The New Old Age:
How the body ages and how to keep it young

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The Joseph B. Martin Conference Center
The New Research Building
Harvard Medical School
77 Avenue Louis Pasteur
Boston, MA 02115

THE Longwood SEMINARS
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The New Old Age:
How the body ages and how to keep it young

Moderator

Amy Wagers, PhD

- Forst Family Professor of Stem Cell and Regenerative Biology at Harvard University and the Harvard Stem Cell Institute
- Senior Investigator, Section on Islet Cell and Regenerative Biology, Joslin Diabetes Center
- Member, Paul F. Glenn Center for the Biology of Aging at Harvard Medical School

Speakers

Sharon Inouye, MD, MPH

- Professor of Medicine, Harvard Medical School
- Director, Aging Brain Center at the Institute for Aging Research, Hebrew SeniorLife
- Milton and Shirley F. Levy Family Chair in Alzheimer's Disease, Hebrew SeniorLife

Bruce Yankner, MD, PhD

- Professor of Genetics and Neurology, Harvard Medical School
- Director, Harvard Neurodegeneration Training Program
- Co-Director, Paul F. Glenn Center for the Biology of Aging at Harvard Medical School

About the Speakers:

Amy Wagers, PhD

Amy Wagers is the Forst Family Professor of Stem Cell and Regenerative Biology at Harvard University and the Harvard Stem Cell Institute. She is a senior investigator in the Section on Islet Cell and Regenerative Biology at Joslin Diabetes Center and a member of the Paul F. Glenn Center for the Biology of Aging at Harvard Medical School. Wagers' research seeks to understand how changes in stem cell activity impact tissue homeostasis and repair throughout life and how these cells may be harnessed for regenerative medicine. Wagers has authored more than 100 primary research and review articles, and her work has been recognized by awards from the Burroughs Wellcome Fund, Beckman Foundation, WM Keck Foundation, Glenn Foundation, Howard Hughes Medical Institute and the National Institutes of Health. In 2013, she received the New York Stem Cell Foundation's Robertson Prize for outstanding achievement. She is the 2015 recipient of the Vincent Cristofalo Rising Star in Aging Research Award.

Sharon Inouye, MD, MPH

Sharon Inouye is a professor of medicine at Harvard Medical School, the Milton and Shirley F. Levy Family Chair in Alzheimer's Disease and director of the Aging Brain Center at the Institute for Aging Research at Hebrew SeniorLife. Inouye's research interests include the epidemiology and outcomes of delirium, reversible contributors to cognitive decline and the interrelationship of delirium and dementia. Inouye developed the Confusion Assessment Method, a method for identification of delirium. She also developed the Hospital Elder Life Program for delirium prevention, which has been implemented in over 200 hospitals worldwide. She directs the Successful Aging after Elective Surgery study, a large Program Project from the National Institute on Aging exploring innovative risk factors and long-term outcomes of delirium. Inouye has authored over 220 scientific articles, and was elected to the National Academy/Institute of Medicine in 2011. Inouye received the M. Powell Lawton Award from the Gerontological Society of America and the A. Clifford Barger Award for Excellence in Mentoring Award at HMS.

Bruce Yankner, MD, PhD

Bruce Yankner is a professor of genetics and neurology at Harvard Medical School, director of the Harvard Neurodegeneration Training Program and co-director of the Paul F. Glenn Center for the Biology of Aging. Yankner's work has contributed to understanding pathogenic mechanisms in Alzheimer's disease, Down's syndrome and Parkinson's disease. The Yankner laboratory has identified a gene network controlled by the master transcriptional repressor REST that promotes neuronal survival and stress resistance in the aging brain and may protect against Alzheimer's disease. He has received the Major Award for Medical Research from the Metropolitan Life Foundation, the Derek Denny-Brown Neurological Scholar Award from the American Neurological Association, the Irving S. Cooper Award from the Mayo Clinic, the Zenith Award from the Alzheimer's Association, the Ellison Medical Foundation Senior Scholar Award, the Nathan W. Shock award from NIA, the Joseph A. Pignolo Award in Aging Research and the NIH Director's Pioneer Award.

Harvard Women's Health Watch

How can you prevent cognitive decline? Try this combination strategy

Hope Ricciotti, MD
Editor in Chief, *Harvard Women's Health Watch*

Four steps — following a healthy diet, getting regular exercise, socializing, and challenging your brain — can improve your mental skills, even as you age.

Observational studies over the past few years seem to be repeating the same message: regular physical activity, a good diet, taking on new mental challenges, and maintaining strong social connections may each help you hang on to your mind. The latest and most impressive study goes a step further by suggesting that if you follow all four practices, you may even reverse lost mental capacity. The results of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) indicated that doing so not only kept cognitive skills from declining, it also improved reasoning skills and speed in performing mental tasks.

What the study involved

The FINGER study — which involved 1,260 women and men and lasted two years — is the largest and longest randomized controlled trial to assess the effects of lifestyle interventions on preserving mental acuity. The participants ranged in age from 60 to 77. They all had a few risk factors for developing cognitive impairment but scored in the normal range on mental function tests. On average, their blood pressure and cholesterol were a little high and they were overweight, but not obese.

The volunteers were randomly assigned to two groups. One set of participants — the study group — received personal nutritional counseling, exercise instruction from physical therapists, and cognitive training. They also underwent seven medical exams during the study period. They frequently met in groups for cooking classes, cognitive training, or exercise instruction. The other participants — the control group — had three medical exams, during which they received general health advice. Both groups were given mental function tests again at the end of the study.

Both groups showed improvement, but the study group's overall scores were 25% higher than the control group's. Moreover, they scored 150% higher than the controls on tasks measuring processing speed (response time) and 83% higher on tests of executive function (organization and reasoning). However, neither group improved in ability to recall lists of words.

The study's results should offer additional encouragement to pursue a healthy, active, engaged lifestyle, says Dr. Scott McGinnis, a neurologist at Harvard-affiliated Brigham and Women's Hospital and author of *The Harvard Guide to Coping with Alzheimer's Disease*. "Healthy lifestyle behaviors can benefit people of all ages. But to have the greatest impact on late-life mental function, get started early," he says.

Whether or not the people in the study group will maintain their new lifestyle habits remains to be seen. It's also unknown whether, over time, the study group will have a lower rate of mild cognitive impairment or dementia than the control group. Both groups will undergo exams and cognitive testing again in 2019.

Is there a message here for you?

You probably already knew that regular exercise, a Mediterranean diet, and challenging mental activities can help preserve your mental acuity. However, the FINGER study told us that it not only helps to combine these practices, it also helps to enjoy them as you do them. When the participants were interviewed by the press, they said they stuck with the study because they were having such a good time and had become friends with others in their training groups. Although the study was demanding, only 12% of participants dropped out. Attendance was over 85% at training sessions, which included three to five exercise sessions a week as well as 10 to 12 sessions of nutrition counseling and 144 cognitive training sessions over two years.

If you're having trouble making healthy changes, a cooking or exercise class may help you get started and open a new circle of friends. Volunteering as a tutor, joining a community choir, or working on a political campaign can offer new intellectual challenges and social engagement. The key to making lifestyle changes is in finding a way to enjoy making them — and that is often among a group of companions who are striving for the same goal.

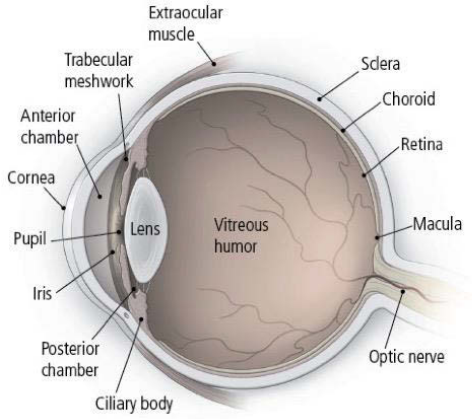
To learn more…
This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from the February 2016 issue of the *Harvard Women's Health Watch*, available at http://hvrd.me/YFhaD.

How to sidestep age-related eye problems

Just as hair turns gray and skin sags with age, the eyes, too, undergo changes as you grow older. Although many of these changes are part of normal aging, some set the stage for more serious eye problems.

As eyes age, eyelid muscles weaken, and skin becomes thinner and more flaccid. This can cause the upper lid to droop or the lower lid to sag. Eyelashes and eyebrows may lose their lushness and thin out considerably.

Eye anatomy: The inside story



Rays of light pass through the cornea, the anterior chamber, and then the lens, which focuses images. The lens is nourished by the aqueous humor, a clear, watery solution that circulates from the posterior chamber into the anterior chamber and helps maintain normal pressure. Light reaches the retina after it passes from the lens through the vitreous humor, a clear gel that fills most of the eyeball. The retina has light-sensitive cells that capture images, which are then sent to the brain via the optic nerve. At the retina's center is the macula, a small region that provides sharp, central vision.

Tear production also drops off, and the oily film that tears provide decreases as lubricating glands in the conjunctiva and lids fail. These changes can lead to a buildup of mucus, resulting in stickiness, or make the cornea dry, causing irritation or an uncomfortable, gritty sensation in the eye.

The conjunctiva turns thinner and more fragile with age and takes on a yellowish tinge from an increase in elastic fibers. The white of your eye (the sclera) also assumes a yellow hue from a collection of lipid, or fat, deposits. Calcium may deposit in the sclera, leading to patches of grayish translucency. The exposed conjunctiva between the lids begins to degenerate, and the cornea can develop an opaque white ring around its edge.

With time, the lens hardens and loses its elasticity. This makes it more difficult to focus on near objects, a common condition called presbyopia. You might also find that your night vision grows poorer. These changes usually occur simultaneously in both eyes.

Practical steps to preserve your vision

You can take steps on your own to protect and preserve your vision. The eyes are priceless and deserve to be treated with care and respect. Following are some of the most important steps you can take to help ward off problems.

Don't smoke. The chemicals in cigarette smoke travel through the network of tiny blood vessels that supply your macula. Eventually, those chemicals can damage the blood vessels and lead to age-related macular degeneration. Smoking has also been linked to an increased risk for cataracts.

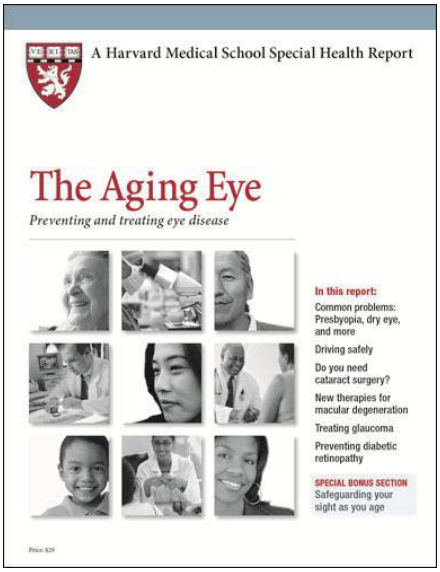
Wear sunglasses and a hat. The hat should have a three-inch brim to protect your eyes from the sun's ultraviolet (UV) radiation, which has been linked to eye damage — particularly cataracts and age-related macular degeneration.

Eat a nutritious diet, with plenty of fruits and vegetables. Just as sunglasses and a hat protect your eyes from the outside, these foods can protect your vision from the inside, helping to ward off certain eye diseases. For example, studies show that people who eat the most foods rich in the antioxidants lutein and zeaxanthin (such as spinach and other dark green vegetables) are less likely to develop cataracts and age-related macular degeneration. These nutrients filter out harmful blue wavelengths of light, protecting your eye cells from damage. It's also a good idea to minimize saturated fats and hydrogenated oils, which contribute to blood vessel damage and can diminish blood flow to your eyes.

Wear safety glasses or goggles. Thousands of eye injuries occur every day, and 90% of them would have been preventable with the use of appropriate safety eyewear. Put on protective goggles or safety glasses whenever you work with power tools, use cleaning supplies or other chemicals, or play sports. If you do get chemicals in your eyes, immediately flush the eye with water in the sink or shower for 15 minutes. Do not bandage it. Seek medical care immediately.

Learn about the aging eye. You should know how to recognize risks and symptoms so you're alert to the warning signs of vision problems and can see a doctor right away, before a condition causes further damage. If you have diabetes, controlling your blood sugar can delay both the start and progression of retinopathy.

Limit your screen time. Spending many hours in front of a television or computer screen or working in poor light does not cause harmful medical conditions, but it can tire the eyes. Follow the 20-20 rule: for every 20 minutes you spend looking at your computer screen, look away for at least 20 seconds to give your eyes a rest.



To learn more…
This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Special Health Report *The Aging Eye*, available at http://hvrd.me/YNQaQ.

How memory changes with age

Many people begin to notice changes in their powers of recall around the age of 50. Some of these changes are relatively predictable and differ from the memory impairment caused by dementia or other conditions that damage the brain. There are ways to tell the difference.

But just because your memory seems to be getting worse with age, that doesn't necessarily mean that age is directly responsible. Your memory can falter as a result of stress, fatigue, or being overloaded. Some memory difficulties may also be caused by medications, poor vision or hearing, sleep disturbances, or depression — in other words, things you can take steps to correct.

Age-related changes in the brain

As you get older, certain characteristic changes take place. You are likely to experience delays in your ability to recall things, which explains why you have to rack your brain to remember a name or word that is familiar to you. It also becomes more difficult to divide your attention among more than one activity or source of information. You may find it difficult to focus your attention, getting more easily distracted than when you were younger.

Over time, changes take place in the brain that may account for these difficulties. Brain regions involved with memory processing, such as the hippocampus and especially the frontal lobes, undergo age-related structural and neurochemical changes. For example, the hippocampus shrinks in size. Some receptors (the lock-and-key structures on the surface of neurons needed for them to communicate with other neurons) may cease to function normally. The result is that as you age, it takes longer to absorb new information and to form new memories. The loss of receptors and of neurons may also make it harder to concentrate.

These changes can undermine the encoding, consolidation, and retrieval of new information. Different kinds of memory can decline with age, including episodic memory (for example, which stock you sold last year from your retirement account), semantic memory (facts, such as the year World War I started), and spatial memory (such as the directions to a new location).

In addition, the ability to perform tasks involving attention and executive function declines with age. Executive function is a group of cognitive activities that involve the overall regulation of thinking and behavior — the higher-order processes that enable us to plan, sequence, initiate, and sustain our behavior toward some goal, incorporating feedback and making adjustments along the way.

When people of all ages encounter new information, they may all take in the big picture, but those who are older may not absorb as much detail. For instance, after listening to a

presentation, a 25-year-old and a 75-year-old may both remember the overall subject and basic ideas, but the 25-year-old may be able to recall more of the specifics.

Reasons for encouragement

These changes may sound disturbing, but they are relatively minor and may simply represent slower processing speed. In other words, age-related changes in the brain may slow down your learning and your recall, but they don't impair your ability to function effectively. Your ability to make sense of what you know and to form reasonable arguments and judgments is well-preserved. Moreover, the wisdom that you've gained from experience over the years remains unscathed.

In addition, you can compensate for the slowdown in information processing and diminished ability to concentrate by working harder to pay attention to any new information you are trying to learn. It's not difficult. For example, try repeating the information several times in your mind or discussing it with friends. Willpower and effort can overcome a fair amount of age-related difficulty. In many instances, if you make the effort to learn something well, you'll be able to recall it as well as a younger person can. And consider this: while processing speed may become slower with age, the general amount of knowledge a person has continues to increase.

Not all memories slip

One of the myths surrounding the term "age-related memory loss" is that all forms of memory are equally affected. In fact, while some information may become harder to recall — and new memories may be harder to lay down in the brain — other memories will remain as accessible as ever. There is truth in the old saying that "you never forget how to ride a bicycle." Procedural memory — by which you remember processes and skills such as how to ride a bicycle, serve a tennis ball, or accomplish routine tasks — does not tend to fade with age.

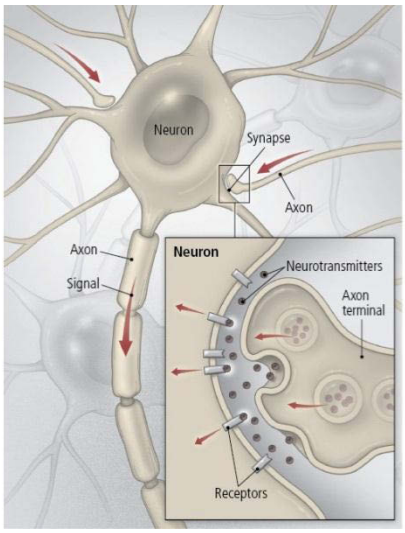
Brain plasticity

While certain brain regions may take a hit from the aging process, the brain is also quite adaptable. The complex network of interconnected neurons through which it processes information is quite dynamic, changing constantly throughout life in response to everyday experiences — a phenomenon called plasticity.

For years, the scientific view of an adult's brain was anything but encouraging. Experts believed that, unlike other cells in the body, neurons did not regenerate. They thought that the brain produced new brain cells only early in life and that once you reached adulthood, the growth of new neurons ceased and existing neurons began to die off. You may have heard the oft-repeated "fact" that you lose 10,000 brain cells a day. The idea was that your brain was shrinking, and that could mean only one thing: as you lost neurons, you also lost some of your capacity to learn, think, and remember. Researchers now know that this neuron degradation is less pronounced than previously thought.

Not only do brain cells not die as rapidly as scientists once thought, but it may even be possible to grow a modest number of new neurons — a process known as neurogenesis. Nearly two decades ago, compelling evidence showed that human adults do sprout new neurons. The significance of this is not entirely clear, and neurogenesis may be less important for memory than maintaining the connections among neurons — the neural pathways that are formed among brain cells as you learn new information or have experiences (see the following figure). Revisiting the information strengthens the pathways. In fact, any activities you engage in frequently — whether related to your job, your hobbies, or running a household — become more sturdily encoded.

A wide web of memories



In order to recall a memory, you must activate a vast network of interconnecting brain cells called neurons (nerve cells). These brain cells deliver and permanently store messages along neural pathways, primarily in the cerebral cortex, the large, domed outer layer of the brain.

One brain cell communicates with another across a space called a synapse, by way of chemicals known as neurotransmitters. These neurotransmitters activate the receptors on the neighboring cell. Revisiting a memory strengthens the connections between brain cells that are responsible for maintaining that memory.

The brain also has some capability to reorganize itself, shifting functions from one network to another, if a particular process starts to weaken. For example, some studies have found that the brains of older and younger adults may engage different brain regions to accomplish the same mental task. Scientists believe that this may be a mechanism of older brains to compensate for diminished function in the area normally used for that task.

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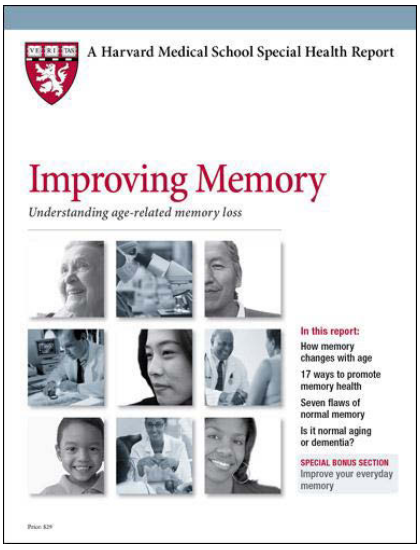
Longwood Seminars, April 19, 2016

The bottom line is this: New connections between neurons are formed as we learn information or take in visual images and other types of stimuli. The more we use the information, the stronger the memory. Even if some brain regions weaken, the brain may be able to compensate. For these reasons, stretching your mind with mentally challenging activities can improve your memory.

Common memory lapses and strategies to overcome them

What you forget	How to remember better
Names	• When you meet someone for the first time, stop and take the time to register his or her name. Many times you may forget a name simply because you didn't notice it being said to you in the first place. • Use a new acquaintance's name in conversation. • Think about whether you like the name. • Think of people you know well who have the same name. • Associate the name with an image, if one comes to mind. For example, link the name Sandy with the image of a beach, and imagine Sandy on the beach. Use as much detail as possible — picture her in a bathing suit, on a beach that's familiar to you. • Write the person's name down in your memory notebook, personal organizer, or address book.
Where you put things	• Always put things you use regularly, such as keys and eyeglasses, in the same place. • For other objects, repeat aloud where you put them. • As you put an object down, make a point of looking at the place where you put it. • If you still don't think you'll remember, write down in your memory notebook or personal organizer where you put the object.
What people tell you	• Ask someone to repeat what he or she just said. • Ask the person to speak slowly; that way, you'll be able to concentrate better. • Repeat to yourself what the person said and think about its meaning.

	• If the information is lengthy or complicated (such as advice from your doctor), record it on your cellphone or a small voice recorder, or take notes.
Appointments	• Write them down in an appointment book, in a calendar that you look at daily, or in your personal organizer.
Things you must do	• Write them down in your personal organizer or calendar. • Write yourself a note and leave it in a place where you'll see it (for instance, on the kitchen table or by the front door). • Ask a friend or relative to remind you. • Put an object associated with the task you must do in a prominent place at home. For example, if you want to order tickets to a play, leave a newspaper ad for the play near your telephone. • If you must do something at a particular time (such as take medicine), set an alarm.
Adapted with permission from Winifred Sachs, Ed.D., Center for Cognitive Remediation and Treatment, Beth Israel Deaconess Medical Center.	



To learn more…
This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Special Health Report *Improving Memory*, available at http://hvrd.me/YNSVo.

Harvard Women's Health Watch

What you can learn from the oldest old

Hope Ricciotti, MD
Editor in Chief, *Harvard Women's Health Watch*

Resilience — a quality shared by the longest-lived women — can be acquired. It will serve you well, whatever your age.

Women are natural survivors. The 10 people with the longest verified life spans are women, as are 85% of centenarians (people between 100 and 110). Scientists studying centenarians have found that good genes and a healthy lifestyle aren't the only factors that increase your chance of seeing your 100th birthday. Most centenarians also share an emotional trait: resilience, the ability to adapt well to stress and adversity.

Dr. Jennifer Moye studies life stage and resilience as a geropsychologist in the Harvard-affiliated VA Boston Healthcare System. In her work with cancer survivors, she has found that older people adapt better to a cancer diagnosis and treatment than those who are younger or middle-aged. "By the time we're older, we've dealt with a lot and are much better at getting back up after we're knocked down," she says. Dr. Moye notes that some people are naturally resilient because they instinctively move on after a crisis. Others may need to reflect on the situation and realize that they're stronger for having survived it.

How to become more resilient

Studies have revealed that some attributes associated with resilience — an outgoing and trustful approach to others, physical fitness, enjoyment of life, ability to adapt to change, learning from setbacks, and sustaining optimism — can be acquired. Here are a few suggestions.

Develop strong social connections. Maintaining a broad-based community of family and friends can ensure that you'll have support during a crisis.

Savor each day. Go for a walk in a park, read a great book, listen to music, or have a good laugh. Think of your life as a gift and strive to make each day meaningful.

Grow from your setbacks. Reflect on the resources you've used to survive other losses and employ them to go forward. You'll realize that those experiences have made you stronger.

Take care of yourself. Do things you enjoy and find relaxing. Eat nutritiously, get enough sleep, exercise regularly, keep your medical appointments, and take your prescriptions.

Keep up hope. If things were better in the past, they can be once again. Practice visualizing the future you want and work toward achieving it.

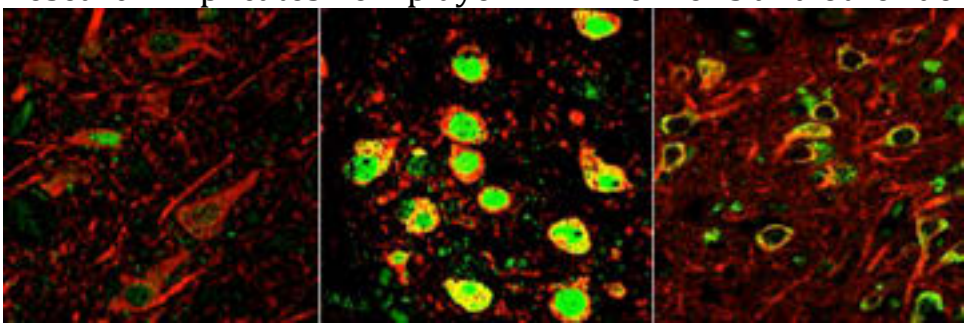
To learn more…
This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from the October 2015 issue of the *Harvard Women's Health Watch*, available at http://hvrd.me/YFhaD.

The aging brain needs rest

March 19, 2014

By Stephanie Dutchen
(From Harvard Medical School News)

Research implicates new player in Alzheimer's and other dementias



A new study shows that a gene regulator called REST, dormant in the brains of young people (left), switches on in normal aging brains (center) to protect against various stresses, including abnormal proteins associated with neurodegenerative diseases. REST is lost in critical brain regions of people with Alzheimer's (right). Image: Yankner Lab

Why do neurodegenerative diseases such as Alzheimer's affect only the elderly? Why do some people live to be over 100 with intact cognitive function while others develop dementia decades earlier?

More than a century of research into the causes of dementia has focused on the clumps and tangles of abnormal proteins that appear in the brains of people with neurodegenerative diseases. However, scientists know that at least one piece of the puzzle has been missing because some people with these abnormal protein clumps show few or no signs of cognitive decline.

A new study offers an explanation for these longstanding mysteries. Researchers have discovered that a gene regulator active during fetal brain development, called REST, switches back on later in life to protect aging neurons from various stresses, including the toxic effects of abnormal proteins. The researchers also showed that REST is lost in critical brain regions of people with Alzheimer's and mild cognitive impairment.

“Our work raises the possibility that the abnormal protein aggregates associated with Alzheimer’s and other neurodegenerative diseases may not be sufficient to cause dementia; you may also need a failure of the brain’s stress response system,” said Bruce Yankner, Harvard Medical School professor of genetics and leader of the study.

“If true, this opens up a new area in terms of treatment possibilities for the more than 5 million Americans currently living with Alzheimer’s disease,” said Yankner, who in the 1990s was the first to demonstrate the toxic effects of amyloid beta, the hallmark abnormal protein in Alzheimer’s.

The results were published Mar. 19 in *Nature*.

Protection at the end of life

The CDC lists Alzheimer’s disease as the sixth leading cause of death in the United States, and a Mar. 5 paper in *Neurology* by a group unrelated to Yankner’s argued that it should be ranked third. A 2013 study by the RAND Corporation found that with an estimated annual toll of as much as $215 billion, Alzheimer’s is America’s most expensive disease, costing more than heart disease or cancer.

“Dementia is not an inevitable result of aging,” said Yankner, who is also co-director of the Paul F. Glenn Laboratories for Biological Mechanisms of Aging. “We know it’s possible for the human brain to work normally for a century or more. So a robust mechanism must have evolved to preserve brain function and keep brain cells alive in long-lived organisms like us. We just haven’t learned what that mechanism is.”

Yankner believes REST may be a key piece in the solution to that puzzle. REST first came to his attention when team member Tao Lu, HMS instructor in genetics, flagged it as the most strongly activated transcriptional regulator—a switch that turns genes on or off—in the aging human brain. The team confirmed the finding through biochemical and molecular tests and high-resolution imaging.

The finding surprised him at first because until then, REST’s only known activity in the brain occurred prenatally, when it keeps key genes turned off until progenitor cells are ready to differentiate into functional, mature neurons. REST was believed to wind down in the brain soon after birth. (It

stays active elsewhere in the body and appears to protect against several kinds of cancer and other diseases.) When Yankner thought more about it, however, it began to make sense.

“When in a person’s life are brain cells most vulnerable?” he asked. “The first time is during fetal development, when loss of young neurons would be devastating. The second is during aging, when you’re bombarded by oxidative stress and misfolded or aggregated proteins, such as the amyloid beta and tau proteins seen in Alzheimer’s disease. It makes sense that a system would come on at those two times to protect neurons, which are largely irreplaceable.”

Having discovered this possible new role for REST, Yankner and team went on to identify the specific genes REST regulates in aging neurons. They found that REST turns off genes that promote brain cell death and contribute to various pathological features of Alzheimer’s disease, such as amyloid plaques and neurofibrillary tangles, while it turns on genes that help neurons respond to stress.

Lab dish experiments revealed that removing REST made neurons more vulnerable to the toxic effects of oxidative stress and amyloid beta. REST appeared to clear away and protect against the free radicals that result from oxidative stress.

To confirm REST’s role, the team engineered mice that lacked REST only in their brains and watched what happened as they aged.

“The mice were okay as young adults, but as they got older, neurons in the brain started to die in the same places as in Alzheimer’s: the hippocampus and the cortex,” said Yankner. “This suggested that REST is essential for neurons to remain alive in the aging brain.”

Together with HMS associate professor of genetics Monica Colaiácovo, the team also uncovered a REST equivalent in the tiny worm *C. elegans*. There, too, the REST equivalent was necessary to protect against free radicals and amyloid toxicity. This suggested the protective function is shared across species.

Diverted from its course

Yankner and colleagues further illuminated the relationship between REST and the aging brain through a combination of lab experiments and studies of brain tissue from elderly people with and without dementia.

The team showed that REST was activated in normal aging brains. The brains of people who developed mild cognitive impairment, by contrast, showed an early decline in REST. The affected brain regions of people with Alzheimer's had hardly any REST left.

"REST loss correlates very closely with memory loss, especially episodic or autobiographical memory, the type that typically declines early in Alzheimer's," said Yankner.

Cell culture experiments suggested REST is activated when stressed neurons send signals to one another, and that once REST is created in a neuron's cytoplasm, it must travel to the nucleus to do its job.

Yankner's group then found that in Alzheimer's, REST gets diverted from its journey to the nucleus, becomes engulfed through a process called autophagy and is eventually destroyed.

The team saw the same striking misplacement of REST when they looked at brain tissue from people with other prevalent neurodegenerative diseases involving dementia, including frontotemporal dementia and dementia with Lewy bodies. In all three dementing illnesses, REST had been swept into the cellular trash bins alongside each disease's abnormal proteins: amyloid beta in Alzheimer's, tau in frontotemporal dementia and alpha-synuclein in Lewy body disease.

"The prevention of REST from getting to the nucleus may be the earliest phase in the loss of REST function. Our laboratory models suggest that this will make neurons much more vulnerable to a variety of stresses and toxic proteins," said Yankner.

Uncovering how REST gets activated and misplaced provides new ideas for how to intercept Alzheimer's. For instance, rather than solely focusing on lowering amyloid beta levels, as clinical trials have done so far without great success, Yankner imagines trying to target REST with drugs such as lithium, which his lab has shown can boost REST function.

REST and dementia-free longevity

Next, Yankner turned to the long-standing puzzle in neurology of how some aging individuals can harbor Alzheimer's disease pathological changes but never become demented.

The team examined brain tissue gathered as part of the Religious Orders Study and the Rush Memory and Aging Project, both funded by the National Institute on Aging. These long-term studies together follow several thousand aging participants and collect donated tissue after death to better understand normal aging, cognitive impairment and neurodegenerative disease.

The team sorted the samples into two groups. One group had Alzheimer's pathology and experienced symptoms of dementia. The second group had the same amount of Alzheimer's pathology but did not become demented. The team found that the group with no dementia had at least three times more REST in the nuclei of their neurons in key brain regions.

"This suggests a person may be able to resist the toxic effects of Alzheimer's pathology if REST levels remain high," said Yankner. "If we could activate this stress-resistance gene network with drugs, it might be possible to intervene in the disease quite early."

"Since Alzheimer's strikes late in life, delaying the onset of disease by just a few years could have a very substantial impact," he added.

In additional studies, the team found that REST strongly correlated with increased longevity. REST levels were highest in the brains of people who lived into their 90s and 100s and remained cognitively intact. Levels stayed high specifically in the brain regions vulnerable to Alzheimer's, suggesting that they might be protected from dementia.

Finally, the team showed that REST increases the expression of several genes known to increase lifespan in model systems of aging.

It remains to be seen how many more pieces will slot in alongside REST in solving the puzzle of aging and dementia. For now, the team's findings offer new ideas for combating a disease that currently has no treatment.

