Toward a Future With Memory

Researchers look high and low for the essence of Alzheimer's

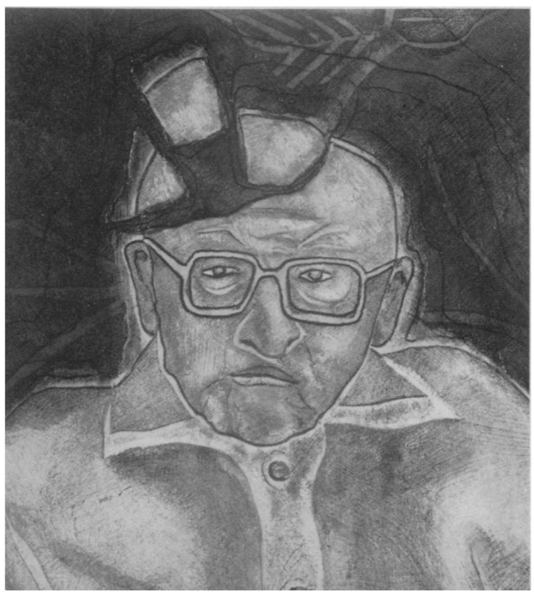
By RICK WEISS

The 51-year-old woman's first signs of trouble, according to her physician, were feelings of jealousy toward her husband. From this somewhat unremarkable (and possibly justified) condition followed other, more baffling personality changes, including fears that someone wanted to kill her, outbursts of loud shrieks and bouts of forgetfulness.

She carried household objects back and forth, hiding them for no apparent reason. