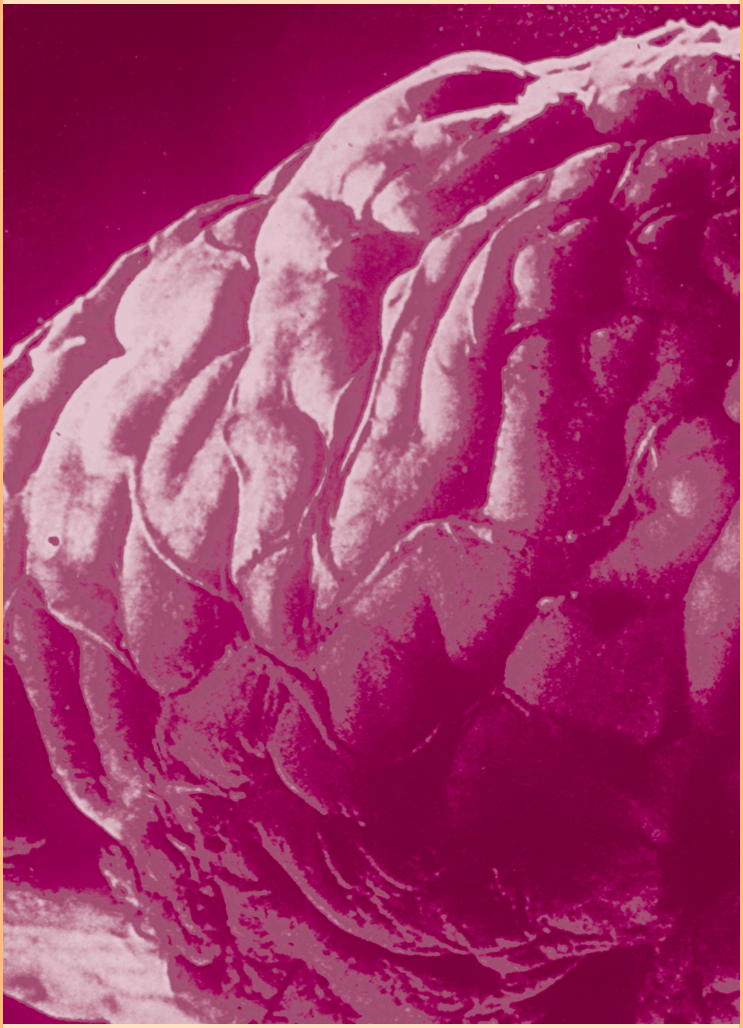
MIND ALERT



Good News About the Aging Brain!
Special Lecture by Marian Diamond and Arnold Scheibel

A Joint Program of
the American Society on Aging
and the MetLife Foundation

The American Society on Aging is delighted to be able to partner with the **MetLife Foundation** and the **Archstone Foundation** to develop the MindAlert program, which seeks to translate new research on our body's ability to keep our mind alert in later life into practical tools for elders and aging-services providers. In this booklet you will find the following:

- A monograph from the **MetLife Foundation MindAlert Lecture Series**, which was established to disseminate the latest research information on maintaining and enhancing cognitive function in late life. The first MindAlert lecture was presented at the First Joint Conference of ASA and the National Council on the Aging, held in New Orleans in March 2001. **Drs. Marian Diamond** and **Arnold Scheibel**, two internationally reknowned researchers, were the invited speakers. This monograph represents an edited transcript of their talk—and is truly good news about the aging brain.

- Brief descriptions of the 2001 winners of the **MetLife Foundation MindAlert Awards**. This awards program was set up to identify and recognize innovative community-based programs that translate research related to enhancing cognitive function in later life into practical mental/cognitive health promotion activities. This booklet presents the key elements from each of the 2001 winning programs. Contact information for the winning programs is also provided for those interested in learning more.

If you would like to learn more about the MindAlert program, including its Web-based clearinghouse of resources on mental fitness, please visit *www.asaging.org/mindalert* or contact Therese McNamee, manager of education, training and special projects at *theresem@asaging.org*.

Good News About the Aging Brain

Marian Diamond

Can I touch your cerebral synapses this morning? We'll see.

I would like to begin with a general introduction before presenting the specific brain research from my laboratory at UC Berkeley that holds the promise of what I call "successful aging."

In our democratic free society, the human brain has the privilege and capacity to determine its own destiny. But no one said it was easy. It has been said that aging is not for sissies, but in fact, life is not for sissies. I frequently use the title "An Optimistic View of Aging" when I present my research. Who wants to listen to a talk called "A Pessimistic View of Aging"? Yet recently I was asked to speak at a retirement conference. I thought to myself, the concept of "retirement" is contrary to my desires and values in life. Should I really accept this challenge? And the answer was "Yes."

Have you ever looked up the word *retirement* in the dictionary? *Retire* definitely has a negative connotation. It means to withdraw, resign, regress, recede, abdicate, depart, and on and on. There is no synonym indicating anything upbeat or forward-thinking or optimistic. We know Robert Browning's famous stanzas "Grow old along with me / The best is yet to be / The last of life for which the first was made . . . " What an exhilarating perspective! His words certainly do not suggest the necessity to resign, retreat, regress, recede or withdraw from life.

In light of the profound social changes and medical advances that have taken place in American society, why has it taken so long to challenge the very meaning of the word *retire*? Can't we find a new word to inspire us to move forward into a period that amounts to almost one-fourth of our potential lifetime? I asked people all over the country to help us find a substitute for retire: a single, acceptable, positive word for this segment of our lives. I finally found one that I think currently fills the need: *redirect*. In fact, the moment I heard the word I was excited. Think about it—isn't redirection what we wish to do when we want to change our style of living after following a specific pattern for so many years? I'm told that AARP wishes to drop the R from its name, the American Association of Retired People. Why not keep the R and change it to "Redirected"?

Redirect suggests moving in a different direction but continuing to surround ourselves with stimuli to fulfill the remaining one-fourth of our one hundred years.

My scientific research for the past many years has focused on the effects of the environment on the brain—the external environment out here and the internal environment inside each one of us. Our laboratory experiments have focused on identifying factors that influence the well-being of the brain, because the brain has the capacity to redirect its own desires. What other cells can do that? That three-pound mass, which I can hold in one hand, has the capacity to conceive of a universe one billion or more light-years across. Just think what those cells can do. The brain is truly a phenomenal structure, and keeping it healthy for our entire existence on earth is a goal we can and should aspire to. I am going to touch upon five basic factors for maintaining brain health. You're going to say there's nothing new about them, but I'm going to be giving some scientific evidence of their benefit.

Number one, and in my mind the most important, is **diet**. What we feed this brain significantly affects its well-being. Two, we must **exercise** the body and brain. Exercising not only the brain but the total body is necessary to maintain a healthy brain. Three, we must **challenge** the brain. It gets bored; we know that well. So we need **newness**, new things in our life. And fifth—last but definitely not least—we must share basic human **love**.

When studying the brain it is essential to keep in mind that development and aging are a continuum. Your brain doesn't just develop in the first part of life and age in the last part. While your brain was forming in the embryo, it was developing nerve cells at the rate of about 50,000 per second. Think

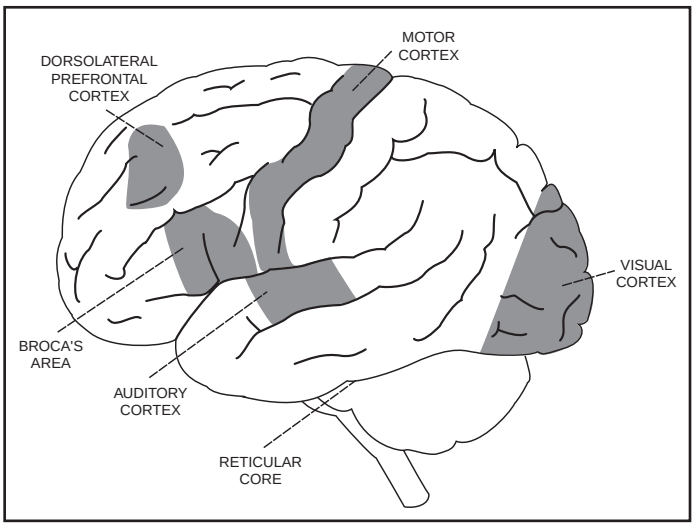


Figure 1a

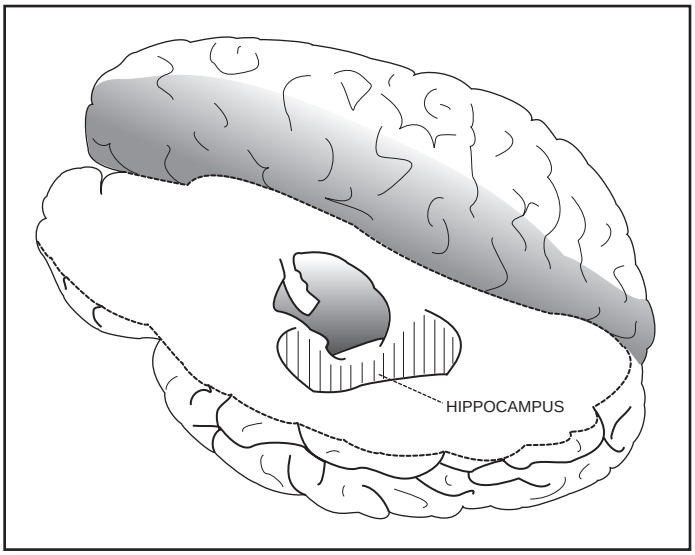


Figure 1b

of that explosive development—50,000 per second. But before you were born you had already lost 50 percent of those cells. Everybody worries about losing cells at the other end of the life cycle when in reality you lost more nerve cells before you were born.

A Look at the Brain

Let's start with a look at the human brain, a phenomenal mass that weighs about three pounds—roughly 2 percent of our total body weight—yet gets a fourth of the cardiac output. Have you ever watched your heart on an echocardiogram? I saw mine the other day. I could see the valves opening and closing. What a thrill to know exactly how it works. With every beat it pumps a fourth of that cardiac output to this precious brain.

Equally wondrous is that no two human brains are alike. No two of you will be listening to this lecture in the same way. No two of you will walk away with exactly the same ideas and information. I hope you will learn the message that I am trying to present about the dynamics of this brain and about keeping the brain dynamic for a lifetime.

How does your brain feel about studying itself? The brain itself has no feeling: You can cut it and it does not feel the injury. Sensory receptors in other tissues initiate the impulses that bring the pain sensations to the brain for analysis. Let us look at this diagram of the brain (see Figure 1a and 1b). For me to be talking to you now, one part of my brain is firing: Broca's area, which deals with motor speech. Some people activate motor speech in a broader area, some a little further toward the front. But it is generally in the inferior frontal area.

For you to be looking at this diagram your visual cortex, in the back of the brain, is firing. You see stars when you get hit on the back of the head because your visual cortex has been jarred. For you to be listening to me, a little area in your superior temporal lobe is being activated. The area of the cerebral cortex responsible for hearing is very small in comparison with the amount of cortex devoted to seeing. For me to be moving my pointer, the motor cortex is firing. The highest cognitive processing is going on in the prefrontal cortex, just behind your forehead. The prefrontal cortex is responsible for such functions as initiative, judgment, working memory, planning ahead, sequencing events, and so forth. Each part of the cerebral cortex has a general function, but it obviously has its very specific functions as well.

Diet and Brain Growth

Let us now return to the five basic factors responsible for keeping our brains healthy

and active during our lives. The first is diet. Yes, diet is vital to the brain just as it is to our body as a whole. For the brain to grow healthily from infancy, it certainly needs protein to maintain and develop its nerve cells and their branches. Here is a nerve cell (Figure 2). In the outer layers of your brain you have several hundred billion nerve cells. The processes developing from the cell body are called dendrites. Dendrites receive input from other nerve cells. Integration of the input takes place in the cell body, resulting in an electrical impulse that continues down the axon, a fiber from the cell body leading to the target tissue. The tips of the axon are not continuous with the receptive dendrites on the next nerve cell adjacent to it—there is a gap between them. An electrical impulse travels down the axon to the tips, and then a chemical is liberated to cross the gap and stimulate the adjacent dendrites. This chemical is called a neurotransmitter. The neurotransmitter is liberated, crosses the gap, and then the electrical impulse continues through the new dendrites.

When we first started working in the field there were perhaps five neurotransmitters known. The other day I called Floyd Bloom, the former editor of *Science* magazine, who is one of the major researchers in the field. I asked him, "How many neurotransmitters are known today?" He said at least a hundred. So you get a glimpse of the magnitude of chemical reactions in our brains. It's a wonder that any two people ever think alike and understand each other with such a dynamic nervous system that must keep all these transmitters in proper balance.

I am spending time on dendrites and axons because, whenever we talk about the growth of the brain during development, we are primarily considering the growth of dendrites and axons and the connections they are making with other cells and target tissues. One nerve cell can get input from as many as 20,000 other nerve cells in one part of the brain. But most cells don't have that much input. Each cell can do a tremendous amount of computation, and we have more than a hundred billion cells.

Now let's take a minute to talk about how dendrites develop. In the frontal lobe of a newborn human's cerebral cortex, just behind the forehead, we can see very few branches on the nerve cells as they begin to develop. By the age of two an enormous amount of branching is going on. However, not all those dendrites have made appropriate connections yet, which is why two-year-olds are sometimes difficult to deal with.

When my husband and I were teaching in Africa in 1988, we found that in Nairobi, Kenya, women would not eat protein while they were pregnant because they learned that they delivered babies that were too large. By reducing their protein intake while pregnant they delivered smaller babies. My immediate question was "What effect does this reduced protein intake have on the infant brain? " When we came back to Berkeley, we started an experiment involving pregnant rats. We fed half the pregnant rats a normal, high-protein diet and gave the other half a low-protein diet. The body weight of babies whose mothers were fed the reduced-protein diet was 50 percent less than that of babies whose mothers had a normal protein diet. And the brains?

