Physiologic Clues

We don't know very much about the few men and women who have lived to 115 years of age or more, but we can assume that they eluded the diseases that kill many people in their 70s and 80s. At 122, Jeanne Calment, for instance, had lived a relatively disease-free life. In fact, escape from infectious disease is the most common reason that all of us can now expect to live longer than our grandparents.

Chronic diseases and disability were once thought inseparable from old age. This view is changing rapidly as one disease after another joins the ranks of those that can be prevented or at least controlled, often through changes in lifestyle.

We now know, for example, that most people can avoid lung disease by not smoking. And heart disease and stroke rates have fallen at the same time that Americans have lowered their fat consumption, begun to exercise more, and quit smoking.

So if chronic disease is not intrinsic to the aging process, as many gerontologists now believe, then what is? Are there universal or "normal" aging processes?

Normal Aging

Unlike most of us, Satchel Paige was never quite sure of his birth year. "My birth certificate was in our (family) Bible, and the goat ate the Bible," he said. But even had he known his chronological age, it may not have shed much light on how old he was physiologically. In fact, gerontologists are discovering that age in years doesn't necessarily correlate with physiological age.

For decades, investigators at the NIA have compiled data on heart function, lung capacity, and numerous other bodily functions in hopes that this information may one day be used to establish definitive measures of physiological aging. In theory, these biomarkers would be more precise indicators of aging than chronological age itself. Once established, these biomarkers could make it easier to study normal aging, diseases, and possible interventions. So far, however, no such biomarkers have been identified in humans.

"How old would you be if you didn't know how old you were?"

– Leroy "Satchel" Paige
Member, Baseball Hall of Fame. The oldest person to pitch in the major leagues – he was in his late 50s.

In the Baltimore Longitudinal Study of Aging (BLSA), volunteers, age 20 to 90, are screened every 2 years for physiological and psychological changes. They undergo a complete physical exam and a series of tests including muscle strength (shown), bone density, aerobic capacity, and glucose tolerance. Each assessment adds detail and focus to the BLSA's slowly growing picture of how we age.

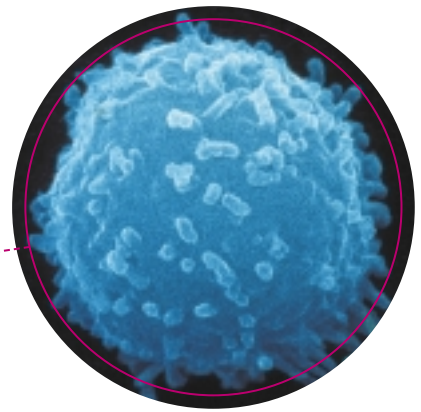
In fact, normal physiological aging is quite variable, according to investigators involved in the Baltimore Longitudinal Study of Aging, a long-term NIA study begun in 1958 that has tracked the lives of more than 1,000 people from age 20 to 90 and beyond. Not only do individuals age overall at vastly different rates, it is quite likely that age-related changes in various cells, tissues, and organs differ as well. For instance, kidney function may decline more rapidly in some individuals. In others, bone strength may diminish faster. The organs that age fastest in one person may not age as rapidly in another. This suggests that genes, lifestyle, and disease can all affect the rate of aging and that several distinct processes are involved.

Although this diversity lessens the likelihood of finding biomarkers of aging in humans, the quest for these indicators has yielded many insights into the physiology of two organ systems that may have important roles in the aging process. One of these is the endocrine system (**See Hormones and Research on Aging, page 26**). The other is the immune system.

The Immune System

When Shigechiyo Izumi of Japan contracted pneumonia and died in 1986 at the reputed age of 120, it was his immune system that failed. One of the many bacteria or viruses that cause pneumonia broke through the elaborate, natural defenses that protect humans from infection. Scientists have long known that these defenses decline with age; now, some of the underlying mechanisms are coming to light.

A multiplicity of cells, substances, and organs make up the immune system. The thymus, spleen, tonsils, bone marrow, and lymphatic system, for example, produce, store, and transport a host of cells and substances—B-lymphocytes and T-lymphocytes, antibodies, interleukins, and interferon, to name a few. Several are of special interest to gerontologists. These include the class of white blood cells called lymphocytes, which fight invading bacteria and other foreign cells.



The organs of the immune system are located throughout the body. White blood cells—lymphocytes—are key operatives of this system. With age, these cells become less active, making the body more vulnerable to bacteria, viruses and other pathogens.

What is Normal Aging?

Individuals age at extremely different rates. In fact even within one person, organs and organ systems show different rates of decline. However, some generalities can be made, based on data from the Baltimore Longitudinal Study of Aging.

HEART > Heart muscle thickens with age. Maximal oxygen consumption during exercise declines in men by about 10 percent with each decade of adult life and in women by about 7.5 percent. This decline occurs because the heart's maximum pumping rate and the body's ability to extract oxygen from blood both diminish with age.

ARTERIES > Arteries tend to stiffen with age. The older heart, in turn, needs to supply more force to propel the blood forward through the less elastic arteries.

LUNGS > Maximum breathing (vital) capacity may decline by about 40 percent between the ages of 20 and 70.

BRAIN > With age, the brain loses some of the structures (axons) that connect nerve cells (neurons) to each other, although the actual number of neurons seems to be less affected. The ability of individual neurons to function may diminish with age. Recent studies indicate that the adult nervous system is capable of producing new neurons, but the exact conditions that are critical for this have yet to be determined.

KIDNEYS > Kidneys gradually become less efficient at extracting wastes from the blood.

BLADDER > Bladder capacity declines. Urinary incontinence, which may occur after tissues atrophy, particularly in women, can often be managed through exercise and behavioral techniques.

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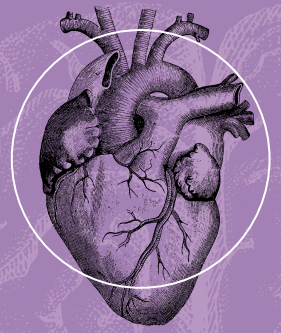
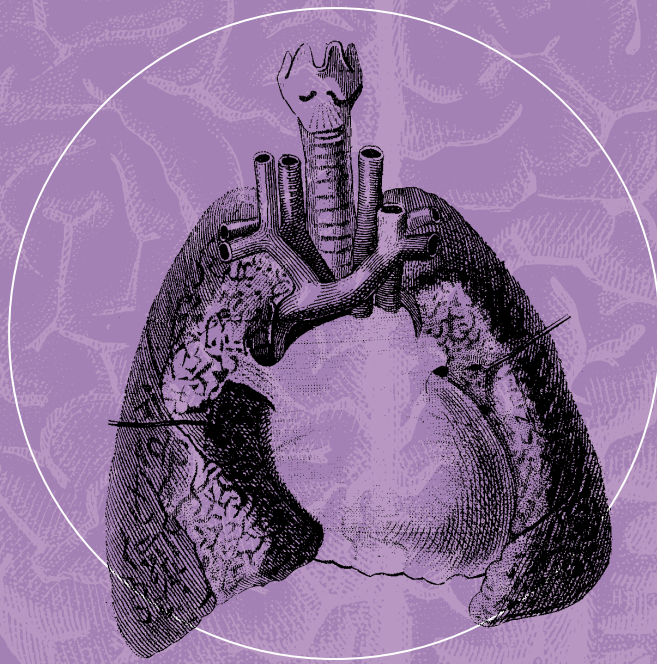
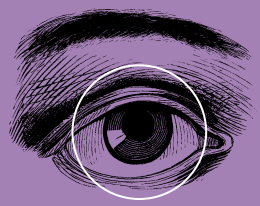
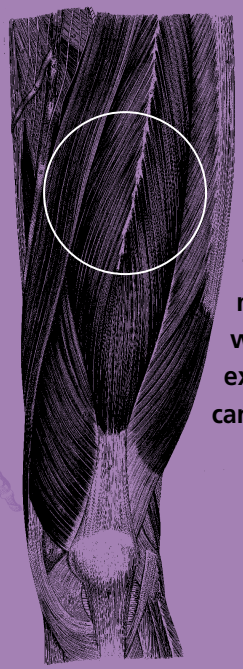




What is Normal Aging?



BODY FAT > Typically, body fat gradually increases in adulthood until individuals reach middle age. Then it usually stabilizes until late life, when body weight tends to decline. As weight falls, older individuals tend to lose both muscle and body fat. With age, fat is redistributed in the body, shifting from just beneath the skin to deeper organs. Women typically have a higher percentage of body fat than men. However, because of differences in how this fat is distributed—on the hips and thighs in women and on the abdomen in men—women may be less susceptible to certain conditions including heart disease.



MUSCLES > Without exercise, estimated muscle mass declines 22 percent for women and 23 percent for men between the ages of 30 and 70. Exercise can slow this rate of loss.

BONES > Bone mineral is lost and replaced throughout life; loss begins to outstrip replacement around age 35. This loss accelerates in women at menopause. Regular weight bearing exercise—walking, running, strength training—can slow bone loss.

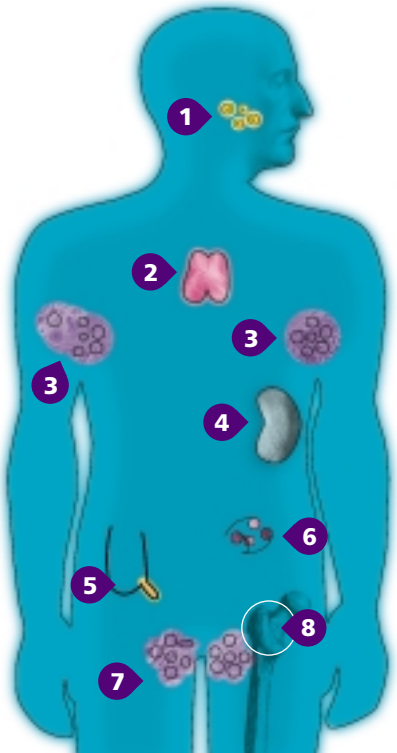
SIGHT > Difficulty focusing close up may begin in the 40s; the ability to distinguish fine details may begin to decline in the 70s. From 50 on, there is increased susceptibility to glare, greater difficulty in seeing at low levels of illumination, and more difficulty in detecting moving objects.

HEARING > It becomes more difficult to hear higher frequencies with age. Even older individuals who have good hearing thresholds may experience difficulty in understanding speech, especially in situations where there is background noise. Hearing declines more quickly in men than in women.

PERSONALITY > Personality is extraordinarily stable throughout adulthood. Generally, it does not change radically, even in the face of major events in life such as retirement, job loss, or death of loved ones. However, there are exceptions. Certain individuals facing these and other life-altering circumstances can and do show signs of personality change during the final years of life. An easy-going individual who loses a job after many years, for instance, may become disillusioned and develop a sullen disposition. But these out-of-character reversals of personality are relatively rare.

Lymphocytes fall into two major classes: B-cells and T-cells. B-cells mature in the bone marrow, and one of their functions is to secrete antibodies in response to infectious agents or antigens. T-cells develop in the thymus, which shrinks in size as people age; they are divided into cytotoxic T-cells and helper T-cells. Cytotoxic T-cells attack infected or damaged cells directly. Helper T-cells produce powerful chemicals, called lymphokines, that mobilize other immune system substances and cells.

T-cells and their lymphokine products have intrigued gerontologists ever since it was learned that T-cells—or more precisely the functioning population of T-cells—declines with age. While the number of T-cells remains about the same, the proportion of them that proliferate and function declines. Studies have also shown that in older people, T-cells destroyed by stresses such as irradiation or cancer chemotherapy take longer to renew than they do in younger people.



