



JOHNS HOPKINS  
M E D I C I N E

MEMORY BULLETIN



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# THE JOHNS HOPKINS MEMORY BULLETIN

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## TABLE OF CONTENTS

<b>Letter</b> .....	1
Mediterranean Diet, MCI, and Dementia .....	1
Cutting Calories to Improve Memory .....	3
A New AD Biomarker .....	6
AD Drug Development .....	9
Memory Athletes .....	17
When Dementia Strikes Early .....	20
Still Alice .....	22
Thomas DeBaggio Update .....	24
Until Next Time .....	26
<b>In-Depth Report</b> .....	27
Young-Onset Dementia .....	
<b>Grand Rounds</b> .....	39

PETER V. RABINS, M.D., M.P.H.  
CO-DIRECTOR, SECTION OF GERIATRIC AND NEUROPSYCHIATRY

Dear Friend,

In 1826, Anthelme Brillat-Savarin the French lawyer, politician, and author of a celebrated work on gastronomy, *Physiologie du Goût* (The Physiology of Taste), wrote, “Dis-moi ce que tu manges, je te dirai ce qui tu es.” For those of you whose French is a little rusty, this translates to “Tell me what you eat and I will tell you what you are.” Today, we are more apt to simply say, “You are what you eat.”

According to the recently published research findings of Nikolaos Scarmeas, M.D., an Assistant Professor of Neurology at the Taub Institute’s Division of Aging and Dementia at Columbia University Medical Center in New York, what you eat can be a crucial factor in not only whether or not you develop heart disease, but possibly also whether you develop mild cognitive impairment, or MCI. MCI is a precursor of dementia and Alzheimer’s disease (AD).

Dr. Scarmeas’s recent observational study in the *Annals of Neurology* reported that a diet rich in vegetables, fish, olive oil, and fruit and low in meat, dairy, and fat—the so-called Mediterranean diet—can possibly help prevent MCI and may also help those with MCI from moving into Alzheimer’s disease.

We already know from previous studies that the Mediterranean diet is extremely heart healthy and has been extolled in cancer studies, too. Now, the same way of eating is possibly associated with improved brain health as well, adding more credence to the mantra, “What’s good for the heart is good for the brain.”

Here is how Dr. Scarmeas’s study worked: The researchers at Columbia reviewed the food-frequency files of 1,393 patients with no cognitive problems and 482 people who had MCI. These patients were then followed for an average of 4.5 years and close attention was paid to whether or not they adhered to a Mediterranean diet.

Dr. Scarmeas reported that:

- 275 of the 1,393 patients who did not have MCI at the beginning of the study eventually developed it.
- Compared with the one third of patients who barely followed the Mediterranean diet, the one third with the highest adherence scores for sticking to the Mediterranean diet had a 28% *lower* risk of developing MCI.



*"These medicines all taste pretty good—let's approve them."*

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- Among the 482 patients with MCI at the beginning of the study, 106 later developed AD within an average of four years. However, those patients with the highest score for Mediterranean diet adherence had a 48% lower risk of developing AD than the one third of patients who barely adhered to the diet.

Granted, this was only an observational study: Participants had to remember what they ate as opposed to eating only what was prepared for them by study investigators, which is what happens in a clinical trial. Even so, since we already know that the Mediterranean way of eating helps improve diabetes, coronary artery disease, and hypertension, it certainly makes sense that it would have some beneficial effect on neurological health as well.

As Dr. Scarmeas and his colleagues noted in their study, the Mediterranean diet may improve cholesterol levels, blood vessel health, and blood sugar levels and cause a reduction in overall inflammation, all of which have been linked previously to cognitive improvement.

Even though you may not be able to make it to Monte Carlo or Cap d'Antibes this season, eating the type of foods you'd readily find there will certainly provide you the same health benefits, minus the jet lag. Why not do your-

self a favor: Make it a point to regularly visit your greengrocer, fish market, and wine shop. The Mediterranean foods you consume should taste great, and you may be protecting your brain as well.

### CUTTING CALORIES TO IMPROVE MEMORY

Here's more news about food and your memory. A study appeared recently in the journal *Proceedings of the National Academy of Sciences* that made me pause. The small study out of Germany titled "Caloric Restriction Improves Memory in Elderly Humans" reported that *reducing* daily caloric consumption could lead to *significant* memory improvement.

The German researchers, led by Agnes Flöel, M.D., an Assistant Professor of Neurology at the University of Munster, took 50 slightly overweight adult women (body mass index [BMI] of 28, which is about 175 pounds for a 5-foot, 6-inch woman) who ranged in age from 50 to 80 (60 years old, on average) and assigned them to three groups to see what effects caloric reduction would have on their memories three months later.

One group cut their daily calories by 30% without being told what to eat. It was recommended that no one consume less than 1,200 calories a day. The second group increased the heart-healthy unsaturated fats in their diets by 20% by eating more fish and other foods, while the third group made no changes in what they ate. All study subjects were given memory and blood tests at the study's start and completion.

The results of the study:

- Those people who cut their calories lost five pounds, on average, and boosted their scores on a test to recall words on a list by 20%. As more weight was lost, verbal scores increased by almost 30%. Other types of memory were *not* affected.
- The women who consumed more unsaturated fatty acids showed no memory improvements.
- The women in the group that made no changes to their diets showed no improvements in memory.

The study results suggested to the researchers that caloric restriction might improve memory. They believe the weight-loss group had improved verbal recall because they became more sensitive to the blood sugar-regulating hormone insulin and had a drop in C-reactive protein levels, which meant less inflammation to damage the brain and other body organs. These two factors have already been linked to improvement in brain function.

Although this small study is the first in middle-age adults to show memory benefits following weight loss—and weight loss is recommended for everyone

## THE MEDITERRANEAN DIET: 10 KEYS TO MAKING CHANGES IN HOW YOU EAT

The so-called Mediterranean diet has been around for thousands of years and became popular in the United States in the 1980s, when the results of the Seven Countries Study were published. This study reported that people living in Greece and southern Italy—who typically eat a diet rich in fruits, vegetables, and whole grains and who get most of their fat intake from foods high in monounsaturated fats (such as olive oil and nuts) and high in omega-3 fats (such as fish)—had a lower risk of heart disease than those living in countries like the United States and Finland, where fruit and vegetable consumption is lower and most of the fat in the diet comes from saturated sources such as red meat and dairy products.

More than a quarter century later, studies are still reporting the heart and

overall health benefits for those who follow a Mediterranean-style diet—whether or not they live in Southern Europe. So, instead of following the latest diet fad, why not try a time-honored route to overall health?

### Why It Works

The secret to the success of the Mediterranean diet is most likely that monounsaturated fats are consumed in place of saturated ones. Replacing saturated fats with monounsaturated fats not only decreases LDL (“bad”) cholesterol levels, but may also raise HDL (“good”) cholesterol levels. And that’s not all. Researchers believe that other characteristics of the Mediterranean diet—the consumption of alcohol in moderation, eating fiber-rich foods, and avoiding trans fatty acids (the diet focuses on eating unprocessed foods)—also contribute to the reduced incidence of heart disease

and premature death.

### Changing Your Diet

Eating the Mediterranean way is much easier than following one of the many fad diets that turn up every year. You don’t have to count calories, make radical changes in your eating habits (like cutting out entire food groups such as carbohydrates), or strictly limit the amount of fat you eat. Instead, the focus is on more healthful food choices—choosing whole foods over processed foods, replacing saturated fats with the monounsaturated fats found in olive oil, nuts, and avocados, and adding omega-3 fats to your diet by eating fish more often.

If you’re already trying to improve your health through diet—perhaps reducing your saturated fat and dietary cholesterol—you probably won’t have to make any dramatic adjustments to adopt a Mediterranean way of eating. Here are the 10 key steps to

with BMIs greater than 25—Esther Oh, M.D., Assistant Professor of Geriatric Medicine and Gerontology at Johns Hopkins, has some reservations with this particular study.

“With so many Americans overweight and obese,” she says, “memory is being affected. Obesity is linked to insulin resistance, and insulin resistance leads to chronic hyperinsulinemia. It is thought that chronically elevated levels of insulin may lead to down regulation (less activation) of brain insulin receptors, which

eating like you're living on the Mediterranean:

**1. Eat plenty of fresh fruits and vegetables, which are packed with fiber and antioxidant vitamins.** For added flavor, sauté vegetables with olive oil and herbs. But don't slather your vegetables with butter or cream sauces.

**2. Emphasize whole foods over processed foods.** When you have the time, make meals from scratch rather than going to fast-food eateries or buying frozen entrées or packaged baked goods.

**3. Choose whole grains instead of refined and processed grains like white bread and white rice.** Whole grains include brown rice as well as cereals, breads, crackers, and pasta made with wheat, oats, bran, rye, barley, or wheat berries. Beware of terms like "wheat flour" and "enriched flour," which indicate the products are not whole grains.

**4. Eat fish once or twice a week.** Choose fish such as

salmon, trout, herring, tuna, and mackerel, which are high in omega-3 fats. If you're worried about mercury, limit how much fresh tuna, canned albacore tuna, swordfish, shark, king mackerel, and tilefish you eat. Brush your fish with olive oil, and then bake, broil, or sauté it. Avoid deep-fried fish.

**5. Limit full-fat dairy products.** Instead, opt for low-fat milk, cheese, and yogurt.

**6. Avoid high-fat red meats such as beef, bacon, and sausage. Instead, buy poultry and lean cuts of meats.** Don't make meat the centerpiece of a meal, and always trim any visible fat from meat and remove the skin from poultry.

**7. Add peas, beans, and legumes to your diet; they are good sources of low-fat protein and are filled with fiber.** They make delicious soups, can be added to salads, and are a great accompaniment to fish.

**8. Choose oils rich in monounsaturated fat.** The best choices are extra-virgin olive oil, canola oil, flaxseed oil, and high-oleic sunflower or safflower oil. Cook with these oils, and use them to make salad dressings. Remember: monounsaturated-rich oils are fats and contain 9 calories per gram, so don't overdo it. Oils to use sparingly include corn, soybean, and peanut oil.

**9. Try nuts and seeds when you have a craving for a snack, instead of potato chips, cookies, or candy bars.** Almonds, cashews, Brazil nuts, sesame seeds, and pumpkin seeds are particularly high in monounsaturated fat. Just avoid nuts coated in salt or roasted in honey.

**10. Enjoy a glass of wine with dinner.** When it comes to alcohol: No more than two drinks a day for men, and a drink a day for women may help boost HDL cholesterol levels.

in turn results in less insulin getting into the brain. Insulin is actually thought to be good for the brain, and acute administration of insulin has been shown to improve verbal memory. This is good."

What Dr. Oh has concerns about is that this was a study with healthy adults. Her major worry is that cutting calories to improve memory may send a wrong message to older people who often are under-nourished, underweight, or have chronic health problems.

She has other reservations as well. “I would *not* recommend caloric restriction for patients who already have dementia. Their problem is mainly decreased intake of food due to decreased appetite and forgetting to eat. Most of the time they (or their family members) are struggling to prevent any further weight loss. The participants in the German study reduced their caloric intake by 30% of their baseline. Most of my patients who have dementia would not do well if they cut 30% of their current intake.”

I have some questions with this study, too:

- Calories were restricted and memory improved, but was it owing to the caloric restriction or the type of foods consumed?
- How long can most people sustain a diet reduced by 30%?
- Most people, if you go by the failure of diets as a guideline, will lose weight and go off the diet soon after, putting right back all the lost weight—plus a few more pounds. Will memory improvements be maintained?
- If the reduction in inflammation was thought to be a reason why verbal memory improved in the study, why have studies of anti-inflammatory drugs failed to improve memory?

If you are overweight, Dr. Oh says that eating a little less is certainly a good health message, and it could do something for your brain, too. But if you want to preserve or enhance your memory without going hungry, here are two other ways:

- **Increase your physical activity.** Regular exercise can boost insulin sensitivity and reduce inflammation, so go out for a daily walk, swim, or go dancing and you will enhance your cognitive health.
- **Challenge your brain daily.** People who spend time reading, playing musical instruments, or playing cards or board games have a lower risk of dementia and AD.