"I'm sure there is something else at play that hasn't been seen or measured yet. REST won't be the end-all. But I think our work will help shift attention to this protective pathway in the aging brain and its role in the prevention of Alzheimer's and other dementing diseases," said Yankner.

"It's a new point of view on the problem."

This study was supported by the National Institutes of Health (Director's Pioneer Award DP1OD006849 and grants P01AG27916, R01AG26651, R01GM072551, P30AG10161, R01AG15819 and R01AG17917) and the Glenn Foundation for Medical Research.

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Amy Wagers—Focusing on stem cell biology

July 11, 2008

By Melissa Jeltsen
(From *Harvard Gazette*)

"No matter what, unless you drop it on the floor, you're going to learn something."

Twenty minutes after her weekly lab meeting is scheduled to begin, Amy Wagers rushes into a conference room on the fourth floor of the Joslin Diabetes Center, where her lab team sits, chatting around a long oval table.

"Sorry I'm late," she calls out, closing the door behind her. "Oh good, the food's here!"

Grabbing half a sandwich and a pickle off a catered tray, she simultaneously grabs a seat and motions for her team to begin its presentations. Lights out. In the darkened room, all eyes turn to the illuminated white screen. There, in all its monochromic splendor, glows an enlarged image of a blood-forming hematopoietic stem cell.

At 34, Wagers is already a Principal Faculty member of the Harvard Stem Cell Institute, an assistant professor in Harvard's new Department of Stem Cell and Regenerative Biology, and also has appointments at Harvard Medical School and Joslin.

In a remarkably short period of time, Wagers and her team have seen their efforts propel the lab from the ranks of start-ups to those of the firmly established. If her team's latest research into the development of muscle continues along the same track, it may some day be possible to harness the power of adult muscle stem cells to make future skeletal muscle transplant possible, offering real hope to patients with muscular dystrophy and other muscle degenerative diseases.

Embryonic stem cells are unique entities with the potential to develop into any cell type in the body. They can multiply without limit, serving as a repair

system by replenishing other cells. Because of these characteristics, they may prove to be invaluable tools for fighting human disease.

Once a week, Wagers meets with her two research assistants, three postdoctoral fellows, medical fellow, and graduate student who staff her lab. Regular meetings give the scientists a chance to present their developing data. Today, it also gives Wagers a chance to have lunch. Shooting out of one meeting early, she immediately heads to another. Much of Wagers' day is spent applying for grants and making phone calls.

Her titles bespeak formality, but dressed in blue jeans and a black fleece, her hair loose, Wagers could easily be mistaken for one of her own lab techs. But those placing their bets on the future of stem cell science look at accomplishments rather than age and titles. And last summer the W.M. Keck Foundation named Wagers a "Distinguished Young Scholar in Medical Research" providing her with $1 million to support her work with adult stem cells over five years.

Using Adult Stem Cells

There are two principal stem cell types, adult and embryonic. Embryonic stem cells are derived from a blastocyst — an early embryo — and are pluripotent, meaning a single stem cell has the ability to give rise to all of the various cell types that make up the body. Adult stem cells are found within adult tissues and are generally limited to differentiating into the various cell types of their tissue of origin.

The Wagers Lab primarily does research on two types of adult stem cells — blood-forming, or hematopietic, stem cells which generate all the red and white blood cells needed to deliver oxygen to body tissues, and muscle-forming, or myogenic, stem cells, which generate muscle fibers.

Bone marrow transplants, which are used to treat a range of diseases, including leukemia, lymphoma, and immunodeficiency, depend on blood-forming stem cells.

So far, blood-forming stem cells are the only adult stem cells scientists have been able to purify and use to treat human disease. However, scientists have reported isolating adult stem cells in the brain, blood vessels, skin, liver, and skeletal muscle, and are still searching for them in other parts of the body.

“[Adult stem cells] are very powerful for targets of tissue regeneration. We have been interested in making bone marrow transplants better and, similarly, making muscle cell transplant possible,” says Wagers.
Shane Mayack, a postdoctoral fellow in her third year with Wagers, studies the factors regulating hematopoietic cell mobilization. She says she interviewed with 15 labs before deciding to work with Wagers.

“I thought the types of questions she was interested in asking were really exciting and important to address, especially for the future of modern science,” Mayack says.

Because the lab focuses on asking fundamental questions about stem cells, such as what extrinsic factors influence their movement and reproduction, Wagers is building a platform of information that people in many fields can use, Mayack says.

Her Story
Over the hum of the projector, Wagers asks questions about what the lab technicians identified in the slides. They refer to the presentation as a “story.” Asked about it later, Wagers explains that a “story” is a series of scientific findings that come together to reveal something new.

Wagers’ own story began in Chicago, where she received her doctoral degree in immunology and microbial pathogenesis from Northwestern University. As an undergraduate, she signed up to be a bone marrow donor. In her senior year, she got an unexpected phone call — she matched a patient who needed a transplant. Although the patient decided not to go through with the procedure, Wagers was fascinated with the blood-forming stem cells that are utilized in the transplant. “I thought, wow, stem cells were really cool,” she recalls. She decided to do her postdoctoral fellowship training in stem cell biology, and went to Stanford to study with Irving Weismann, who since 2003 has been the director of Stanford’s Institute for Stem Cell Biology and Regenerative Medicine.

Wagers began her postdoc work studying the trafficking of blood-forming stem cells in the body. A year into her research, a rash of scientific papers were published that seemed to prove adult stem cells were pluripotent. With

the debate over embryonic stem cell research becoming super-heated, the new findings took on enormous political importance.
"Folks were taking the data and saying 'we don't need embryonic stem cells. The blood-forming stem cell is pluripotent, and can make anything; we'll just do bone marrow transplants and we'll cure heart disease,'" Wagers says.
She realized the systems she had already set up to study the trafficking of stem cells were perfect to study whether or not the cells were in fact pluripotent.

In 2002, she released a paper titled "Little Evidence for Developmental Plasticity of Hematopietic Stem Cells." Her paper was a direct refutation of previous papers published in high-profile journals, and disproved evidence from other labs suggesting that adult stem cells were pluripotent.

"The whole idea was that stem cells run around in your blood looking for damage, and then when they find it they just become whatever it is they need to become, magically," she says. "People still have this idea of stem cells. They're not magic. But people want them to be," she adds.

Embryonic and adult stem cells
"Studying adult stem cells informs embryonic stem cell research," Wagers explains.

"I study adult skeletal muscle stem cells — they know how to make muscle. I mean, they really know how to make muscle. That is all they do — they are professional muscle-making cells," she says.

In order to force an embryonic stem cell to make muscle, Wagers says, the best thing to do is to learn from the muscle stem cell. She says her lab would be transitioning into more embryonic stem cell research in the future.

"Our strategy is to inform ourselves in the adult [stem cell] and then take that to embryonic stem cells. We've just got to the level of sophistication with the adult [stem cells] that I think it's time to move," she says. "For human models of disease, there's a lot of opportunity [with embryonic stem cells] that is difficult to study using adult cells."

Because stem cell biology is a relatively new field, each question you answer gets you five more questions, Wagers says.

Being curious is one of the essential character traits of a scientist.

The most important trait according to Wagers? “Stubbornness,” she answers, laughing, “no, that’s not quite the right word. Perseverance. Ninety percent of what you’re going to do in science is not going to work. To be successful, you have to be able to forgive yourself for all the mistakes you’re going to make, and want to get up and do it again the next day. Am I going to learn something no matter whether it fails or works? I love those experiments. No matter what, unless you drop it on the floor, you’re going to learn something.”

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The three-minute reveal

October 21, 2014

By Bonnie Prescott
(From Harvard Medical School News via Beth Israel Deaconess Medical Center)

Delirium is a state of confusion that develops suddenly, often following an acute medical illness, a surgical procedure or a hospitalization. Although delirium is estimated to complicate hospital stays for more than 2.5 million elderly people in the U.S. each year, this common condition often goes undetected. The result can be serious complications with sometimes devastating consequences for vulnerable hospitalized elders.
Now, investigators at Harvard Medical School and Beth Israel Deaconess Medical Center have developed a three-minute diagnostic assessment for delirium and demonstrated that it is extremely accurate in identifying the condition in a group of older hospital patients.

