Alzheimer’s disease (AD) afflicts 4 million people in the United States and is expected to strike 14 million by the year 2050, as the population ages. Researchers are scrambling to find genetic risk factors, decipher disease mechanisms, and develop reliable diagnostic tests that detect the illness at its earliest, potentially most treatable stage. Using these findings, they hope to devise new therapeutic approaches. Current clinical trials are testing novel techniques that stall or reverse AD-like neuropathology in mice.

“Alzheimer’s is in fact like an insidious fog, barely noticeable until everything around has disappeared. After that, it is no longer possible to believe that a world without fog exists.”
—From Elegy for Iris, by John Bayley, describing his wife Iris Murdoch’s descent into Alzheimer’s disease.

Introduction
Alzheimer’s disease (AD) is one of the spookiest ailments around. It steals victims’ memories, changes their personalities, and renders them speechless and unable to think coherently. But what makes the disease so frightening is not just its symptoms but its prevalence. One in 10 people older than 65 suffer from AD; above 85, the odds rise to almost 50%.

In contrast, research activity on AD is anything but spooky: Its rapid progress is demystifying the disease. Thanks to the past decade’s insights into the genetics and underlying biological processes of the illness, “we can begin to think about doing something for [Alzheimer’s patients], instead of just labeling them,” says Don Price of Johns Hopkins University in Baltimore. Indeed, three different strategies for alleviating or preventing some of the neuropathological symptoms of AD are being assessed in clinical trials now, and other lines of research are pointing to additional disease-fighting strategies.

Mountains of unanswered questions still loom, however. The field of AD research “has really blossomed,” says Colin Masters of the University of Melbourne in Australia. “But it hasn’t reached its peak yet. There’s never been a better time for a young investigator since I’ve come into this area. There’s just so much going on.”

Diagnosis
Alzheimer’s is tricky to diagnose. In its earliest stages, it can mimic depression, reactions to prescription drugs, a variety of other diseases, and normal aging. Some neuropsychological tests predict better than others who will develop more clear-cut symptoms of AD (†). Although subtle at first, “over time, the disease declares itself,” says Don Price. Memory, language, and decision-making skills decline steadily as confusion grows, sometimes accompanied by belligerence, anxiety, or hallucinations (see Honig case study*). Excluding other causes and observing the rate and type of decline can allow a clinician to diagnose AD with as much as 90% accuracy.

But because other dementias cause similar symptoms, ultimately only an autopsy can confirm that someone suffered from Alzheimer’s. Using staining techniques and a microscope, a pathologist can spot the diagnostic plaques and tangles that riddle an AD patient’s brain (Fig. 1). The so-called amyloid neuritic (or senile) plaques are found outside the cell and consist of amyloid protein knotted up with tendrils of malformed brain cells; the neurofibrillary tangles are made of a protein called tau, and they bunch up inside of neurons. Although plaques and tangles are still the defining characteristics of AD, the set of quantitative criteria used by neuropathologists to make the diagnosis is somewhat arbitrary and has changed in recent years.

Fig.1: The evidence. Extracellular deposits, called amyloid neuritic plaques (top), accumulate preferentially in certain regions of the brain in people with Alzheimer’s disease; neurofibrillary tangles (bottom) build up inside of neurons.
Sometimes the disease is called “dementia of the Alzheimer’s type” (DAT) to reflect the uncertainties about how to define it as well as whether AD is a single disease rather than a collection of different ailments that cause similar symptoms.

As potential therapies snake through the drug-approval pipeline, better tools are needed to figure out who should get the therapies, says Don Price. Ideally, treatments would reach people at risk for AD during the so-called preclinical stage—before they lose too many precious, largely irreplaceable neurons. If there were a benign treatment, he says, “when you joined AARP [the American Association of Retired Persons], you’d get your pill.” The classic signs of AD—plaques and tangles—gunk up the brain well before people show symptoms of AD, according to autopsy studies that include nondemented people (2). Such studies imply that “the disease has already started before it can be clinically detected,” says Joe Price of Washington University in St. Louis. And people who have been diagnosed with the mildest, early stage of AD already suffer from a substantial loss of neurons in memory areas of the brain (3), he adds.

