cial incentives for families to take care of their elders. One model is a system adopted by Chile in 1981, in which all wage earners are required to contribute 10% of their pay to one of a number of private pension funds that invest the money on their behalf. Singapore has both a compulsory savings plan for workers and tax breaks and preferred access to government housing for those who have older relatives living with them. Singapore and Hong Kong, like many developed nations, also have multitiered health systems that include hospices for the dying and visiting nurses for the elderly.

But in the countries where the bulk of the developing world's population resides, government social security programs or employer-subsidized pensions will be filling only a fraction of old peoples' needs. China has even taken a step backward, says Liang: "Before the economic reform, two-thirds of the population was covered by some sort of health insurance." But now "much of the collective and public infrastructure and services have deteriorated [and] are not being replaced."

In countries that can't afford the more expensive social services, people will have to rely instead on developing community systems that will supply both support and information on care for the elderly. Kalache says it will be crucial to promote low-tech and cost-effective interventions, such as inducing people to take an aspirin a day to lower the risk of heart attack.

In Jamaica, a pioneering step in this direction has been fostered by Denise Eldemire, a public health worker at the University of West Indies. Eldemire has designed a course to train community members on how to care for elders that covers subjects such as the aging process, basic hygiene, working with the family, and foot care for diabetics. One thing the students learn is how to build a walker. "There's no way we can fund a lot of programs, so we have to enable families and caregivers to provide care," says Eldemire.

Efforts like these are necessary, says Kalache, who has a pitiful annual budget of $18,000 to try to wake up the world about its aging populations: "Ignoring aging as a development issue will erode the foundations for socioeconomic development." The young will be shortchanged, because "if you don't have policies for the aging, the very nature of the problems of old age will take over," he says.

Bobadilla, for one, is not optimistic about what the already overstressed governments will be able to do. "The fact that the elderly are going to be poor and are going to be many," he says, "doesn't [automatically] make them a priority."

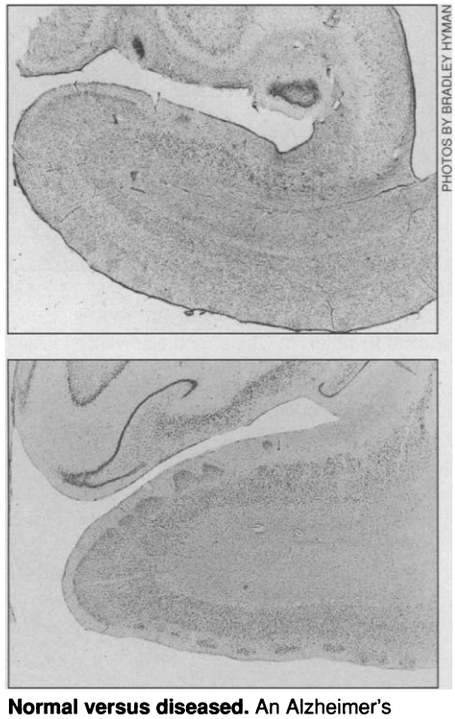
–Constance Holden

THE AGING BRAIN

For the Cortex, Neuron Loss May Be Less Than Thought

Nearly everyone fears the changes that advanced age will bring to his or her mind. And some change is almost inevitable: As people get older, they become more forgetful and find learning new things more difficult. But careful study reveals that for healthy brains, as opposed to those beset by Alzheimer's disease, age-related changes are selective and hardly incapacitating. Movie plots are remembered, for example, even as their details are lost. Facts can still be learned, although their source may vanish. And now, in a departure from what was previously thought, several groups of neurobiologists are proposing that the biological changes in the healthy aging brain are similarly subtle—and possibly correctable.

Just a decade ago, almost all experts thought that widespread cell death in the brain caused the cognitive changes of normal aging. But in the past few years, better methods of telling normal subjects from those with neurodegenerative diseases and more sophisticated techniques for examining the brain have started to yield results challenging that notion—especially for the neocortex, the brain area governing much of human cognition. A similar picture may also be emerging for the hippocampus, a structure important in memory (*Science*, 1 March, p. 1229). "The field of [brain] aging is undergoing a major reassessment," says neuropsychologist Mark Moss of Boston University School of Medicine. "It's an exciting time."



PHOTOS BY BRADLEY HYMAN

Normal versus diseased. An Alzheimer's brain *(above)* shows extensive neuronal loss in the entorhinal cortex compared to a normal brain *(below)*.