#### A NEW AD BIOMARKER

Most leading AD experts are in agreement that biomarkers are going to play a key role in AD diagnosis and treatment in the future. What are biomarkers, you might be thinking. These various traits (anatomic, physiologic, biochemical, or molecular) are associated with the presence and severity of AD. Biomarkers are detectable and measurable by a variety of methods including physical examination; laboratory tests of blood, urine, and cerebrospinal fluid; and medical imaging. Using biomarkers, researchers hope to not only predict AD, but to predict how a person’s disease progresses or how a person may respond to AD drug therapy.

There is now a global hunt in progress using a variety of AD biomarkers to help identify the initiation (sometimes years in advance of the onset of an AD

symptom such as memory loss), development, and ongoing cascade of damage caused by AD. Unfortunately, the search for biomarkers has been painstakingly slow, especially when compared with the great successes achieved in the past two decades by heart disease and diabetes researchers using their own particular set of biomarkers. You are surely familiar with the most common biomarker for heart disease, the blood test for cholesterol (HDL and LDL) levels. For people with diabetes, the A1c test is a biomarker used primarily to monitor the glucose control of diabetes patients over time. The goal of those with diabetes is to keep their blood glucose levels as close to normal as possible. The A1c test helps determine how elevated uncontrolled blood glucose levels have been. The test may be ordered several times while control is being achieved, and then several times a year to verify that good control is being maintained.

We now know that AD just doesn't appear out of the blue one day and a person then starts exhibiting signs of this insidious disease. Instead, evidence is beginning to mount that AD slowly damages the brain for many years before the person, family members, or doctors pick up on any symptoms. Therefore, by having a biomarker that can identify these presymptomatic sufferers of AD, we should be able to diagnose the disease long before symptoms appear and hopefully offer treatments that will slow or eradicate the disease.

With an effective biomarker, children of parents with AD could have a diagnostic test performed. Many patients already come to our AD clinic at Johns Hopkins for precisely this reason. They say, "My father and his mother died of Alzheimer's. Is there anything I could do to lessen my chances of developing the disease?" If there were a reliable biomarker tied with an effective therapy, we could certainly help. Another important value of a biomarker is to determine who will respond to existing or future drugs.

Although AD scientists still have a ways to go to develop an AD biomarker that's on a level with those for heart disease and diabetes, progress is definitely being made. Anne Fagan, Ph.D., an Associate Professor of Neurology at Washington University School of Medicine in St. Louis, was on the phone to the *Memory Bulletin* recently to discuss how she and her colleagues have now linked a potential biomarker of AD to brain damage in humans with *no* signs of mental problems.

That's right: The test subjects in Dr. Fagan's recent study published in the journal *Annals of Neurology* appeared to be cognitively normal, but in fact they harbored the earliest signs of AD. "What was really neat about our study," says Dr. Fagan, "was that we could see changes already in people as young as 60 who were seemingly okay."

Although their cognitive and neurological assessments were normal, study participants with lower levels of a substance known as amyloid beta 42 (A-beta

42) in their cerebrospinal fluid (CSF) had *reduced* whole brain volumes. This suggests, says Dr. Fagan, that AD changes might already be damaging their brains.

“We had previously demonstrated in another study that low CSF levels of A-beta 42 mark the presence of amyloid deposition in the brain, a key diagnostic marker of the amyloid plaques that characterize Alzheimer’s disease. What is new in our most recent study is that you can see the same amount of A-beta 42 in a subset of people who were not demented. We had already predicted this based on what we know of the pathology of AD. When we look at studies, we know that the damage starts a long time before the presence of full-blown symptoms. We term this the preclinical AD phase.”

For the recent study, Dr. Fagan and her colleagues analyzed CSF samples and magnetic resonance imaging (MRI) brain scans of two groups of subjects at the university’s Alzheimer’s Disease Research Center. The first group of 29 volunteers had very mild cognitive impairment; the remaining 69 volunteers were cognitively normal. Their ages ranged from 60 to 91.

The researchers used a computer program to analyze the MRI scans and determine whole brain volume, a measurement of the amount of space taken up by a patient’s gray and white matter minus the CSF fluid circulating in the skull.

Participants with normal levels of A-beta 42 in their CSF had whole brain volumes within expected ranges. However, in both the cognitively impaired subjects and cognitively normal volunteers with decreased CSF A-beta 42, the size of the brain was smaller.

In addition to A-beta 42, researchers analyzed CSF levels of a family of proteins called tau proteins. These proteins are a component of structures called neurofibrillary tangles that increase as AD progresses. Scientists believe increased levels of tangles in the brain lead to increased CSF tau levels. *The St. Louis researchers found CSF tau levels did not increase until subjects became mentally impaired.*

According to Dr. Fagan, AD experts had thought that amyloid builds up first in the brain followed by an increase in tangle accumulation. What her study provides is some of the first evidence in living people that this concept may be right: Large scale changes in amyloid seem to precede large-scale changes in tau, which are then linked to the onset of clinical dementia symptoms.

Dr. Fagan and her Washington University researchers will follow cognitively normal subjects with reduced CSF amyloid levels and brain volumes to see if they eventually become demented, potentially confirming A-beta 42 as an

antecedent biomarker for Alzheimer's disease. They will also continue to look for additional Alzheimer's biomarkers in CSF samples and brain scans.

"Hopefully, the scientific community will see the value of biomarkers and identify people early enough and put them in the clinical trials for new AD drugs," says Dr. Fagan.

"We have had a number of experimental AD drugs that have recently failed. But this is not surprising," she says, "because we have been screaming for years to the drug companies and the researchers, 'You are testing people too late. You want to put non-demented people in these trials.'

"It's a tough sell, but it will have to come down to that. You can't be treating someone with an experimental drug who is severely demented and already has a head full of amyloid; the neurons that are going to die have already died. Why would you expect that an experimental drug is going to help these test subjects at an advanced stage of illness?"

The key, therefore, according to Dr. Fagan, is to get volunteers with preclinical AD and see how an experimental drug works for them. "That's one of the real values of a biomarker," she says. And it could help us prevent AD or at least delay it from starting to cause problems. This would certainly be a major achievement in our battle with AD.

#### **AD DRUG DEVELOPMENT**

There are currently an estimated 5.1 million people in the United States living with Alzheimer's disease and according to the Alzheimer's Association, that number is expected to more than triple by 2050. Recent studies show that a potential Alzheimer's pandemic could potentially bankrupt the U.S. health-care system. For now, no treatment can prevent or halt the mental ravages associated with AD. However, the successful development of a disease-modifying drug for Alzheimer's could potentially save the U.S. health care system an estimated \$4 trillion dollars. While our hopes are high, there doesn't appear to be such a drug on the horizon just yet.

At present, there are four AD drugs available in the United States: Aricept (donepezil) is the most widely prescribed, followed by Namenda (memantine), Razadyne (galantamine), and Exelon (rivastigmine). When these drugs work—and in a third of patients they have little or no effect—they affect only disease *symptoms*, with no impact whatsoever on disease *progression*. Three of the drugs, Razadyne, Aricept, and Exelon—the cholinesterase inhibitors—do this by reducing the breakdown of acetylcholine, an important brain messenger (neurotransmitter) that the brain produces.

On the other hand, Namenda, the most recent AD drug approved (in 2003) by the U.S. Food and Drug Administration (FDA), is prescribed for moderate to severe AD and is thought to work in a completely different manner—by blocking the activity of glutamate, another neurotransmitter that is thought to kill cells when it is in too high a concentration or too active.

Many *Memory Bulletin* readers have contacted me about AD drugs over the past year. Some want to know what is in the AD drug pipeline that can potentially slow progression of the disease. Others want to know why it takes so long to get a drug approved by the FDA and why it takes so long to bring a drug to market. Still others want to know why the new medications have to cost so much.

I will try to answer these questions—and others—by telling you about a new drug, MSL (monosodium luminol), that is currently being tested for ataxia-telangiectasia (A-T), a rare genetic, multisystem disorder that also causes progressive neurologic impairment. If all goes according to plan, this drug may eventually prove valuable for treating AD and other chronic neurological diseases. The reason I say this is because A-T is sometimes called “the Rosetta Stone of medical research.” It’s believed that unlocking its mysteries could then translate into an understanding of a myriad of degenerative diseases involving the nervous and immune systems, including various cancers and Alzheimer’s.

The story with MSL picks up in Austin, Texas, a city that prides itself as the Live Music Capital of the World, with more than 1,900 bands and performing artists living in and around the city. On a warm night in late September there were close to 500 people, music lovers most of them, decked out in white and black cowboy hats, snug jeans held up by impressive hand-tooled leather belts with oversized, custom-made silver rodeo buckles, and a wide array of Tony Lama lizard boots. They had gathered for a pickin’ party at the Darrell Royal Auditorium at the Barton Creek Resort & Spa, on the outskirts of Austin. It was a chance to be serenaded by three of Nashville’s top award winning country songwriters who were there to play (pick) their guitars and sing for two hours. In the boisterous, fun-loving crowd was Coach Darrell Royal himself, the winningest football coach in University of Texas Longhorn history. Coach Royal, 84, now has Alzheimer’s.

The pickin’ party also offered the concertgoers a chance to lend their support to Robert Howard and Connie Cole for their Longevity Foundation, which has been raising money for the past 17 years to find a cure for the inflammation that causes A-T. Their foundation has also been supporting research efforts at the University of Texas M.D. Anderson Cancer Center, Northwestern University, Texas A & M University, Baylor College of Medicine, and the University of Texas at Austin that may lead to effective treatments not only for AD, but also Lou Gehrig’s disease, heart disease, multiple sclerosis, diabetes, and a host of other chronic ailments that linked to low-grade inflammation.

For those of you who don't know, low-grade inflammation isn't the kind you can see in an infected cut. Such acute inflammation is usually a sign of a properly functioning immune system that is working hard to heal the wound and fend off invading viruses and bacteria. Once the immune system has finished these tasks, it shuts down the inflammatory response.

By contrast, chronic, low-grade inflammation may persist for years, many times for decades. Although it initially causes no symptoms, it sets in motion an insidious process that damages tissues, disrupts biological processes, and culminates in the development of chronic and often life-threatening diseases, including heart disease and, possibly, AD.

Before the Nashville all-stars came on, Mr. Howard took to the stage, and while poignant family photos flickered on the large projection screen behind him, he talked briefly about his son Patrick, who was diagnosed with A-T when he was five years old. Patrick, the boy with the bright smile that lit up a room, was also an extraordinarily gifted painter whose work had already caught the eye of Bill Worrell, the noted Texas artist. Patrick struggled valiantly with his disease but in 2000, when he was 14, A-T finally got the best of him. Mr. Howard also briefly mentioned the ongoing research with an interesting drug called MSL that was being tested by Bach Pharma Inc., a North Andover, Massachusetts company. The drug has already shown promise in laboratory studies at relieving low-grade inflammation and preventing neurodegeneration.

The investigational drug MSL has a very interesting and colorful history, one that goes back to the Soviet Union and their space program in the 1960s. What many people don't realize is that the first group of cosmonauts that were sent into space hurtled back and forth in capsules that were not adequately shielded against radiation. These Russian space heroes eventually developed health problems due to radiation exposure, such as leukemia, lymphoma, and skin cancers. When the medical issues became pronounced, a secret military group was quickly assembled to find a cure for the cosmonauts. After going through thousands of potential molecules, they finally settled on one called Galavit, or GVT.

Theodor Von Keudell, director of the Medical Press Agency in Germany, was on the phone to the *Memory Bulletin* in early February. Mr. Von Keudell, an investigative reporter with an interest in cancer and one of the leading medical journalists in Germany, wanted to talk about his "discovery" of Galavit in the Soviet Union a decade earlier and how he was eventually able to introduce it to the West.

"In the late summer of 1999, a German businessman with Russian connections asked if I would like to do a story about a Russian drug that had been developed for the Russian cosmonauts. He also pointed out that the drug was currently used in Russia for the treatment of malignant tumors as well as for the modulation of the immune system.

“I was soon on my way to Moscow with my two camera crews. On our first night in Moscow, my whole team was invited to a dinner where we were introduced to some Russian doctors who had done much of the research with Galavit. We also met with General-Major Victor Lutov, who was the Chief of Medical Services for Military and Space Defense at the Defense Ministry of the Russian Federation. Here is a transcript of what he had to say:

*“Since we had begun to send cosmonauts into space, we were looking for methods to protect the immune system against radiation. Finally, it was our radiological institute in Obninsk that struck gold. They invented a new drug that activated and protected the immune system. After these results were confirmed and successfully proven by other institutes in the Soviet Union, we began using the drug during the preparation of our cosmonauts and during rehabilitation after their return from space. This development and testing took more than 15 years to get a drug that met our requirements in protection, prevention, and rehabilitation.*

*“We are convinced that the sensational results of this treatment was the reason why none of the Russian cosmonauts and none of the allied nation astronauts became ill with radiation-related cancer—either during their expeditions into space or 10 years later. These positive results encouraged us to use the drug with traditional cancer treatment, too. If we look at the experiences with our cosmonauts with Galavit, we have results of about 300 people. If we include soldiers and their family members who were also treated successfully with this immune modulator so far, we reach between 25,000 and 30,000 people.”*

Mr. Von Keudell continued with his story. “The next morning, we drove to the Yuri Gagarin Cosmonauts Training Centre outside of Moscow, where we met our guide, Gennadi Michailowitsch, the famous Russian cosmonaut who had spent more than 300 continuous days in space. We spent the day interviewing doctors and then left for Obninsk, the mysterious city where the Russians had concentrated all their radiation research. We met seven scientists there who had done most of the basic research with GVT, including their animal studies.

“The interesting thing that came across in all the interviews with the Russian doctors: None of them said that GVT could cure cancer. However, they all said that they would use it as a complementary medicine—in combination with surgery, chemotherapy, and radiation therapy and that it would dramatically improve the results of the classic treatments, decrease the side effects of therapy, and increase quality of life. Finally, they said that in addition to its use as an adjunct cancer treatment, they used it as an efficient immune modulator and as an anti-inflammatory drug for a variety of diseases.

“Their reserved judgment about Galavit, their scientific knowledge, their professional behavior, and the studies they had done so far, including the ones which were still in progress, persuaded me that the Russians had found a drug

that could be useful for all of mankind. In my opinion, they wanted to share their findings and knowledge with me (and through me with the world). They were proud of their science and research. I knew that they would never have the money or the management to repeat this research in the Western Hemisphere, nor would they be able to market the product there.

“My first thoughts about the drug and its potential use were that if everything that the Russians had told me was true, then they had come up with a drug similar in importance to penicillin. If just half of their findings and conjectures were right, this drug could effectively treat many of the severe diseases that mankind was suffering from.

“My second thought was, how could I get this drug to the West and develop it further? I felt a deep respect for the Russian scientists, but I also knew that they had no money to pay for all the additional research that would be necessary to get this drug approved in Western countries. And I felt pity and a little bit of guilt that none of the scientists who had discovered this drug would benefit financially from the sale of rights. At this time, a Russian researcher earned less than \$90 a month!”

Some time after Mr. Von Keudell’s story ran on German TV, Galavit was being used as a cancer treatment in a clinic in Bad Karlshafen, Germany where some unscrupulous doctors announced that the drug could cure cancer. Charging more than \$13,000 for a course of treatment valued at less than \$500, they began treating scores of desperately ill cancer patients who had come from around the world in hopes that the miracle Russian drug would save their lives. Sadly, Galavit did not do what it had been advertised to do. All of the patients eventually died.

The Galavit story doesn’t end here. Last summer, following a 16-month trial, three people who ran the clinic were sentenced to serve three to seven years in jail for fraud. The judge in the trial said the businessman, doctor, and journalist who ran the Galavit scam had been encouraging false hopes among the dying and profiting from it.

Although the promising Russian drug certainly had a horrible introduction in the West, it still had its believers. After negotiating with Russian officials for rights to Galavit, Bach Pharma Inc., the Massachusetts drug company, eventually began the laborious process of translating the reams of available research from Russian and German into English, and then started their own laboratory studies to validate that the drug actually worked. “We were sufficiently happy with the results,” says Mark O. Henry, the Bach Pharma Chief Executive and Financial Officer. “The drug was renamed MSL and the requisite laboratory and animal trials were begun to see what the drug could really do.”

## HOW PRESCRIPTION DRUGS MAKE IT TO YOUR PHARMACY

**Y**ou may encounter some surprises along the road to treatment with prescription medications. The first could be when your doctor says that the promising AD treatment you just read about in the newspaper will not be available for years. The second surprise may come much later at the pharmacy counter when you finally receive your new pills: Why do they cost so much?

Developing a new drug for use in humans is an extraordinarily expensive gamble. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), researchers may screen as many as 10,000 different molecules to identify only 250 worthy of preliminary testing in test tubes, cell cultures, and laboratory animals. Of those 250 candidate drugs, only five might be suitable for testing in people. Only one of those five may end up on the pharmacy shelf.

Along the way, pharmaceutical companies typically spend hundreds of millions of dollars and 10 to 15 years to create and market a new medication. The most expensive drugs to develop are those involving biotechnology techniques, such as geneti-

cally engineering bacteria to produce a medication. An independent estimate by the Tufts Center for the Study of Drug Development pegged the average cost of developing a new biopharmaceutical at \$1.2 billion.

Sometimes, the industry loses the gamble. In December 2006, for example, the pharmaceutical company Pfizer pulled the plug on development of a promising medication for high cholesterol, torcetrapib, when research suggested it might raise the risk of heart attacks and death. In clinical trials, torcetrapib raised “good” high-density lipoprotein (HDL) cholesterol levels and was expected to become a blockbuster product. The company had already invested \$800 million when it halted development.

Despite the costs, the industry continues to invest heavily in new products. In 2007 alone, drug developers tested 277 drugs for heart disease and stroke—the leading causes of death in Americans—according to a PhRMA report.

### **Drug Discovery**

Underlying the discovery of promising new medicines is basic biomedical research,

largely paid for in the United States by the National Institutes of Health and many private foundations. In the same way that doctors may specialize in particular organs or diseases, biomedical scientists may devote entire careers to a single cell type or even a single gene or molecule.

Having identified a substance that appears to have a desired effect, laboratory scientists must then assess how well it is absorbed, how it acts in the body, and how toxic it is. Typically, the first studies are conducted in cells in tissue culture, and later studies are conducted in laboratory animals. The drug won't be approved for use by humans until a large volume of scientific data is conveyed to the U.S. Food and Drug Administration (FDA). As mentioned earlier, the overwhelming majority of candidates never get that far.

### **The FDA Approval Process**

People have been promoting patent medicines and nostrums in America since before the Revolutionary War. In the mid-1800s, entrepreneurs at carnival sideshows and advertisements in almanacs peddled many remedies—some of dubious effectiveness. In 1906, the

Pure Food and Drug Act established authority for a regulatory agency that eventually became the FDA.

Today, the FDA decides whether and how pharmaceutical companies may test drugs in Americans and, ultimately, whether the companies will be allowed to sell a drug. What occurs between the first news report about a promising drug and the prescription in your hand is a lengthy process that involves a structured series of studies. If all goes well, the testing process leads to FDA approval: the legal right to sell the drug in the United States.

When a newspaper article ends with the statement “further testing is required,” that’s a reference to the three phases of clinical testing that occur between the laboratory tests in animals and FDA approval.

#### **Phase I**

The first clinical studies involve a relatively small number of patients or healthy volunteers, usually 20 to 80 people. In Phase I studies, researchers determine the biological effects of the drug in the human body at various doses—including harmful side effects—and measure

how well the drug is absorbed, how it is metabolized, and how long it stays in the body before it is eliminated. A candidate drug could be rejected in this phase for a number of reasons. The drug may turn out to be too toxic or the body simply may not absorb it well enough. Many drugs that look promising in mice and in test tubes fail to pass muster during Phase I clinical trials.

#### **Phase II**

If the Phase I trials are favorable, the next step is to test the drug in a larger number of subjects, typically around 100 to 300. Again, researchers look at safety, but now they also try to establish whether the drug provides a benefit in treating people with a specified disease or condition. Pharmacologists refer to this as a drug’s “indication.” For example, the FDA-approved indication for cetirizine (Zyrtec) is to treat allergy symptoms. In Phase II testing, it was tested in people with respiratory allergies to see if their symptoms improved without causing worrisome side effects.

#### **Phase III**

To reach Phase III testing, a drug must be sufficiently safe

in Phase II testing and show clear signs of being effective for a specific indication. Phase III trials usually involve about 1,000 to 3,000 people. At this stage, researchers better define the risks and benefits of the drug, its side effects, and how frequently the side effects occur, especially compared with other drugs used for the same disease. In short: How good is this new drug? Whom does it help? How much does it help? And what can go wrong?

One important goal of Phase III trials is to determine the circumstances under which the drug would be dangerous to use. These conditions are called contraindications. For example, if a drug is somewhat toxic to the liver, it could be life threatening for a person with pre-existing liver disease. For this hypothetical drug, therefore, liver disease is a contraindication.

Ultimately, doctors make their prescribing decisions based on the expected benefits of the drug compared with its risks. Your doctor or pharmacist can provide an information sheet with your prescriptions, which explains

*continues on following page*

## HOW PRESCRIPTION DRUGS MAKE IT TO YOUR PHARMACY (CONTINUED)

the drugs' main indications, potential side effects, and known contraindications in language designed to be understandable and useful to you. You should read it carefully before taking the first dose and if you develop new problems after starting the medication.

### After FDA Approval

FDA approval means that clinical studies have proven a drug to be more helpful than harmful for specific diseases and conditions. But FDA approval does not guarantee that a drug is absolutely safe and universally effective. Instead, it signifies that a drug is sufficiently safe and effective when used within the limits defined by its testing for indications, side effects, and contraindications. Even so, the demonstrated risks and benefits may change once a drug is tested in a larger and more diverse group of patients.

When you fill a prescription for a relatively new drug, you are entering, in effect, a vast and unregulated human experiment. Statistically, a Phase III clinical trial involving several thousand people has its limits. A rare side effect—for example, one that affects only one in 50,000 individuals—may not show up during the trials. But once the drug is on the market and prescribed to millions of people, uncommon side effects may start to show up.

Then why not require all drugs to be tested in 50,000 or more people? Such a policy would be extremely expensive and would substantially increase the cost and time it takes to bring new medications to market. To address the issue of rare adverse effects, the FDA requires post-marketing studies, in which the drug's manufacturer monitors a sample of people using the drug and reports any new adverse reactions.

Physicians, pharmacists, and patients themselves can also report drug side effects or problems with the use or quality of medical products by using the FDA's MedWatch system. The MedWatch website gives you the option of printing out a report form to take to your doctor or filling out a form online yourself. To make a report, go to [www.fda.gov/medwatch](http://www.fda.gov/medwatch) and click on "How To Report" and then "Reporting by Consumers." You can also call the FDA at 800-FDA-1088 to request a "MedWatch Voluntary Reporting" form via the mail.

By reporting side effects or problems with medical products, you can help the FDA to identify risks to yourself and other consumers. In some cases, the FDA decides on the basis of this post-marketing surveillance that a new drug is too dangerous after all and orders it to be withdrawn from the market.

"To date, we have spent more than \$16 million in research," said Steven Stroup, M.D., during a phone call to the *Memory Bulletin*. Dr. Stroup, a Nashville, Tennessee radiologist, is Director of Medical Research for Bach Pharma. "We know that our drug has multiple uses. As an anti-inflammatory, it works as an immune modulator and works across the host in multiple ways. If you modulate the inflammation process, you can have an impact on a variety of autoimmune diseases that are caused by inflammation, from AD and rheumatoid arthritis to Crohn's disease, multiple sclerosis, and psoriasis."