In a study in the October 21 issue of the Annals of Internal Medicine, the authors report that the assessment, the Three-Minute Diagnostic Interview for CAM-Defined Delirium (3D-CAM), detected delirium with greater-than-90-percent specificity and sensitivity when compared with a reference standard. Of particular note, 3D-CAM was shown to be highly accurate in identifying delirium in patients with dementia, a group for whom diagnosis can be particularly challenging.

“Prompt recognition of delirium is the first step to timely evaluation and treatment, preventing complications and keeping older patients safe while in the hospital,” said lead author Edward Marcantonio, HMS professor of medicine and director of the Institute for Aging Research in the Division of General Medicine and Primary Care at Beth Israel Deaconess. “As growing numbers of older adults are being hospitalized, it’s critically important that doctors, nurses and other hospital care providers be able to recognize delirium. We wanted to develop a brief and simple method to make this easier to accomplish, and we are extremely happy with the 3D-CAM results. It appears that this easy-to-administer interview could significantly improve

detection of this common and morbid condition in vulnerable older hospital patients."

Delirium affects 30 to 40 percent of older medical patients and between 15 and 50 percent of older surgical patients. The condition remains distressingly under-recognized, with average detection rates of only 12 to 35 percent in most clinical settings. Moreover, the cases of delirium that are identified tend to be those of agitated patients who are disruptive to patient care, while the patients with hypoactive delirium, who are quiet and lethargic, often are undiagnosed.

The CAM (confusion assessment method) algorithm was originally developed in 1990 by the study's senior author Sharon K. Inouye, director of the Aging Brain Center in the Institute for Aging Research at Hebrew SeniorLife and HMS professor of medicine in the Division of Gerontology at Beth Israel Deaconess. To date, the CAM has been used in over 4,000 original studies and has been translated into more than 14 languages. The CAM diagnostic algorithm requires that the assessor determine the presence or absence of four key features of delirium: 1) acute change and fluctuating course, 2) inattention, 3) disorganized thinking and 4) altered level of consciousness. To be diagnosed with delirium, a patient must have features 1 and 2 and either 3 or 4.

"We have found that there are many different cognitive tests that the person rating the CAM can use to assess for these four features, and we've shown that the quality of the assessment makes a big difference in the accuracy of identification of delirium," explained Inouye. "The 3D-CAM is a major advance since it provides a brief, easy-to-administer approach that operationalizes the CAM algorithm in three minutes and provides highly accurate results compared to a gold-standard clinical assessment."

To develop the 3D-CAM assessment tool, the investigators reduced an original list of 160 questions and observations down to 20 items. To do this, each item was evaluated using a modern measurement approach called item response theory, which is also used to create educational tests such as the SAT. Only the most informative items for delirium diagnosis were selected for inclusion in the final 3D-CAM assessment. Examples included patient questions about symptoms ("Have you been feeling confused?"), structured observations ("Did

the patient fall asleep during the interview?") and cognitive testing of attention and orientation.

After selecting the 20 best items and assembling the 3D-CAM interview, the authors embarked on a prospective validation study by enrolling 201 patients over age 75 who were hospitalized in Beth Israel Deaconess's general medicine service between 2010 and 2012.

The authors first conducted a gold-standard clinical assessment for delirium and dementia, in which an experienced clinician conducted a full patient evaluation including a cognitive exam, a review of the patient's medical records and conversations with the patient's nurse and family caregiver. This assessment took between 60 and 90 minutes and resulted in data similar to a doctor's initial evaluation.

An expert panel then reviewed all of the data and made a judgment as to the presence or absence of delirium and dementia. The gold-standard assessment determined that 42 of 201 participants (21 percent) had delirium, 88 percent of which was hypoactive or "quiet." They also found that 56 patients (28 percent) had dementia prior to being admitted to the hospital. In some cases, patients had both delirium and dementia. Research assistants subsequently administered the 3D-CAM assessment without knowledge of the gold-standard results.

"First, we timed the test, and found that, on average, it did indeed take only three minutes to administer," said Marcantonio. The researchers then compared the results of the 3D-CAM with the gold-standard assessment and found that the 3D-CAM correctly identified 95 percent of the patients with delirium (95 percent sensitivity) while correctly identifying 94 percent of patients without delirium (94 percent specificity). When a second research assistant went back and administered the 3D-CAM without knowledge of the first test results, the answer was the same 95 percent of the time (95 percent reproducibility.) Importantly, the 3D-CAM performed nearly as well in patients with dementia, which is a particularly challenging group in which to diagnose delirium.

"Given its brevity, ease of use, and excellent accuracy and reproducibility, the 3D-CAM could be an important component of a program to improve recognition and management of delirium in older hospitalized adults," said

Marcantonio. Added Inouye, "Hospitals throughout the world are increasingly recognizing the importance of delirium as a major preventable adverse event. The 3D-CAM holds great promise as an important advance for delirium care specifically and for acute care of elders more generally."

The 3D-CAM instrument and instructions are available at **www.hospitalelderlifeprogram.org**.

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Making old hearts new

2013

By Johnathon Henninger
(From *Science In The News*)

Although the heart is commonly thought of as something that causes us emotional joy and pain, while also providing us with the urge to make reckless decisions, we have to give it more credit. In actuality, this incredible organ will beat more than 2.5 billion times in an average adult lifetime, pumping 5-6 quarts of blood throughout the body every minute [2]. This vital function provides oxygenated blood to the entire body, ensuring that our other organs can do their jobs. As with any machine, however, constant use and degrading maintenance mechanisms can lead to decreased function. Debilitating disorders like heart disease and heart failure are on the rise in an aging population; this has given researchers powerful motivation to study these disorders with the hope of finding potential therapies.

Heart Regeneration and Aging
Many of our organs, including the skin, skeletal muscle, intestines, blood, and even the liver, can naturally regenerate. In some cases, this regeneration ability is due to resident adult stem cell populations which have two main properties: they are able to self-renew, ensuring that we don't lose them, and they have the ability to become any of the cell types found within their respective tissues. For instance, the most well characterized adult stem cell, the hematopoietic (blood) stem cell, is able to differentiate, or become more specialized, into all the cell types of the blood, including red cells, white cells, and platelets.

Scientists have been searching for resident adult stem cell or progenitor cell populations in the heart, but the majority of the evidence indicates that these populations are either very rare or do not exist. Whether these cell populations exist or not, research has made it clear that our hearts do regenerate, albeit at an extremely slow pace, most likely due to the division of existing, mature cardiomyocytes (heart muscle cells). In a fascinating study, researchers cleverly used the historical nuclear bomb tests of the 1950's to look at human heart regeneration. These nuclear tests released many

radioactive isotopes into the atmosphere, including carbon-14. This carbon was incorporated into the tissues of people living at the time. By observing the levels of carbon-14 in these individuals over time, the researchers were able to demonstrate that the heart does indeed replace itself very slowly [3].

Whether new cardiomyocytes are generated throughout our lifetimes remains an area of intense research. Interestingly, studies in animal models, including zebrafish and salamanders, have demonstrated that these creatures are able to robustly regenerate heart tissue. For instance, you can simply cut away 20% of a zebrafish's heart, and, within a few weeks, it will completely regenerate [4]. In mammals, the situation is entirely different. After injury to a mouse or human heart, the natural response is to generate permanent fibrous scar tissue that may impede heart function. It is important and promising to note, however, that zebrafish also produce scar tissue during heart regeneration, but for some unknown reason, this scar tissue is eventually degraded and replaced with healthy heart tissue. This suggests that sometime during our evolution, we either lost the ability to regenerate the heart, or the ability still exists but is repressed.

These results are exciting because they suggest that we may be able to enhance heart regeneration through some type of therapy, which is desperately needed. Heart failure, or the inability of the heart to pump enough blood to support other organs, is the primary cause of more than 55,000 deaths per year in the U.S., and it is estimated that this disorder costs the U.S. $34.4 billion dollars per year [5]. One of the main causes of heart failure is cardiac hypertrophy, or the growth in size of individual cardiomyocytes. Due to the enlargement of individual cells, the heart has to work harder to pump less blood, which ultimately leads to the inability to properly support other organs. Unfortunately for us, cardiac hypertrophy naturally increases with age, but therein lies the potential for discovery. By comparing old and young individuals, scientists have been trying to identify factors that can return the heart to a youthful state, with the ultimate hope of identifying factors that promote natural regeneration.

