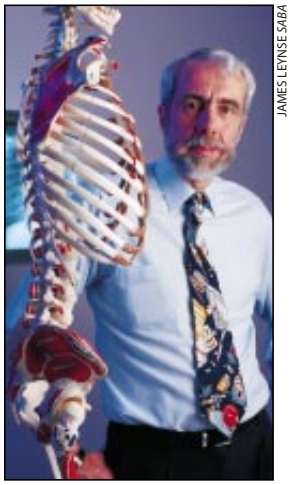
Q&A

Osteoporosis

Donald P. McDonnell, Ph.D.

M. J. SHARP



JAMES LEYNSE *SABA*

Robert Lindsay, M.B.Ch.B., Ph.D.

It's hard to envision a thin, athletic woman as a hip fracture victim waiting to happen. Unfortunately, research shows that women athletes who often diet and don't get enough calcium have among the highest risks for developing osteoporosis when they reach their 50s and 60s. Some young female athletes are also at risk because they lose so much body fat that they stop having their menstrual periods, which lowers their estrogen levels and leads to bone loss. Osteoporosis is characterized by decreased bone mass and an increased risk of broken bones. According to the U.S. National Osteoporosis Foundation, more than 28 million people in the U.S. are at high risk of developing the potentially crippling disorder—and most of them are women. That figure is predicted to jump to 41 million by 2015, when women in the baby boom generation will be beyond menopause.

***KARYN HEDE**, special correspondent for SCIENTIFIC AMERICAN, discusses what women should know about osteoporosis with **DONALD P. McDONNELL, Ph.D.**, associate professor of pharmacology and cancer biology at Duke University Medical Center, and **ROBERT LINDSAY, M.B.Ch.B., Ph.D.**, chief of internal medicine at Helen Hayes Hospital in West Haverstraw, N.Y. McDonnell's research focuses on a new class of compounds called selective estrogen receptor modulators (SERMs), which offer hope for preventing and treating osteoporosis without the side effects of estrogen. Lindsay is founding director of the metabolic bone disease unit at St. Luke's–Roosevelt Hospital in New York City and is the author of over 200 publications on osteoporosis and estrogen replacement therapy.*

Q ***What causes osteoporosis? And why are women particularly prone to the disease?***

A **McDONNELL:** To answer that, I need to describe what usually happens in normal bone. Bones are very complex and dynamic organs. There are basically two types of bone cells: osteoblasts, which make bone, and osteoclasts, which break down bone. Normally, these cells function in concert throughout life to resorb old, worn-out bone and replace it with new bone. In osteoporosis, this balance gets thrown off in favor of the osteoclasts.

The hormone estrogen, which is present in much greater quantities in women than in men, regulates the bone deposition process. A number of sex hormones may be involved in maintaining bone mass. In men, estrogen and androgens are involved. Men have more estrogen than women after menopause, so they are relatively more protected. But men do get osteoporosis, just in lower numbers.

Women have two stages of bone loss: from about age 35 to menopause, and after menopause. We don't really understand the first stage, although estrogen levels have already begun to drop during that time of life. But after menopause, osteoporosis results from the lack of estrogen.

What is known about the role of estrogen in maintaining healthy bones?

McDONNELL: This is a case in which the clinical data have been way ahead of basic science. For years, all we knew was that when you put women on hormone replacement therapy, they stop losing bone and actually regain a small bit of bone mass. But we've had some revealing developments in the laboratory within the past few years. It's becoming clear that estrogen binds to estrogen receptors in bone progenitor cells, the cells that give rise to the osteoblasts and osteoclasts. After menopause, a lack of estrogen actually stimulates production of both cell types—but with a net increase in osteoclasts, which results in a net loss of bone.

LINDSAY: We still do not understand exactly how estrogen controls skeletal remodeling. But when women go through

menopause, the normal bone-remodeling process goes crazy. After the ovaries stop secreting estrogen, the number of sites where the bone cells are breaking down old bone and making new bone increases. Theoretically, the amount of old bone removed should be exactly equal to the amount of new bone laid down. But after menopause there's an imbalance between bone resorption and bone formation in favor of resorption. As a consequence, after each remodeling cycle you end up with slightly less bone.

Who is at risk for developing osteoporosis?