Whether or not MSL will ever be shown to be effective and succeeds in gaining FDA approval for A-T, AD, or any other disease remains to be seen. While Bach Pharma has already spent millions on research, according to a study by Bain & Company, a global business consulting firm, it is now estimated that the average cost to develop a new prescription drug and get FDA approval is well over \$1.7 billion. In these days of trillion-dollar deficits and billion dollar corporate bailouts, money may have lost some value for you. Here is another way of looking at the money needed for new drug development: If counted out in \$1,000 bills, the amount of money would create a stack almost 500 feet high.

In the AD research field, the road is already littered with some mighty casualties that failed before reaching the finish line. In just the past year, four well-financed drug trials for AD—Flurizan (tarenflurbil), Alzhemed (tramiprosate), IGF-1 (insulin-like growth factor), and bapineuzumab—came up empty owing to lack of efficacy or safety concerns, dashing the hopes of doctors, patients, caregivers, and the company executives who had invested billions of dollars in the trials.

“It’s been very frustrating and challenging to develop this drug,” admits Dr. Stroup of MSL. “But MSL has huge potential and we believe in it, and we are going to continue with our efforts.”

As always, I will keep you apprised of further research with all promising AD drugs as they move through the various testing steps. Perhaps, if all goes according to plan, MSL might turn out to be one of those drugs, but the failure of so many drugs that seem to hold promise emphasizes how important necessary careful study is.

#### **MEMORY ATHLETES**

The top memory athletes recently journeyed to New York City for the 12th USA Memory Championship, an annual event that puts the best minds of this country through rigorous tests against the clock that are designed to maximize the power of their billions of gray cells. The 52 contestants for this year’s event ranged in age from 12 to 60 and went head to head in a series of memory tests. After spending 15 minutes studying first and last names linked to the photos of 99 people, they were then quizzed for 20 minutes. A random series of digits was then shown to each contestant and they had five minutes to learn them before their quiz. The “speed card” event entailed memorizing the random order of a shuffled deck of playing cards. Finally, contestants were allotted 15 minutes to memorize the 50 lines of an unpublished poem before having to repeat it back from memory.

Practice makes perfect. While you may struggle to remember where your eyeglasses are, contestants in the Memory Championships are never fazed,

because these people constantly work at remembering. Just like you might spend hours working at your golf game or piano practice, these people work at remembering long strings of numbers and other arcane facts. What this practice does is help them organize the way that they store and retrieve information in their brains. For example, Chester Santos, the returning champion from San Francisco, practices three hours a day the month before the championship, while Thomas Sowell, a 42-year-old Texan, practices two hours a day and every Saturday he puts himself through a four-hour mock competition. These memory athletes are determined not to forget anything.

What these memory champions do is the same thing that you do when you learn and remember—only they take it to extremes. What you learn and are able to remember depend on your ability to make associations, or mental linkages, among experiences, store them in an organized fashion, and then search for them efficiently when retrieval is needed. This involves the functioning of several brain regions and the neurons (brain cells) within each region.

What competitors utilized the most in the national Memory Championships was mnemonics. A mnemonic is any technique used to help you remember; the more meaningful something is, the easier it is to remember. For example, instead of studying each playing card, competitors assigned visual images to every card. Salma Hayek became the “Queen of Hearts” for one contestant. When memorizing lists, names, and addresses, many will alphabetize them or group them as an acronym—a word made from the first letters of a series of words (for example, NATO stands for North Atlantic Treaty Organization).

Another mnemonic technique is called an acrostic. Acrostics use the first letter of each item to create new words that form a sentence or phrase (for example, “Every good boy does fine” helps you remember the order of the treble-clef line notes on sheet music: E, G, B, D, F). In addition, many will create personal stories that connect each element to be remembered, and they find this to be helpful in remembering not only words but also numbers. The more compact or meaningful the mnemonic or story, the easier it will be to remember the information.

While you may not aspire to be a memory champion, there are many ways that you can improve and protect your memory abilities. Inheriting good genes is certainly a good start! Like virtually all cognitive capacities, including overall intellect, individual differences in memory are, to some extent, inherited. Since we cannot select our parents, however, there are a number of things you can do to maximize your memory functioning at any age:

- **Exercise your mind.** Staying mentally active is the key to maintaining memory as well as other cognitive skills. Working crossword puzzles, studying a for-

eign language, learning to play a musical instrument, starting a new hobby, reading, and maintaining social interactions are excellent choices.

- **Eat sensibly.** A balanced diet low in cholesterol and including nine servings daily of fruits and vegetables can improve alertness and energy and minimize your risk of memory-impairing conditions. Foods rich in omega-3 fats (especially wild salmon, mackerel, trout, sardines, walnuts, and flaxseed) may be particularly beneficial for brain function. For most senior citizens, a daily multivitamin is recommended.

- **Stay physically active.** An adequate blood supply to the brain is necessary for all mental functions, including memory. Regular physical activity helps get more blood to the brain and thereby promotes better mental functioning. Exercising 30 or more minutes every day is recommended. Improved aerobic fitness translates into better cognitive function. Regular aerobic exercise seems to keep brain cells healthy and encourages the growth of new neurons.

Exercise also helps optimize blood pressure and increases production of an important protein called brain-derived neurotrophic factor (BDNF). Animal studies have recently revealed that the more animals voluntarily exercised on a running wheel, the higher their levels of memory-enhancing BDNF.

Not only can you improve your overall health through regular exercise, you can also improve your ability to think. In a study published in the *Proceedings of the National Academy of Sciences*, older adults who were physically active were found to have better concentration skills than those who did not exercise as much. In that study, one group of adults (ages older than 60) walked for 15 minutes three days a week, eventually working up to an hour a day after three months.

A similar group spent the same amount of time stretching and strengthening their muscles but did not do any aerobic exercise. In the end, the group that walked had significantly better concentration.

- **Treat high blood pressure.** Over time, hypertension can damage brain cells and trigger transient ischemic attacks, mini-strokes that may impair memory. Keeping blood pressure controlled (at 120/80 mm Hg or less) maximizes blood flow to the heart and brain. It is estimated that 42 million Americans have hypertension (blood pressure above 140/90 mmHg) but only 10 million have their blood pressure safely controlled.

- **Drink alcohol only in moderation.** Studies have found that people who drink excessively—more than three drinks daily—were 1.5 times more likely to develop both memory problems and dementia.

- **Wear protective headgear for active sports.** If you ride a bike, horse or motorcycle, inline skate, ski, or ice skate, protect your head with a good helmet. Traumatic brain injury, even early in life, appears to be a risk factor for developing AD and other forms of memory-impairing disorders in later life.

- **Get enough sleep.** Sleep deprivation impairs brain function, which can affect your ability to concentrate, learn, and recall information. There is also some evidence that the synthesis of certain proteins important for memory is increased during sleep.

- **Place commonly lost items in a designated spot.** If you are prone to losing certain items, such as keys or eyeglasses, choose a place to leave them and always put them in that spot when you are not using them.

- **Write things down.** If you have trouble remembering phone numbers or appointments, write them down and place the list in a conspicuous spot. Making a daily “to do” list will remind you of important tasks and obligations. The simple acts of writing notes and making lists reinforce memory.

- **Say words out loud.** Saying “I’ve turned off the stove” after doing so will give you an extra verbal reminder when you later try to recall whether the stove is still on. Incorporating people’s names into the conversation immediately after you have met them serves the same purpose. For example, saying “Very nice to meet you, Mr. Williams” will help consolidate your memory of the name.

- **Use memory aids.** Use a pocket notepad, personal digital assistant, wrist-watch alarm, voice recorder, or other aids to help remember

- **Use visual images.** When learning new information, such as a person’s name, create a visual image in your mind to make the information more vivid and, therefore, more memorable. For example, if you have just been introduced to a Mr. Hackman, visualize him hacking his way through a dense jungle with a machete.

#### WHEN DEMENTIA STRIKES EARLY

Jim Mueller, a former sheet-metal worker, is young and active. He and his wife, Michelle, have three daughters under the age of 15. Unfortunately, Mr. Mueller entered a select group four years ago when he was diagnosed at the Rush Alzheimer’s Disease Center in Chicago with young-onset Alzheimer’s disease. He was 36 years old.

While AD is a traditionally a disease of older people, the Alzheimer’s Association estimates as many as half a million Americans now have young-

onset Alzheimer's, an incurable condition that develops before age 65. And because these patients are often in the midst of raising families and building careers, the diagnosis is not only devastating for the patient, but the collateral damage it causes to the family is life altering.

Jim Mueller lost his \$80,000 job soon after his AD diagnosis. With no income, he and his wife soon depleted their savings, eventually losing their home, and their car. With no health insurance, Medicare picks up some of the cost for Jim's AD drugs, Exelon and Namenda. Free prescription samples from understanding doctors help immensely.

Eric J. Hall, President and Chief Executive Officer of the nonprofit Alzheimer's Foundation of America (AFA), was on the phone to the *Memory Bulletin* to talk about young-onset dementia. Last year, the AFA held a conference in New York City called "Preparing for the Crisis: Diagnosing & Caring for People in Their 30s, 40s & 50s With Young-Onset Alzheimer's Disease."

"Healthcare professionals and social service agencies must put young-onset dementia on their radar screens," Mr. Hall says. "AD poses enormous challenges for anybody, but its onset at a young age intensifies them enormously. In addition to receiving a proper diagnosis, these individuals need help with an entirely different set of emotional, financial, and family issues."

Although she is slowly losing her husband to AD, Michelle Mueller speaks openly about the disease in order to help others, and to push for much-needed support and social programs. "People need to be aware of the fact that this is not just for old people," she says. "There needs to be programs to address young-onset AD. There needs to be change so that people like my husband can be taken care of. It is a real struggle to put food on the plate. We sometimes have to use the food pantry, and my children don't get to do all the things that other children get to. I sometimes wish there could be an Alzheimer's community where low-cost housing and low-cost medicine were made available."

Jim Mueller took the phone from his wife, and he talked effusively about his new job, serving as the coach for a local high-school girl's softball team. He is also a part-time high school basketball and soccer coach.

"I was told that I never would be able to get a high school coaching job because of my condition, and that really fired me up," he says. In order to remember the names of his players, he has a photograph of each, with their uniform number and name on it. He refers to the photos to make his lineups and substitutions.

Michelle was back on the phone. As the sole caregiver to her family, she has

her hands full. “I certainly do,” she admits. “It is only by God’s grace that I am able to do this. I never thought in my wildest dreams that I would be going through what I am now. When I married Jim, I was 13 years older than he was, and I actually thought that he would take care of me when I got older. Life has some strange twists and turns.”

For more on young-onset dementia, turn to the In-Depth Report by Brian Appleby, M.D. on page 27.

### **STILL ALICE**

“*Still Alice*,” a *New York Times* best seller, is a gripping book of fiction based fact, a stunning in-depth look at a vibrant, intelligent woman. The protagonist is 50-year-old Alice Howland, who has to confront her young-onset AD diagnosis at the peak of her academic career at Harvard. Terrified at what is happening to her, she is initially afraid to break the news to a husband and three children who love and depend on her.

Told from the point of view of Alice, the novel takes readers into two years of her ever-changing life. We see her struggling as she tries to come to grips with the impact that the disease is having on her brain. We witness the ensuing chaos in her professional career as an esteemed professor of cognitive psychology, and we read of her changing personal interactions with her husband and children.