That reassessment is still incomplete, as not everyone thinks that the new data, some of which haven't yet been published, have proved that cortical neurons are preserved during aging. "There's no definitive study on cell loss and normal aging," says neurobiologist Paul Coleman of the University of Rochester School of Medicine and Dentistry in New York. "It's a messy area." But if the new findings are correct, they might have implications for developing drugs that bolster aging memories.

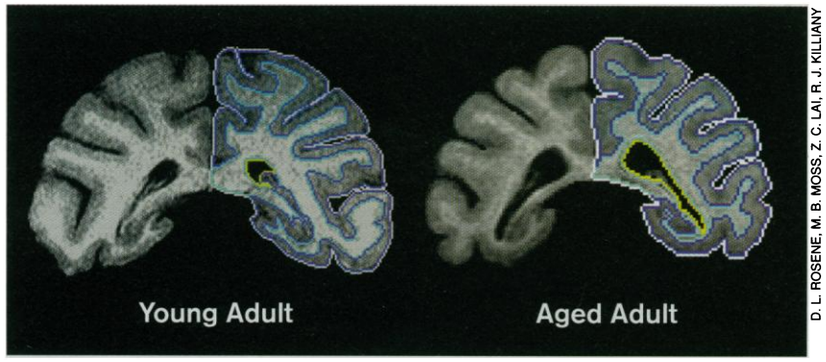
That's because it might be possible to compensate for some of the other brain changes being considered as contributors to the cognitive deficits of age. They include, for example, a decrease in the density of certain of the receptor proteins through which neurons respond to neurotransmitter signals and a breakdown of myelin, the fatty sheath that insulates nerve fibers and thereby facilitates their ability to transmit signals. Such alterations, unlike actual neuronal loss, might be remedied with drugs. "If the brain is preserved structurally, there's hope that we'll be able to reconstitute its function [with drugs]," says Bradley Hyman, a neuroscientist at Massachusetts General Hospital in Boston.

The long-standing belief that neurons are lost during aging got its major impetus in 1955, when anatomist Harold Brody at the State University of New York, Buffalo, published the first study correlating neuronal counts in the neocortex with age. Studying brains from 20 human subjects, from newborns to 95-year-olds, Brody saw extensive cell loss in a number of neocortical areas, including the cognitive areas of the frontal and temporal cortex. Follow-up studies by Brody's own group, as well as by several others, indicated that the cortex could lose up to 40% of its neurons during aging.

Although no one knew for sure how such massive cell death related to mental ability, experts thought it could cause rather dramatic declines in cognitive abilities in the normal, healthy elderly. Additionally, it

was assumed that these changes were inevitable and almost impossible to reverse. In any case, the belief that the cortex loses neurons with age went without a serious challenge until 1984.

In that year, anatomist Herbert Haug and his colleagues at the Medical University of Lübeck in Germany published results suggesting that a common method of preparing brain tissue for microscopic study causes young cortical tissue to shrink more than old tissue. This raised the possibility that the earlier studies, which were based on cell density measures, showed higher densities in young brains simply because the tissue had shrunk more. Indeed, taking this shrinkage into account, Haug's group found no evidence of cortical neuron loss with age in a study of 120 normal human brains.



D. L. ROSENE, M. B. MOSS, Z. C. LAI, R. J. KILLIANY

No shades of gray. These MRI images show loss of white, but not gray, matter in the brain of a 32-year-old rhesus monkey *(right)*. The young adult is 5 years old.

At the time, that conclusion was roundly criticized. The critics pointed out that differential shrinkage should not have been a problem for all the earlier studies, as some investigators had also noticed the problem and attempted to correct for it, while others used tissue preparation methods that didn't cause shrinkage. But in 1987, results obtained by neuropathologist Robert Terry of the University of California, San Diego, and his colleagues suggested that something else might have led the older studies astray. Because the methods used to screen for brain pathologies were not as sensitive as those developed later, Terry suggested, earlier researchers may have inadvertently included brains with Alzheimer's disease or other dementias known to cause rampant cell death.

Consistent with that idea, when Terry and his colleagues examined 51 normal brains, carefully screened to eliminate those showing signs of Alzheimer's or other pathologies, they saw a decrease with age in the number of large neurons, but they also found an equal increase in the number of small neurons. The conclusion: Neurons shrink but don't disappear. "Brody is an excellent scientist, but I'm confident that he included Alzheimer's cases and that these lowered his cell counts," Terry says.

Since then, other results have buttressed the idea that normal brains, unlike those of Alzheimer's patients, show little loss of cortical neurons. Some of these come from Alan Peters, Mark Moss, Doug Rosene, and their colleagues at Boston University School of Medicine, who have been studying rhesus monkeys. Although these animals don't develop Alzheimer's disease, they do suffer a humanlike cognitive decline with age—but with no apparent loss of cortical neurons.