LINDSAY: The major risk factors are age and race: Caucasian and Asian women who have reached menopause have the greatest risk. Having a family history of osteoporosis increases risk because there's a genetic component to the overall amount of bone you start with as an adult. Beyond that, other risk factors are a thin physique, smoking, excessive alcohol consumption and a history of low calcium intake. In addition, some medications, such as steroids, the anticoagulant heparin and anticonvulsants, can accelerate bone loss.

Lowering Your Risk

So what should women with these risk factors do?

LINDSAY: If you have three or more risk factors, you ought to think seriously about having a bone-density scan around the time of menopause. A bone-density scan, technically called dual-energy x-ray absorptiometry (DXA), is used to measure bone mineral density in the spine, hip and wrist, the most common sites for osteoporotic fractures. Bone scans take just a few minutes and result in very low x-ray exposure—about one tenth that of a standard chest x-ray.

Women with low bone density at menopause are very likely to develop fractures; the lower your bone density, the higher your risk. Measurements are based on the mean bone density of a young woman at peak bone mass. Based on the results of the scan, a patient and her physician can decide among several courses of action.

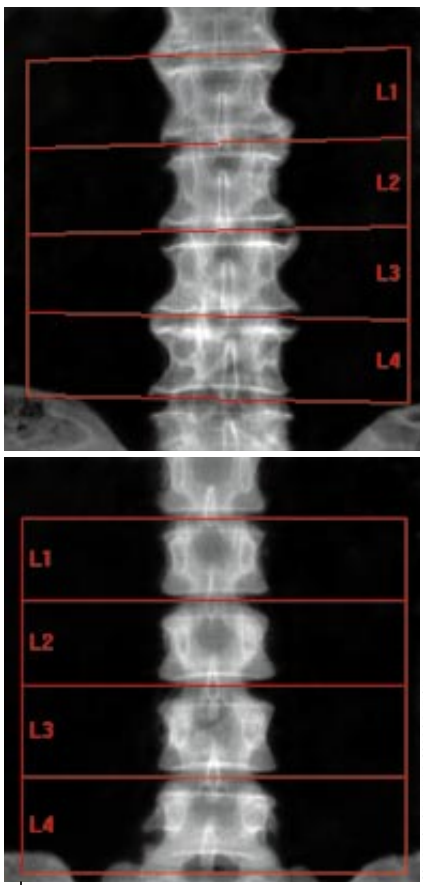
If a woman has high bone density, greater than one standard deviation above normal, her doctor might say, "You don't need to worry; you're not going to get osteoporosis." To a woman with average bone density who is just entering menopause, a physician might say, "We don't know whether you are going to lose bone or not, so come back and get a measurement in two to five years." To get the best reading, that woman should go back and have the measurement done at the same place, on the same machine and preferably with the same technician.

If a woman's bone density is a little lower than average for her age—greater than one standard deviation below normal—and she's 55 years old, her doctor might say, "Here are things you can do to change your lifestyle: stop smoking, reduce your alcohol intake, increase your calcium intake and increase your physical activity." Moderate physical activity not only helps bones grow stronger, it also reduces the risk of falling and breaking a bone better than anything else. That woman's physician would also want to measure her bone density again in a couple of years to see whether she was losing bone rapidly.

A woman with bone density lower than 2.5 standard deviations below normal is at particularly high risk for a fracture and should consider pharmacological intervention.

How accurate is bone-density scanning in predicting a woman's future risk of a bone fracture?

LINDSAY: Bone density is a better predictor of fracture than cholesterol is for heart attack or blood pressure is for stroke. Roughly speaking, a 10 percent reduction in bone density doubles a woman's risk of fracture after menopause.



COURTESY OF LUNAR CORPORATION

A bone scan of the lower spine of a 68-year-old woman with osteoporosis (top) *looks less opaque than a similar scan of the spine of a 52-year-old woman without the disease* (bottom). *The osteoporotic woman's spine is slightly crooked, as indicated by the red lines between the vertebrae. It also bears two abnormal bony growths called osteophytes at the right side of lumbar vertebrae L2 and L3.*

Should premenopausal women have their bone density checked?

