THE NIH

Word on Health

Consumer Health Information Based on Research from the National Institutes of Health

April 2004

New Fronts in Alzheimer's Research

Potential for Prevention, Earlier Detection

An estimated 4.5 million older people currently have Alzheimer's disease, and researchers predict that by 2050 the number could nearly triple to 13.2 million. But several promising recent developments in the study of Alzheimer's disease may one day lead to new methods of diagnosing, preventing and slowing the disease's progress. These include a new way to look inside the brains of people with the disease as well as new methods for preventing buildup of a protein, called amyloid, which forms plaques that scientists believe may be involved in causing Alzheimer's symptoms.

Detecting Alzheimer's disease at an earlier stage is a major research goal. In one compelling study that may lead to crucial earlier diagnosis and prevention efforts, scientists created a compound that allows them to use positron emission tomography (PET, an imaging tool used to view body function and diagnose disease) to look at early signs of the abnormal clumps of amyloid proteins (called plaques) that form in the brains of people who have Alzheimer's. Called Pittsburgh Compound B, the substance was developed by researchers at the University of Pittsburgh School of Medicine and Sweden's Uppsala University. Their work — aimed at being able to intervene sooner in people with Alzheimer's, possibly as the plaques begin to form — was supported in part by a grant from the National Institute on Aging (NIA), part of NIH.

"We are moving toward earlier and earlier detection of Alzheimer's disease," notes Dr. Neil Buckholtz of NIA's Neuroscience and Neuropsychology of Aging Program. "Research at Pittsburgh and elsewhere is bringing us closer to the day when we can look in the brain, see if the characteristics of the disease are there, and then develop therapies that hopefully can change the progression of the disease and its clinical course." Buckholtz heads a new effort in which NIA is bringing together government, academic and industry scientists to accelerate the use of imaging in research and, ultimately, in the diagnosis and treatment of Alzheimer's disease.

Stopping Alzheimer's Plaques

Understanding the formation and activity of beta amyloid, the primary component of Alzheimer's plaques, is a major focus of research. Investigators continue to work intensely to figure out the process by which amyloid precursor protein (APP) is snipped by enzymes to release the beta amyloid fragments that clump together to form the sticky plaques. One of these enzymes is called beta secretase. In a mouse study at Johns Hopkins University School of Medicine, scientists developed a transgenic mouse in which the gene for BACE1, a beta secretase enzyme, is eliminated, or "knocked out." The scientists found that with BACE1 eliminated, beta amyloid protein fragments were no longer produced in brain cell cultures of the knockout mice. This finding has resulted in a focus on the design of drugs that could inhibit BACE1 activity.

Earlier NIH-supported studies also discovered potential mechanisms to clear amyloid plaques. Researchers at the Salk Institute and their colleagues elsewhere found that gene transfer of an enzyme may help clear out plaques. The human enzyme, neprilysin,

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was injected into the brains of transgenic mice with human amyloid plaques. After the treatment, the enzyme appeared to help degrade existing plaques and help reduce growth of new plaques.

Teams of scientists in New York and California have suggested that astrocytes, one of the three principal types of brain cells, can break down amyloid and eliminate it from the brain. Astrocytes nourish and protect neurons in the brain and are located close to brain plaques. Researchers have a theory that some astrocytes may be impaired, making them unable to, in Alzheimer's case, completely clear amyloid from the brain.

"Our studies on the biology of Alzheimer's disease give us an increasingly clear picture of what happens in the brain and how the communications among cells are compromised," says Dr. Stephen Snyder of NIA's Etiology of Alzheimer's Section. "With this knowledge, scientists are now able to demonstrate ways in which the culprits involved in Alzheimer's might be interfered with and even eliminated."

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Treatments Under Study

Some research is turning to old drugs for their potential promise in treating Alzheimer's disease. In one study at Massachusetts General Hospital, scientists funded by NIA and NIH's National Institute of Mental Health (NIMH) examined a rarely used antibiotic that seemed to dissolve the plaques. The drug, clioquinol, was chosen because it draws zinc and copper from the body. Some scientists believe that when amyloid is

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The Word on NIH

The National Institutes of Health (NIH) is one of the world's premier biomedical research organizations. A government agency within the U.S. Department of Health and Human Services, NIH is composed of 27 Institutes and Centers, each with its own research focus.

NIH supports and conducts medical research to understand how the human body works and to gain insight into diseases and disorders. NIH translates research results into medical interventions and distributes current medical information to patients, health care providers and the general public.

NIH provides leadership and financial support to researchers in every state and throughout the world, investing billions of dollars in scientific research each year. About 10% of NIH's budget supports over 2,000 research projects in its own laboratories. Most of its budget, however, is awarded through almost 50,000 competitive grants and contracts to researchers at over 2,800 hospitals, universities, medical schools, and other research institutions.