Parabiosis

One can imagine that the simplest way to rejuvenate an aging heart would be through treatment with some type of drug or protein that could easily travel through the blood. Although cell therapies, including reprogramming cells from other parts of the body into heart muscle, have gained significant

research interest, they have considerable technical and regulatory hurdles to overcome. To help identify factors that could promote rejuvenation or regeneration of an aging heart, some researchers have turned to a centuries old technique known as parabiosis, or the surgical joining of two animals to develop a single, shared circulatory system (Figure 1 top). By physically joining old and young mice together, parabiosis allows researchers to expose the old heart to a youthful blood environment, or conversely, a young heart to an old environment. The beauty of this technique is two-fold. First, it does not require that you know exactly what is in the blood to see an effect, and second, any factor that you may find is already natural to the system, increasing the likelihood that it may be safe to use.

Parabiosis experiments have already been used to show that exposure to a youthful blood environment can greatly enhance muscle and neural regeneration in old mice. Recently, Richard Lee, Amy Wagers, and their colleagues at the Harvard Stem Cell Institute extended this technique to look at cardiac hypertrophy in aging mice, a study that gained considerable media attention [1]. Remarkably, they found that, when exposed to a youthful blood environment, cardiac hypertrophy was reversed in old mice. The entire heart in the old mouse significantly decreased in size after one month. Importantly, they showed that this was not due to changes in blood pressure or behavior due to the parabiosis surgical procedure. It is also interesting to note that the young mouse hearts did not increase in size during this procedure. This suggests that the old mouse blood is simply lacking the factors that cause this effect rather than containing factors that actively increase heart size.

Of course, it would not be practical to start joining the circulatory systems of children and teens to aging adults, therefore the researchers set out to find the factors responsible for this remarkable change in heart size. Initially, they did not find any differences in metabolic factors; however, when they compared the protein composition of young blood to old blood, they found 13 factors that were significantly different. One factor, which they decided to follow up on, was the protein, growth differentiation factor 11 (GDF-11).

What is Growth Differentiation Factor 11?

GDF-11, also known as bone morphogenetic protein 11 (BMP-11), is a protein that belongs to a family of cell signaling molecules known as the transforming growth factor beta (TGF-b) superfamily. This family of proteins is important

for regulating embryonic development and adult tissue. GDF-11 is similar in structure to myostatin, a protein well known to regulate skeletal muscle size. Using purified protein, the researchers in this study treated old mice with GDF-11 and were able to reproduce the findings of the parabiosis experiments, namely the reduction of cardiac hypertrophy (Figure 1 bottom). The cardiomyocytes themselves, when treated with GDF-11, had reduced expression of proteins that lead to increased cell growth, and interestingly, GDF-11 only had an effect on age-related cardiac hypertrophy. When hypertrophy was induced in young mice, this protein had no effect.

Caveats and Limitations

These remarkable findings suggest that purified GDF-11 could be used in older individuals to help reduce age-related cardiac hypertrophy. Treatment with this protein could potentially reduce the incidence of heart failure; however, we also must be aware of certain caveats and limitations in this study.

Since this study was conducted in mice, it is not guaranteed that this protein will work similarly in humans. Significant testing will need to be done before there are broad human clinical trials. The study also only considered naturally aging hearts with no indication of whether this protein could help with any heart-related diseases, which are common causes of heart failure. Moreover, it is not clear from the study whether heart function was actually improved after treatment with GDF-11. The researchers did not test heart rate, blood pressure, or the ejection fraction, a measure of how much blood volume the heart pumps in one contraction, in mice only treated with GDF-11. Although cardiac hypertrophy was significantly reduced, this is not the only significant factor regulating heart function. For instance, it is known that as we age, our heart muscle cells increase their ploidy, or the number of copies of the genome that they each contain. Although the majority of the cells in our body contain two copies of the genome, as the heart gets older and cardiac hypertrophy takes place, many of the cardiomyocytes contain anywhere from 8 to 16 copies of the genome, which may significantly alter their biology. This study did not investigate the ploidy of the cells, so it is unclear how well GDF-11 returns the heart to a ‘youthful’ state. With respect to GDF-11, it is also clear that this is not the only factor having an effect, indeed, the researchers found 12 other potential factors that could be interesting to study. Finally, GDF-11 is highly produced in the spleen, and it is possible that treatment with this protein in older mice could affect other organ systems.

The exciting finding that GDF-11 can reduce age-related cardiac hypertrophy will certainly lead to a host of additional studies down the road. This study highlights the fact that scientists can discover rejuvenation or regenerative factors through interesting techniques like parabiosis. Investigating differences between old and young animals could potentially lead to a variety of therapies that may ultimately help our aging population.

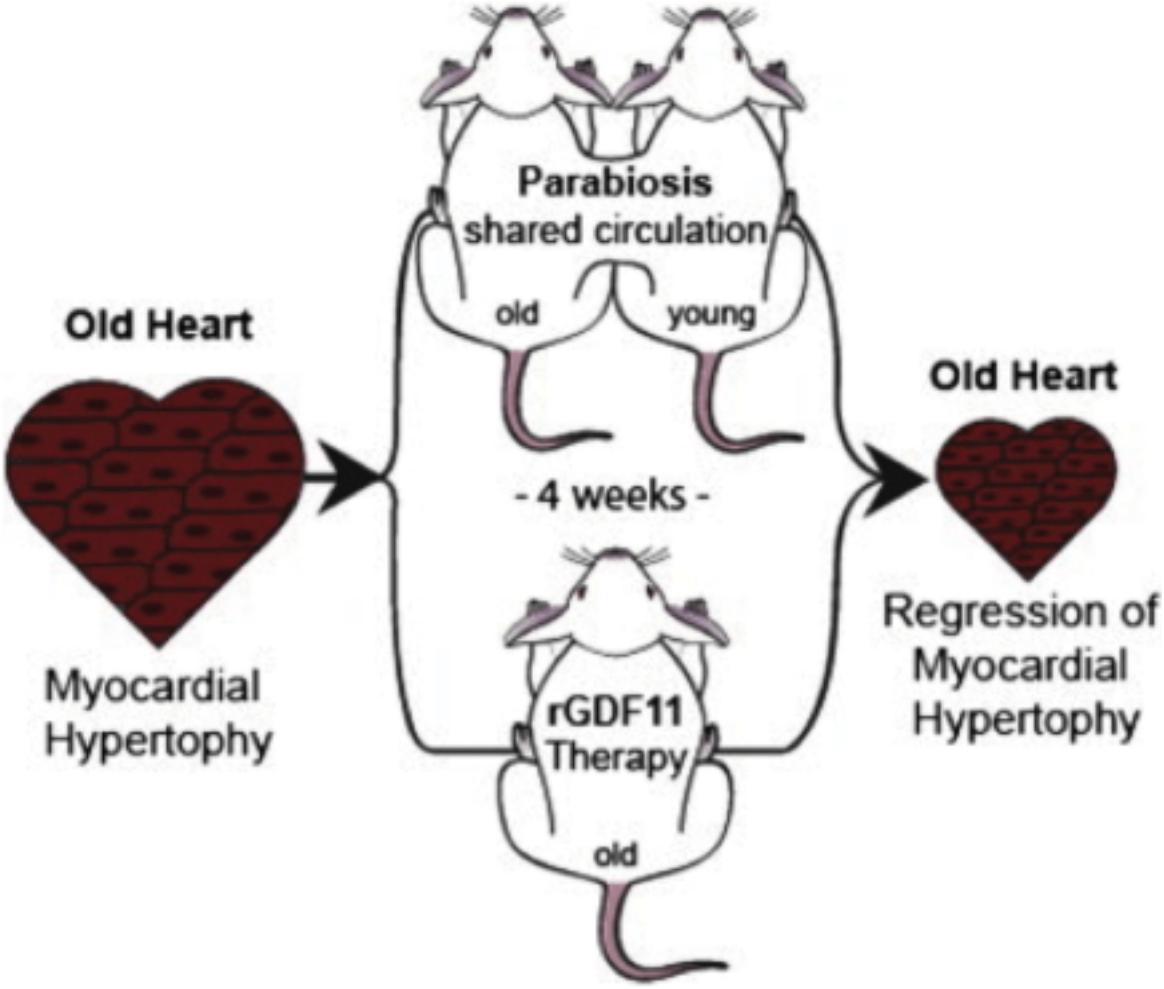

Figure 1: *This figure shows an overview of the paper published in the journal Cell by researchers from the Harvard Stem Cell Institute. At the top, a young and old mouse are surgically joined by parabiosis, and after 4 weeks time, researchers found that the old mouse heart had decreased in size. When they examined the blood of old and young mice, they found a protein, GDF-11, that when injected into old mice had the same effect on heart size (bottom). [1]*

Jonathan Henninger is a graduate student in the Biological and Biomedical Sciences Program at Harvard University.