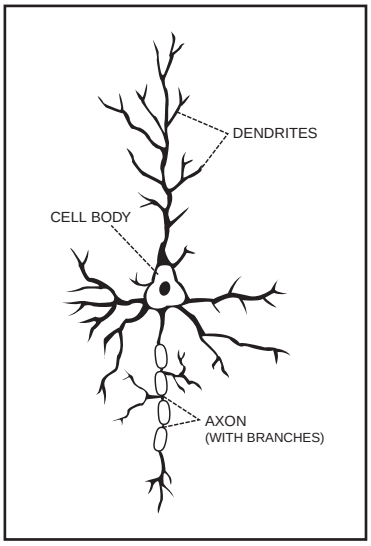


Figure 2

Dendrites in those baby rats whose mothers had reduced protein just did not develop fully. When we put those babies in enriched environments with lots of objects to explore, their dendrites did not increase significantly, as they did in babies whose mothers had a normal diet and enriched living conditions. We learned that it is important to have a protein-rich diet to grow healthy nerve cells that can respond positively to enriched living conditions.

In a follow-up experiment, we gave the low-protein-diet mothers high-protein diets after delivery and gave their babies high-protein diets after they were weaned—and then we got those dendrites to grow. Furthermore, when we put the babies in enriched environments, their brains benefited from the stimulation. These experiences and my ongoing studies give me

cause to worry about well-intentioned programs that focus on children ages three through five. I believe that considerable money should be directed toward good prenatal care. You can be certain that well-developed embryonic and fetal brains are far more able to benefit later from Head Start and other enrichment programs.

Returning to the dietary components that are key to developing and maintaining a healthy brain, it has been validated that choline is extremely important in the diet. Choline is necessary to form an important neurotransmitters, acetylcholine, as well as enzymes that help acetylcholine function appropriately. We have learned from Richard Wurtman at the Massachusetts Institute of Technology that if you don't have enough choline in the diet, the cell cannibalizes its own membrane to make acetylcholine. So it's extremely important to have choline in the diet.

What are dietary sources of choline?

(1) *Soybeans and soy products.* These days you will find an increasing number of soy-based products on the shelves. We tofu advocates have it with marmalade for breakfast.

(2) *Egg yolks.* You say you are not going to eat egg yolks because of their cholesterol, but if you have low cholesterol levels, you can have egg yolks.

(3) *Peanuts.* These are somewhat high in fat and sodium, but use them moderately along with other source foods. My father always had a big bowl of peanuts for us when we came home from school.

(4) *Liver.* There are those who do enjoy liver! I do.

I mentioned only one neurotransmitter, acetylcholine, but remember, you have about 100 different neurotransmitters serving your body's chemical needs. Other important ones are dopamine, serotonin, and glutamate. You can look up the dietary sources for these neurotransmitters in your spare time.

We have known for some time that vitamin B is essential for the well-being of the nervous system. Let's just take one B vitamin, vitamin B_6. B_6 is important in the metabolism of amino acids, which are related to the structure of protein. Vitamin B_6 is vital to the creation of neurotransmitters. What happens if we have a vitamin B_6 deficiency? Our memory is impaired, causing trouble with our ability to register, retain and retrieve memory. A shortage of B_6 also can lead to nerve damage in the hands and feet. A few vitamin B_6 sources: potatoes, bananas, chicken breast, beef top round, turkey white meat, rice bran, carrot juice, rainbow trout. Just a selection taken from the literature to show you that there are many sources for B_6.

Antioxidants are other important substances for the care and feeding of the brain. Most everybody knows the major antioxidants, vitamin C and vitamin E, and their food sources. The American Chemical Society website lists rich sources of antioxidants—including blueberries and strawberries. How many of us are aware that these are rich sources in antioxidants?

We continue on just a little more on to the interaction of calcium and your parathyroid gland. Most people are familiar with the thyroid gland in the neck, but did you know the parathyroids are right there too? Usually four of them. They regulate the amount of calcium in your blood. If you have low blood calcium, hormones from your parathyroid glands act on cells in your bones to extract calcium from the bone in order to raise your blood calcium. Everybody knows that calcium is important for bone structure, but did you know that it is also important for nerve impulse conduction? It is important for muscle contraction.

Exercise

Now let us turn to our second key factor in maintaining a healthy brain: exercise. A recent article I read mentioned that lack of exercise was responsible for increased incidence in sugar diabetes, cardiovascular problems, obesity and depression. We know that exercise improves skeletal muscle tone and function and that it helps our venous return in our legs, indicating the importance of keeping our legs active. Exercise is essential to bring oxygen to all parts of the body—especially the brain. What area of the brain has been shown to be subject to what we call anoxia, or a reduced amount of oxygen? The hippocampus (see Figure

1b). The hippocampus deals with the processing of recent memory and visual spatial processing. As we age and our blood vessels become less efficient, it is very important to exercise to get the oxygen through the vascular system up to the hippocampus, as well as to the rest of the brain and body.

I like to always emphasize swimming as a good form of exercise. When we get older, we may walk a good deal using our lower extremities, but do we use our upper extremities? Swimming exercises the entire body including both upper and lower extremities. How many of you feel depressed after you have sat indoors for several hours? I know I certainly do. Exercise has been shown to benefit the balance of your neurotransmitters.

I also learned the other day that exercise has been shown to benefit children with hyperactivity problems. Are our children getting enough exercise sitting in front of their computers and video games all day long? Everyone should have planned exercise for possibly one hour each day—just as you brush your teeth and eat your breakfast daily.

Challenging the Brain

I have come to challenge, a third vital component of brain health. What I am about to say has been validated by my years of laboratory research. In terms of successful aging, it is not enough to continue activities in the same groove, year after year, with the same expenditure of mental and physical energy. Remember Alice in Wonderland, who discovered that on the other side of the looking glass a person had to move very fast to stay in the same place? The underlying laws of physics Lewis Carroll was playing have their correlate in neurophysiology: the brain needs new challenges if it is to remain a healthy, functioning organ. Translated, if you like to do crossword puzzles and you've been doing the same kind of crossword puzzles year after year, try more complicated puzzles next time or introduce a new game that will challenge different skills that are lying dormant.

In order to get ideas about human brain function we look at rat brains, which have many of the same basic patterns of brain structures as humans, only rat brains are the size of pecans whereas our brains are the size of cantaloupes. I offer the results of one of our rat experiments dealing with "enriched" and "impoverished" environments. In the enriched environment, 12 rats live in a large cage and have objects to play with. It is very important to have something challenging in the cage with these rats. In contrast, the impoverished environment houses a rat who lives all by itself with no objects to challenge it. These two experimental conditions were compared with a control group of rats living three to a cage in a small cage, which is the standard laboratory way of housing rats.

Examining and comparing brain tissue from each of the three groups yields a wealth of information. The outer layers, just like those in our brains, are called the cerebral cortex. *Cortex* means "bark." The cortex is a dynamic structure—parts of the human cortex have sent humans to the moon. The thickness of the cortex is one of the first measurements we make because it is simple and lets us know if changes are occurring in the constituents of the cortex, namely, neuron number and size, dendritic growth, synaptic growth. In our little rats we can measure what happens to the cortex when we put the animals in different environments. First, we measured the difference in cortical thickness between 24 pairs of enriched and nonenriched male rats. We found that the rats living in enriched environments demonstrated some changes (increased thickness) in the frontal area, no changes in the general sensory area and dramatic changes—7 percent—in the visual cortex.