NIH's own scientists, and scientists working with support from NIH grants and contracts, have made countless medical advances in the last century. More than 100 of these scientists have received Nobel Prizes in recognition of their achievements.

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A Word to the Wise...

What Are the Symptoms of Alzheimer's Disease?

Alzheimer's disease begins slowly. At first, the only symptom may be mild forgetfulness. People with Alzheimer's may have trouble remembering recent events, activities, or the names of familiar people or things. Simple math problems may become hard to solve. Such difficulties may be a bother, but usually they are not serious enough to cause alarm.

However, as the disease goes on, symptoms are more easily noticed and affect a person's ability to do everyday tasks, eventually becoming serious enough to cause people with Alzheimer's disease or their family members to seek medical help. For example, people with the disease get to the point where they forget how to do simple tasks, like brushing their teeth or combing their hair. They can no longer think clearly. They have problems speaking, understanding, reading, or writing. Later on, some people with Alzheimer's disease may become anxious or aggressive, or wander away from home. Eventually, patients need total care.

The seven warning signs of Alzheimer's disease are:

1. Asking the same question over and over again.
2. Repeating the same story, word for word, again and again.
3. Forgetting how to cook, or how to make repairs, or how to play cards — activities that were previously done with ease and regularity.
4. Losing the ability to pay bills or balance the checkbook.
5. Getting lost in familiar surroundings, or misplacing household objects.
6. Neglecting to bathe, or wearing the same clothes over and over again, while insisting that they have taken a bath or that their clothes are still clean.
7. Relying on someone else, such as a spouse, to make decisions or answer questions they previously would have handled themselves.

Source: Alzheimer's Disease Education & Referral Center, a service of NIH's National Institute on Aging

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present, it attracts zinc and copper, paving the way for destructive brain plaques to form. The team found that treatment with clioquinol reversed the deposition of amyloid in the brains of mice with AD. Despite these encouraging findings, researchers need to proceed very cautiously when investigating this compound for human use, as small amounts of these metals are necessary for many chemical reactions in the body.

Other widely used medications are currently being tested. One population study published two years ago found that people with elevated levels of a compound called homocysteine in their blood had nearly double the risk of developing Alzheimer's. Blood levels of homocysteine can be reduced by increasing intake of folic acid (or folate) and vitamins B6 and B12. Researchers are now examining whether lowering homocysteine levels in the blood with B vitamins and folate might reduce the risk of Alzheimer's. Results of this trial are expected in 2006.

Researchers are also studying simvastatin, a cholesterol-lowering drug, in people who already have Alzheimer's disease to see if the drug might slow down the rate of Alzheimer's progression. Earlier studies have associated the use of cholesterol-lowering drugs in this class with a positive impact on brain function and reduced risk of Alzheimer's. Results of this trial are expected in 2006.

Where Research Is Headed

In addition to looking for ways to diagnose and treat Alzheimer's earlier, researchers are examining lifestyle and genetic factors that might affect a person's chances of developing the disease.

Diet and exercise, for example, are under close study. Another interesting avenue being explored is the influence of formal education on a person's memory and learning skills. Researchers are trying to determine if the amount of formal education a person has somehow affects the brain so that it facilitates a person's potential to work around or reduce the effect of the brain abnormalities associated with Alzheimer's.

To examine how heredity and genes play a role in Alzheimer's, NIA recently stepped up its Alzheimer's Disease Genetics Initiative. The initiative teams up NIA, academic researchers at Indiana University and Columbia University, the NIA-supported network of 29 Alzheimer's Disease Centers around the U.S., and the Alzheimer's Association. Scientists hope to create a large bank of data and blood cells containing genetic material from 1,000 families in which at least two living siblings have been diagnosed with late-onset Alzheimer's disease. By studying families with the late-onset form of Alzheimer's, the most common form

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of the disease, scientists hope to understand more about how Alzheimer's develops as well as new methods of prevention and treatment. To find out how to participate in the study, families should contact the National Cell Repository for Alzheimer's Disease (NCRAD) toll-free at 1-800-526-2839 or visit the website www.ncrad.org.

"Finding the additional risk factor genes for late-onset AD is critically important to move our understanding forward," says Dr. Creighton Phelps, director of the program that supports the NIA Alzheimer's Centers. "Working intensively with a large number of families will, we hope, allow scientists to find these genes sooner rather than later."

Scientists still need to learn a lot more about what causes Alzheimer's disease. By studying genetics, education, diet, environment, and other factors to learn what role they might play in the development of this disease, researchers hope they will find ways to diagnose, prevent or even treat this devastating illness.

To keep up to date on new developments, visit http://www.alzheimers.org/nianews/nianews.html or subscribe to the ADEAR Center e-mail alerts at http://www.alzheimers.org/maillist.htm.◆

—Written by NIH Word on Health and NIA staff

For a more detailed description of Alzheimer's, get the free booklet *Alzheimer's Disease: Unraveling the Mystery*. This and other free information is available from the Alzheimer's Disease Education and Referral (ADEAR) Center online at www.alzheimers.org or toll-free at 1-800-438-4380. ADEAR information specialists can also answer questions and provide other publications about Alzheimer's disease and research.

For information on participating in Alzheimer's disease clinical trials, please visit the Alzheimer's Disease Clinical Trials Database, a joint project of the U.S. Food and Drug Administration (FDA) and NIA, at http://www.alzheimers.org/trials/index.html or http://clinicaltrials.gov/.

Alzheimer's Impact Growing; Caretakers Need Love, Too

The most dramatic increase in the number of people with Alzheimer's disease will be in the population age 85 and older, when about 8 million cases of the disease are expected in this group by 2050. With the impact of Alzheimer's disease growing as more of the U.S. population heads into their senior years, the National Institute on Aging (NIA), part of NIH, is conducting research aimed at making sure that people who take care of those with Alzheimer's get help, too.

Not only does a diagnosis of Alzheimer's have an enormous effect on the person with the disease, but the progressive nature of the disease also places a tremendous strain on the person's family, friends and especially the primary caretaker. Depression and high levels of stress are seen commonly in family caregivers of people who have Alzheimer's, according to a multi-site study called REACH, or Resources for Enhancing Alzheimer's Caregiver Health. REACH is funded by NIA and the National Institute of Nursing Research (NINR), another component of NIH.

In a separate report, study investigators found that Alzheimer's caregivers could benefit from bereavement and counseling services before death of the family member, because of the long periods of steady decline associated with the disease. Education on pain control, coping and other social support could also help reduce the burden of caregiving and depression, scientists say.

"As we search for ways to treat and ultimately prevent Alzheimer's disease, we must continue to provide information and strategies to help caregivers and policymakers cope with the social and behavioral aspects of the disease," says Dr. Sidney Stahl of NIA's Behavioral and Social Research Program.

For more information for family members and friends of people with Alzheimer's, a free booklet, *Caregiver Guide*, is available from NIA. The guide, NIH publication #01-4013, is available in both English and Spanish. Another free resource, "Home Safety for People with Alzheimer's Disease," is also available. To receive these booklets or fact sheets and other information on Alzheimer's without charge, contact the Alzheimer's Disease Education and Referral (ADEAR) Center at www.alzheimers.org or call toll free 1-800-438-4380.

Men Can Get Osteoporosis Too

Most people don't think that men develop osteoporosis. This disease, in which bone becomes thin and fragile and can fracture easily, is mostly associated with women. Doctors don't often discuss the issue with their male patients. But men can get the hip and other bone fractures that come with osteoporosis, too, and it's no less painful or debilitating for them than it is for women.

Men are usually diagnosed with osteoporosis only when they have fractured a bone. Men don't generally experience the rapid bone loss in their 50's that women do, but by age 65 or 70, they are losing bone mass at the same rate as women. Hip fractures occur at older ages in men, which might explain why men who break a hip are more likely to die of complications than women. More than half of all men who suffer a hip fracture go from the hospital to a nursing home, and 79 percent of those who survive for one year still live in nursing homes or intermediate care facilities.

Studying Osteoporosis in Men

Scientists are trying to learn more about the causes, diagnosis, treatment and prevention of osteoporosis and its related fractures in men as well as in women. In 1999, NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and two other NIH components, the National Institute on Aging (NIA) and the National Cancer Institute (NCI), launched a seven-year study that is following 5,700 men, age 65 or older. "Mr. OS," as it is called, aims to determine the extent to which the risk of fractures in men is related to bone mass and other factors such as their bone structure, lifestyle and tendency to fall.

In the NCI component of "Mr. OS," scientists are trying to answer the question of whether having a high bone mass is associated with an increased risk of prostate cancer. In women, if you have a high bone mass, you have a higher risk of getting breast cancer. Both types of cancers are thought to be associated with your whole lifetime exposure to the sex hormones your own body makes.

NIH's National Heart, Lung, and Blood Institute (NHLBI) is also supporting a part of "Mr. OS" that is looking at the role of sleep in the health of older men.

Treatment and Prevention

Men are more likely than women to have a high risk of fracture due to secondary causes, like a specific disease (such as celiac disease, in which a person's intolerance to a protein found in wheat and other grains interferes with their intestinal absorption of calcium) or taking medications that can affect bone mass (like the steroids used to treat asthma, rheumatoid arthritis and other diseases). Knowledge of the diseases and conditions that can affect bone mass can help to prevent men as well as women from reaching the point of fracture before diagnosis.

Getting enough calcium is very important for preventing osteoporosis. Adults 19 - 50 years old need 1,000 milligrams (mg) of calcium every day; those over 50 need 1,200 mg. The best way to get enough calcium is through your diet. Buy fortified orange juice and cereals, and eat lots of green leafy vegetables and low-fat dairy products like cheese, milk, ice cream and yogurt.

You should also get enough vitamin D. If you spend 15 minutes outside in the sun each day, your body should make enough on its own. If you have limited sun exposure, scientists currently recommend 200 to 400 international units (IU) if you are under age 70 and 600 if you are over.

It's also important to do regular weight-bearing exercise, such as walking, jogging, stair-climbing, tennis, weight-training and dancing. These exercises may strengthen your bones and may also help with your balance. That will reduce your risk of falling and thus reduce your chances of breaking a bone.

If you already have osteoporosis, doctors are prescribing most of the same medications that they are giving to women. Alendronate (brand name Fosamax®) and risedronate (brand name Actonel®) both now come in a once-a-week pill. But they can cause problems with your stomach or esophagus (the tube that connects the mouth with the stomach) if not taken exactly as directed. The Food and Drug Administration has approved teriparatide (brand name Forteo®) only for those who are at high risk of fracture; the drug must be injected daily for no longer than two years. Be sure to talk with your doctor about your options.◆

—Written by Bobbi Bennett

For more information about osteoporosis, go to http://www.osteo.org/ or contact the NIH Osteoporosis and Related Bone Diseases~National Resource Center at:

NIH ORBD~NRC
1232 22nd Street, NW
Washington, DC 20037-1292
Phone: 800-624-BONE or 202-223-0344
TTY: 202-466-4315
FAX: 202-293-2356
E-Mail: orbdnrc@nof.org

Understanding Risk

What Do Those Headlines Really Mean?

Lately it seems to happen almost every day — you hear about a new result of medical research on television or read about it in the paper. Often it's about your "risk" or chance of having a disease or health problem. After reading the story did you worry because the numbers made your chance of getting sick seem high? Or, did the story confuse you because you remember a news item not too long ago about the same health problem, but with a very different finding? What does it all mean? Which stories can you trust?

A new publication from NIH's National Institute on Aging (NIA) might be able to help. *Understanding Risk: What Do Those Headlines Really Mean?* explains different types of scientific studies, different types of risk, and suggests some questions you can ask yourself when reading or listening to the next story about research results.

Types of Studies

The first step in understanding medical research reports is to know the difference between types of research studies. Some projects involve *laboratory studies* using microscopic cells or creatures such as yeasts, viruses, or bacteria. Some of these studies may not immediately seem relevant to humans, but very often studying other organisms helps us to understand our own bodies and what can go wrong with them to cause diseases and disorders.

Some studies involve animals like mice which can serve as a "model system" for how the human body works. Investigators looking at human diseases, though, eventually need to turn to studies in people.

When studying people, scientists often use *observational studies*. In these, researchers keep track of a group of people for several years without trying to change their lives or provide special treatment. This can help scientists find out who develops a disease, what those people have in common, and how they differ from the group that did not get sick. What they learn can suggest a path for more research. However, observational studies have certain weaknesses. Sometimes differences between groups are caused by something the investigators are not aware of. Only further research can prove for sure whether their finding is the actual cause of illness or not.

A *randomized controlled clinical trial (RCT)* is considered the best way to learn whether a certain treatment works or not. A clinical trial can involve thousands of human volunteers. They are assigned to two or more study groups by chance (randomly). One of the groups, the control group, receives a preparation such as a pill that looks just like the treatment or drug being tested, but actually does nothing (a placebo). This is the only way to really compare and see if the treatment is effective.

Clinical trials are usually conducted in phases. The trials at each phase have a different purpose and help scientists answer different questions: In Phase I trials, researchers test a new drug or treatment in a small group of people (usually 20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify possible side effects. In Phase II trials, the study drug or treatment is given to a larger group of people (often 100-300) to see if it is effective and to further evaluate its safety. In Phase III trials, the study drug or treatment is given to even larger groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely. In Phase IV trials, post-marketing studies gather additional information about the drug's risks, benefits, and optimal use.

A clinical trial, especially a larger one, sometimes yields different results than earlier studies in laboratories, in animals, or even in people. But, the clinical trial results will be more meaningful to you because the research involved people and because of the way these studies are designed.

How a Clinical Trial Works

First, the scientists sign up volunteers. These volunteers are randomly divided into two groups. One receives the test drug, and the other, the control group, gets a placebo. The study is also masked, meaning that neither the doctors nor the volunteers know who is getting the test treatment or the placebo.

Then the investigators keep track of each group over time. They watch for side effects of the drug. At the end of the study period, everyone learns which group was getting the test drug and which was on placebo, and the results are analyzed.

For more information, or if you are interested in participating in a clinical trial, visit http://clinicaltrials.gov/.