The Immune System

1. Tonsils and Adenoids
2. Thymus
3. Lymph Nodes
4. Spleen
5. Appendix
6. Peyer's Patches
7. Lymphatic Vessels
8. Bone Marrow

Most research on the aging immune system now centers on these cells. One group of T-cell products, interleukins, is found at different levels as people age. The interleukins—there are more than 20 identified so far—serve as messengers, relaying signals that regulate the immune response. Some, like interleukin-6, rise with age, and it is speculated that they interfere in some way with the immune response. Others, like interleukin-2, which stimulates T-cell proliferation, tend to fall with age. Gerontologists study the interleukins, not only for clues to the mechanisms of aging, but also for their potential in the detection and treatment of immune problems.

Meanwhile, compelling evidence suggests one intervention—caloric restriction—may counteract some of the natural declines in the immune system as well as in other physiological systems of aging animals.

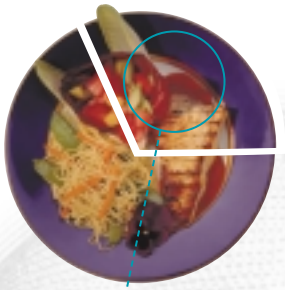
"To lengthen thy life, lessen thy meals."

– Benjamin Franklin, (1706-1790)

Caloric Restriction

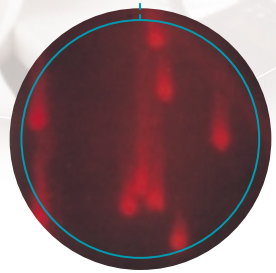
An inventor, statesman, diplomat, and scientist, Benjamin Franklin was a true Renaissance man renowned for his sage advice. Among his many pearls of wisdom: "To lengthen thy life, lessen thy meals." Nearly 275 years later, gerontologists are finding those words may turn out to be amazingly prophetic.

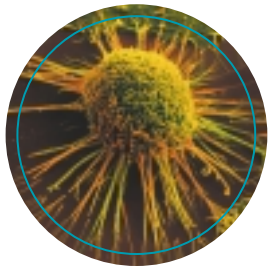
Since the 1930s, investigators have consistently found that laboratory rats and mice live up to 40 percent longer than usual when fed a diet that has at least 30 percent fewer calories than they would normally consume. The animals that eat this nutritionally balanced diet, which provides healthful

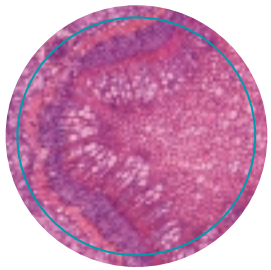


Feeding animals 30 to 40 percent fewer calories than normal appears to delay age-related degeneration of nearly every physiological system. But it remains uncertain whether caloric restriction could have the same effect in humans.

Data from animal studies suggests caloric restriction may help neurons resist dysfunction and death (top). Caloric restriction also might help the body fend off cancer (center), and other age-related cellular changes (bottom).







amounts of protein, fat, and vitamins and minerals, also appear to be more resistant to age-related diseases. In fact, caloric restriction appears to delay normal age-related degeneration of almost all physiological systems. And so far, caloric restriction has increased the lifespans of nearly every animal species studied including protozoa, fruit flies, mice, and other laboratory animals. Now investigators are exploring whether and how caloric restriction will affect aging in monkeys and other non-human primates, our closest relatives in the animal kingdom.

Why calorically restricted animals live far beyond their normal lifespans remains unclear. Because cutting down on calories slows metabolism, and free radicals are by-products of metabolism, caloric restriction may reduce oxidative damage to cells. Calorie restricted animals also have less glucose circulating in their blood than their freely feeding counterparts. This may lessen the potential for protein crosslinking, a biochemical process implicated in cellular aging. And because caloric restriction lowers body temperature slightly, cells may sustain less genetic damage than at normal body temperature. In addition, scientists speculate that caloric restriction preserves the capacity of cells to proliferate, and that it keeps the immune system functioning at youthful levels. Caloric restriction also may work through other mechanisms. It may, for instance, influence hormonal balance, cell senescence, or gene expression. Or, it might work through a combination of all of these mechanisms, plus other factors.