Both Prices (who are unrelated) point out that several approaches might yield decent diagnostics for Alzheimer’s. Blood or spinal fluid might carry the signatures of the proteins that compose plaques and tangles; neuroimaging techniques could theoretically be designed to highlight deposits of β amyloid, the main ingredient in plaques; and the search continues for genes that predict someone’s risk of Alzheimer’s. So far, three genes—Presenilin 1 (PS1), Presenilin 2 (PS2), and APP—have been linked to rare, early-onset forms of the disease that usually strike people before they reach age 60; each child of such a patient stands a 50% chance of inheriting the gene and thus succumbing to the disease if he or she lives long enough (4-9). And one version of a fourth gene, APOE, increases a person’s risk of AD but doesn’t impose an absolute sentence like the others do (10).

But the early-onset genes account for less than 5% of Alzheimer’s patients. A strong genetic component contributes to the common type of illness that hits people when they’re older, but that form of the disease isn’t due to a single gene’s defect. As a result, it’s harder to study than the rare, early-onset form.

The hunt for AD genes is still on. “To me, the genetics [of AD] is just starting,” says Rudolph Tanzi of Harvard Medical School in Boston. “The tools are in place,” including the human genome sequence, identification of single-nucleotide polymorphisms (SNPs), and studies of families with high incidence of Alzheimer’s. Researchers hope that new genes will hint at the disease’s etiology, which molecular pathways it hijacks, and where drugs might aim to block Alzheimer’s. Recently, Tanzi’s team and others identified a region of chromosome 10—but not yet a particular gene—linked to sporadic, late-onset AD (11-13). And Ellen Wijsman of the University of Washington, Seattle, estimates that at least five or six genes remain to be found that predict a person’s risk of AD at least as reliably as does APOE (14).

Pathology

During much of the 1990s, great rhetorical battles rumbled between two camps of Alzheimer’s researchers. Hoisters of the β-amyloid flag held senile plaques primarily responsible for AD neuropathology. Their rivals insisted that neurofibrillary tangles, composed of the protein tau, caused the nervous system more significant damage. That battle, still commonly known as the battle of the Baptists (for β-amyloid protein) versus the Tauists, has subsided somewhat, although it has left plenty of questions.

β amyloid, the active ingredient in neuritic plaques (15), is a fragment sliced out of the middle of a protein called β-amyloid precursor protein (APP), which weaves in and out of the cell membrane. Two enzymes, β- and γ-secretase, snip β amyloid free from APP and allow it to float away from the cell (Fig. 2). This process usually doesn’t cause trouble; β amyloid shows up in many healthy body tissues, although no one knows what it does. But when β amyloid is overproduced in the brains of people with AD, it bands together first in fibrils and then in plaques. These clumps probably irritate nearby neurons in a variety of ways: They activate scavenger cells of the immune system, called microglia, which can misguidedly attack healthy neurons while clearing up detritus in the brain; they cause oxidative damage to nearby cells with the help of metals embedded in the plaques (see “The Two Faces of Oxygen”); they possibly stimulate apoptosis, or programmed cell death (see “More Than a Sum of Our Cells”); and they probably physically block neuron-to-neuron connections. β amyloid can also gum up capillaries and arterioles, fine blood vessels that are often deformed in Alzheimer’s. Some investigators believe that β amyloid, perhaps in some prefibrillar form, does its damage inside of the cell. In any case, the genetic data strengthen the case that β amyloid drives AD; PS1 and PS2 (genes that are required to produce active γ-secretase) and APP all are linked to familial forms of the disease.

Tau, meanwhile, works a different side of the street. The protein normally builds and stabilizes microtubules, tiny tracks along which supplies are carted throughout the cell. When tau goes bad—in most cases no one knows how or why—it twists up in pairs. These protein couples tangle together within the neuron, where they eventually distort the cell physically and hobble its internal machinery. Tau tangles are seen in several unrelated neurodegenerative diseases. One was considered a type of AD until it was found to be a pure tau pathology, without any trace of AD’s other defining feature, amyloid plaques. That disease is now called frontal-temporal dementia; it’s caused by a mutation of the tau gene (16-18).
β amyloid and tau pathologies seem to operate fairly independently at early stages of the disease, says Don Price. Plaques first accumulate throughout the cortex, the outer portion of the brain responsible for most high-level cognition. Tangles, meanwhile, concentrate in the hippocampus, a subcortical area crucial for memory. Then, “at some stage, the two pathologies become interactive, facilitating each other,” says Don Price, although no one’s quite sure why or how. Any hypothesis about how AD works, he says, will have to explain both plaques and tangles; most researchers agree, allowing the Baptists and Tauists to reach a truce.

