Alzheimer’s: Forestalling the Darkness

In his magical-realist masterpiece One Hundred Years of Solitude, Colombian author Gabriel García Márquez takes the reader to the mythical jungle village of Macondo, where, in one oft-recounted scene, residents suffer from a disease that causes them to lose all memory. The malady erases “the name and notion of things and finally the identity of people.” The symptoms persist until a traveling gypsy turns up with a drink “of a gentle color” that returns them to health.

In a 21st-century parallel to the townspeople of Macondo, a few hundred residents from Medellín, Colombia, and nearby coffee-growing areas may get a chance to assist in the search for something akin to a real-life version of the gypsy’s concoction. Medellín and its environs are home to the world’s largest contingent of individuals with a hereditary form of Alzheimer’s disease. Members of 25 extended families, with 5,000 members, develop early-onset Alzheimer’s, usually before the age of 50, if they harbor an aberrant version of a particular gene.

Early-onset Alzheimer’s, passed down as a dominant genetic trait from only one parent, accounts for less than 1 percent of the 27 million Alzheimer’s cases worldwide documented in 2006, but its hallmark brain lesions appear to be identical to those in the more common late-onset form, in which symptoms do not appear until after the age of 65.

The predictability of disease onset in the Medellín families has attracted the attention of a group of scientists and pharmaceutical companies who are considering a novel approach to research that will test drugs in patients before the first signs of dementia appear.

In recent years a number of drug candidates for treating mild or moderate Alzheimer’s have failed, persuading researchers that much of the disease pathology—accretions of aberrant proteins and loss of brain cells or circuits—begins well before the memory loss becomes apparent. This growing realization, confirmed by new technologies that can track the disease years before the first symptom, suggests that to be most successful, treatment must start during the many years when the insidious disease process is already under way, even though a patient’s memory remains intact.

Consequently, a major thrust of much Alzheimer’s research is shifting toward arresting the disease in advance of symptoms—not only with drugs but also with lifestyle measures that would be safer and less costly than filling a drug prescription for 10 or 20 years.

Interventions before symptoms appear could be key to slowing or stopping the leading cause of dementia

By Gary Stix

KEY CONCEPTS
- The incidence of Alzheimer’s disease continues to rise as the population ages, but effective treatments are lacking.
- Some new drugs may have failed because they were tried too late.
- New techniques to track the disease before symptoms arise may allow testing of drugs at a stage when they may be more effective.

—The Editors
**An Early Start**

The Colombian Alzheimer’s families stand in the vanguard of prevention research. Francisco Lopera, the neurologist who 28 years ago first came across the families who were later discovered to bear the paisa mutation (named after the moniker for the people of the region), has begun to contact hundreds of still healthy family members. He wants to probe their willingness to participate in a test of drugs that would remove or stop the buildup of toxic protein fragments, amyloid-beta peptides, that damage brain cells early in the disease process. “The contribution made by these families may shed a lot of light on the treatment and prevention of both early- and late-life Alzheimer’s,” Lopera says.

In the planned trial, which could begin as early as next year and is part of a broader effort called the Alzheimer’s Prevention Initiative (API), healthy, mutation-bearing family members around the age of 40 would start to receive anti-amyloid therapies (a drug or vaccine) already tested for safety in Alzheimer’s patients. Talks are under way to send a cyclotron—a small particle accelerator—to be shared by a group of hospitals in Medellín for making radioactive tracers needed for imaging studies that would reveal whether the drug is hindering amyloid buildup.

The trial will evaluate whether a treatment can delay or stop the inexorable silent progression of the disease if administered seven years before the average age of diagnosis in family members who carry the gene. Beyond testing specific therapies, the designers of the Colombian trials also plan to see whether tracking of Alzheimer’s-specific biomarkers can indicate whether an experimental treatment is working. (A biomarker is a measurable indicator—such as a concentration of a particular protein—that changes in concert with progression or regression of a disease.) A reliable set of biomarkers would allow drug researchers and clinicians caring for patients to evaluate success of a therapy relatively quickly, by measuring changes in such silent benchmarks, instead of having to wait to assess overt symptoms. The API plans to undertake a similar set of trials with a U.S.-based group made up of carriers of two copies of a gene variant, APOE4, that increases susceptibility to Alzheimer’s, although carriers are not guaranteed to get the disease.

If successful, the API would serve as a model for making biomarker-based Alzheimer’s prevention trials commonplace. Proving that a drug prevents a disease takes much longer and costs...
much more than ascertaining whether it works in a patient who is already sick. “A pharmaceutical company is not going to invest in the longer duration of a prevention trial for an unproven agent that may not be efficacious,” notes Maria Carrillo, senior director of medical and scientific relations for the Alzheimer’s Association.