As in most of the work now done with laboratory animals, we wanted to determine whether female rats would respond in the same way. When we measured the difference in cortical depth between 23 pairs of enriched and impoverished nonpregnant female rats, we saw some changes in the frontal area, some changes in the general sensory cortex, and 4 percent change in the visual cortex, not quite as much as in the males. My students suggested that we challenge the enriched females to see if we could bring that visual cortex up to the

level of the males. Sure enough, we did. How? We put obstacles in front of their food cups. Every time they wanted to eat they to climb over all those obstacles. Now, did we try to bring the male general sensory cortex up to that of the female? No, that's an experiment we saved for future students to complete.

Why is thicker better? Psychologists have tested the rats living in enriched or impoverished conditions and found the enriched rats ran maze tests faster than did the impoverished. Evidently more dendrites—thicker cortices—indicate a greater ability to solve problems. With humans, we purposely have to work harder as we age to set up challenges for us. It's easy to take the simple route. It's hard to add additional challenges.

There are obviously different kinds of challenges. Here's another experiment we conducted on rats. We put a rat in one corner of a maze and food in the opposite corner. The rat ran right to food. The next day we put one barrier in the box. The rat had to run around the barrier to find his food. The next day another barrier and so forth. Pretty soon we had 19 barriers, so he really had to learn to get through barriers to find food. Simple task. How much of the brain changes when we challenge it with a simple task? We found 6 percent changes, but only in his visual cortex. That's a statistically significant difference, but only in one area because the rat is only dealing with one kind of challenge. In multisensory enriched environments we change most of the cerebral cortex, not just a single area.

A single-input challenge changes just a single area of the brain. So children (or adults) sitting in front of computers all day long are being fed a specific input. Multisensory enriched environments involve varied toys, sociability and changing stimuli. Now, you may ask, what is most important in the enriched environment? Sociability—having all the rats living together—or just being surrounded by challenging objects? Other investigators conducted experiments in which 12 rats were put in an enrichment cage with no toys. An increase in the cerebral cortex occurred but it was not as much as when 12 rats were in a cage with toys. Then one rat was placed in the enrichment cage by itself with the toys. Its cortex changed much less than that of rats who lived with toys and other rats. So both sociability and challenge are important. I can tell you how researchers got the rat living alone with the toys to experience greater changes: They gave it methamphetamine, and it ran around and interacted with the toys. We certainly do not recommend this approach! Thus, we've been able to show that these experimental conditions, the stimulus objects plus the friends, were both necessary to create the most significant changes to the brain.

Another condition we wanted to investigate besides the thickness of cortical tissue in these experimental groups was the impact of enriched and impoverished environments on a substance called *lipofuscin*. Lipofuscin is an "aging pigment" that accumulates in your brain as you age. It is thought to interfere with the normal functioning in nerve cells. You do not want nerve cell bodies filled with an aging pigment because they normally are busy producing proteins to supply their many functions. We found that rats put in enriched environments produced less of this aging pigment in their brains. Just another plus for having challenge and activity in the brain throughout one's lifetime.

Brain Challenges and the Immune System

Our most recent research has focused on human beings. A secret passion of mine was to find a relationship between the cerebral cortex and the immune system. The immune system is, of course, extremely important to our health at all ages, and certainly it is critical to successful aging. The results of our research, which are just being published now, made it into the press around the world. We learned a great deal about people who challenged their cerebral cortex to affect their immune systems, even though they didn't know that's what they were doing.

From our animal studies we've learned that the dorsolateral frontal cortex was related to the functioning of the immune sys-

tem: The dorsolateral frontal cortex was deficient in immune-deficient animals. How did we learn that? In 1980, the French stripped off most of the cerebral cortex in their mice and they found that this process affected the number of circulating T cells in the blood. We had to find out which part of the large cortex specifically affected the immune system.

Eventually we found an area on both the right and left cortices that was thinner in immune-deficient female mice. (These immune-deficiency studies were all done with female mice because the French started with females.) The immune-deficient mice had no thymus gland, which is responsible for producing T cells. The thinner cortical area is called the dorsal lateral frontal cortex. The rest of the cortex was fine as far as we could measure. When the thymus was transplanted back into the immune-deficient animal, the deficiency in the cortical area was reversed. So we know we have an area of the cerebral cortex related to the immune system.

It was my dream to find this area of the cerebral cortex, because it is under voluntary control. I say I want to pick up this pointer, I do it. That's voluntary control. Can we voluntarily, then, stimulate this area? We learned that experimenters had given schizophrenic patients what is called a Wisconsin Card-Sorting Test, which is good for clinically testing psychological factors. While the patients were undergoing the card-sorting test, they had a PET scan, which showed that the test activated the dorsolateral frontal cortex.

Most people haven't heard of the Wisconsin Card-Sorting Test because it's primarily used clinically. We wanted a card game that everybody has heard of—say, bridge. The game of bridge uses working memory. It uses planning ahead. It uses sequencing and initiative and judgment. All of these are functions of this part of the cortex.

We had 12 women come to the lab to play bridge with one another. We took blood from them before they started playing to measure the initial level of their T cells. Then we took blood from them after playing bridge for an hour and a half, and found that they had significantly increased a specific type of T cell. The before-and-after data were exciting to us because we found a significant increase in their CD4-positive T lymphocytes. We did not find such a T cell increase in the blood samples of the control women who did not play bridge, but sat listening to quiet music during the time the others were playing bridge.

We were terribly thrilled with these new results. Clearly, the cerebral cortex plays a role in controlling the immune system. Now we have to learn to "educate" that dorsolateral cortex and help keep our immune system healthy. This is just a preliminary study. It has to be replicated and followed through. But to me it was a very exciting moment.

Now, what happens if the brain is damaged? Our students conducted another series of experiments in the late 1980s to find out. We found that if you lesion the left motor cortex in a young, sexually mature rat, it will lose the function of its right forepaw. They did this to a number of rats, and then they put half in nonenriched (control) environments and half in enriched environments. When they looked at the brains of rats placed in nonenriched conditions, they found that dendrites did not grow very much around the lesion, on the opposite side or back in the sensory area of the cortex. But in the enriched environment those dendrites grew significantly. The dendrites grew around the lesion. They grew in the opposite side and they even grew back in the somato-sensory cortex. From these findings we can only conclude that, even when brain damage is present, animals living in a stimulating environment are able to compensate for the damage. Look at the promise that holds for our species who receive some degree of brain injury.

Newness Versus Overstimulation

What happens if you overstimulate or overenrich the brain? My conversation with a pediatrician concerned that children are being constantly bombarded with new experiences inspired the following experiments. In our previous experiments with rats we just changed the toys in the cage

two or three times a week. "Newness" is an important part of challenge, so we had to change the toys. Otherwise, the brain at first increases and then decreases with boredom. It needs stimulus to keep those dendrites extended. In our new experiment, instead of changing toys two or three times a week, we changed the toys at seven o'clock at night, eight o'clock at night, nine o'clock at night, four nights a week for four weeks.

We bombarded those little rats with stimulation. We didn't know if we were going to see huge brains, or not—that's the fun of research. It seems that the significantly different results we had recorded between the enriched and nonenriched rats in our original experiments did not continue to increase when we stepped up the frequency of changing the toys for the enriched group.