Tanzi says the Baptists-versus-Tauists debate has subsided in part because recent research suggests that neither plaques nor tangles initiate the sequence of neuropathological train wrecks, such as cell death and disrupted neurotransmitter systems, that characterize Alzheimer's. Instead, plaques and tangles might be “tombstones” that mark sites of earlier carnage, he says. Before these tombstones are erected, free-floating fibrils of β amyloid—not yet clumped together in plaques—appear to damage neurons. Compared to the β-amyloid fibrils, amyloid plaques are relatively benign, says Tanzi.

Regardless, Melbourne’s Masters points out that there’s still a “big gap” between the field’s recognition that β-amyloid overproduction is one of the earliest malfunctions in AD and an understanding of how β amyloid might drive later symptoms, including amyloid plaque deposition and tangle formation. “One of the major challenges” facing the field of AD research, says Masters, is to “prove or disprove the amyloid hypothesis”—the theory that amyloid sets off and maintains the cascade of AD neuropathology—“by actively intervening” in β-amyloid production. If drugs that prevent buildup of the peptide the progression of AD—including the formation of tau tangles—“everyone will be satisfied” that β amyloid is key to AD, he says.

A quicker test of the amyloid hypothesis might come from animal studies. A new transgenic mouse model develops both amyloid plaques and neurofibrillary tangles, so researchers are now able to explore the relation between the two. The presence of β amyloid appears to accelerate the accumulation of tauopathies, suggesting that β amyloid can spur formation of both types of damage (19).

Plaques and tangles are AD’s most definitive marks, but the disease causes plenty of other neuropathology as well. In later stages of AD, communication between surviving neurons sputters and sparks; they share fewer synapses, the points of near-contact where neurons exchange chemical signals. The resulting loss of activity can be striking when viewed under the Technicolor lens of a positron emission tomography scan (Fig. 3).

If we step back from the microscope for a moment, we can see that the brain as a whole looks shrunken after years of AD (Fig. 4). The gross atrophy cuts a distinctive swath across the cortex, which Tanzi likens to a tornado that topples some houses and skips over others. Alzheimer’s disease chews up some parts of the cortex—the frontal, parietal, and temporal lobes, which are associated (grossly and respectively) with higher cognition, spatial abilities, and memory—while leaving the occipital cortex, which processes vision, largely unscathed. Below the surface of the brain, the olfactory bulb, amygdala, and hippocampus suffer the greatest neural losses. These neural clusters are responsible (again, grossly and respectively) for smell, emotions, and memory.

Alzheimer’s corrupts the brain’s neurochemistry as well. Another subcortical structure, the nucleus basalis, shrinks dramatically in Alzheimer’s. It produces acetylcholine, one of the main ingredients in the neurotransmitter soup that swirls around, conveying messages in the brain. Acetylcholine regulates sleep and facilitates higher cognitive functions as well. Drugs that inhibit the breakdown of this neurotransmitter improve thinking skills in people with mild or moderate Alzheimer’s.

Prevention

Sometimes the abundance of diseases that plague one’s later years proves fortuitous—for scientific observations, at least. Researchers noticed in the 1990s that people who suffer from rheumatoid arthritis don’t develop AD as often as do their peers. After some head scratching, this observation led to several studies showing that certain types of pain killers—nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin and ibuprofen but not acetaminophen—delay the onset of AD (20).

Although the NSAID studies were inspired more by unexpected observations than by theory, the results fit with basic research showing that β amyloid inflames surrounding microglia. These immune system cells release inflammatory cytokines, nitric oxide, and other neurotoxins that can destroy nearby neurons; alternatively, the microglia might turn phagocytic and chew up plaques, they might free β amyloid to roam around the intercellular space. Whatever the mechanism, cooling off inflammation might restrain some of AD’s early progression.