With a set of biomarkers in hand, a pharmaceutical company could test whether a drug changes levels of amyloid or another biomarker in the same way that physicians test cholesterol levels as a gauge of whether a statin is helping to prevent heart disease. “We need to move presymptomatic treatments forward. Otherwise we could lose a whole generation,” says Eric M. Reiman, executive director of the Banner Alzheimer’s Institute in Phoenix, who, along with colleague Pierre N. Tariot, launched the API.

The challenges of prevention trials still loom large: the drawbacks posed by inevitable drug side effects are more difficult to weigh against potential benefits in patients who do not yet have symptoms. Moreover, no one can predict whether a drug that proves helpful for early-onset Alzheimer’s will also work in patients who lack the particular gene mutation that brings on the early-onset form of the disease. But the urgency of finding new treatments—and the lure of a multi-billion-dollar drug—has given momentum to prevention strategies. An organizational meeting for the API in January drew 19 U.S. and European pharmaceutical and biotechnology companies to a Phoenix airport hotel to discuss the possibility of forming a noncompetitive partnership in which academics and industry would collaborate on clinical studies and share results freely.

Some therapies for Alzheimer’s do exist, but they do little to delay disease progression. A true disease-modifying treatment would meet with overwhelming patient demand. Statisticians predict that by the middle of the century, the global prevalence of Alzheimer’s will quadruple, reaching 107 million. A treatment that delays disease onset by even five years would halve the number of people who die from the disease.

**Inside Your Head**

An Alzheimer’s prevention trial based on biomarkers would have been dismissed as fantasy as recently as five years ago. Such an endeavor may come to fruition because imaging and other technologies, now flourishing worldwide, can track biomarkers to reveal the nature of the underlying disease process. In the U.S. since 2004, the Alzheimer’s Disease Neuroimaging Initiative (ADNI), a collaboration among pharmaceutical companies, academics and the National Institutes of Health, has been developing methods to better assess the effectiveness of drugs tested in individuals suffering from the disease, a goal that quickly expanded to look at what is happening during the time before an actual diagnosis is made.

One intriguing report of progress in the field came January 21, when Clifford R. Jack, head of the group within ADNI studying biomarkers that can be detected with magnetic resonance imaging (MRI), described a model of how the disease likely progresses and paired it with biomarkers that seem able to track this pathology. Jack presented his work, which also appeared in a technical paper, to an online audience of more than 100 people during a Web seminar on Alzheimer’s forum, a gathering that included many leading researchers in the field. Co-founded by June Kinoshita, a former *Scientific American* editor, Alzheimer’s forum is a meeting place for the exchange of ideas, a repository of research information and a source of perhaps the most in-depth journalism anywhere on Alzheimer’s research.

At the Web seminar, Jack noted that the biomarker measurements have demonstrated that the disease process begins years before the defining symptoms that allow a diagnosis to be made. During this time (estimated to range from five to 20 years), a particular type of amyloid peptide...
[PROGRESS TOWARD PREVENTION]

NEW TOOLS DETECT SILENT EARLY SIGNS

The disease process underlying Alzheimer’s (below) starts years before symptoms would lead to a diagnosis. Researchers can now track it in living patients with tools—including brain imaging and spinal fluid tests (far right)—that monitor Alzheimer’s-related biomarkers: signs of biological changes (such as mounting levels of toxic proteins) that routinely occur in the course of the disease. Researchers hope that one day biomarker testing will identify incipient disease in people and that treatment in this early stage will delay or prevent dementia.

**AMYLOID ACCRETION**

5–20 years before diagnosis of Alzheimer’s dementia

Early on, a protein fragment called amyloid-beta aggregates in the brain centers that form new memories. The amyloid buildup, a biomarker detected by the presence of plaques, results in damage to synapses, the interface between neurons (detail). Amyloid blocks chemical signals (neurotransmitters) from reaching receptors on receiving neurons. This buildup can be captured by various forms of neuroimaging, including positron-emission tomography (PET), that detect a radioactive compound, Pittsburgh imaging compound-B (PIB), able to bind specifically to amyloid. A spinal tap can also be used to gauge the amyloid biomarker.