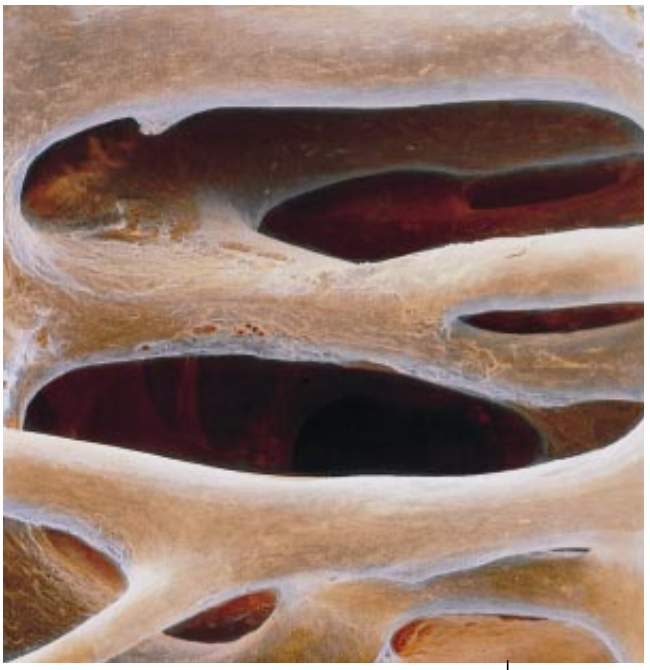
LINDSAY: By and large, premenopausal women don't need to have a bone-density measurement unless they have very clear risk factors for osteoporosis, such as anorexia and problems with the function of their hypothalamus, a region of the brain that's involved with hormone regulation. The time for women to consider a bone scan is somewhere around the perimenopausal years, from the early 40s to the early 50s.

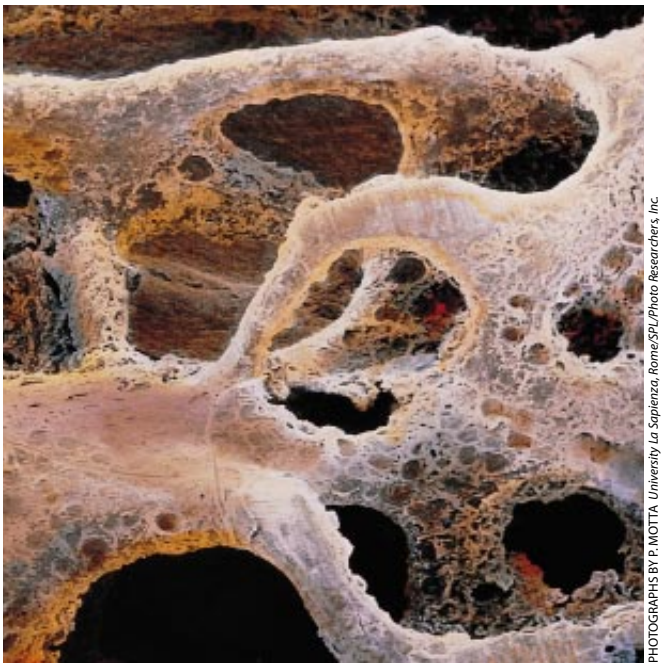
What can premenopausal women do to reduce their future risk of osteoporosis?

LINDSAY: The key to preventing osteoporosis—and many other diseases of aging—is a healthy way of life, particularly a good diet high in calcium. In general, nonpregnant women should take in between 1,000 and 1,500 milligrams of calcium per day, whether in food or as a dietary supplement. The National Health and Nutrition Examination Studies found that the average calcium intake in the U.S. is only about 600 milligrams a day.

The elderly who are homebound or have chronic illnesses must also ensure that they get enough vitamin D, which helps the body use calcium. Most multivitamins contain vitamin D; intake should be five to 7.5 micrograms a day.

Being physically active is also important. Having regular periods is crucial because young women who don't menstruate usually have low estrogen levels, which can mean losing bone mass. And here's yet another reason why a woman should stop smoking: it's as bad for your bones as it is for your lungs and heart.