Other epidemiological research uncovered promising hints that estrogen replacement therapy might protect women from Alzheimer’s. The early studies weren’t case-controlled, however, and a recent, more rigorous clinical trial from the Women’s Health Initiative (WHI) turned up no evidence that estrogen alleviates the clinical symptoms of women with mild or moderate AD (21). However, a separate, post-mortem neuroanatomical study from the WHI showed that at a cellular level, at least, estrogen did seem to exert a positive effect. Women with early signs of AD who had taken estrogen lost fewer neurons in vulnerable brain regions than did women who had taken placebos (22).

The AD-prevention hypothesis dearest to the hearts of many researchers goes by several different names: the cognitive reserve hypothesis, the cortical reserve hypothesis, or the “use it or lose it” hypothesis. According to the theory, stimulating the brain, say, by regularly reading research articles, decreases the risk of developing Alzheimer’s. Although the mechanism for such a protective factor is a bit murky—scientists talk about building extra neural connections that somehow compensate for early AD neuropathology—a few studies have backed up initial observations that people with more years of

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education are less likely to develop Alzheimer’s. For instance, those with AD were less likely to have engaged in intellectual activities in early and middle adulthood than their nondemented peers (23).

Some of the most intriguing evidence for the cognitive reserve hypothesis comes from a longitudinal study of nuns in convents. These women are an epidemiologist’s dream: They live in similar rooms, eat the same kinds of foods, and have similar chores and hobbies, thus reducing the number of confounding variables that normally plague population studies. Researchers analyzed writing samples gathered when the young women entered their convents. Low grammatical and cognitive complexity correlated with likelihood of AD (24); in contrast, one particularly sharp woman lived to age 101 with all her wits, even though her brain was studded with plaques and tangles at autopsy (25), providing more anecdotal evidence for the cognitive reserve hypothesis.

Treatment

Alzheimer’s disease used to be one of the grimmer areas of research, but these days, AD researchers are remarkably optimistic. New transgenic and knockout mouse lines offer “ways to get into the nervous system of living animals,” says Don Price. And the potential for helping millions of people live fuller, longer lives contributes to the new sense of urgency and enthusiasm.

Three major strategies are being subjected to clinical trials now. Their approaches and underlying logic differ, but their goal is the same: to prevent the accumulation and clear existing deposits of β amyloid. One treatment aims to block the secretase enzymes that clip β amyloid from APP. Another chelates the heavy metals zinc and copper from amyloid plaques, where the metals spur oxidative damage. The third, a vaccination model, attempts to rope the immune system into the battle against Alzheimer’s.

Although most researchers have one or more favorites, they all agree that, as Tanzi says, “those three trials are the main ones to keep an eye on.” And the results from any or all are expected shortly. “We have to get ready for any one [strategy] to break out as being particularly useful only 5 years from now,” he says.

When it comes to cutting APP, “there’s a good way to process it and a bad way to process it,” says George Martin of the University of Washington (UW), Seattle. The enzyme in the white hat, α-secretase, clips APP straight through the heart of the β-amyloid amino acid sequence. The bad guys—and the ones implicated in AD—β-secretase and γ-secretase, cut APP at either end of what floats free as β amyloid.

β-secretase and γ-secretase are “intriguing” therapeutic targets, says Don Price. A gene called BACE1 encodes β-secretase (26). As predicted, mice that lack BACE1—which don’t appear to suffer from the gene’s absence—can’t cleave APP in the β-secretase spot. BACE1 knockout mice also don’t accumulate amyloid deposits, even when they carry a gene that churns out buckets of APP.

A close kin of BACE1, called BACE2, appears to act as an α-secretase. It clips APP in a good way, breaking into bits the amino acid chain that would otherwise become β amyloid. BACE1 is relatively concentrated in the brain; BACE2 is more common in other tissue—leading Price to conclude that the ratio between the two enzymes “is the first possible explanation for why β amyloid is a neuronal disease.” Meanwhile, two genes have been proposed as γ-secretase builders, Presenilin 1 (PS1) and Presenilin 2 (PS2) (27). Constraining these enzymes likely to cut APP close to the end that would become β amyloid might make sense, Price suggests, because “β amyloid is a neuronal disease.”
trovercy abounds about whether these genes’ products are, in fact, γ-secretase, but at the least, they’re necessary cofactors for its activity. Blocking them prevents γ-secretase from liberating β-amyloid from APP (28).