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Study shows activity increases life expectancy

November 12, 2012

By Aemilia M. Phillips
(From *The Harvard Crimson*)

Staying active and maintaining an average body weight can lead to a 7.2-year gain in life expectancy, according to a study released by researchers at Brigham and Women's Hospital last week.

The study, conducted in collaboration with the National Cancer Institute, surveyed 650,000 individuals of all ethnicities and body mass indexes, aged 21 – 90. Results show that gains in life expectancy are much greater for those who begin regular physical activity earlier in life.

"Those active at a young age also tend to be more active as they grow older, so it is good to start being active at a young age," wrote Harvard Medical School professor and senior author of the study I-Min Lee in an email.

Despite the busy schedules of college students that can make it difficult to follow an exercise regiment, exercise is crucial even at this early age, according to Meir Stampfer, professor of nutrition and epidemiology at the Harvard School of Public Health.

"People have a tendency to only think of years added on when they're 89 years and older. But for a young person, the benefit of physical activity might be preserved vitality," he said.

Finding opportunities to exercise can be difficult in an increasingly sedentary society, according to the study. The report examined "brisk walking," an accessible alternative for those intimidated by intense fitness regiments.

Lee's work shows that someone who walks 150 minutes per week, the amount of exercise recommended by the federal government, will add 3.4 years to someone's life expectancy. A lesser workout of 75 minutes per week would add 1.8 years.

“I think people neglect the benefits gained from brisk walking. It seems daunting for people [but it’s] just a matter of prioritizing,” said Stampfer.
One of Stampfer’s studies also explores the benefits of exercise for people with varying states of health. This study involved monitoring physical activity in prostate cancer patients.
“Exercise prevents illness, but is also beneficial during illness,” Stampfer said. “In the prostate cancer patients who exercised, there was a decreased death rate compared to those who did not.”
In Lee’s study, the results were consistent for those with higher weights.
“Many individuals in the US are overweight or obese. For such persons, it is often difficult to reduce weight,” wrote Lee in an email. “What is encouraging is that our study shows that by being physically active, even overweight/obese persons can increase their life expectancy compared to someone their weight who is not active.”

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Living Longer with a Healthier Immune System

By Anna Kuchnir
(From *Science In The News*)

While man's eternal search for "the fountain of youth" continues, a study published recently in the Proceedings of the National Academy of Sciences suggests that we (at least the gourmands among us) may not like what we find. Scientists have known for decades that reducing the amount of food consumed can extend the lifespan of multiple organisms, ranging from yeast to rats. Exactly how reducing the number of calories consumed prolongs life is unknown, but theories abound. Some researchers believe that ingesting fewer calories slows down the rate at which our bodies metabolize, or break down, food and turn it into energy, thereby slowing the aging process. Others believe that decreased calorie consumption sets loose fewer free radicals, the harmful particles generated as a side effect of metabolism. The most recent theory, proposed by researchers at the National Institute on Aging (NIA), is that long term calorie cutting, or caloric restriction (CR), prolongs life in part by delaying the aging of the immune system.

One of the major health problems affecting the elderly is an increased susceptibility to infections and greater severity of disease. For instance, the yearly flu epidemic is rarely more than an inconvenience for a healthy young adult, while to an elderly person it can be life threatening. One of the many possible reasons why the elderly become more frequently and more seriously ill than the young is a gradual decline in the effectiveness of the immune system as the body ages.

What is the immune system and what does it do for us?
Your body's immune system is responsible for fending off pathogens, or organisms that cause disease, such as bacteria, viruses and parasites. This complex and finely tuned system employs many different strategies to keep pathogens from gaining a foothold in the body and causing disease. The NIA study focused on a particular branch of the immune system, a population of immune cells called T cells, which circulate in the blood stream searching for invading pathogens. So-called "naïve T cells" are those that have never interacted with a pathogen. When a naïve T cell finds a pathogen, it signals for the destruction and clearance of the invader. The naïve T cell then turns into a

"memory T cell", which is capable of remembering and responding to that particular pathogen forever, enabling a swifter and more powerful response than can be provided by a naïve T cell.

T cells are made in a gland called the thymus. The thymus is largest in size and most active at birth, pumping out many T cells. As we age, the size and T cell-making capacity of the thymus gradually and steadily shrinks. The thymus of an elderly person generates far fewer naïve T cells than that of younger one. Additionally, the immune system of an elderly person has encountered many different pathogens over a lifetime, and more naïve T cells have become memory T cells. Since fewer naïve T cells are made by the thymus and a large portion of T cells have been converted into memory cells, the variety of new pathogens that the immune system of an elderly person can recognize is reduced. This slow decline in the ability to fight off new infections, or immune senescence, may be partly responsible for the increase in the frequency and severity of infections later in life.

The effect of reduced calorie intake on the immune system

To determine whether the life-prolonging effects of caloric restriction (CR) in monkeys were due in part to a delay in the onset of immune senescence, researchers at the NIA fed young adult monkeys either a normal diet or 30% less of the same diet, thereby decreasing caloric intake while maintaining adequate nutrition. Both sets of monkeys were maintained on their respective diets for 10 to 14 years, at which time, the monkeys' immune systems were comparable to those of 60 to 70 year-old humans. The functioning of the monkeys' immune systems, specifically of their T cells, was then tested over a period of three years.

In every test performed, T cells from CR monkeys showed fewer signs of aging than those of monkeys maintained on a normal diet. The CR monkeys had a higher level of naïve T cells than monkeys on the normal diet and these T cells responded to pathogens like those of a younger animal. A healthier immune system may mean that the CR monkeys can fend off pathogens and stay free of disease better than monkeys on a normal diet, although this has yet to be directly tested.

Why do we need to worry about aging and disease *right now*?

Aging and age-related diseases are a big concern for the medical and general communities alike. Statistics show that the number of people aged 65 and

over is increasing at a faster rate than the rest of the population. It is anticipated that by 2029, people 65-74 years of age will make up 10% of the population. While 10% does not sound terribly alarming, we should keep in mind that facilities and professionals, such as nursing homes and health care providers, will have to grow in step with the aging population. Projections show that in the future, there is likely to be a shortage of health professionals, such as nurses and pharmacists, needed to take care of the elderly population. Additionally, occupancy rates for nursing home beds are already over 90% in a number of states. Looking ahead to the next few decades, it becomes clear that certain adjustments will have to be made to accommodate the elderly.

Scientific advances that can either delay or decrease immune senescence may one day enhance both quality and duration of life by helping the immune system fight off disease. So, is CR the path to a long, healthy life? While the results of this and other studies suggest that caloric restriction may be beneficial to long term health, cleaning out the fridge and going hungry may be premature. Waiting for scientists to unravel the mechanism responsible for maintaining the immune system in a youthful state while leading a healthy lifestyle, seems a more attractive option.

— *Anna Kushnir, Harvard Medical School*

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http://sitn.hms.harvard.edu/flash/2007/issue30/

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Forever young: How long can humans live? (video)
October 22, 2014
Science In The News
http://sitn.hms.harvard.edu/seminars/2014/foreveryoung/

Hospital elder life program (HELP)
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Blood young mice shown to reverse aging
Carolyn Y. Johnson
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Wagers laboratory
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The IOM cognitive aging report
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Preventing falls in hospitals
Agency for Healthcare Research and Quality
http://www.ahrq.gov/professionals/systems/hospital/fallpxtoolkit/index.html

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