So, with too much coming in we did not increase the enrichment effect; it was less. Stress reduces the cortex at the same time that enrichment tries to increase it. What stress factor is involved? Corticosteroids coming from the adrenals. Corticosteroids reduce the cortical thickening. We take out the adrenals and the cortex grows significantly. It shows how much the cortex is normally being held back by corticosteroids.

The lesson for humans? Too much stress decreases the dimensions of the cortex and is detrimental to our well-being at any age. So when we teach for the schools we mention that children must learn in environments with more enrichment than stress. Too much stress decreases the dimensions of the cortex.

Love and Nurturing

Our last subject, oddly enough, is love. A little background: We had started our experiments using young rats, which are readily available and easy to work with. We found they were growing dendrites with enrichment. We then decided to raise our rats to see if we could change the brain in middle-aged rats. So we raised rats up to 600 days of age, equivalent to 60-year-old humans. We put half in enriched conditions and half in nonenriched conditions, and we could still find increases in the cerebral cortex with enrichment to the brain. But we were beginning to lose the animals at 600 days, so we could not come up with conclusive results on middle-aged rats.

Following the publication of our findings, I was invited to the German Academy of Sciences to report on my work. While I was there, I was struck when a scientist there who said that the German rats lived to be 800 days. I came back to Berkeley wondering how were we going to get our rats to live longer?

We tried to figure out what was missing in the design of our experiment. When I would talk with groups of older folks around the country, I felt that many of them just weren't getting enough attention, enough TLC, enough daily kindness. Sure, they had their televisions, they had good food, but where was the love? We didn't see it. So we decided to give our rats love.

Instead of just putting them in little cages when the rat cages were being cleaned, we held the rats against our lab coats and we petted them. We got those rats up to 766 days, put half of them in enriched environments and half in nonenriched environments, and at 904 days—equivalent to 90-year-old people—we were still finding thicker cortical tissue among those rats maintained in enriched conditions. Number one, we got them to live longer. Number two, we got those brains to change. How can we not conclude that stimulating the brain works its magic right up until the end, and may even prolong life? Why do you think Arne and I haven't retired?

We used to believe as scientists that the loss of dendrites was an inevitable correlate of the aging process. It was simply our fate. Yes, it takes concerted attention to stave off the "inevitabilities" we have accepted for so long, but is the price really that high? Is it too much work to follow a healthy diet, enjoy plenty of exercise, seek out new challenges and get lots of love? My own life and work have been enriched immeasurably by two statements I absorbed many years ago. How fortunate that my English family crest states, "Love conquers all." My Swiss grandmother added, "In spite of all difficulties, upward and onward."

A good combination.

Arnold Scheibel

It's a pleasure to have the opportunity to follow Marian's wide-ranging presentation of some of the things that we feel are quite important. Today, I will talk briefly about a few more things. First, we'll start with the bad stuff: How does the brain age in a worst-case scenario? We don't, for a moment, believe that any of us will follow that route but we want to take some measures—measures that rise, in part, directly out of Marian's work.

Next, I'll talk about how the human brain responds to an enriched input.

Marian has shown you the basic research in rats that led us to look at the importance of brain enrichment. I can show you material from human brain tissue that supports and perhaps expands on these findings.

Marian mentioned to you several facts that came out in research, for instance, the fact that enrichment is enrichment only when there's effort involved. You know what they say, no gain without strain. We want to show you why it seems to be that the strain has to be there in order for enrichment to be effective.

Aging-Related Changes to the Human Brain

Let me start with the sexiest picture I have: the human brain (Figure 3a). I show it to you not just for its essential beauty but also because it makes an example. This is what a normal, intact adult human brain should look like. It is pink because it is a highly vascularized structure. As you know, the surfaces are deeply creased. We call the little hills *gyri* and we call the little valleys *sulci*.

Human cortices are built this way as opposed to the very smooth cortices on the little animals that Marian has worked with. This kind of gyration (meaning the brain has a geological landscape) increases the surface area of the brain, where all the thinking occurs, without massively increasing its bulk.

In this second brain (Figure 3b), you see that the gyri are narrower and the sulci much deeper. Look how deep the great lateral fissure is.

This is quite typical of the brains of old people who have undergone brain atrophy. Now, some degree of atrophic change occurs in the majority of people. We still are not sure what allows some of us to escape a certain amount of atrophy almost completely. Some of us undergo small amounts of atrophy that apparently don't affect our cognitive function. And then, of course, a fraction of us will experience some kind of senile dementia. Alzheimer's is perhaps the best known dementia, although by no means the only one.

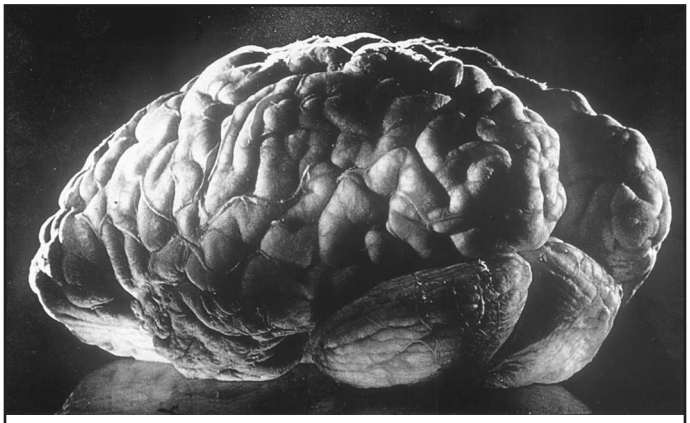


Figure 3a: The normal human brain.

Figure 3b: The brain of a patient with senile dementia of Alzheimer's. Note the enlarged spaces (*sulci*) between each fold (*gyrus*) of brain tissue due to progressive atrophy.

Data from recent studies are highly suggestive that although the severe forms of senile dementias are, to some extent, genetically predetermined, our future does not necessarily lie in our genes. And what we do with our brain tissue may have a great deal to do with the way we spend the latter parts of our lives. It's an interesting concept—we must take our living brains into our own hands, so to speak.

Here's a picture of a typical cortical cell (Figure 4). We call it a pyramidal cell because its cell body is pyramidal in shape, rich with dendritic branches. Notice the progressive loss of dendrites.

In a sense the dendrite is the visible coin of the realm. The richer your dendritic extensions, the richer your dendritic plexi. Cells of people with dementia actually shrivel into themselves. The synaptic connections that depend upon the extent of the dendrites are progressively lost as the dendrites disappear. As that happens your levels of cognitive function also diminish. It's like spending a good deal of your years now with a wonderful computer with a hundred gigabytes. All of sudden you come in one morning and the poor little thing has only fifty kilobytes of function.

This is why Marian and I have been more and more sensitized to the need to keep the dendritic system alive and growing.

We would like to make it possible for people, exclusive of those who are unlucky enough to follow an Alzheimer-type pattern, to avoid the shriveling entirely and keep the cells richly branched and pyramid-shaped.