Although stifling either β-secretase or γ-secretase would prevent β-amyloid production, most researchers see β-secretase as an easier target. It cuts APP at a site outside the cell membrane, whereas γ-secretase somehow cuts APP in a segment embedded in the cell membrane, where it’s hard to target drugs. γ-secretase has another disadvantage, Don Price points out: Blocking it could interfere with the Notch pathway, which is necessary for cell maturation. Although the brain doesn’t produce many new cells, a drug that shuts down Notch systemically would derail the production of the immune system’s lymphocytes, for example.

Researchers from several drug companies are searching for secretase inhibitors, many by using high-throughput screening that can scan millions of compounds for hidden anti-β- or anti-γ-secretase superpowers. Don Price predicts that the research might shake up a cocktail of drugs that keep β-amyloid production in check.

Other researchers have engaged a different foe than β-amyloid proper: the metals that spur β-amyloid to aggregate. Ashley Bush of Harvard Medical School discovered years ago while working with Tanzi that zinc causes loose strands of amyloid peptide to clump together in the test tube. Chelating zinc reverses the process. And in brain slices from people who died with AD, zinc chelators dissolve amyloid plaques (29).

“Nobody understands what free zinc is doing in the brain,” says Melbourne’s Masters, a collaborator on the project. Even in healthy people, it congregates in the parts of the brain most prone to AD damage, and it appears to interact with the neurotransmitter glutamate. The zinc somehow prompts β-amyloid to aggregate, and then it sucks copper into the clumps as well. Together, the metals generate hydroxyl radicals that probably cause oxidative damage to nearby tissue. Mopping up these heavy metals, the researchers reasoned, would squelch some neurotoxicity and either prevent plaques or, in the best case, dissolve plaques that have already taken root.

Bush announced at the Society for Neuroscience meeting in November 2000 that high-throughput screening had identified several candidate compounds that chelate copper and zinc. Conveniently, one chelator, called clioquinol, had already been approved by the U.S. Food and Drug Administration for use as an antibiotic (although it was later recalled due to adverse reactions in some people in Japan). The drug prevented plaque formation when given at a young age to animals engineered to mass-produce amyloid deposits (30). The drug is being tested in humans with AD now, and Masters says he expects results sometime in 2002.

A third promising approach to clearing β-amyloid deposits from the brain treats them like a germ. Dale Schenk of Elan Pharmaceuticals in South San Francisco pioneered the approach, which involves vaccinating animals with β amyloid to induce an immune response. In mice, at least, the vaccination triggers antibodies to β amyloid, some of which make it past the blood-brain barrier. As in the chelation studies, vaccinating young mice prevents buildup of amyloid plaques, and vaccinating older animals clears plaques that have already formed; neither group reported obvious side effects (31).

Clinical trials with a similar vaccine approach are under way in people with early AD; so far, the subjects tolerate the treatment well. It’s too soon to say whether antibodies to β amyloid could clear plaques in humans with Alzheimer’s. But even if the vaccination dissolved plaques, would it restore patients’ cognitive skills? Animal studies show that plaque-ridden, demented mice given the vaccination regain memory abilities, suggesting that the vaccine could, at its best, not just slow the progression of AD but also reverse some of its symptoms (32, 33).

Vaccinating against a naturally occurring protein is risky, however. Enough antibodies must seep into the brain, attach to β amyloid, and signal the immune system to clear out the garbage. But too many antibodies, Don Price says, “could stir up an autoimmune response.” And Harvard’s Tate points out that activating microglia, as the vaccination strategy appears to do, might exacerbate the neural inflammation that probably promotes AD, given the results from the NSAID studies.

While some researchers fine-tune these strategies and await results from human clinical trials, others are searching for new techniques. For instance, a sluggish protein-degradation system could allow bad β amyloid to accumulate in the brain; stimulating enzymes that break down β amyloid might fight AD (34).

Despite the auspicious early results from treatments that block or clear β amyloid, Masters points out that researchers are still debating whether the other AD villain, tau, would make a good target for future therapies. For instance, tangled tau is phosphorylated, and some have suggested that preventing or reversing this phosphorylation might clear tangles. However, researchers are still trying to determine whether phosphorylation triggers the tangles.

Another quirky strategy for fighting AD might arise out of recent research on stem cells. These fairly undeveloped cells zero in on many types of damage in the nervous system, including tumors, bruises, and strokes. At the Society for Neuroscience meeting in November 2000, Tate reported that stem cells also migrate to amyloid deposits in the mouse brain. One of the major questions in stem cell biology is why they seek particular spots in the brain, and Tate isn’t sure what signal amyloid deposits send that brings stem cells running. But theoretically, she says, stem cells could be “engineered to repair damaged tissue, deliver therapeutics, or replace” neurons killed by Alzheimer’s.

While most researchers are focused on neuropathological mechanisms in AD, says UW’s Martin, many tend to overlook the number one risk factor for AD: aging. If half of all people develop the neuropathological features and clinical symptoms of AD after a certain age, he says, it makes more sense to think of AD not as a disease but as a “common senescent phenotype.” In order to figure out AD, he says, researchers will have to understand the fundamental mechanisms of aging.

Laura Helmuth is a staff writer at Science. She uses her brain as much as possible.
Also called Aβ. The short amyloid protein that is clipped out of β-amyloid precursor protein. Can be either 40 or 42 amino acids long. Aβ42 appears to be more likely to clump into free-floating fibrils and then senile plaques. “β amyloid” in the context of AD refers to Aβ42.

ApoE Apolipoprotein E gene. Comes in three major flavors: ApoE2 and ApoE3 are either harmless or protective against AD; ApoE4 increases a person’s risk of Alzheimer’s disease, particularly if present in two copies. It’s not yet clear how other, less common types of ApoE relate to Alzheimer’s.

APP β-amyloid precursor protein. Probably involved in neurogenesis. When cut by β-secretase, it yields harmless peptides. When cut by γ- or γ-secretase, it gives rise to β amyloid. Mutations in its gene—designated APP—are responsible for some cases of early-onset, familial Alzheimer’s.

β-secretase One of the enzymes necessary for clipping β-amyloid from β-amyloid precursor protein.

DAT Dementia of the Alzheimer’s type. This abbreviation is frequently seen in research publications. It acknowledges that Alzheimer’s disease is an umbrella term for what may prove to be many symptomatically similar yet etiologically distinct diseases.

γ-secretase One of the enzymes necessary for clipping β amyloid from the β-amyloid precursor protein.

Presenilin 1 Presenilin 1 (PS1) and Presenilin 2 (PS2) are similar genes on different chromosomes. Their protein products either are γ-secretase or they facilitate its action. Mutations in the PS1 and PS2 genes are responsible for some cases of early-onset, familial Alzheimer’s.

Presenilin 2 Presenilin 1 (PS1) and Presenilin 2 (PS2) are similar genes on different chromosomes. Their protein products either are γ-secretase or they facilitate its action. Mutations in the PS1 and PS2 genes are responsible for some cases of early-onset, familial Alzheimer’s.

SNPs Single-nucleotide polymorphisms. Common, single-base-pair variations in DNA.

Tau A protein that normally stabilizes microtubules in the cell. In Alzheimer’s and some other neurodegenerative diseases, it bunches up to form neurofibrillary tangles.

Further Reading

John Bayley, Elegy for Iris (Picador USA, New York, NY, 2000).

The Alzheimer Research Forum, an excellent source for debates, summaries of research publications. It acknowledges that Alzheimer’s disease is an umbrella term for what may prove to be many symptomatically similar yet etiologically distinct diseases.

The Alzheimer’s Association, mainly focused on resources for patients and families. Their protein products either are γ-secretase or they facilitate its action. Mutations in the PS1 and PS2 genes are responsible for some cases of early-onset, familial Alzheimer’s.

Check up on your favorite Alzheimer’s disease. The Women’s Health Initiative estrogen replacement therapy is neurotrophic and neuroprotective. The Women’s Health Initiative estrogen replacement therapy is neurotrophic and neuroprotective. The Women’s Health Initiative estrogen replacement therapy is neurotrophic and neuroprotective.