Understanding Scientific Results

How do you understand the results you read in a news story? Different types of numbers can be used to explain the same facts, and the way these numbers

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are presented can change how you feel about the results. For example, let's say you heard that only one percent of people in the U.S. had a disease. You might not think that was very much until you realize that that's almost three million people! When you hear numbers like these, it's important to try to put them in context to understand how important they really are.

When investigators report their findings, especially from large clinical trials, they often talk about risk. They might mention *relative risk*, *absolute risk*, or both. These are different ways to explain how likely someone is to have a certain health problem. Relative risk is usually shown as a ratio or a percent. An absolute risk is nothing more than a number found by subtraction. How these numbers are presented to you can sway how you feel about the finding and affect whether you change your behavior.

Consider an imaginary new drug. After testing this fictitious drug in a large clinical trial, the investigators learn that the *relative risk* of getting a certain side effect from the medicine is 2.0, which means the risk is increased by 100%. Sounds serious. But that doesn't mean that all of the people using the drug will have that side effect. It means that twice as many people on the drug get the symptom as those not taking the drug (news reports often phrase it this way, too). So, if six people out of every 10,000 normally have a symptom in one year, then twelve people out of 10,000 using the medicine might have it. The *absolute risk* of this side effect is twelve minus six, or six more people out of every 10,000 using the medicine. Many people who really need a new medicine might not consider six in

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A Word to the Wise...

Ask Yourself

When you learn about a new medical finding, ask yourself:

- **?** Was it a study in the laboratory, in animals, or in people? The results of research in people are more likely to be meaningful for you.
- **?** Does the study include enough people like you? You should check to see if the people in the study were the same age, sex, education level, income group, and ethnic background as yourself and had the same health concerns.
- **?** Was it a randomized controlled clinical trial involving thousands of people? They are the most expensive to do, but they also give scientists the most reliable results.
- **?** Where was the research done? Scientists at a medical school or large hospital, for example, might be better equipped to conduct complex experiments or have more experience with the topic. Many large clinical trials involve several institutions, but the results may be reported by one coordinating group.
- **?** Are the results presented in an easy-to-understand way? They should use absolute risk, relative risk, or some other easy-to-understand number.
- **?** If a new treatment was being tested, were there side effects? Sometimes the side effects are almost as serious as the disease. Or, they could mean that the drug could worsen a different health problem.
- **?** Who paid for the research? Do those providing support stand to gain financially from positive or negative results? Sometimes the Federal government or a large foundation contributes funding towards research costs. This means they looked at the plans for the project and decided it was worthy of funding, but they will not make money as a result. If a drug is being tested, the study might be partly or fully paid for by the company that will make and sell the drug.
- **?** Who is reporting the results? Is the newspaper, magazine, or radio or television station a reliable source of medical news? Some large publications and broadcast stations have special science reporters on staff who are trained to interpret medical findings. You might want to talk to your health care provider to help you judge how correct the reports are.

The bottom line is: Talk to your doctor. He or she can help you understand the results and what they could mean for your health. Remember that progress in medical research takes many years. The results of one study often need to be duplicated by other scientists at different locations before they are accepted as general medical practice. Every step along the research path provides a clue to the final answer—and probably sparks some new questions also.

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10,000 a large enough risk to prevent them from taking it, even if the side effect is quite serious.

It's important to be critical when reading or listening to reports of new medical findings. The next time you read or hear about a medical study in the news, ask yourself the questions in the accompanying list (see Ask Yourself) to see how important the finding may be to you. If you're not sure, turn to your health care provider for help.◆

—Written by Karin Kolsky

To view or order a free copy of *Understanding Risk: What Do Those Headlines Really Mean?* online, go to http://www.niapublications.org/engagepages/risk.asp. Or, you can call 1-800-222-2225 (TTY: 1-800-222-4225) for this fact sheet or other information on subjects related to aging from NIA.

New Senior Health Web Site

People 60 and older constitute the fastest growing group of Internet users in the United States. So isn't it time they had their own web site for reliable health information?

NIH has answered with an enthusiastic "Yes!" by launching NIHSeniorHealth.gov (http://www.nihseniorhealth.gov), a new talking web site with formats and topics tailored to the needs of older people. The senior-friendly site takes advantage of techniques developed by the National Institute on Aging (NIA) and the National Library of Medicine (NLM) designed to encourage older people to use the Internet, and this site in particular, as a resource for the best information on health and medical research.

The site was unveiled at a recent Capitol Hill briefing requested by Sen. Tom Harkin (D-IA). Harkin, whose state is among those with a high percentage of people age 65 and older, said, "As our population ages, good health will be important on both a policy and personal level. For all of us, that starts with the right information on prevention and treatment, which NIH is now providing seniors by means of this new and innovative web site."

NIA and NLM brought together researchers who study cognition, web site designers and communications experts to fashion a site that is easy for older adults to read, understand, remember and navigate. The site features large print and short, easy-to-read segments of information repeated in a variety of formats such as open-captioned videos and short quizzes to increase the likelihood it will be remembered. Consistent page layout and prompts help older adults move from one place to another on the site without feeling lost or overwhelmed. Each topic provides general background information, quizzes, frequently asked questions (FAQs), open-captioned video clips, transcripts for the videos, and photos and illustrations with captions.

NIHSeniorHealth.gov also has a "talking" function, which allows users the option of reading the text or listening to it as it is read to them. Finally, in addition to being senior-friendly, the new site complies with section 508 of the Rehabilitation Act of 1973, making it accessible for people with disabilities.

Because the risk of many diseases increases with age, site sponsors are focusing on topics of particular interest to older people, including Alzheimer's disease, arthritis, balance problems, breast cancer, colorectal cancer, exercise for older adults, hearing loss, lung cancer and prostate cancer. In coming months, topics will include aphasia, diabetes, falls, osteoporosis, sensory loss and vision changes, among others.

Along with NIA and NLM, many other NIH components contribute topics to the site.

NIHSeniorHealth.gov is expected to serve as a

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model for web designers seeking to make sites accessible for older adults. NIA and NLM have developed a booklet, *Making Your Web Site Senior Friendly: A Checklist*, which gives guidelines that can be used to update any web site with cognitive aspects of aging in mind. To order a copy or to get more information about the web site, contact the NIA Office of Communications at 301-496-1752.◆

—Written by NIA staff

Research Capsules

Diabetes and Mental Decline

A new study has found that women with type 2 diabetes are at increased risk of cognitive decline, as measured by a series of tests assessing their verbal and memory skills. Finding a way to slow or prevent this cognitive decline can have important public health benefits. The good news is that diabetic women in the study who took glucose-lowering pills, called oral hypoglycemic agents, for their condition had a risk similar to women without diabetes.

Previous research has found links between diabetes and early cognitive decline, but few studies have followed cognitive change over time. A Harvard research team supported by NIH set out to investigate the connection in older women, an age group disproportionately affected by type 2 diabetes. The researchers gave cognitive tests by telephone to women of ages 70-81 from the nurses' health study, a long-running study of registered nurses. The women were then retested starting about two years later. Over 16,500 women completed the study.

Women with diabetes had greater cognitive declines over the two years than those without. The longer they had lived with diabetes, the greater their odds of decline. For example, the odds of poor cognitive performance of those with diabetes for 15 or more years was 50% higher than for women without diabetes. Women taking insulin for their diabetes had similar results to those not taking medication for their diabetes, but those on oral hypoglycemic treatment had cognitive declines similar to those without diabetes.

According to the National Diabetes Statistics Fact Sheet, 18.2 million people — 6.3 percent of the population — have diabetes, with type 2 diabetes accounting for up to 95 percent. Type 2 diabetes is most common in adults over the age of 40, and is strongly linked to obesity, inactivity, family history of diabetes, and racial or ethnic background. It is the main cause of kidney failure, limb amputations, and new onset blindness in adults, and is a major cause of heart disease and stroke.

This new study adds to the growing number of reasons to focus on preventing type 2 diabetes, and on controlling your blood sugar if you have it. If you have type 2 diabetes, make sure to talk to your doctor about controlling your blood sugar. And if you're in danger of developing type 2 diabetes, learn what you can do to prevent it.◆

—Written by Harrison Wein, Ph.D.

Source: *British Medical Journal 328:548*

A study of diabetes treatment and cognition is being supported by NIH's National Institute on Aging as part of the ACCORD trial, currently recruiting patients. For information, see http://clinicaltrials.gov/ct/show/NCT00000620?order=1.

Learn more about preventing and controlling diabetes at the National Diabetes Education Program's web site: http://

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www.ndep.nih.gov/diabetes/diabetes.htm. Materials are also available in Spanish and six Asian American and Pacific Islander languages at http://www.ndep.nih.gov/diabetes/pubs/catalog.htm#PubsAsianAm. Or contact:
National Diabetes Information Clearinghouse (NDIC)
1 Information Way
Bethesda, MD 20892-3560 (Use 9-digit ZIP code.)
Phone: 1-800-860-8747 or 301-654-3327
Fax: 301-634-0716
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Also see *Dealing With Diabetes* from NIH's National Institute on Aging at http://www.niapublications.org/engagepages/diabetes.asp; a Spanish version is available at http://www.niapublications.org/spnagepages/diabetes-sp.asp. Or contact:
National Institute on Aging (NIA) Information Center
P.O. Box 8057
Gaithersburg, MD 20898-8057
Phone: 1-800-222-2225
TTY: 1-800-222-4225

The Pain of Rejection

Physical pain exists to keep us alive. Neural circuits and chemicals tell us when something is wrong so we can take action and survive another day. Our sense of pain tells us to remove our hand from a hot stove top, cradle a broken arm, or remove an eyelash from our eye. But are these same neural circuits involved in other kinds of pain? Do they prompt us to cry when separated from our moms as infants, feel devastated after a bitter break-up, or get distressed when picked last for the company softball team? Pain is the word we use to describe what we feel in these situations, but can these social pains really come from the same region of the brain as physical pain? New research shows that they do.

A research team funded by NIH's National Institute of Mental Health (NIMH) devised a clever experiment. Participants played a virtual ball-tossing game while they lay in a functional magnetic resonance imaging (fMRI) scanner that monitored blood flow to their brains. Participants first just watched two other players toss a ball (observation). They were told that they could not join in the game of "Cyberball" because of technical difficulties. Eventually they joined in the game of catch (inclusion). However, after a few tosses, the other players stopped throwing the ball to them (exclusion). Although the participants were led to believe that the other players existed and were also in scanners, their Cyberball playmates were really created by a preset computer program. Afterwards, the participants filled out questionnaires about their level of social distress and how excluded they felt.

The researchers found that during exclusion from the game, the area of the participant's brain that became active was the anterior cingulate cortex (ACC), the same area that is active during physical pain. The greater the reported feeling of social distress, the more active this area of the brain had become. In addition, another area of the brain, the right ventral prefrontal cortex (RVPFC), also became active in an apparent attempt to lessen the distress of being shunned.

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These remarkable findings reveal that feelings of social pain and physical pain arise from similar regions in the brain. This sharing of neural machinery highlights the importance of social connections. Social attachment and support are crucial to our minds, regardless of whether the inclusion consists of bonding with your newborn child or joining a game of catch.◆

—Written by Carol E. Torgan, Ph.D.

Source: *Science 302: 290-292, JAMA 290:2389*

For more information on pain, visit http://www.ninds.nih.gov/health_and_medical/pubs/pain.htm.

Visit the MEDLINE plus information page on pain at: http://www.nlm.nih.gov/medlineplus/pain.html.

Gene Therapy in Salivary Glands

Scientists at the National Institute of Dental and Craniofacial Research (NIDCR) have taken another step toward making gene transfer into salivary glands a therapeutic reality. The new results may open up possibilities for treating diseases and conditions that are resistant to conventional treatments.

Salivary glands can secrete substantial amounts of protein into saliva. The glands are easily accessible through the mouth via their excretory ducts, and infusing fluid into the ducts causes little discomfort for patients. These attributes mark salivary glands as potential 'factories' for producing secreted proteins to treat both oral and systemic disease.

Scientists can induce salivary glands to produce new proteins through gene transfer, which involves delivering a gene into a cell that then expresses the

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protein encoded by the gene. Therapeutic proteins have been produced by the salivary glands of many types of animals using this technique, but only in an unregulated, continuous manner that could create problems for clinical use.

The NIDCR scientists set out to adapt a method that had proven effective in other tissues, and succeeded in creating a gene expression system they could turn on and off in rat salivary glands. The system is controlled by administering the drug rapamycin, which turns the gene on and thereby induces protein production. When the drug is not given, the gene is inactive and no protein is made. The researchers demonstrated that the production of human growth hormone (hGH), used as a "model protein," and its secretion into the saliva of rats could be generated by rapamycin at least three times over a 16-day period. Rats not given rapamycin had no hGH in their saliva.

These results could potentially lead to new treatments for oral or systemic diseases. Oral fungal and bacterial infections, for instance, usually require treatment for about 10-14 days — a period the scientists showed could be achieved with their system. Therapeutic genes administered to the salivary glands can provide a higher local concentration of medications than is possible with injections into the bloodstream or muscle. The approach might also enable doctors to deliver therapeutics that cannot be given systemically.◆

—Written by Beatrijs Lodde, M.D.

Source: Gene Therapy 2004 Jan 22 [online publication]

For more information about gene transfer, see the *Gene Transfer* NIH Backgrounder at http://www.nih.gov/news/backgrounders/genetransferbackgrounder.htm.

For information about oral health, visit the Oral Health Information Index at http://www.nidcr.nih.gov/health/newsandhealth/oralDiseases.asp.

Heard It From a Fly

Think those tiny, pesky flies circling the fruit bowl in your kitchen are simply a nuisance? Think again! Scientists continue to learn secrets about human health from basic research with simple organisms such as insects, worms, mice, and rats. Fruit flies have been a particular favorite for researchers investigating the role of heredity in the formation of tissues and organs. Both insects and people develop according to a genetically determined body plan, and scientists know that many of the genes involved in this process are very similar among animals

Using fruit flies as a model system, National Institute of General Medical Sciences (NIGMS) grantee Grace Boekhoff-Falk of the University of Wisconsin in Madison recently made a fundamental discovery about hearing. She and her coworkers discovered an insect gene nicknamed "spalt" that profoundly affects flies' ability to hear. The scientists found that experimental flies created to lack the spalt gene were deaf, as measured by direct tests of the flies' hearing organs located inside their antennae.