In work begun about 10 years ago, the Boston workers found no relation between either cell counts and age or cell counts and cognitive function in areas of the neocortex as diverse as the visual cortex, motor cortex, and prefrontal cortex, a region involved in problem-solving tasks that require holding complex information in mind and manipulating it. "When we first began looking at monkeys, we assumed there'd be a loss of neurons from the cortex," Peters recalls. "It took a long time to find out there isn't."

And human work that is just now being published also finds little or no loss of cortical neurons in normal aging. In a study that began 16 years ago and is still continuing, John Morris, Leonard Berg, and their colleagues at Washington University Medical School in St. Louis have been following more than 200 subjects who were all healthy when they entered the study. The researchers test the cognitive abilities of the participants annually and also interview their close relatives, looking for subtle signs of mental slippage that augur early dementia. When the subjects die, Hyman's team at Mass. General examines their brains for evidence of pathology, including cell loss.

Results on the first 10 normal subjects, which will appear in the 15 July issue of the *Journal of Neuroscience*, show no age-related differences in cell numbers between ages 60 and 90 in the entorhinal cortex, a structure critical to memory and a way station for signals passing from the neocortex to the hippocampus. And, in as yet unpublished work on 28 normal brains, the Mass. General team detected no cell losses between the ages of 57 and 98 in an area of the neocortex called the superior temporal sulcus that is involved in a number of cognitive functions.

In contrast, a group of age-matched patients with early dementia had lost half the cells in the entorhinal cortex, and a third group with more advanced Alzheimer's disease was missing up to 65% of the cells in both of the brain structures examined. "If one thing seems clear," says Dennis Dickson, a neuropathologist at Albert Einstein College of Medicine in the Bronx, New York, "it's that normal aging is different from Alzheimer's disease."

Nevertheless, because so much older data supports the idea of extensive neuronal loss, even in normal aging, many researchers want more evidence before they discard the idea. For example, some experts think that more areas of the brain need to be sampled in healthy people. "Additional work is needed to map out the locus of the most salient age-related changes in carefully screened subjects," says Mony de Leon, who studies brain aging at New York University School of Medicine.

Skeptics also point out that all studies based on neuronal counts suffer from uncertainties. One problem is that tissue can undergo structural changes after death but before it is scientifically scrutinized. Another is that researchers can perform only one count—at the age of death—from any given individual. As a result, they don't have a baseline for telling whether that particular brain lost neurons. "If a neuron left behind a signpost when it died, then we could directly measure cell loss," says Dickson. Instead, scientists must infer a loss of cells by comparing the brains of subjects who die at different ages—a tricky comparison because individuals can vary in the number of cells they start with.

What's more, imaging studies have shown that the brain shrinks with age, and many people interpret that shrinkage as cell loss. For example, in work published 4 years ago, Stanley Rapoport, chief of the neuroscience laboratory at the National Institute on Aging, used magnetic resonance imaging (MRI) on the brains of healthy men and saw a 10% drop in total brain volume in men over 60 versus that of men more than 25 years younger. Rapoport's team also has data suggesting that some of the shrinkage is occurring in gray matter, which contains neuronal cell bodies, although his data point most clearly to loss in subcortical nuclei.

"There likely is a real loss of neurons that occurs with healthy aging," Rapoport maintains. De Leon's team saw something similar when comparing images of the cortex from young adults in their 20s and 30s with those from people in their 60s and 70s. They found a small but significant loss of both gray mat-

ter and white matter, which contains the axons, the long nerve projections that carry electrical messages between neurons.

But other imaging studies indicate that brain shrinkage might be due almost exclusively to loss of white matter. In an MRI study of 70 healthy human brains reported 3 years ago, Marilyn Albert of Harvard Medical School and her colleagues found almost no change in the gray matter, but an 8% drop in white matter, between the ages of 30 and 80. "It used to be thought that we lose neurons every day of our lives. That's just not true—at least for the cortex," says Albert.

Peters and his colleagues go one step further: They have evidence that changes in white matter may account for the cognitive changes in aging rhesus monkeys. They originally got this idea 5 or 6 years ago when they saw a breakdown of the fatty sheaths of myelin that insulate axons in old monkey brains, but not in young ones. Then, over the last 2 years, the researchers followed up on this observation, examining how the change might relate to the animals' cognitive status.