One other thing appears in photographs of brain tissue in far-advanced cases of Alzheimer's disease. Masses of dense fibers choke the nerve cells to death. We call these masses neurofibrillary tangle material. These great masses here are masses of an unusual protein we call *amyloid*.

Many of you have probably heard of amyloid. We know now that one of the hallmarks of abnormal, toxic aging is the progressive laying down of amyloid masses. Not only do they destroy the connections around them, they appear to be directly toxic to nerve cells. We want to get amyloid out of the way.

The Good News

Here's the good stuff. How do dendrites grow? They grow by adding branches, and branches off those branches.

This process appears to be active all through life if we give brain cells the proper kind of stimulation, or "enrichment." I want to share with you a couple of straightforward experiments done with human brains.

Now, for ethical reasons and for the kind of things we all empathize with we do not want to do experiments on individuals. However, very often individuals will their brains to science. And this is very important. It's one thing to look at the brain of someone who is deceased. It's another thing to have enough information about that individual to know how he or she lived his or her life. What were the high points? What were the negative, the degrading components?

When we put this background information together with study of the deceased person's brain we can learn a great deal. For example, we stain the nerve cells, and this is perfectly easy to do, to get a picture of the person's typical *apical* (upper) dendrites and *basilar* (lower) dendrites.

The simplest way to measure our results is to have a group of concentric circles in the eyepiece of the microscope we use to study brain cells. We center the cell body in the middle and then count the number of dendrites that cross each circle. Let's say the inner circle has three or four crossings. As we go out to the third, fourth or fifth circles we get 10, 15 crossings. As we go out farther the crossings obviously become fewer. Then we graph the number of crossings against the number of circles, and connect the lines.

What we get is a graphic pattern. And essentially, the area under that graph directly represents the amount of dendritic tissue that this cell has generated. If the graph is higher or if it comes out at a leisurely angle, we can be sure that the cell had more dendritic tissue that is distributed in a richer way.

This is a very simple way to do some rough quantitative measurements on dendritic richness or poorness.

In one study, we used this process to look at the brains of a group of 10 or 12 people

about whom we had data as to how they spent their lives.

For example, one person was a clerk-receptionist, apparently a very fine typist. Another individual was a major-appliance repairman. A third fellow was a tailor, a fourth an office-work typist, a fifth a mechanic.

What did we want to do with the brains? Marian indicated to you that specific parts of the cerebral cortex serve specific functions and specific parts of the body. Knowing this, we sampled a part of the brain that we knew took care of hand and finger motions and contrasted that with an adjacent part of the brain that took care of sensory inputs from the surface of the chest. We can immediately infer there should be an enormous functional difference. I don't sense my environs by rubbing my chest against the wall. I sense it by touching the wall, right? So the hand-finger part of the cortex gathers very powerful, subtle input, and the chest part of the cortex gathers gross, uneducated input. If more input—enriched input—makes dendrites grow, we should be able to see in the hand-finger area a much richer dendrite pattern than in the chest area.

We found consistently dramatic differences—for all but three of the individuals.

Do you know what we found with the fellows that fooled us? We found that two of them were left-handers, so they were not using the right hand as the leading hand. There was very little difference between left-handed function and chest function. The third individual turned out to be a salesman. He was a right-hander but we learned from his wife that he was very clumsy; he never could use his hands effectively. The dendritic pattern told the story.

Here's another, similar experiment. As you all know, most of us are "left language dominant." The left hemisphere of our brain takes care of all the computational work in language. The right hemisphere, also very important, is not interested in semantics and syntax and computation. It's interested in the flow, the sound of speech, what we call the melody and the prosody. Without my right hemisphere I would speak in a rhythmless monotone, and you all would leave the room as soon as you could.

There's a tremendous difference in what these cortical systems do. We inferred—and this was a dangerous inference—that the dendritic tissue on the left-language-dominant side should be much more complex than over on the same area of the right side because we feel that cognition must be more subtle than emotion. It's a dangerous presumption: Sometimes it's true and sometimes it's not. We sampled cells from the area that computes language output and other cells from the area just behind it, which enervates the muscles of the tongue, larynx and pharynx to carry out the commands.

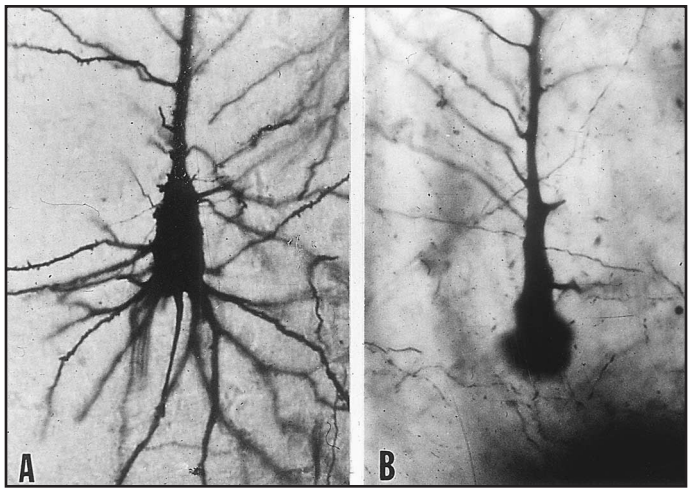


Figure 4: Contrast between a normal cortical pyramidal cell in the human cerebral cortex (A) and a similar cell, showing advanced degenerative changes in senile dementia (B).

Everything worked out as we expected with the left language area far surpassing all others, including the right language area, except in one person.

We were disturbed to find that in his right language area the dendritic systems were more complex. It turned out that this individual was a lifelong lefty. He was one of the relatively small number of people who are right language dominant, and it showed very clearly. We learned, then, that form follows function. The more you use a system the more your dendritic tissue grows in that system. It's a valuable lesson to remember.

One last bit of data: In another study that I did with my graduate student, Bob Jacobs, we looked at the brains of people. We

always work without knowing the characteristics so the knowledge doesn't modify our judgment when we're counting dendrites. We found that the group could be broken into three groups on the basis of the data. One group had a certain amount of dendritic tissue, the second had more, and the third group had even more. We couldn't figure out what caused these differences until we examined the data we had on the individuals' lives. You know what we found? The first group only had an elementary school education. The second group had gone through high school and perhaps a year of college. The group with the highest number of dendrites had completed college and graduate school. It was an eye-opener.

What I'm reporting to you is a correlation between the amount of dendritic tissue and the amount of education. The results say nothing about cause or causality. You might argue, well look, the poor folks who had less dendritic tissue couldn't make it out of elementary school. That's perfectly possible. However, on the basis of what we know from the animal work of Marian and others, it does look as though challenge, constant input and new information were at stake here. The third group could undoubtedly live richer, more fulfilling lives because of a higher education level.

Now, I want to finish up with the third, last component of our discussion. What are the possible mechanisms that are basic to the processes that Marian has told you about, that we've hinted at here?

Inside the brainstem is an area that we haven't mentioned before. It's a very old area known as the reticular core of the brainstem. Sensory input—it doesn't matter whether it's touch, vision, audition, any of these—comes in through the brainstem through the thalamus, where it has a number of connections. Then it goes through this curious little half-moon structure, which is actually a filter system, up to the cortex. From the cortex, in this case the direct sensory cortex, the input is disseminated to various parts of the cerebral hemispheres.