Many gerontologists are particularly intrigued by findings suggesting that animals on calorie restricted diets have reduced rates of disease. In one of the largest studies to date, Roderick Bronson, D.V.M., at Tufts University found that caloric restriction not only extended lifespan in mice, but also prevented or slowed down development of every disease and all types of tumors. Other rodent studies have found that caloric restriction may increase resistance of neurons in the brain to dysfunction and death. These results, described as "stunning" by gerontologists, have raised hope that further study of caloric restriction will help uncover the mechanisms responsible for disease in old age.

However, whether caloric restriction might have the same effect in primates remains a major question. In studies underway at NIA, rhesus and squirrel monkeys are growing up on a calorically restricted diet. Similar studies are also ongoing at the University of Wisconsin and the University of Maryland. Preliminary results from these studies show some promising early signs of improved health—including greater resistance to diabetes and heart disease—in these primates as they age. (**See The Next Step: Caloric Restriction in Primates, page 36**).

In the 1930s, investigators discovered that rats and mice fed fewer calories lived longer than rodents allowed to eat as much as they liked. Since then, caloric restriction has increased the lifespan of nearly every animal species studied.

The Next Step: Caloric Restriction in Primates

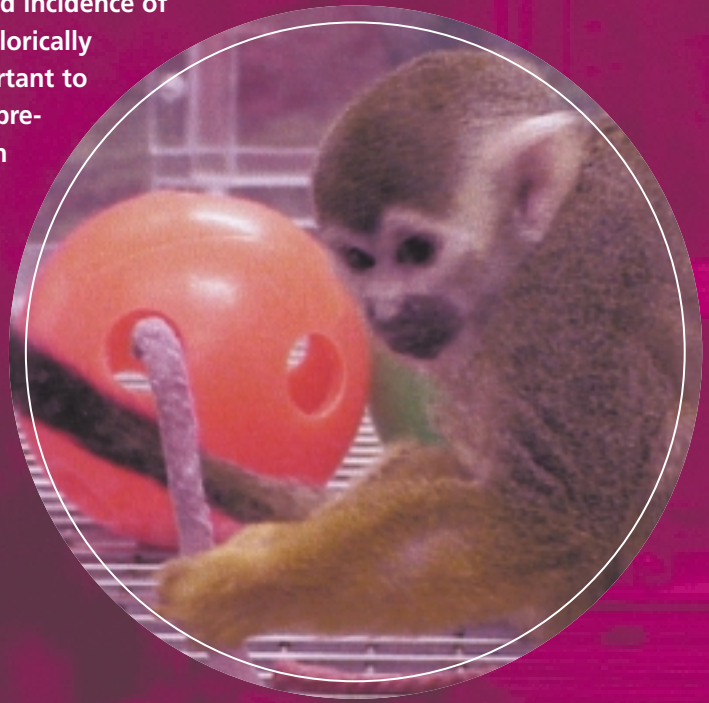
At the NIH Animal Center in Poolesville, Maryland, about 75 rhesus and squirrel monkeys are on diets; they eat 30 percent less than they would normally but get all the necessary nutrients. Another 75 monkeys, the control group, are eating as much as they want. The differences between the two groups, as they age, are beginning to provide insights into how caloric restriction influences lifespan.

The monkeys that arrived at the Poolesville laboratory in 1987 have responded to caloric restriction as expected; their maturation, measured by factors such as skeletal development and onset of puberty, has been delayed by about a year or year and a half. This is comparable to the delays in maturation seen in calorically restricted rodents.

As the monkeys continue to grow into middle age and beyond, Donald Ingram, Ph.D., and his colleagues at the NIA's Gerontology Research Center in Baltimore, where the project is coordinated, are monitoring dozens of signs of aging, ranging from immune response to activity level to antioxidant levels to fingernail growth. The measurements are being compared with those of the monkeys in the control group and should provide leads to some of the mechanisms at work in caloric restriction.

