vitamin D and its active forms as

well as the role vitamin D plays in the body. These investigations revealed that vitamin D is a hormone activated by sunlight. Vitamin D boosts calcium levels in the body by fostering the ability of intestines to absorb calcium from the diet. A lack of vitamin D triggers a cascade of reactions resulting in increased bone resorption.

Once this basic research had revealed the nature of vitamin D, clinical researchers began toying with the idea that the compound might prove beneficial to women suffering from postmenopausal osteoporosis. The elderly, in general, tend to be prone to vitamin D deficiency, studies show. Some studies also show that dietary supplements of vitamin D and calcium given to elderly women can reduce their risk of hip fracture. For these reasons, doctors often prescribe vitamin D supplements to women with postmenopausal osteoporosis, especially elderly women not exposed to much sun.

Explosion of research

The repertoire of drugs doctors have at their disposal to prevent or treat osteoporosis is likely to expand greatly in the near future as a result of the explosion in basic research on bone biology that has been fostered by the availability of a variety of new research tools. These tools, which include antibodies designed to seek out and bind to specific proteins, genetic probes, cell cultures of osteoblasts and osteoclasts, and rodents whose ovaries have been removed as well as genetically engineered animal models, have enabled researchers to fine-tune their explorations of what exactly controls bone remodeling. Hormones such as estrogen, parathyroid hormone, and vitamin D may be the kingpins in bone remodeling, but they cannot affect this process without the aid of other molecules that operate in the vicinity of bone to control its resorption or formation.

But what are those molecules? Insight into this mystery came in the 1960s, from researchers at Cornell and Harvard Universities who were conducting basic anatomy studies on the newt. These scientists used radioactive tracers to show that cells that become bone-eating osteoclasts start out as white blood cells in the bone marrow. Building on this finding, Donald Walker of Johns Hopkins University in Baltimore showed in the 1970s that he could cure mice of a bone disease caused by faulty osteoclasts by giving them bone marrow transplants. Apparently osteoclasts that developed from the bone marrow restored bone resorption in these animals. This indicated that in mice the osteoclast shares its origins with white blood cells; they both develop from parent cells in the bone marrow. Shortly after Walker's discovery, other researchers found that human osteoclasts also originate from marrow cells.

At the time these discoveries were made, other basic researchers discovered that cells of the immune system (which include white blood cells and their parent cells) secrete a variety of substances, called cytokines, that influence these cells' own development and activity. Could these same

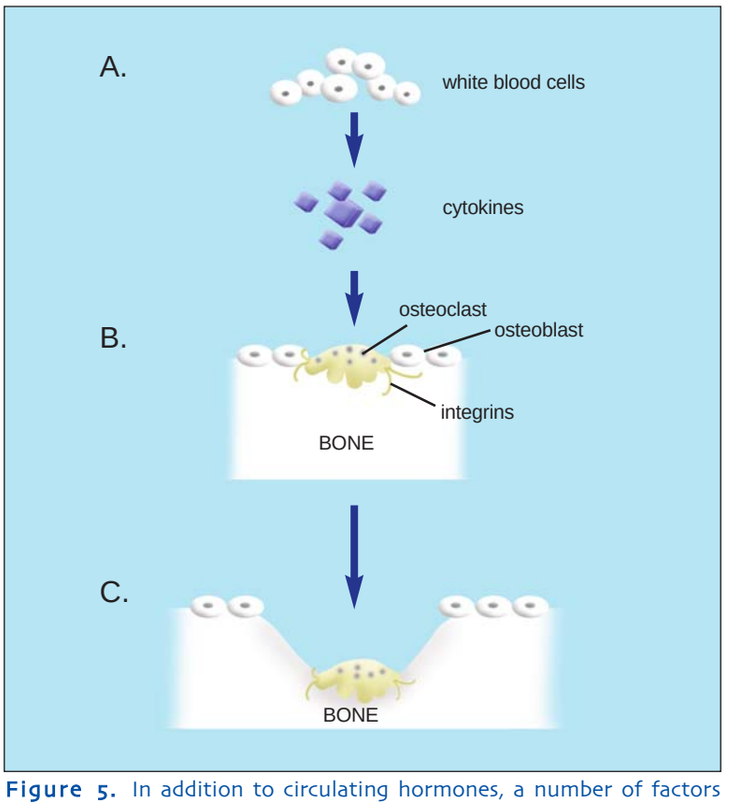

Figure 5. In addition to circulating hormones, a number of factors control bone resorption. Cytokines propel white blood cells (A) to fuse together and develop into osteoclasts. The integrin proteins that jut out from the surface of the osteoclast anchor the cell to bone (B). Once anchored, acids and enzymes released by the osteoclast dissolve a cavity in bone (C). *Designed by Corporate Press.*

cytokines also be influencing the development and activity of osteoclasts?

A number of investigators set out to answer this question and discovered that several cytokines do indeed propel immature white blood cells to become bone-eating osteoclasts (fig. 5). One of these cytokines also increases the life span of each osteoclast formed. Other researchers showed that estrogen plays a major role in reining in the production of these cytokines, which explains why postmenopausal women, who lack the hormone, have elevated numbers of osteoclasts. This population explosion of long-lived osteoclasts tips the balance away from bone formation and toward bone resorption such that more bone is lost than formed.

The discovery of cytokines that promote bone resorption offers new targets for anti-osteoporosis drugs, which researchers are avidly pursuing. Investigators are also dissecting the biochemical pathways that these cytokines influence, and have uncovered several key compounds that could also serve as drug targets. Another recently discovered therapeutic target is the molecule that anchors osteoclasts to bone. Such anchoring is a necessary first step in bone resorption, so drugs that can prevent anchoring may be effective anti-osteoporosis drugs of the future.

Researchers are also beginning to uncover some of the compounds that stimulate the production and activity of bone-forming osteoblasts. This research offers the possibility that, in the future, doctors will be able to use drugs to restore and not just prevent bone loss. Although parathyroid hormone, a compound known to prompt bone formation, is likely to be used as an osteoporosis drug in the near future, all the drugs currently used to treat osteoporosis work by stemming bone resorption.

Even without these potential new drugs to counter postmenopausal osteoporosis, the disorder has already undergone a remarkable transformation from an accepted and inevitable consequence of a woman's aging to a preventable and treatable disease. All of this would not have been possible without the efforts of a cadre of researchers over the past 250 years from fields as disparate as anatomy, biochemistry, pathology, and physiology. These investigators pursued such basic questions as, how does bone grow, what role does estrogen play in bone remodeling and in breast cancer, how does the body maintain its delicate calcium balance, why are some diets insufficient, and what cells give rise to osteoclasts? Without the curiosity of these scientists fueling basic insights into bone biology, drugs for osteoporosis would never have been discovered—and many women would continue to have no option but to enter their golden years stooped over and in pain.

Biographies

Margie Patlak writes about biomedical research and health from the Philadelphia region. She has written for Discover, Glamour, Physician's Weekly, Consumer Reports on Health, The Washington Post, the Los Angeles Times, the Dallas Morning News, and numerous other publications. She also writes frequently for the National Institutes of Health and the National Academy of Sciences.

Steven L. Teitelbaum, M.D., is the Wilma and Roswell Messing Professor of Pathology at Washington University School of Medicine and a Past-President of the American Society for Bone and Mineral Research.

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