**TAU BUILDUP**

1–5 years before diagnosis

Before symptoms would justify an Alzheimer’s diagnosis, a protein called tau inside neurons begins misbehaving. Normally tau helps to maintain the structure of tiny tubes (microtubules) critical to the proper functioning of neurons. But now phosphate groups begin to accumulate on tau proteins (detail), which detach from the microtubules. The tubes go on to disintegrate, and tau then aggregates, forming tangles that interfere with cellular functions. A sample of spinal fluid can detect this process.

**BRAIN SHRINKAGE**

1–3 years before diagnosis

As the underlying disease process advances, nerve cells start to die, and patients and family notice memory and other cognitive lapses. Cell death shrinks the brain in areas that involve memory (the hippocampus) and higher-level brain functions (the cortex) and thus can be tracked with a form of magnetic resonance imaging that measures brain volume. Such shrinkage accelerates and ultimately involves many areas of the brain.
begins to aggregate outside of brain cells and damage synapses, the contact points between neurons. A radioactive tracer molecule, such as Pittsburgh imaging compound-B (PIB), can bind to amyloid in a patient’s brain and then be imaged using PET (positron-emission tomography). The imaging technique, abbreviated PIB-PET, has shown that this aggregation process starts to level off before definitive symptoms arise.

Later on, but also before a diagnosis, a class of proteins called tau, which normally assist in providing structural support to neurons, become detached from the cells’ scaffolding and clump into tangles, wreaking havoc inside the cells. The tau buildup can be detected by examining a sample of cerebrospinal fluid. This test can also look for decreasing levels of amyloid-beta, which occur as the peptides get removed from the fluid to form deposits in the brain. Together, decreasing levels of amyloid-beta and an increase in tau in the cerebrospinal fluid give a strong signal that the disease process is advancing.

Anywhere from one to four years before a person is diagnosed with Alzheimer’s, a phase called mild cognitive impairment sets in. It is characterized by symptoms that range from memory lapses to poor decision making. Mild cognitive impairment can arise from causes other than Alzheimer’s, but in those who are on the road to Alzheimer’s dementia, mild cognitive impairment occurs because neurons in certain brain areas are damaged or dying—a loss that accelerates over time. (If memory problems are the primary symptom, the patient often progresses to Alzheimer’s.) This stage can be tracked with a form of imaging called volumetric MRI, which measures shrinkage of the brain as neurons expire. The cascade of events, including the early accretion of amyloid, disrupts cell metabolism and can be monitored with a form of PET, fluorodeoxyglucose-PET (FDG-PET), that gauges the metabolic status of neurons.

**But Does the Patient Get Better?**

Using biomarkers as the basis of clinical trials for prevention poses a set of challenges to both pharmaceutical companies and regulators—and constitutes a barrier to moving ahead with the API and other prevention efforts. To be approved, an Alzheimer’s drug needs to show that it provides cognitive benefits for the patient (in memory, language or a related measure) better than a placebo does.

If a biomarker is tracked instead of symptoms in a prevention study, researchers need to be sure that the measurements truly presage whether a subject is likely to develop dementia. For instance, investigators do not yet know whether changing amyloid-beta levels will ultimately prevent dementia, despite the large body of evidence suggesting that amyloid-beta contributes to disease development.

In fact, in one early trial of an amyloid therapy, the levels of the peptide decreased in some patients, but there was almost no evidence that cognition improved. “We’re concerned that we might have a drug that affects a marker in the way that we predict but that it doesn’t affect patients’ clinical picture,” says Russell Katz, director of the division of neurology products for the Food and Drug Administration. “In other words, their disease continues to progress, and they don’t get any better.” Katz says a better approach to incorporating biomarkers in clinical trials would be to first show that reducing levels of amyloid or another biomarker benefits patients who have mild cognitive impairment or who are newly diagnosed with Alzheimer’s and to attempt to use biomarkers in people without symptoms only afterward. “The best way to get there in my opinion is to start with patients who have symptoms, maybe very, very early patients, and then work backward,” Katz says.

But the researchers in the Colombian prevention trials assert that they may already be capable of using biomarkers to detect subtle changes in memory, thereby allaying Katz’s concern. And Reiman cites work from his group that might offer another way to help ease regulator concerns. In that study, carriers of the APOE4 gene variant showed a small decline in scores for memory on psychological tests many years before any cognitive deficit became noticeable. This level of sensitivity, Reiman says, means that applying a cognitive test along with a biomarker measure in a prevention trial might suffice to indicate, say, whether prospects for avoiding dementia really do improve as amyloid levels drop. For the moment, Katz still needs convincing. “What is the evidence that these patients, despite their diminished cognitive status, will actually go on to develop Alzheimer’s?”