PHOTOGRAPHS BY P. MOTTA *University La Sapienza, Rome/SPL/Photo Researchers, Inc.*

Healthy bone (left) *appears smooth and sturdy when viewed under the microscope. In contrast, bone from someone who has osteoporosis* (right) *is porous and fragile, making it more susceptible to fracture.*

Treating Osteoporosis

Estrogen is frequently prescribed for menopausal and postmenopausal women to prevent osteoporosis. Yet the use of estrogen has been associated with an increased risk for breast cancer and cancer of the endometrium, the lining of the uterus. Is estrogen still the best treatment for osteoporosis?

McDONNELL: Estrogen has been on the market now for 50 years, and it has an excellent record not only in treating osteoporosis but also in reducing a woman's risk of cardiovascular disease. It also reduces other unwanted side effects of menopause, such as hot flashes. There is a small increase, however, in the incidence of breast cancer among women who take estrogen, although new evidence suggests that women who take estrogen have a lower overall mortality rate. So on balance, the beneficial effects of estrogen for most women greatly outweigh its potential risks. Estrogen with progestin, in a combination called hormone replacement therapy, reduces the risk of endometrial cancer. Still, the breast cancer issue remains at the front of women's minds.

LINDSAY: The gold standard for treatment of osteoporosis is hormone replacement therapy. If women are already on hormones for other reasons—to control menopausal symptoms or because they are concerned about heart disease—then they need do nothing more. Hormone replacement therapy is the first-line therapy for osteoporosis because it has proved to be the best protection against bone loss.

Are there other drugs that can protect against bone loss, without estrogen's side effects?

McDONNELL: One of the newest therapies is a class of drugs called the bisphosphonates, of which the best known is alendronate, or Fosamax. The bisphosphonates do not work like hormones. They do not bind to the estrogen receptor in bone progenitor cells; they enter the bone directly. One hypothesis is that the bisphosphonates reduce the activity of osteoclasts, thereby reducing bone resorption. These agents are very effective in the treatment of osteoporosis. But every drug has a positive side and a negative side. The negative side is that these agents have no beneficial effect on the cardiovascular system and that they do not reduce the other symptoms of menopause, such as hot flashes.

LINDSAY: The people who are most likely to use a bisphosphonate drug such as Fosamax are those who have the highest risk of developing osteoporosis. The problem with Fosamax is that at the higher dose used for treatment, 10 milligrams, it has been associated with some upper gastrointestinal symptoms—heartburn and dyspepsia. That's why it's a second-line therapy for most people. And in rare instances, Fosamax can cause esophageal ulcers.

A new drug called Evista was approved by the Food and Drug Administration last December for treating osteoporosis. How does it work?

McDONNELL: Evista, or raloxifene, is the first approved selective estrogen receptor modulator, or SERM. Other SERMs are now being tested in clinical trials. These drugs function as estrogens in the bone but not in the other organs. In fact, Evista functions as an antiestrogen in the breast by blocking the estrogen receptor, which can spur breast cancer growth. So although it remains to be proved, SERMs might actually reduce a woman's risk of breast cancer. Several small studies have shown that SERMs decrease breast cancer by 70 percent. They can also reduce the risk of endometrial cancer. Long-term studies are still needed to see if that holds up over the long run.

The SERMs have also introduced totally new issues for women to consider. Evista is only about one half to one third as effective as estrogen in preventing bone loss, and the preliminary data suggest that it doesn't begin to match up to estrogen

in protecting against cardiovascular disease. But new SERMs are in development that are likely to show more promise in this regard. Another downside is that current SERMs not only don't protect against hot flashes, they actually induce hot flashes—the reason most menopausal women go to their doctors in the first place. On top of all that is the question of how SERMs will affect the estrogen receptors in the nervous system: Will SERMs decrease cognitive function or increase the risk of Alzheimer's disease? Those are going to be important issues.

How can SERMs act selectively in some tissues but not in others?

McDONNELL: When estrogen binds to its receptors in cells, it activates them by converting them from a square shape into a circular shape. The circular shape is then able to complete all the effects of estrogen in the cell, including turning on some genes. What SERMs do is warp the receptors into new and different shapes. We found that different cells have different abilities to recognize these shapes. For instance, cells in the breast can recognize only a circle. But bone cells aren't that choosy. They can recognize either the circular shape or an alternative shape. So compounds like SERMs that can mold estrogen receptors into another shape can activate the receptors in the bones but can also block the receptors in the breast and endometrium. Using this approach, I believe we will eventually be able to "dial in" certain properties of estrogen, such as protection against heart disease, and "dial out" others, such as its ability to contribute to breast cancer and endometrial cancer.