The monkeys on the restricted diet are smaller and weigh about 20 percent less than monkeys in the control group. However, the calorically restricted monkeys are no less physically active than animals allowed to eat at will.

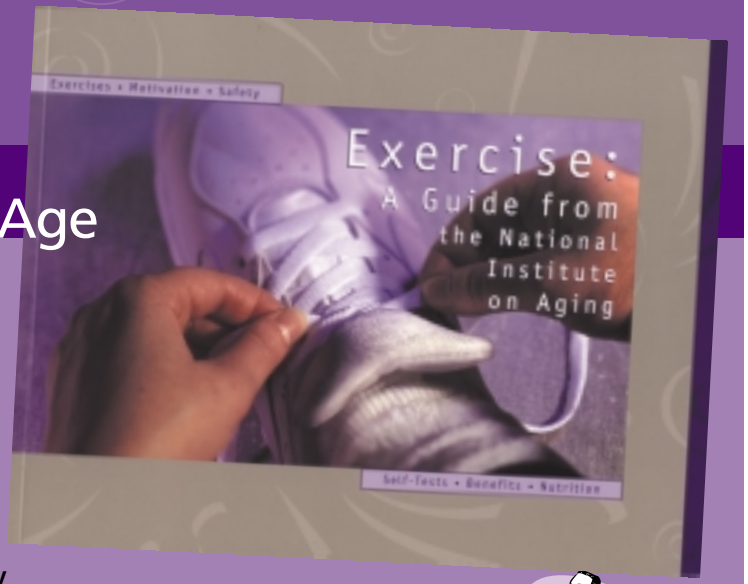
So far, some positive trends have been detected, including the possibility of reduced incidence of heart disease and cancer in the calorically restricted monkeys. But it is important to keep in mind that these data are preliminary, and investigators caution that it may be many more years before it can be determined if caloric restriction does indeed improve the health and extend the lifespan of aging primates.



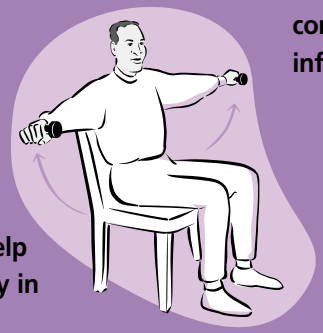
Exercise: It Works at Any Age

Regular physical activity may be the most important thing an older person can do to stay healthy and self-reliant. In fact, the more exercise you can do in later life, the better off you'll be.

Studies suggest regular, sustained exercise can help prevent or delay some diseases and disabilities as people grow older. And, in some cases, it can actually improve some of these conditions in older people who already have them. In a study conducted at Tufts University in Boston, for instance, some people age 80 and older were able to progress from using walkers to using canes after doing simple muscle-building exercises for just 10 weeks. In addition, physical activity can improve your mood, lessen your risk of developing adult-onset diabetes, slow bone loss, and reduce your risk of heart attack and stroke.



Endurance exercises such as brisk walking increase your stamina and improve the health of your heart, lungs and circulatory system. Strength exercises build muscles and reduce your risk of osteoporosis. Balance exercises help prevent a major cause of disability in older adults: falls. Flexibility or stretching exercises help keep your body limber. As part of a daily routine, these exercises and other physical activities you enjoy can make a difference in your life as you get older.



For a nominal fee, an exercise book and a 48-minute companion video are available from NIA. For more information about the book and video contact:

NIA Information Center
P.O. Box 8057
Gaithersburg, MD
1-(800)-222-2225
1-(800)-222-4225 TTY

Yet even if caloric restriction is successful in primates, it is unlikely that most people could maintain a diet of 30 percent fewer calories without drastic and, in all probability, unpalatable changes in their eating habits. For this reason, most gerontologists doubt that caloric restriction will ever become a widespread means of extending the human lifespan. But investigators are exploring the question of whether drugs might mimic its effects, negating the need for sweeping alterations in diet. In rodent and other animal studies, gerontologists are testing a number of synthetic substances that

produce some of the same effects as caloric restriction, such as reducing body temperature and lowering the amount of insulin in the blood. So far, the preliminary results have been promising. However, none of these substances has yet proved to extend lifespan, and some have potentially toxic side effects that may make human use impractical. Still, the search goes on. Meanwhile, it is becoming increasingly clear that lifestyle—particularly diet and exercise—can have a powerful influence on how people age.