On its way into the cortex the sensory input adds information to the reticular formation or reticular core. The reticular core is like the telephone operator in a little New England town about 75 years ago. Everything came through her switchboard. Right? She rerouted all the calls and gradually became familiar with everybody's business. That's what the reticular core does. It is continuously listening to everybody's business. Now, unlike the New England telephone operator who remembered all the awful secrets of the town forever, the reticular core has a very short, fickle memory. It is interested only in what is new, different, exciting and unexpected. That which is dull and repetitive it just forgets and ignores. Its own activity goes down steeply unless what's coming in is exciting and new.

That's important to us because the role of the reticular core is to project to all parts of the cortex, not just to a single part. The core actually determines the levels of activity all throughout the cortex, including the levels of genomic activity, activity that produces the protein that may produce dendrites. So, when Marian was stressing to you the importance of the fact that sensory input be fresh and engaging and new and different, it was because this input is necessary for the reticular core to get involved and help us actually grow new dendritic tissue.

Remember the half-moon-shaped filter that I told you about? This filter is actually a series of little gates, or gatelets, that control access to the cortex. The prefrontal cortex (the area responsible for the highest levels of cognitive function) has a direct level of control over these gatelets. Since you—the highest level of you—are really a prefrontal cortex, you can learn to control these gatelets. That's how biofeedback works. That's how autohypnosis works. That's why the yogi can lie on a bed of nails and not only not feel the pain but not even get scratched or begin to bleed. With practice, you can gain control over what comes into your brain, by the use of this prefrontal cortex working on this system. So this gives you, at least potentially, another measure of control over your brain and yourself.

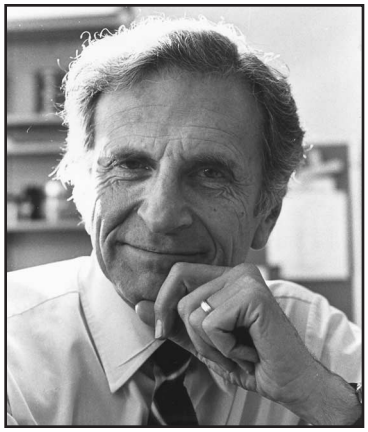
Finally, the exciting data that Marian has presented shows that if we stimulate this prefrontal cortex through something challenging like playing bridge, we can actually make positive changes in our immune sys-

tems. In the case that she studied she was able to show these changes in a certain form of lymphocyte, the CD4 cell.

Where do these changes occur? Well, the sources for immune system activity in adults are usually in the spleen and in the shafts of the long bones. The prefrontal cortex also turns out to be the only cortical area that projects directly to our hypothalamus and pituitary. And the hypothalamus in turn, this great visceral center, is in charge of the immune system working in the spleen and long bones. You see, you can actually plot out schematically the routes by which these wonderful effects of enrichment occur. For me the most exciting thing is that it gives us a significant degree of control over ourselves and our future. And I think this is our major challenge as we age.

The Lecturers

Marian Diamond, PhD, is professor of human neuroanatomy and total body anatomy in the Department of Integrative Biology at the University of California, Berkeley.



Arnold Scheibel, MD, is a professor in the Department of Neurobiology at the University of California, Los Angeles, Medical Center.

2001 MINDALERT AWARDS

The ASA–MetLife Foundation MindAlert Awards were established in 2001 to recognize innovations in mental fitness programming for older adults. The awards recognize programs, products or tools that promote cognitive fitness in later life. Programs are judged for their innovation, their basis in research, demonstration of their effectiveness, their potential for replicability, and the extent to which they are accessible to diverse populations of elders. The following are descriptions of the 2001 award winners.

The Adult Activities Center

Adult Day Services of Orange County Costa Mesa, CA

One of the 2001 MindAlert Awards recognized the achievements of the Adult Activities Center at Adult Day Services of Orange County in Costa Mesa, Calif. The Adult Activities Center, directed by Cordula Dick-Muehlke, offers a continuum of services to address the unique needs of people in the early stages of Alzheimer's disease and their caregivers.

While advances in the diagnosis and treatment of Alzheimer's have led to earlier identification of individuals with dementia, California's system of care remains focused on serving those with moderate-to-severe impairment. The Adult Activities Center offers a comprehensive set of services for people in the early stages of the disease.

The New Connections Club is a day program that incorporates research-based interventions such as memory retraining, exercise and reminiscence therapy to enhance cognitive, physical and emotional functioning. The Activities Club is an outings-based day program for those who are relatively independent but can no longer benefit from cognitive interventions. "Memory Boosters" is the title of a 10-week set of memory retraining classes offered at the center and in the community. "You're Not Alone" is a 10-week set of parallel support groups for early-stage individuals and their caregivers. And "Living With Alzheimer's Disease," a three-week psychoeducational series, is offered for caregivers.

Each component of the services offered at the Adult Activities Center is designed in light of studies demonstrating the effectiveness of particular approaches with early-stage individuals and with their caregivers. By drawing on existing research, the Adult Activities Center differs from the handful of other early-stage programs, which are recreationally focused and take the typical "whatever works" approach to dementia care. Although it is commonly believed that even early-stage individuals cannot benefit from memory retraining, Adult Activities Center participants have, for example, shown significant improvements in their ability to identify famous faces and places following 12 weeks of practice.

A survey of caregivers whose loved ones have participated in the Adult Activities Center for a minimum of 3 months revealed a variety of benefits. Of the 43 respondents, the majority reported that their loved ones were happier (83%), less depressed (62%), more interested in life (62%), and less anxious (54%) as a result of participation. Benefits experienced by caregivers included having more time for personal activities (85%), feeling less stressed (88%) and more relaxed (83%), gaining a better understanding of dementia (78%), being less isolated (64%) and finding it easier to continue working (64%).

Mind Your Mind: Workshops for Mental Fitness

Presented Around the United States

A second MindAlert Award was given to Mind Your Mind, a systematic, well-rounded mental activity program that promotes mental fitness in older adults. Beatrice Seagull, professor emeritus at Rutgers University, New Jersey, has presented Mind Your Mind workshops to nearly 2,000 par-

ticipants since 1992. Mind Your Mind is an educational workshop activities program that systematically promotes mental fitness in older adults. It is designed specifically for groups in senior centers and adult community facilities; participants range in age from 65 to 85-plus.

Based upon the idea that continued intellectual stimulation is a tremendous benefit to successful aging, the program empowers its participants by strengthening their minds and by enhancing their feelings of control over their lives. Emphasis is on the potential for self-improvement. Older adults consistently express their fears about declining memory and decreasing mental abilities. By directing attention to the concept of mental fitness, participants are encouraged to work on keeping the mind in peak shape. In a classroom setting, the workshop activities provide a structure for them to reflect upon their cognitive capacities, practice their thinking skills and increase their self-confidence.

The Mind Your Mind program is a complete "mind workout," similar to a physical workout, with exercises designed to stimulate multiple parts of the brain. The theoretical framework is based on distinct cognitive skills—memory, flexible thinking, perception, using language, reasoning—which are clearly defined and described. The activities for each skill provide practice in that area. Included are warm-ups; mind benders; riddles; verbal and perceptual tasks; and exercises to promote memory and retrieval, flexible thinking, spatial relationships and problem solving. The activities range from easy to more complex. Some of the tasks are generational, connected to knowledge acquired during a lifetime of experiences.