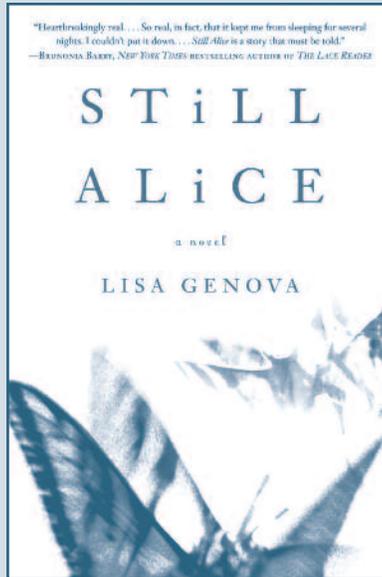
“*Still Alice*” is a beautiful, poignant, well-told tale—and one that almost never got to be told because many literary agents and publishers had told Lisa Genova, Ph.D., the author, that no one would be interested in reading about AD. After Dr. Genova self-published the book and then sold it from the trunk of her car, one smart publisher, Pocket Books, finally saw the many merits in this lyrical work and bought the rights for \$500,000.

Dr. Genova had watched as her own beloved grandmother was taken care of by her aunt and uncle for four years after her AD diagnosis, eventually dying at the age of 89. Armed with a Ph.D. in neuroscience from Harvard, Dr. Genova, who had never written a book, felt driven to write a first-person account of someone suddenly diagnosed with AD, not when they were old like her grandmother, but when they were relatively young and still expected they would have many more productive years to live.

“My grandmother was doing her best to make sense of her situation, given the information she was able to access in her brain,” says Dr. Genova, who recently called the *Memory Bulletin* from her Cape Cod home to discuss her book.

“She told everyone that my aunt, who had moved in to her home to be her

## STILL ALICE: A BOOK TO REMEMBER



*Despite the escalating erosion of her memory, her brain still served her well in countless ways. For example, at this very moment, she ate her ice cream without dripping any of it onto the cone or her hand by using a lick-and-turn technique that had become automatic to her as a child and was probably stored somewhere near the information for how to ride a bike and how to tie a shoe. Meanwhile, she stepped off the curb and crossed the street, her motor cortex and cerebellum solving the complex mathematical equations necessary to move her body to the other side without falling over or getting hit by a passing car. She recognized the sweet smell of narcissus and a brief waft of curry emanating from the Indian restaurant on the corner. With each lick, she savored the delicious tastes of chocolate and*

*peanut butter, demonstrating the intact activation of her brain's pleasure pathways, the same ones required for enjoying sex or a good bottle of wine.*

*But at some point, she would forget how to eat an ice cream cone, how to tie her shoe, and how to walk. At some point, her pleasure neurons would become corrupted by an onslaught of aggregating amyloid, and she'd no longer be capable of enjoying the things she loved. At some point, there would simply be no point.*

*She wished she had cancer instead. She'd trade Alzheimer's for cancer in a heartbeat. She felt ashamed for wishing this, and it was certainly a pointless bargaining, but she permitted the fantasy anyway.*

**From "Still Alice," by Lisa Genova (Pocket Books, 2009).**

caregiver, was a homeless woman who had no place to live. She couldn't understand that my Aunt Mary was her daughter and she had no idea what the heck she was doing living with her in her house.

"Before my grandmother developed AD, whenever I thought about Alzheimer's, I always pictured an elderly grandparent in the end stage of the disease, someone with a totally vacant stare, not knowing who anyone was. The seed of my book, however, came when I began to imagine what it would be like at the beginning stages of the disease for my grandmother. What did it feel like to look into the mirror and not understand completely what she was looking at as she

touched her face? For “*Still Alice*,” I had this—and many other things—happen to a 50-year-old woman.

“As I worked on the book I never thought I would be an AD advocate; my goal was to tell a story and tell it well. Along the way, however, I realized that if the book ever reached a general audience, it would be a tremendous opportunity to help with awareness, education, and advocacy for Alzheimer’s. Now that the book is published, I know that my grandmother would have been proud. It’s not just that the book entertains, but it’s one that helps people get some idea of what AD diagnosis, treatment, and living with AD are all about.”

The movie rights to “*Still Alice*” are in the process of being sold. But don’t wait for the movie. If you have young-onset disease yourself, if you are a caregiver for someone with AD, or even if you have no connection with AD at all, the book is a page turner that is bound to move you.

#### THOMAS DEBAGGIO UPDATE

I first told you about Tom DeBaggio several years ago, shortly after he was diagnosed with Alzheimer’s disease at the age of 57. For years, Mr. DeBaggio operated a successful herb farm and nursery in Arlington, Virginia. He had written a popular book about herbs, and shortly after his AD diagnosis, the former newspaper journalist began writing what it was like to have young-onset AD.

Mr. DeBaggio worked tirelessly to get his thoughts down on paper before it was too late. It would be a difficult race but it was one he knew he had to complete. “At first, I viewed the diagnosis as a death sentence” he told me in our phone conversation. “Tears welled up in my eyes uncontrollably; spasms of depression grabbed me by the throat. I was nearer to death than I anticipated. A few days later I realized good might come of this. After 40 years of pussyfooting with words, I finally had a hell of a story to tell. Alzheimer’s is something I have to live with. Unfortunately, it’s getting more difficult to live with. Life isn’t anywhere near as much fun as it used to be,” he says.

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*For me now, any questions of identity become profound and difficult. Without memory you lose the idea of who you are.—Thomas DeBaggio*

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Mr. DeBaggio is the only active Alzheimer’s patient to have written a book, and it wasn’t easy. He would sit down and write and then stumble out of his room when he couldn’t take it anymore. There was just so much frustration. He’d scream and pound his desk, saying that he couldn’t come up with the

words that he couldn't remember anymore. It was not uncommon for him to call his wife Joyce and ask her how to spell some particularly difficult words.

*"Losing My Mind: An Intimate Look at Life with Alzheimer's"* (Free Press), was published in 2002 to great acclaim. The book records Mr. DeBaggio's memories from early childhood onward, and details his daily battles as he tries to cope with the disease. *"When It Gets Dark: An Enlightened Reflection on Life with Alzheimer's"* (Free Press) was published a year later, and in this poignant memoir he laments about a life with his family that is being cut short by AD.

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*"My memory, which had been a sacred touchstone, was failing long before I expected. I was losing the ability to remember things important to me. I had difficulty recognizing the names of my plants, and even friends I saw infrequently. I was fifty-seven this year, and not eager to acknowledge that now I might be tied to a teetering mind that had begun a slow descent into silence."*  
—Thomas DeBaggio

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Joyce DeBaggio, Tom's wife, was on the phone to the *Memory Bulletin* one sunny morning in late winter to talk about her husband, his writing, and his deteriorating physical and mental condition. Tom no longer lives at home with her and he is literally fighting the disease that has destroyed his life.

"I just got a call this morning from the nursing home where Tom now lives," she says. "Tom had to be moved into another unit because he has deteriorated so much. He still recognizes me but because he can't walk and because he has started to scream a lot when they try to change his diaper or try to help him, it is becoming more difficult for people to handle him. That's why he had to be moved. This is Tom's second nursing home. Last July he was asked to leave the first nursing home because he was so combative."

I asked Mrs. DeBaggio how she was holding up. "It breaks my heart every time I see him," she said. "I have been on antidepressants for a while and I have not been functioning well, although I am beginning to feel a little better. I am an artist but I gave up my art studio. I didn't want to pick up a piece of paper for the longest time. Everything just disappeared for me."

When Joyce DeBaggio speaks of her husband, she is mournful but ever proud of what he was able to accomplish so that others could understand first-hand what he was going through as he began his "slow descent into silence."

"I want Tom to be remembered for his writing. He has kind of been the

poster boy for Alzheimer's, which is okay, but he was really a great writer. I don't want him to be forgotten."

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*"It is lonely here waiting for memory to stop, and I am afraid and tired. Hug me, Joyce, and then let me sleep."—Thomas DeBaggio*

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#### UNTIL NEXT TIME

As I write this, snow flakes are falling over Baltimore, a final gasp of winter weather that is dusting the grounds white. But I am already looking past this storm and thinking about spring, which arrived at 7:42 this morning. That's because I'm an optimist, and spring is the traditional season of optimism: Those blustery days of winter 2008/2009 will soon give way to budding trees, the promise of warm weather, and a chorus of birds outside my office window.

Spring also represents renewal. My hope for you is that this new season brings with it a growing inclination to live actively and optimistically. Why not invite your spouse, family members, and friends to dinner to welcome in the new season? See it as an opportunity to celebrate your drive toward better health and wellness. Sitting down to a convivial meal with people you love is the best medicine for just about anything that ails you. Happy spring!

Until next time, I wish you and your family the best of health.

P RABINS MD

Peter V. Rabins, M.D., M.P.H.



## IN-DEPTH REPORT

### YOUNG-ONSET DEMENTIA

**Brian Appleby, M.D.**, is Director of the Creutzfeldt-Jakob Disease Program and Co-Director of the Frontotemporal Dementia and Young-Onset Dementias Clinic at Johns Hopkins. His research focus is on the clinical and translational aspects of Creutzfeldt-Jakob disease (CJD) and other human prion diseases.



Why can't I focus on a work-related task like I used to? Why do I struggle to balance my checkbook? Why is it such an effort to think of the right word to say? Isn't that my business partner, what's his name? Why am I opening the oven door? Why am I feeling so down? Did I have that important business meeting today, or is it next week? Did I lock the doors of the car last night? And where did I park the car?

What's going on here? Aren't these typical signs of dementia, the "old timer's disease" that only strikes those in their 70s and 80s? What does it mean if you have these complaints in your 30s, 40s, or 50s—and they are worsening? According to the Alzheimer's Association, for hundreds of thousands of Americans, many of whom are in their peak earning years and raising children, these could be undiagnosed symptoms of young-onset dementia.

"Dementia" is a general term that refers to decline in multiple areas of thinking and/or memory while an individual is awake and alert; the decline is enough to interfere with normal daily functioning, whether on the job or at home. The term "young-onset dementia" refers to dementia that begins before the age of 65, sometimes as early as the 30s and 40s. This is to be differentiated from "early-stage dementia," which has nothing to do with age. Rather, it refers to the beginning of a dementia syndrome regardless of the age at which it starts.

Young-onset dementia can be caused by frontotemporal lobar degeneration (FTLD), Alzheimer's disease (AD), cerebrovascular conditions (e.g., multi-infarct disease, stroke), Parkinson's disease, Huntington's disease, prion diseases (e.g., CJD), and other conditions. (See chart on page 28). The Alzheimer's Association now estimates that there are between 220,000 and 640,000 people under the age of 65 with young-onset dementia or Alzheimer's disease (AD) in the United States today.

These early dementias are devastating neurological conditions that exact a tremendous emotional and financial toll on patients and their families and present a host of challenges never envisioned by the young patients. The condition



## IN-DEPTH REPORT

### Young-Onset Dementia

#### DEMENTIA-CAUSING DISEASES

##### Degenerative Brain Diseases

- Alzheimer's disease
- Parkinson's disease
- Pick disease
- Frontotemporal degeneration
- Huntington disease
- Progressive supranuclear palsy
- Spinocerebellar degenerations
- Multiple sclerosis

##### Prion diseases

- CJD
- fatal familial insomnia
- Gerstmann-Sträussler-Scheinker Disease

##### Cerebrovascular Diseases

- Multiple infarct disease
- Binswager disease
- Subcortical leukoencephalopathy
- Thalamic infarct

##### Cerebral Vasculitides

- Lupus
- Temporal arteritis
- Giant arteritis

##### Infectious diseases

- Syphilis
- Tuberculosis
- HIV
- Prion disease (Creutzfeldt-Jakob disease)
- Fungal encephalitides
- Viral encephalitides

##### Psychiatric disorders

- Major depressive disorder
- Schizophrenia

##### Traumatic Brain Injuries

- Closed head injury
- Open head injury
- Subdural hematoma
- Vitamin deficiencies
- Vitamin B<sub>12</sub> deficiency (pernicious anemia)
- Vitamin B<sub>6</sub> deficiency (pellagra)
- Vitamin B<sub>1</sub> deficiency

##### Endocrine Diseases

- Hyperthyroidism
- Hypothyroidism
- Growth hormone deficiency
- Hyperparathyroidism
- Cushing disease
- Conn disease

##### Cerebral Tumors

- Intrinsic brain tumor
- Metastatic cancer

##### Toxin Exposure

- Alcohol
- Heavy metals (lead, arsenic, mercury)
- Volatile hydrocarbons
- Medications

##### Other

- Normal pressure
- hydrocephalus

Adapted from: *Practical Dementia Care*, Peter V. Rabins, Constantine G. Lyketsos, Cynthia D. Steele. Oxford University Press, 1999.