Some companies are already trying to gain a better understanding of how to use biomarkers. Bristol-Myers Squibb has been sampling the spinal fluid of patients with mild cognitive impairment to try to predict which ones are likely to progress to Alzheimer’s. Those who exhibit a low level of amyloid-beta and a high level of tau will be qualified to participate in a trial of a drug.
[STATE OF THERAPY]

WHY TREATMENTS LAG

Any drug that substantively delayed or stopped Alzheimer’s would be an immediate blockbuster, perhaps exceeding sales for Prozac or Lipitor. No such drugs are on the market because investigators are still trying to understand how to alter the underlying mechanisms by which the disease causes dementia.

Drugs that impede amyloid buildup offer a case in point: a number of drug possibilities at various stages of testing can purportedly inhibit amyloid accumulation or foster its clearance. Yet several antiamyloid drugs tested in clinical trials have already failed. (The table below lists major classes of Alzheimer’s drugs under development.) Some researchers wonder whether too little emphasis has been placed on interfering with other processes that contribute to the disorder. Among the 100 or so agents under development are prospective drugs that target the cell-damaging tau protein. Some are intended to quell inflammation, boost the functioning of mitochondria, enhance cerebral insulin levels or provide other protection for neurons. The most recent high-profile failure involved Dimebon, a drug that did not target amyloid. As with cancer and HIV, it may be necessary to combine several of these agents to slow or halt Alzheimer’s. —G.S.

<table>
<thead>
<tr>
<th>DRUGS UNDER STUDY</th>
<th>WHAT THEY DO</th>
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<tr>
<td>Inhibitors of enzymes that produce amyloid-beta</td>
<td>Such inhibitors block or modify the action of enzymes that cut a large protein (the amyloid precursor protein) in a way that releases the amyloid-beta peptides.</td>
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<tr>
<td>Vaccines or antibodies that clear amyloid-beta</td>
<td>Vaccines induce the body to produce antibodies that bind to amyloid and clear them from the brain. Unfortunately, in clinical trials, both vaccines and antibodies have induced side effects of varying severity in some patients.</td>
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<td>Amyloid-beta aggregation blockers</td>
<td>Agents that prevent amyloid fragments from clumping could prevent damage to neurons.</td>
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<td>Antitau compounds</td>
<td>These agents, although fewer in number than those that target the amyloid pathway, take various approaches, such as blocking production of the toxic form of the tau protein or impeding its aggregation into tangles.</td>
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<tr>
<td>Neuroprotective agents</td>
<td>Different strategies attempt to boost natural brain chemicals that enhance the health of neurons. In one, a gene is delivered into the brain to start production of a protective substance.</td>
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Absent effective drugs, some researchers and clinicians are exploring diet along with mental and physical exercise as preventive steps.

That blocks an enzyme, called gamma secretase, involved in producing the amyloid-beta peptide. “If you don’t have the biomarker associated with Alzheimer’s pathophysiology, you won’t be eligible to be enrolled into the treatment arm of our study,” notes Vlad Coric, medical director for global science clinical research at Bristol-Myers Squibb. The ability to target only the patients who are more likely to get a diagnosis of Alzheimer’s will facilitate assessment of whether the drug really works, results that would be less clear if the trial had included participants who have little chance of getting the disease. “Looking into the future, one would perhaps start drug trials even earlier, during the presymptomatic phase,” Coric adds.

A Cognitive Shop

The Colombian Alzheimer’s families at the center of the API have also served as inspiration for another innovative approach to prevention. Neuroscientist Kenneth S. Kosik, who has worked with the Colombian families for nearly 20 years and who helped to identify the paixa mutation, established last year what he calls a “cognitive shop” in a residential neighborhood of Santa Barbara, Calif. It was Kosik who arranged a pivotal meeting in Medellin to bring Lopera and the Colombian families into the API.

The cognitive shop—known more formally as the center for Cognitive Fitness & Innovative Therapies (CFIT)—is a refuge for both those with the mild memory complaints that sometimes precede full-fledged Alzheimer’s and the worried well. They go to the Mediterranean-style building to receive advice, based on the best existing evidence, about life changes they can make to perhaps help ward off the specter of dementia—or to better cope with it if it does arrive.

Kosik took the idea for CFIT from Casa Neurociencias, a less sumptuous outpatient clinic near the central hospital in Medellin, a place he spent many hours working alongside Lopera. Alzheimer’s patients with the paixa mutation, along with, at times, dozens of family members, would take a long bus ride from the countryside to spend the day in the clinic’s open space, where the medical staff and family members had easy access to one another. “It was remarkable that there, where the medical system was not so developed, the caring side and the ancillary services were more available,” Kosik says.