Boekhoff-Falk and her team also discovered that the spalt gene is nearly identical in flies and people. That means that what she learns about spalt in fruit flies may also apply to humans, and her work may help scientists find new approaches to diagnosing certain inherited hearing disorders.◆

—Written by Alison Davis, Ph.D.

Source: *Proceedings of the National Academy of Sciences 100,18:10293-10298*

Basic Studies Yield Myeloma Drug

A series of lab studies begun in the 1970s by NIGMS grantee Alfred L. Goldberg of Harvard Medical School has led to a promising new cancer drug now on pharmacy shelves. The medicine, named Velcade™, was approved by the U.S. Food and Drug Administration in May 2003 to treat a deadly type of bone marrow cancer called multiple myeloma. Velcade is now being tested in more than 30 different clinical trials to determine if it can be helpful in treating many other types of cancer.

Velcade is a brand-new kind of cancer drug that targets a molecular machine found in virtually all cells. Goldberg was a pioneer in the discovery that our cells use this machine, called the proteasome, to continually break down their own protein components in order to remove improperly made or damaged proteins and to control cell growth and other vital processes. He reasoned that small molecules that block proteasome function might be useful in treating different diseases. Goldberg and other researchers founded a small biotechnology company that went on to design and make Velcade based on detailed chemical knowledge of how the proteasome cuts up proteins.

The discovery and development of this drug differs from the traditional approach, which relies on the screening of large numbers of chemicals to find those that that can slow the growth of cancer cells. The findings also show how advances in understanding basic biology can help scientists find new and better ways to treat diseases.◆

—Written by Alison Davis, Ph.D.

For information about detection, symptoms, diagnosis, and treatment of multiple myeloma, see http://www.cancer.gov/cancerinfo/wyntk/myeloma or call 1-800-4-CANCER.

New and Notable

The following new or revised NIH publications are available free to the public:

An Activity Book For African American Families – Helping Children Cope with Crisis. National Institute of Child Health and Human Development, NIH Publication 03-5362B, September 2003. E-mail: NICHDInformationResourceCenter@mail.nih.gov or call 1-800-370-2943. View online at: http://www.nichd.nih.gov/publications/pubs/hccc/helping_children_cope_with_crisis.pdf.

Brain Basics: Understanding Sleep. National Institute of Neurological Disorders and Stroke, NIH Publication 04-3440-c, (no date). Call 1-800-352-9424. E-mail: ninds@iqsolutions.com. View online at: http://www.ninds.nih.gov/health_and_medical/pubs/understanding_sleep_brain_basic_.htm.

Gastroesophageal Reflux in Infants. National Institute of Diabetes and Digestive and Kidney Diseases, NIH Publication 04-5419, November 2003. E-mail: nddic@info.niddk.nih.gov or call 1-800-891-5389. View online at: http://digestive.niddk.nih.gov/ddiseases/pubs/gerdinfant/index.htm.

Ojo Con Su Vision! National Eye Institute, NIH Publication 04-5209, December 2003. E-mail: 2020@nei.nih.gov or call 301-496-5248. View website at: http://www.nei.nih.gov/health/espanol/saludable.htm.

Rett Syndrome. National Institute of Neurological Disorders and Stroke, NIH Publication 04-4863. E-mail: ninds@iqsolutions.com or call 1-800-352-9424. View online at: http://www.ninds.nih.gov/health_and_medical/pubs/rett.htm.

Systemic Lupus Erythematosus. National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH Publication 03-4178, August 2003. E-mail: namsic@mail.nih.gov or call 301-495-4484. View online at: http://www.niams.nih.gov/hi/topics/lupus/slehandout/index.htm.

The Seventh Annual Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute, NIH Publication 03-5233, December 2003. E-mail: NHLBIpriority@prospectassoc.com or call 301-592-8573. View online at: http://www.nhlbi.nih.gov/guidelines/hypertension/index.htm.

Understanding Vaccines. National Institute of Allergy and Infectious Diseases, NIH Publication 03-4219, July 2003. E-mail: ocpostoffice@niaid.nih.gov or call (301) 496-5717. View website at: http://www.niaid.nih.gov/publications/vaccine/pdf/undvacc.pdf.

When Someone in Your Family Has Cancer. National Cancer Institute, NIH Publication 04-2685, December 2003. E-mail: cis@icic.nci.nih.gov or call 1-800-422-6237. View online at: http://www.cancer.gov/cancerinformation/whensomeoneinyourfamily.

—Compiled by Jan Ehrman

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