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## IN-DEPTH REPORT

### *Young-Onset Dementia*

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causes a unique problem not only because it is so unexpected but because most of the potentially helpful programs and services that a younger patient needs have all been carefully designed and targeted for much older people.

Because it is rare, getting a proper diagnosis for young-onset dementia is never easy. Since dementia has historically been considered a condition of older people, it is not usually expected in people younger than 65. Therefore, it is not uncommon that when a younger person goes to a doctor with symptoms of dementia, such as problems finding or saying the right word or forgetting how to use an ordinary object such as a computer, the doctor may not even think of dementia as a possible diagnosis. Instead, depression may be deemed the culprit. In many cases, Attention Deficit Hyperactivity Disorder, or ADHD, may be suggested as the cause. Medication is often prescribed, and while it may relieve some symptoms, in some cases it may exacerbate the problem.

In a survey conducted by the Alzheimer's Association, young-onset patients indicated that it took more than a year from the time they first sought medical attention to the time when a diagnosis of dementia was finally made. Some people had to wait as long as six years, and many received several wrong diagnoses and were treated with a variety of medications before finally being diagnosed with dementia.

One of the major problems with young-onset dementia is that it cuts down a person in their prime wage-earning years. While most older people with dementia are retired, many people with young-onset dementia are still working when they are diagnosed. AD and some other diseases that cause young-onset dementia have a gradual onset and many patients are unaware of the subtle changes they are experiencing. During this time, these people lose their ability to perform their usual job tasks. They are regularly befuddled and they don't understand the reasons behind their feeling like that. What was once routine or even simple at work now becomes a major chore. Appointments are made and forgotten. Tasks are late to be completed and not done correctly. There is often anger and confusion with the patient (and co-worker) who suspects that something may be wrong, but is not sure what it is. Depression? A brain tumor? Multiple sclerosis?

The person may lose his or her feelings of self-worth as the disease progresses. He or she also fears that, if found out, he will lose his job. Many people with young-onset dementia are eventually deemed "unproductive" by their employers and they are placed on disability or their job is terminated. Because of mounting pressures and knowing that they are not pulling their weight at work, some people leave on their own, not knowing what's wrong with them, but knowing that they can no longer work as well as before.



## IN-DEPTH REPORT

### Young-Onset Dementia

#### DEMENTIA

**D**ementia is a clinical syndrome caused by a wide range of diseases that affect the brain. Its core feature is a decline in cognition. Dementia has many presentations as well as causes. It can be stable or progressive. It can afflict the young or the old. It is associated with a wide range of mental and behavioral disturbances, many of which are reminiscent of other psychiatric disorders. Dementia involves functional impairment that derives from the impairment in cognition but can also result from behavioral disturbances. Dementia renders individuals more vulnerable to the effects of coexisting medical conditions and medication. Finally, dementia occurs in a family context and affects the lives of many others. Caring for the dementia patient is a complex endeavor. It requires several skills and the involvement of the patient, family care providers, and health professionals.

The word *dementia* derives from the Latin *de mens* and means “from the mind.” Its mention in the Bible and in early Egyptian, Greek, and Roman writings suggest that it has affected humankind since the dawn of time. To many, the word dementia implies craziness, irrationality, and hopelessness. None of these is an accurate description of the syndrome. Many terms have been proposed to replace the word dementia, but all have acquired the same undesirable connotations. This suggests that it is not the word that is frightening, but the disorder it describes.

Dementia is best described as a *syndrome*, a pattern of clinical symptoms and signs. The first element of the definition is a decline, or deterioration, in the cognitive or thinking capacities. This decline from a previous level of ability distinguishes dementia from disorders of cognition that have been present since birth—for example, mental retardation and learning disabilities.

The second element of the definition requires that more than one area of cognition be impaired. Almost every disease that causes dementia affects memory; the other cognitive impairment in judgment, perception, language, abstraction, persistence, and calculation depend on the specific disease and the stage of the illness. This criterion distinguishes dementia from disorders in which only a single cognitive ability is impaired, such as aphasia, in which language disorder is present, and the amnesic syndrome, in which only memory is impaired.

**From:** *Practical Dementia Care*, Peter V. Rabins, Constantine G. Lyketsos, Cynthia D. Steele. Oxford University Press, 1999.



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## IN-DEPTH REPORT

### *Young-Onset Dementia*

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Once a job is lost when a person is in their 30s, 40s, 50s, or 60s, the financial implications are often huge. Unlike almost all older people who have had a lifetime to build a career and plan for retirement, people under age 65 generally do not have enough money set aside to cover their expenses and they quickly find themselves—and their families—in dire straights. Loss of health insurance compounds the problem, even moreso for those who have chronic conditions such as diabetes, heart disease, arthritis, or cancer. Those people with young-onset disease who try to buy health insurance are frequently denied policies because of their dementia. Those who manage to get a policy have to pay high premiums, deductibles, and co-payments.

Early dementia has many causes. AD is the most common neurodegenerative cause of young-onset dementia. Genetic mutations account for only 1 to 2% of all cases of AD, including those with young-onset AD. Many people with young-onset dementia do not have AD pathology in the brain but instead have one of several types of abnormalities grouped under the category of frontotemporal lobar degeneration, or FTLN. (See page 36 for a more detailed description.) Unlike Alzheimer's, which initially causes a loss of short-term memory, FTLN causes behavioral personality changes (i.e. frontotemporal dementia, or FTD) or a progressive loss of language (primary progressive aphasia) or word meaning (i.e. semantic dementia) in the earliest stages. It is estimated that there is a hereditary factor in 30% of cases with FTLN.

**I examine many patients with young-onset dementia and the majority of them are under age 65. Many are referred to Johns Hopkins by physicians in the region and around the country who are confounded by the atypical symptoms they note in these patients. To follow are some of the most frequent questions I am asked about young-onset dementia by doctors, patients, and loved ones alike, and my answers to them.**

**Q. How common is young-onset dementia?**

**A.** The Alzheimer's Association now estimates that one person in every 1,000 below the age of 65 develops dementia.

**Q. What is the cause of young-onset dementia?**

**A.** Although many people suspected that young-onset dementia was caused by Alzheimer's disease, that is not always the case. A study last year from Mayo Clinic researchers reported that young-onset dementia is most often caused by neurodegenerative disease (AD, frontotemporal lobar degeneration [FTLN], familial prion disease, or Huntington's disease) or autoimmune/inflammatory



## IN-DEPTH REPORT

### Young-Onset Dementia

#### SIGNS AND SYMPTOMS THAT SHOULD TRIGGER CONSIDERATION OF A DEMENTIA EVALUATION

##### 1. Cognitive Changes

New forgetfulness, more trouble understanding spoken and written communications, difficulty finding words, not knowing things the person should know (such as the president and how to complete frequently performed tasks), disorientation.

##### 2. Psychiatric Symptoms

Withdrawal or apathy, depression, suspiciousness, anxiety, insomnia, fearfulness, paranoia, abnormal beliefs, hallucinations.

##### 3. Personality Changes

Inappropriate friendliness, blunting and disinterest, social withdrawal, excessive flirtatiousness, easy frustration, explosive spells.

##### 4. Problem Behaviors

Wandering, agitation, nosiness, restlessness, being out of bed at night.

##### 5. Changes in Day-to-Day Functioning

Difficulty driving, getting lost, forgetting recipes in cooking, neglecting self-care, neglecting household chores, difficulty handling money, making mistakes at work, trouble with shopping.

*From: Practical Dementia Care, Peter V. Rabins, Constantine G. Lyketsos, Cynthia D. Steele. Oxford University Press, 1999.*

conditions (multiple sclerosis or lupus). However, according to a 2006 study, most causes of young-onset dementia are caused by vascular disease, traumatic brain injuries, and alcohol.

#### **Q.** Are head injuries a contributing factor in young-onset dementia?

**A.** We are actually looking at the data from our clinic, and there is an association with head injuries and some of the young-onset dementias. Many of our patients have a history of head trauma several decades before their dementia, so concussions and other brain injuries could be a possible worry factor. In the case of an athlete who gets hit hard in the head a couple of times during his career and suffers a series of concussions, there is some evidence that it could lead to problems later on in life—and has in many instances (e.g., Muhammad Ali [boxing], John Mackey [football], and, probably, Chris Benoit [wrestling]).



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## IN-DEPTH REPORT

### *Young-Onset Dementia*

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**Q. What is the profile of the typical young-onset patient that you see in your clinic?**

**A.** Because our clinical and research interests, the majority of patients that we see have AD, FTLN, or a prion disease. They are often in their 50's, and have previously been fairly productive, doing well, and excelling at their jobs. Many have families. In their late 40s or early 50s, however, they gradually began to decline at work. They didn't speak as well, they forgot things, and they began to take profuse notes to remind themselves of what had to be done. Many make common errors that they had never made before. For some, there were subtle personality changes or they made inappropriate comments that they normally would not have made.

After a year or so, co-workers may have caught on to the changes but often assumed that the person was going through a midlife crisis or something like that. Often, as the condition becomes more obvious, an employer will try some type of remediation, which obviously doesn't work because the employee has the beginning of a dementing illness. Eventually the person has to leave his or her job or else take an early retirement.

**Q. How is someone diagnosed with young-onset dementia?**

**A.** The cornerstone of the diagnosis is the clinical history. Often the diagnosis is clear after an initial evaluation. In our clinic, the initial evaluation takes three hours, which includes speaking to the patient, querying many family members and friends, and examining motor, cognitive, and other neurological functions, as well as looking at laboratory reports and brain scan images. After reviewing this information, I will usually have a clinical suspicion. Typically, neural imaging is obtained if not performed already. A magnetic resonance imaging (MRI) or computed tomography or (CT) scan is used to rule out other dementia causes.

**Q. What is the reaction of the patient after being diagnosed with young-onset dementia?**

**A.** It varies depending on the person. Often we see people who have already been to multiple doctors, so they already may have been told they have young-onset dementia. These people are not surprised. Then we see people who are sad and depressed and obviously affected by the disease, as we all would be. However, many bounce back and try to make the best out of it. Finally, I see patients who say they are going to "beat the disease." Unfortunately, there is no way to "beat" the majority of dementias and although it can sometimes be slowed, it typically cannot be stopped. Often, the greatest problem in many young-onset patients is that



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## IN-DEPTH REPORT

### *Young-Onset Dementia*

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there is a lack of insight. In the vast majority of cases it is hard for patients to recognize they have the disease.

**Q. Do patients become depressed after being diagnosed with young-onset dementia?**

**A.** There is a large prevalence of mild depression or depressed mood either preceding the diagnosis, when the patient suspects that something is wrong and is fearful or anxious, or starting right after being diagnosed by a doctor.

**Q. Are patients upset with the diagnosis or are there brain changes that trigger the depression?**

**A.** I think both come into play. The patients are doing well and in the prime of life and suddenly everything gets turned upside down when they are told that they have a dementing illness and may not live much longer. But even before they know the diagnosis, patients and family members alike note signs of depression or apathy.

**Q. What happens after a positive diagnosis is made?**

**A.** When the diagnosis is young-onset dementia, the patient and family members have a myriad of important issues to review. They need to consult with their doctor about what to expect in the near future, and later on when the condition begins to progress. The doctor should suggest other medical specialists who will help in the patient's and family's treatment and care. This will include a psychiatrist and/or neurologist, therapists (e.g., physical, occupational, recreational, speech, and language), nurses, social workers, and counselors. Together, this team will help the patient and family to work on ways to keep the patient as independent as possible for as long as possible.