Taking into consideration the pros and cons of SERMs, who should take them?

McDONNELL: I think SERMs are going to appeal to women who are skeptical of hormone replacement therapy because of the side effects or who have a family history of breast cancer. SERMs might be effective as chemopreventatives against breast cancer and endometrial cancer. Perhaps most important, these new drugs are going to increase women's overall awareness of hormone replacement therapy. When women have more options, they will have more incentive to seek some type of therapy during and after menopause.

The hormone calcitonin is sometimes offered to women as a treatment for osteoporosis. What is calcitonin?

LINDSAY: Calcitonin is normally produced by the thyroid gland to help the body maintain appropriate concentrations of calcium. It is given either as a subcutaneous injection or as a nasal spray, because it is a protein and would be broken down in the stomach if taken by mouth. Before SERMs, calcitonin was the third-line choice for the treatment of osteoporosis because it is not as potent as either alendronate or hormone replacement therapy. Its major advantages are that it is safe and the side effects are modest: some nasal irritation and flushing of the face in the first few weeks of use. It's been around for a long time, and there are no major side effects associated with it. It's used mainly for those who can't or won't take hormones and who can't take alendronate because of gastrointestinal complaints.

If some people have a genetic predisposition to osteoporosis, what will it mean for women if a gene for osteoporosis is found?

LINDSAY: The genetics of osteoporosis is a fascinating field that is growing rapidly. The major approach has been to look for candidate genes and then to evaluate whether different forms of those genes are associated with differences in bone density or the risk of a fracture. The genes that have been looked at include the genes for collagen, which makes up cartilage; the vitamin D receptor; and the estrogen receptor and various growth factors. The very fact that there are all these candidate genes suggests that there may be no single gene that will be useful in a clinical test for osteoporosis risk. Some of the genes are seen more frequently in people who develop fractures, but generally they confer only modest differences in risk.

Another approach has been to look at osteoporosis that runs in families to see if you can identify a common gene in those families. Very little has come out of that work thus far.

I think a genetic test would be of considerable value in terms of guiding lifestyle. We know that lifestyle during the time of young adult life is responsible for about 10 to 20 percent of the variability in bone mass. If we knew there was a gene that had a high prevalence in a family with osteoporosis, physicians could encourage women in such families to build as much bone as possible while they are young through a healthy way of life and getting plenty of calcium.

On the Horizon

What are the most promising therapies coming in the next five years?

McDONNELL: In my mind, we're going toward what I call designer therapies. A woman may go to her doctor and have a family history of osteoporosis but no problems with cardiovascular function. A SERM might be fine for her because she gets protection against bone loss, in the organ where she is most at risk. She's not overtreated. Women themselves are going to decide the market. A woman might say to herself, "SERMs produce hot flashes, so I'll take estrogen for a few years and then switch over to Evista." Women want choices; they want to be much more involved in the treatment of their own menopause.

LINDSAY: I think the most interesting work is being done with agents that might repair the skeleton. Researchers first noted in 1929 that parathyroid hormone can add bone to the skeleton. But that finding was basically ignored until the 1970s, when parathyroid hormone was first synthesized in the lab. Now the first controlled clinical trials of parathyroid hormone as a treatment for osteoporosis have appeared. Last August we published a paper in the journal *Lancet* outlining the results of a three-year study of this hormone. We found that it produces a dramatic increase in bone density—much larger than you see with any of the current therapeutic options. It also appears to reduce the number of spinal fractures. So parathyroid hormone or an analogue might be developed for the treatment of osteoporosis.

I think there's a very rosy outlook for osteoporosis. We have the mechanisms now for diagnosing it, we have some treatment options, and over the next few years we can expect more and better treatments. With all of this, the disease ought to disappear in the next millennium. SA

For more information, visit the National Osteoporosis Foundation at http://www.nof.org on the World Wide Web or call them at 202-223-2226. The association also offers a series of patient education brochures, including one entitled "Osteoporosis: A Woman's Guide."