Using preserved tissue from seven old monkey brains from their previous work, they ranked the degree of myelin erosion in one small part of the neocortex. In work not yet published, they discovered that the extent of disorder paralleled the monkeys' degree of cognitive impairment. "We're beginning to think that myelin breakdown might be bringing about most of the changes with age," Peters says. Now the researchers also have indirect clues using MRI that this breakdown occurs throughout the cerebral hemispheres, which include the neocortex, resulting in a 10% shrinkage in white matter in old monkeys. At the same time, they reported at last fall's Society of Neuroscience meeting, they found no age-related differences in the volume of the animals' gray matter.

Myelin loss might contribute to the cognitive deficits of aging because it is necessary for the rapid conduction of impulses along an axon. While the Boston University biologists theorize that myelin breakdown slows neural traffic everywhere in the brain, it may have its greatest impact in the prefrontal cortex because speed may be most critical to the problem-solving tasks performed there. Indeed, it is these types of tasks that elderly people perform less quickly and accurately than do young adults. "Changes in white matter could have significant effects on the brain," says Peter Rapp, a neuroanatomist at the State University of New York, Stony Brook. "But [the Boston group's] observations need to be confirmed in larger numbers of animals" and with quantitative measures of myelin pathology.

Myelin is not the only neuronal component that may atrophy with age, possibly leading to a decline in nerve cell function. In one of the few quantitative, molecular studies of normal brain aging, John Morrison and Adam Gazzaley at Mount Sinai School of Medicine in New York City and their colleagues have discovered evidence for an age-related drop of about 30% in the density of the *N*-methyl-D-aspartate (NMDA) receptor for the neurotransmitter glutamate, which is thought to play a critical role in learning and memory. The receptor loss occurs in nerve cells at the end of the perforant path, a critical neural circuit that funnels information from the neocortex to the hippocampus and is "extremely vulnerable to aging," Morrison says. Moreover, the perforant-path nerve terminals and the neurons to which they connect were both intact, suggesting that the NMDA receptor decrease occurs without associated structural degeneration of nerve cells.

Not only the receptors but the neurotransmitters themselves may decline with age, impairing nerve cell function. Although cells may not die off in large numbers in the cortex, they are lost in other parts of the brain, such as the brainstem, and the loss changes brain chemistry. For example, some brainstem neurons produce dopamine, a neurotransmitter whose levels decline with age in the monkey neocortex, and that drop, Amy Arnsten, Patricia Goldman-Rakic, and their colleagues at Yale University have shown, contributes to the kind of memory deficits seen in normal aging.

But as long as cortical neurons remain alive, there may be ways to boost their function and stave off mental decline in old age. This might be accomplished, for example, by drugs that compensate for neurotransmitter deficiencies, or provide an extra tweak for the remaining receptors, or help prevent myelin loss, if that is indeed contributing to neuronal dysfunction. And those prospects raise hopes that one day, even the subtle memory deficits of old age will become a distant memory.

–Ingrid Wickelgren

Additional Reading

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NEURODEGENERATIVE DISEASE

Searching for Drugs That Combat Alzheimer's

... Last scene of all,
That ends this strange eventful history,
Is second childishness, and mere oblivion,
Sans teeth, sans eyes, sans taste, sans everything.

With those pessimistic words, William Shakespeare, astute observer that he was, described the final stage of life. Unfortunately, his description is still depressingly apt for many people. As medical science has prolonged human life, it has also brought a sharp increase in the numbers of people suffering from one of the most calamitous afflictions of old age: Alzheimer's disease, which steals a person's mind, ultimately making him or her as helpless and needy of care as any newborn infant.

Alzheimer's also exacts a crushing social toll. According to figures compiled by the Alzheimer's Association, some 4 million people currently have the disease in the United States alone, at a total cost of up to $100 billion per year, much of it for long-term custodial care in nursing homes. And with the population aging, "the size of the problem is going to grow extremely over the next decades," says Denis Evans, an epidemiologist at the Rush Center for Aging in Chicago. Evans's gloomy forecast is based in part on a prospective study of 3809 elderly in Boston that he directed. Called the East Boston Survey, it found that nearly half of people over age 85 have Alzheimer's—and that age group is growing more rapidly than any other. Based on these trends, the Alzheimer's Association estimates that there could be up to 14 million cases by the middle of the next century.

But in spite of these dismal forecasts, scientists studying Alzheimer's disease are beginning to see the first glimmerings of hope that this devastating disease might be checked. For years, Alzheimer's was considered a more or less inevitable consequence of aging. But growing evidence suggests that it's not. Normal brains do not seem to suffer the widespread neuronal loss typical of Alzheimer's (see p. 48). What's more, Alzheimer's devel-