**Q. What happens to the spouse when a patient is diagnosed with young-onset dementia?**

**A.** Several things come to mind: exasperation, exhaustion, extreme frustration, fear, worry, anxiety, depression, and even divorce, particularly with patients who experience profound personality/behavioral changes from FTD.

**Q. If young-onset dementia is suspected, whom should someone go for help?**

**A.** Young-onset dementia exacts a high economic and emotional toll on family and caregivers. Accurate diagnosis is crucial because it tends to provide an



## IN-DEPTH REPORT

### *Young-Onset Dementia*

#### WHEN A SPOUSE HAS YOUNG-ONSET DEMENTIA: WHAT YOU NEED TO KNOW

**Here are the things you need to do if your loved one develops young-onset disease:**

**Gather information.** Although there is no cure, there are coping strategies. Educating yourself about what your loved one is going through will help you deal with this condition.

**Seek support.** Find ways to express your emotions, frustrations, and fears. Talking to another person experiencing young-onset dementia in a spouse can prove to be incredibly helpful. Contact the Alzheimer's Association for a support group nearest you.

**Check for benefits.** This illness may cause your loved one to stop work at a much younger age, and the loss of salary and benefits can be monumental. Check to see if your loved one is eligible for Social Security disability or other benefits. Unfortunately, many social-support programs will not provide assistance unless the person is over 65.

**Explain.** Children often experience a wide range of emotion, from sadness, fear, resentment, and embarrassment, to anxiety, anger, and depression. Talk openly to them about their parent's diagnosis—and the changes you are experiencing because of the disease. Answer all of their questions. Find ways to support them. Invite them to support group meetings. Include them in counseling sessions. Help them deal with their grief and seek medical attention if it is warranted.

**Speak to your own doctor.** Depression is not uncommon for the spouse of a patient with young-onset dementia. If you are feeling depressed or anxious about the life changes that you and your loved one are facing, speak to your doctor. As the disease progresses, you will no longer be in a joint partnership as you had been in your previous married life. As you assume the role of caregiver, you will lose the intimacy with your spouse and take on a parent-child relationship.

explanation to a chaotic and devastating clinical presentation. In addition, it gives a real direction for future management of the patient.

A good geriatric clinic, behavioral neurology clinic, or neuropsychiatric clinic



## IN-DEPTH REPORT

### Young-Onset Dementia

#### FRONTOTEMPORAL LOBAR DEGENERATION

Name a brain disorder that causes dementia or language problem, has no cure, and can devastate families, sometimes within just a few years of diagnosis.

If you said Alzheimer's disease (AD), that's a correct answer, but it's not the only one. Frontotemporal lobar degeneration (FTLD), a disease that causes the same percentage of dementia cases in the under-65 population as AD does in the *over*-65 age group, is a devastating brain disorder that often leaves its victims struggling to find words that once came with ease. Other FTLD victims become apathetic. It's also a brain disorder that can cause people to become extremely withdrawn or inappropriately extroverted. Some are arrested for their behavior, completely unaware or unconcerned that whatever they did was actually dangerous, socially inappropriate, or unlawful. It is a brain ailment that is extremely variable, in both the nature of the symptoms and the severity, depending on what part of the brain is affected.

Frontotemporal lobar degeneration comprises a group of related dementing

conditions that are caused by the loss of brain cells and that share common features as the disease progresses. All of these related dementias, as its name suggests, stem from a progressive shrinking and degeneration of the frontal (anterior) and temporal (side) lobes of the brain. These regions, located just behind the forehead, are involved with speech as well as abstract thinking, personality, and judgment. The damage of FTLD, which often runs in families, is devastating, bringing about significant changes in a person's behavior, personality, and/or language abilities.

FTLD is a clinical syndrome caused by a number of related diseases. One of the underlying diseases is called Pick's disease, an ailment named after Arnold Pick, a Czech psychiatrist and neurologist who first described the strange case of a 71-year-old male patient who had presented with progressive loss of speech and dementia in 1892. When the patient died, his brain was found on autopsy to be atrophied, with shrinkage and death of brain cells in localized areas. Dr. Pick's case study, "On the Relationship Between

Aphasia and Senile Atrophy of the Brain," is still a standard reference for generalized degenerative diseases of the brain. Interestingly, Dr. Alzheimer first described the microscopic hallmark of the disease, called the "Pick body" in 1902.

Frontotemporal lobar degeneration is sometimes known as frontotemporal dementia, or FTD. However, as brain and dementia research has intensified over the past few years, and it became evident that there are significant variants of the classic symptoms during the course of this disease, the name was switched to FTLD. FTD, as you will read later on, is now considered a variant of FTLD.

No one knows why some diseases strike only certain parts of the brain, and coming up with that answer to this is certainly worthy of the Nobel Prize in Medicine. In the beginning of the illness, Alzheimer's disease typically affects the hippocampus and the amygdala, located in the middle of the brain, and this significant brain insult leads to distinct memory issues. By contrast, when a person has FTLD, the frontal lobe, which is associated with decision-



## IN-DEPTH REPORT

### *Young-Onset Dementia*

making, emotions, and behavior control, is initially involved or the temporal lobes, which are involved, may also be damaged.

It is not uncommon for patients with FTLD to lose their language skills rapidly, sometimes over the course of several months. Some patients left speechless by FTLD later go on to develop newfound music or artistic skills that are as impressive as they are surprising. (Read “Musicophilia,” the new book by Oliver Sachs). In some individuals, the deterioration of language is very slow and is not associated with change in personality or behavior. Unfortunately, others with FTLD engage in behavior that is bizarre, unpredictable, and even unlawful that they are often thought to have a psychiatric disorder. And with an undiagnosed (or, worse, a misdiagnosed) FTLD patient spiraling out of control, a family is thrown into crisis, battling grief while trying to make sense of what’s going on and keeping its loved ones under control.

At its worst, loss of judgment, incessant swearing, financial improprieties, lack of empathy, hypersexual behavior, shoplifting, deterior-

ation in personal hygiene, and radical change in religious belief, politics, wardrobes, musical tastes, and even eating habits are hallmarks of the ailment. It’s not uncommon for a person’s personality to be completely erased or altered, with the patient showing no insight into how inappropriate their behavior has become and absolutely no concern for its effect on family and friends. Left in the patient’s place, however, is sometimes a person that a spouse, family member, and friend no longer recognizes or even likes. However, some individuals have a much slower decline and never have such severe changes in personality or function.

The exact prevalence of FTLD is unknown. Some experts estimate that FTLD affects 300,000 to 500,000 Americans and comprise as many as 4% to 20% of patients at memory-disorder or dementia clinics. Men are affected more than women (60% versus 40%). What distinguishes FTLD from other dementias is the gradual and progressive decline in a person’s behavior, language, or both parameters, at the very beginning of the illness.

Often FTLD progresses more rapidly than AD. From time of diagnosis, some people will live for two years, but others may survive a decade or longer (average 6-8 years).

Thus, like all dementing illnesses, FTLD can shorten life expectancy. But what makes FTLD even worse is that it often occurs early in life, striking people in their 40s, 50’s, and 60s (some as early as 21, others as old as 80), peaking at the age of 62, when many men and women are at the height of their careers. By contrast, AD typically strikes in the seventh decade of life and increases with age. Moreover, like AD, there is no known cause and no cure. However, many symptoms are treatable. The rate of progression of FTLD also is variable. As the disease progresses over a period of years, patients often need 24-hour care, monitoring at home, or institutionalization.

—**Argye Elizabeth Hillis, M.D.**, Professor, Departments of Neurology and Physical Medicine and Rehabilitation, and Executive Vice Chair, Department of Neurology at The Johns Hopkins University School of Medicine



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## IN-DEPTH REPORT

### *Young-Onset Dementia*

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should be able to make the diagnosis. At the Johns Hopkins Memory and Alzheimer's Treatment Center, we will often work with patients who come to the clinic from all over the country. We have a dedicated clinic for patients, with a support group for their family members.

**Q. What services does the Frontotemporal Dementia and Young-Onset Dementia Clinic at Johns Hopkins provide?**

**A.** The young-onset dementias present a number of challenges. These challenges include delayed or ambiguous diagnosis, rapid progression in some forms, threats to family income, issues pertaining to dependent children and to parenting, lack of age-appropriate respite-care services and a long-life expectancy for spouses who survive the patient.

Our clinical services for young-onset dementias are designed to directly address these problems by providing a comprehensive clinical care program that integrates traditional dementia care with an array of support services. These services include:

- Clarification of diagnosis
- Treatment of symptoms associated with dementia
- Dementia-care education
- Support groups (in partnership with the local Alzheimer's Association chapter and several national support groups).
- Practical assistance in the management of employment and retirement, and in completing disability applications
- Guidance in the planning of long-term care and in the long-term management of social and financial resources
- Clinic liaison with respite and residential programs
- Guidance with issues pertaining to dependent children
- Home visits (in certain circumstances)

For more information, contact Mary Anne Wylie, M.S., R.N., A.P.N.  
✓ Coordinator, The Johns Hopkins Frontotemporal Dementia and Young-Onset Dementias Clinic, Division of Geriatric Psychiatry and Neuropsychiatry, 550 North Broadway, Suite 308 ✓ Ò Baltimore, MD 21205. You may telephone the Clinic at 410-502-2981.



## GRAND ROUNDS

PETER V. RABINS, M.D., M.P.H.

*Hospitals regularly present Grand Rounds for their physicians. A doctor describes a case history along with clinical presentation and possible treatments. In the Memory Bulletin, Grand Rounds offers readers a chance to present questions about memory, with a Johns Hopkins physician offering responses. (These responses cannot replace the specific advice of your physician, however.)*

*Please e-mail your questions to [prabins@memorybulletin.com](mailto:prabins@memorybulletin.com). Or send your queries to The Memory Bulletin, MediZine LLC, 500 Fifth Avenue, Suite 1900, New York, NY 10110. Due to space limitations, not all queries can be answered.*

### GENETIC TESTING

**Q.** I am 51 years old and take care of my 81-year-old father, who has had AD for the past two years. His father died of dementia when he was 74. Of course, now that my father has AD and my grandfather may have died of it, I wonder about the inevitability of getting it or some form of dementia when I am older. What are your thoughts about genetic testing for AD? **Knoxville, TN**

**A.** At the present time, I do not think that genetic testing provides meaningful information unless there is a history of dementia beginning before age 60. Many studies have shown that 20 to 30% of people at age 80 suffer from dementia. If you have a family history, your chances of developing dementia are 30 to 40%, while a person without such a family history has a 10 to 15% chance. That is, your chances are about three times greater than someone whose parents lived to old age and did not develop dementia. It is not clear that genetic testing for the apolipoprotein E (APOE)  $\epsilon 4$  allele will provide more information. In fact, everyone is at risk for Alzheimer's disease (AD), but some people are at higher risk. I believe we all should consider the possibility that we are at risk and act accordingly.

### AD TIME SPAN

**Q.** My father was just diagnosed with AD. At 80 he looks and acts like someone 20 years younger. For someone in such good physical condition, what is the average lifespan from diagnosis to death for an AD patient? **Timonium, MD**

**A.** Studies in out patient clinics find that life expectancy from first symptom to death averages about 10 years, and my clinical experience agrees with this. Epidemiologic studies suggest a shorter time period for some reason. My guess is that the community epidemiologic studies are less accurate, although it is also possible that people who come to clinics are not representative of the average person.



## GRAND ROUNDS

PETER V. RABINS, M.D., M.P.H.

### CAUSES OF DEMENTIA

**Q.** Is dementia always triggered by AD, or are there other causes? **Jackson Hole, WY**

**A.** There are at least 75 distinct diseases that cause dementia. The word “dementia” is part of a broad medical category, called a syndrome, which includes any disease that causes a decline in two or more aspects of thinking and occurs in an alert, attentive individual. This is a very general definition, equivalent to “brain failure.” It signals to the clinician that the person must be evaluated to identify the specific cause of the dementia. In fact, anytime a person or his or her family is concerned about a possible diagnosis of memory loss or Alzheimer’s disease, the person should be fully evaluated by a physician.