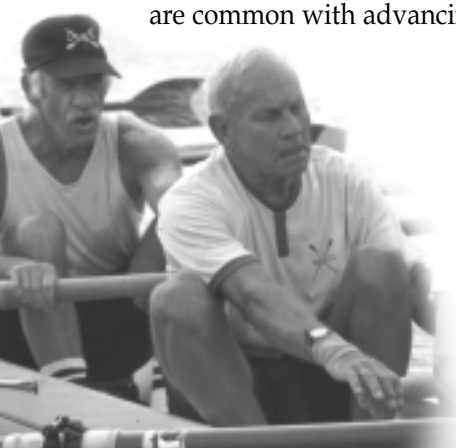
Behavioral Factors

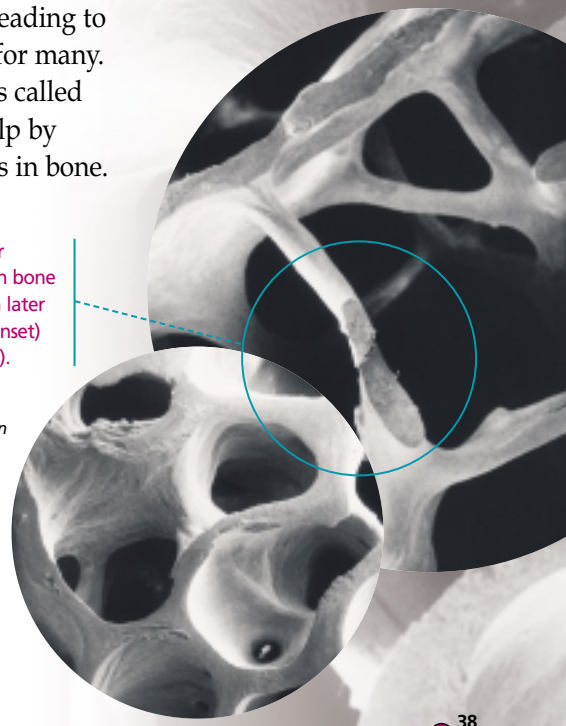
Diet and exercise are thought to have a major impact on a constellation of changes that are common with advancing age. These include higher levels of fats or lipids in the blood, changing levels of blood sugar and insulin, a tendency toward obesity, and increased central body fat that settles around the waist and abdomen. These changes are so prevalent among older people that they have been given a name, syndrome X. Many gerontologists are studying the possible relationship between this syndrome and cardiovascular diseases.

Syndrome X may be preventable through low-fat and low-cholesterol diets, but these are not the only aspects of nutrition that may influence life expectancy. Gerontologists have been scrutinizing a wide range of nutrients with an eye toward their role in aging processes. Calcium and vitamin D, for example, help reduce the thinning of bones that accompanies aging in almost everyone but particularly in older women, many of whom are at high risk for osteoporosis.

Researchers are also studying exercise as a behavioral factor that may have an impact on how long we live or at least on how healthy we are in old age. One landmark study at Tufts University in Boston has shown that exercise can strengthen muscles, improve mobility, and reduce frailty even among 90-year-olds.

Exercises that put weight on bones, such as jogging, walking, and weight-lifting, have been shown to strengthen them. Researchers, as a result, are exploring the potential of exercise to reduce the risk of osteoporosis. This condition, with its fragile, easily broken bones, is a major cause of fractures among older people, frequently resulting in disability, and eventually leading to institutionalization for many. In some cases, drugs called bisphosphonates help by slowing calcium loss in bone.





A balanced diet and regular exercise can help strengthen bone and prevent osteoporosis in later life. Normal bone (bottom inset) and osteoporotic bone (top).

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