The program combines practice in thinking skills with concise factual information about the aging process. A series of "mini-talks" on directed topics are given at intervals during the course to provide the factual material. These topics include "The Aging Mind: Normal Changes," "The Brain and Blood," "The Neuronal Network and Neurotransmitters," "The Evolving Brain," "You and Alzheimer's Disease," and "Enhancing Brain Function—What You Can Do."

Strategies for improving mental fitness in everyday situations complement the exercises and factual material. The strategies refer to common experiences of older adults, offering simple problem-solving solutions as well as opportunities for group discussion and interaction.

Mind Your Mind approaches the concept of mental fitness as an ongoing undertaking rather than as a statistically measurable characteristic. The message of the program is that just like physical fitness, mental fitness can be constantly improved. Scientific research regarding the continuing capacity of the brain to grow in later life, such as that conducted by Professors Diamond and Scheibel, provides the primary motivation of the program: "Use it or lose it."

Elder Rehab

Department of Speech
and Hearing Sciences,
University of Arizona
Tucson, AZ

The Elder Rehab program, the third winner of the 2001 MindAlert Awards, is a cognitive, language, physical-fitness and "partnered volunteering" program for people with mild to moderate Alzheimer's disease. The purpose of the program, which is directed by Sharon M. Arkin, is to improve the quality of life of people with dementia and their caregivers and to slow the rate of cognitive decline.

Twice-weekly interventions are provided by undergraduate "rehab partners." These students provide a weekly session of physical fitness training during which they administer between 10 and 12 different memory and language stimulation activities. Participants' responses to the various activities are recorded so that the program can be monitored. The program includes four components:

Memory Training. Memory training uses research-based methods to help dementia sufferers retain still-remembered personally significant facts about their lives and relearn those that they may have forgotten.

Language Activities. These activities build on preserved abilities—social graces and

pragmatic communication skills such as turn-taking; the ability to respond to cueing and external stimuli; songsheets for "oldtime favorites"; word games and quizzes; verbal fluency exercises; and the ability to discuss topics that don't depend on personal or historical facts, but draw on accumulated life experiences and personal values.

Exercise. To experience the benefits of exercise on health, psychology and mood, Elder Rehab student partners serve as motivators, drivers, personal trainers and conversation partners to make what could be an onerous chore a stimulating, ego-building and fun experience.

Volunteer Work. Participants in the program are encouraged to step out of the role of care recipient and provide meaningful services to others. This social involvement and the positive feelings received from contributing to the welfare of others has been demonstrated to have physiological and psychological benefits.

More than 40 people have participated in the program to date. Standardized measurements of 11 participants showed that these individuals maintained their level of language and cognitive function over a two-semester period while showing significant gains in the recall of autobiographical facts and improvement in their mood and overall quality of life.

HONORABLE MENTIONS

My Turn Program

Kingsborough Community College,
City University of New York
Brooklyn, NY

Rivier Institute for Senior Education (RISE)

Rivier College
Nashua, NH

AWARDS REVIEW COMMITTEE

ASA expresses its gratitude to the review committee for their work in reviewing award submissions: Carol Cober, AARP-Health and Wellness Unit, Washington, DC; Sandra Cusack, Gerontology Research Centre, Simon Fraser University, Vancouver, BC; Marian Diamond, Integrative Biology Department, University of California, Berkeley; Nancy Emerson Lombardo, Center for Research on Women, Wellesley College, Wellesley, MA; Marge Engelman, University of Wisconsin, Madison; Barbara Ginsberg, My Turn Program, Kingsborough Community College, Brooklyn, NY; Judy Goggin, Elderhostel, Boston, MA; Paul Nussbaum, Neurobehavioral Services, Aging Research and Education Center, Mars, PA; and Arnold Scheibel, Neurobiology Department, UCLA Medical Center, Los Angeles, CA.

ABOUT THE MINDALERT AWARDS

New research is showing that cognitive decline is not an inevitable part of the aging process. The brain is able to grow new nerve extensions at any age, and emerging evidence suggests that brain cells are capable of regeneration in the hippocampus—an area of the brain vitally important to the laying down of new memories and information.

New knowledge about the brain means that mental stimulation should be maintained throughout life. These findings offer a striking new model of aging that suggests that elders have the opportunity to lead qualitatively better lives filled with more knowledge and wisdom—and an increased capacity to contribute to society.

To promote the translation of this new research on cognitive fitness into practice, the MetLife Foundation has joined with the American Society on Aging (ASA) to create the MetLife Foundation-ASA MindAlert Awards. This awards program identifies and recognizes programs that provide valuable information and activities supporting enhanced cognitive function in later life. The award not only rewards successful and innovative programs, it provides a wealth of ideas and guidance for organizations seeking to create or improve their own programs.

American Society on Aging

With 7,500 members, the American Society on Aging (ASA) is the United States' largest association of professionals in the field of aging. Founded in 1954, ASA's mission is to promote the well-being of aging people and their families by enhancing the abilities and commitment of those who work with them. To that end, ASA offers a wide variety of conferences and networking opportunities and Web-based training every year. The society also publishes a bimonthly newspaper, a quarterly journal and nine quarterly newsletters for its members. To obtain more information on ASA and to join, visit *www.asaging.org*.

MetLife Foundation

MetLife Foundation (formally known as the Metropolitan Life Foundation), established in 1976 by the Metropolitan Life Insurance Company, has been involved in a variety of initiatives related to the issue of aging. Since 1986, the foundation has supported research on Alzheimer's disease through the MetLife Foundation Awards for Medical Research program and has contributed over $7 million to efforts to find a cure. In addition, the foundation has provided support for a new traveling exhibit on memory, an Alzheimer's Association public-education video for use by caregivers and families of persons with Alzheimer's disease and the distribution of the association's quarterly newsletter. MetLife Foundation has contributed more than $165 million to support health, education, civic and cultural programs throughout the United States. For more information about the foundation, please visit its website at *www.metlife.org*.

Further Information About Brain Research

Accessible information about research on successful aging and the healthy brain can be found in the books *Aerobics of the Mind* by Marge Engleman and *Keep Your Brain Alive* by Lawrence Katz, as well as in the article "New Brain Research Suggests Link Between Wellness and Lifelong Learning" by Judy Goggin, published in the *Older LEARNer* (the newsletter of ASA's Lifetime Education and Renewal Network) and posted online at *www.asaging.org/networks/learn/ol-072.html*.

The MindAlert Program, sponsored by the American Society on Aging, the MetLife Foundation and the Archstone Foundation, is dedicated to sharing the findings of new research showing that cognitive decline is not an inevitable part of the aging process.

This book contains the transcript of a series of exciting lectures given by noted researchers Marian Diamond and Arnold Scheibel. The speakers discuss their research on factors that influence the well-being of the brain and offer readers concrete suggestions for keeping their brains healthy and active as they age.

Also profiled inside are the winners of the 2001 MindAlert Awards, which recognize programs that support enhanced cognitive function in later life.

MetLife Foundation

ASA American Society on Aging