### AGE AND AD

**Q.** Both my wife and I are 82 and, so far, our memories seem intact. We walk an hour a day, get plenty of rest, and are in very good physical condition. As far as we know, no one on either side of our family has had AD or any other form of dementia. That said, what are the odds of either one of us developing AD in the next five to 10 years? **Bowie, MD**

**A.** In general, individuals who are 80 to 85 years of age have a 1%- to 2%-per-year risk of developing dementia—not high enough that you should worry, but not low enough, unfortunately, that you have nothing to worry about.

### STROKE AND AD

**Q.** My 78-year-old wife suffered a mild stroke four months ago. She recovered very well from the weakness on her right side caused by the stroke and no longer needs physical therapy. Betsy was always “sharp as a tack” when it came to names, appointments, and details, but I have noticed that now she sometimes has to pause to recall, for example, the name of a play that we saw last year. Yesterday, she couldn’t remember the word “pen” and said, “You know, that thing you use to write with.” Thirty seconds later she remembered “pen.” I am worried that something could be going on with her memory. Should I make an appointment with her doctor, or is this a temporary problem that should pass? **Atlanta, GA**

**A.** Since you are concerned, it would be good to ask the physician who treated her stroke to assess if she has a disorder of naming or memory. While it is possible that she suffered another small stroke or has the beginnings of a dementia,



## GRAND ROUNDS

PETER V. RABINS, M.D., M.P.H.

this does not seem likely, since she was able to come up with the correct word for pen on her own relatively quickly.

### ASPARTAME AND AD

**Q.** Something came up at my recent AD caregiver support group meeting that made me upset. One of the caregivers said that using aspartame sweetener can cause AD. My wife has diabetes, and ever since aspartame was approved in the mid-1990s she would search out products that used this artificial ingredient. Is there a possibility that her AD (it's considered mild now) was caused by aspartame? **Palm Beach, FL**

**A.** I do not know of any convincing evidence that consuming aspartame (NutraSweet) is a risk factor for developing dementia or Alzheimer's disease. Diabetes is a risk factor for dementia, however—a risk not fully explained by the increased risk of stroke due to the diabetes.

### ELEVATED CHOLESTEROL AND AD

**Q.** Before I started taking a statin medication three years ago, my cholesterol level was always above 200 mg/dl and at one time was as high as 315 mg/dl. I am 51 years old now, and my cholesterol is 198 mg/dl and well managed. From what studies have revealed, are elevated cholesterol levels a possible cause of AD or any other form of dementia? If they are, will keeping cholesterol levels low reduce that risk, or, as in my case, is “the horse already out of the barn”? **Lenox, MA**

**A.** The jury is still out on whether a high total cholesterol or high low-density lipoprotein (LDL) cholesterol level increases the risk of Alzheimer's disease, and it is still not known whether statin drugs lower the risk of developing AD. Elevated cholesterol levels do increase the risk of stroke, which of course can lead to cognitive impairment and dementia, so keep up the good work. I hope you are also exercising and taking other steps to live a “heart-healthy” lifestyle.

**Q.** Just a quick question: Does AD affect a person's ability to walk? My husband was just diagnosed with AD. He is 54 years old. A longtime member of the Adirondack Mountain Club, he has hiked all the major peaks and has gone on weekend hikes with me and other club members for as long as we have been together. I know that we will have other major issues to deal with, but I need to know if his early AD might make it difficult for him to walk. Thanks for your help. **Lima, OH**



## GRAND ROUNDS

PETER V. RABINS, M.D., M.P.H.

**A.** Alzheimer's disease does commonly cause walking or gait disorders later in the illness, usually after five or six years of symptoms. It generally comes on gradually and is associated with falls. The evidence that continued exercise can delay or slow progression of AD is not very convincing, but some preliminary studies suggest this is possible. Therefore, I would suggest that the two of you walk together as long as you enjoy it and it is safe.

### DEPRESSION MIMICKING AD

**Q.** My 77-year-old husband has battled depression since his college days. He will go for the longest periods where everything seems fine, and then, seemingly out of the blue, he goes into what he calls his "funk." This funk can last for a few days to as long as several weeks before he comes out of it and returns to the Walter that I know. With the memory problems and listlessness that Walter exhibits when he is depressed, I often fear that it is not his funk that is bothering him but the onset of Alzheimer's. I try to push that thought out of my mind, but it's a fear I cannot get rid of. Is there any link between depression and AD that I should be on the lookout for? **Algoma, WI**

**A.** Some studies suggest that depression in early life increases the risk of developing later depression, but other studies have not confirmed this. Since all antidepressants can prevent the recurrence of depression, I hope that your husband is being treated by someone who can help him find a drug that lowers his risk of having continued depressive episodes.

### VITAMINS AND AD

**Q.** I am determined to live as long as my parents, both of whom are in their late 90s. I am in good health. I jog daily, lift weights three times a week, and have been a vegetarian for the past 48 years. My question has to do with prevention of AD. To your knowledge, are there any vitamins I should be taking that can help reduce my chances of developing Alzheimer's? **Star Valley, AZ**

**A.** Despite many studies, there is no convincing evidence that any vitamin lowers risk. A few researchers have found that people who take vitamin C or E or who eat foods high in these vitamins are at lower risk, but many other studies have not found this to be true. I recommend eating a well-rounded, heart-healthy diet, and make sure that your blood pressure, cholesterol, and blood sugar are under good control.



## GRAND ROUNDS

PETER V. RABINS, M.D., M.P.H.

### HRT AND AD

**Q.** I am 54 years old and just began hormone replacement therapy for my hot flashes. I understand the possible health risks associated with HRT, but I don't have breast cancer in my family so I will take the hormones for as long as possible. I am writing to you because I heard that one of the possible side benefits of HRT is memory preservation. Is this true, or is this something that, like most medical issues that I read about these days, still needs more study? **Tarrytown, NY**

**A.** The best study to date, the Women's Health Initiative (WHI) study, found that taking HRT consisting of estrogen plus progestin actually *increased* the risk of developing dementia in women older than 65. We don't have prospective data on women under that age, but some epidemiologic studies have found that midlife HRT is protective. Most experts believe that exposure to HRT, especially progestin, should be limited in postmenopausal women because of the WHI study. Even without a family history of cancer, the risk of ovarian and breast cancer is still elevated.

### OA, AD, AND ANTI-INFLAMMATORIES

**Q.** I am curious; I have been taking Celebrex for my painful right knee for the past five years. I was diagnosed with severe osteoarthritis, caused in part by too much football when I was younger, a torn anterior cruciate ligament from skiing 20 years ago, and four decades of singles tennis. I am now 71, and I have been reading up on things to do to protect the brain from Alzheimer's and came across mention of anti-inflammatory drugs. Since I have been taking Celebrex pretty regularly for such a long time, do you think I have also been getting brain protection? **Bishopville, MD**

**A.** While older, retrospective studies did find that individuals taking drugs like ibuprofen (Motrin) were at lower risk for developing dementia than similar-age individuals who did not, a recently completed prospective study in which individuals received Naprosyn (naproxen), Celebrex (celecoxib), or a placebo pill showed that those receiving the drugs had an *increased* likelihood (that was not statistically significant) of developing dementia. While a single study does not convincingly prove that these drugs increase risk, I think it unlikely that a better-designed study will be done in the near future.

### CHOLINESTERASE INHIBITOR CHOICE

**Q.** My 82-year-old grandmother was just diagnosed with AD and will be starting on a cholinesterase inhibitor. Given a choice of the three available drugs, would



## GRAND ROUNDS

PETER V. RABINS, M.D., M.P.H.

you choose Aricept, Exelon, or Razadyne? Why? **Hurlock, MD**

**A.** I believe the evidence suggests that all three are equivalent in the ability to modestly improve cognition in people with AD; I cannot recommend one over another for that reason. Exelon (rivastigmine) comes in a patch form, Razadyne (galantamine) is taken by mouth twice a day, while Aricept (donepezil) is taken once a day. These are convenience differences and matter to a few—but not most—people.

### GINKGO BILOBA AND HUPERZINE A

**Q.** What are your thoughts on ginkgo biloba and huperzine A as memory-protecting supplements for people without AD? **Point of Rocks, MD**

**A.** A large, recently published study convincingly shows that ginkgo does not prevent the development of dementia. I believe huperzine A is still under study, but it may have more side effects than the other available medicines that are thought to work by increasing availability of the brain neurotransmitter acetylcholine.

### “IMAGINARY” ATTACKS

**Q.** My mother was diagnosed with vascular dementia and Alzheimer’s four years ago. She takes Aricept and Risperdal for agitation. She hasn’t exhibited any agitated behavior for several years and is generally in a good mood, although she is often quite confused. Mom has live-in full-time care in her apartment. Recently, at a family dinner when the caregiver was not present, some of us were praising her caregiver as a very nice person when my mother abruptly said that she wasn’t nice at all, that she was mean and pulled my mother’s hair. When we asked her why that happened, she said that once it was because she tried to make a joke, which the caregiver didn’t like, and once she hadn’t liked some clothes the caregiver bought for her. She said this with great vehemence and then, as the discussion continued, she began making very bizarre faces.

I have no way to check out these disturbing claims. There is no physical evidence of injury to my mother, and she hasn’t had any doctor visits for “accidents” or bruises. I stayed with her and her caregiver for four days recently, and my mother didn’t appear to be afraid or shrink from the caregiver; nor does the caregiver ever try to isolate her from the rest of the family (my brother lives half a block away). In fact, if anything, they seemed to have a closer relationship than they did the last time I visited a year ago. How should we approach this “problem”? **Via email.**



## GRAND ROUNDS

PETER V. RABINS, M.D., M.P.H.

**A.** This is a challenging problem. You indicate that you have been unable to verify the accusation by finding either evidence of injury or evidence in your mother's behavior that she is afraid. As a start, I suggest you ask your mother about this issue again when you and she are alone. If she is unaware of her previous statements alleging abuse, that indicates that either her memory is not good enough to reliably report such abuse or she does not want to tell you about it. If she has had dementia for this long, and AD is part of the diagnosis, then she is likely suffering from a severe impairment of memory and her ability to recall a single incident in the past such as this is unlikely but not impossible.

Have there been any other accusations made about this or other persons that are clearly false? Delusions (false, unshakable ideas that are unique to that person) are common in people with dementia, and if there have been others, that would increase the likelihood that this abuse is a false idea. Ultimately, you should talk to the caregiver. If you believe the idea is likely to be false, I suggest you tell that to the caregiver but say that that you wanted to inform her so she would be knowledgeable about the situation.

### HOMOCYSTEINE LEVELS

**Q.** Both my parents have had dementia. My father died of Alzheimer's disease 10 years ago. I am 60 years old and concerned about my risk of dementia. I am in good vascular health: Total cholesterol is 198 mg/dl, HDL is 65 mg/dl, triglyceride level is 78 mg/dl, LDL 117, and blood pressure is 93/58 mm Hg. However, my homocysteine level is relatively high at 12.1 micromoles. Two years ago, it was 12.5 and I doubled up on the amount of folic acid I was taking; the next year it dropped to 9.1. I now take a B complex vitamin with 50 mg of B6, 50 mcg of B12, and 400 mcg of folic acid. I take an additional 400 mcg of folic acid. Should I be concerned about this increase in homocysteine level? Is there anything I can do to bring it down? **Via email.**

**A.** There is a lack of evidence that lowering one's homocysteine level prevents dementia. I do not think that the B complex vitamin will harm you but the likelihood of benefit is very low. I suggest you participate in a regular exercise program if your physician concurs, make sure you do not have diabetes or are obese, and stay mentally active.



JOHNS HOPKINS  
MEDICINE

The information contained in *The Johns Hopkins Memory Bulletin* is not intended as a substitute for the advice of a physician. Readers who suspect they may have specific medical problems should consult a physician about any suggestions made.

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