During his trips, Kosik contrasted the atmosphere favorably to the clinical efficiency of Harvard Medical School, where he had co-founded a memory disorders clinic at Brigham and Women’s Hospital before moving to the University of California, Santa Barbara, in 2004. “I developed a frustration with the fact that people would come into the clinic and we would say, yes, this is looking like Alzheimer’s, and then it was adios,” he says. “We would see them and follow up every six months, but we couldn’t do much except document their decline.”

CFIT combines the informality of Casa Neurociencias with lifestyle recommendations, much of them based on a still evolving body of scientific evidence derived from recent epidemiological or animal studies suggesting that different behaviors might aid cognition. Epidemiologists follow a selected group to determine whether exercise, diet or a multitude of other activities might reduce the risk of a disease such as Alzheimer’s, although more rigorous types of studies are needed to make definitive conclusions.

After a physical and psychological evalu-
tion, a client (the word “patient” is never used) receives a series of personalized recommendations that may include adopting the Mediterranean diet (healthy fats and high fruit and vegetable consumption), engaging in aerobic exercise and playing online brain games. The center engages in some activities that have yet to become standard practice at places such as the Harvard-affiliated memory clinic. As an acknowledgment of the reality of a new era in which patients want more control of their medical care, Tonya Kydland, a cognitive psychologist, acts as a “navigator” to guide people through the morass of medical information on the Internet. She projects a large image of a Web browser on a wall of a darkened conference room and takes a client, page by page, through clinical trials or recent studies on curcumin or another dietary supplement purported to protect brain cells, explaining the weight of evidence for one compound versus another.

CFIT also undertakes the controversial practice of coordinating testing for the APOE4 gene variant. The test is done after counseling the client about the implications of learning the results: if positive, siblings and children may also carry the same gene version and thus be at higher risk. Medical groups discourage testing because it is more control of their medical care, Tonya Kydland, a cognitive psychologist, acts as a “navigator” to guide people through the morass of medical information on the Internet. She projects a large image of a Web browser on a wall of a darkened conference room and takes a client, page by page, through clinical trials or recent studies on curcumin or another dietary supplement purported to protect brain cells, explaining the weight of evidence for one compound versus another.

Kosik, who was a co-author of one of the early papers on the toxic tau protein, denies that he has become a “hot tub” physician who endorses flaky ideas. His laboratory at U.C. Santa Barbara still does studies on the tau protein and other esoteric basic biology. CFIT is intended to fill the gap until the API or some other venture can uncover drugs or other measures that have been proved to work. “The solutions we have here are ultimately not the best solution,” Kosik comments. “But we don’t know when a drug is going to arrive that treats the disease the same way penicillin treats an infection. I think it’s irresponsible to tell people it’s going to be five or 10 years, because I don’t think we know that.”

In coming years, CFIT’s approach to prevention will receive closer scrutiny in rigorous government-funded clinical trials designed to find out whether diet and exercise can really delay the disease or whether the evidence from the epidemiology was just a statistical fluke. One major question for the lifestyle work, says Reisa Sperling, associate professor of neurology at Harvard Medical School, is whether interventions have different effects in people whose brains are currently normal than in those already showing Alzheimer’s-related changes. “Some of these interventions may modulate risk, but if you’re already on the road—if you’ve got the genes, and you’ve already got a head full of amyloid—these interventions may be less able to slow the progression, and so it’s important to test these ideas using biomarkers to see if they really work.”

Ultimately, PET technology or a lumbar puncture may determine whether olives, goat cheese and half an hour every day on the treadmill help to preserve cognition or are just a mere chimera. If such biomarkers do prove useful, biological and behavioral research may finally come together into a true science of Alzheimer’s prevention.

IMPORT FROM COLOMBIA:
Neurologist Francisco Lopera (pointing his left finger) established a standard of care for the world’s largest contingent of families with a hereditary form of Alzheimer’s disease at a clinic in Medellin, Colombia. The community-centered treatment approach instituted by Lopera and his colleagues served as an inspiration for a “cognitive shop” in Santa Barbara (right), where clients engage in programs of physical exercise and other activities aimed at reducing the risk of dementia.

MORE TO EXPLORE


Gabrielle Strobel of Alzforum led a discussion on January 21 about disease-tracking “biomarkers” with a number of leading researchers: www.alzforum.org/res/for/journal/detail.asp?liveID=179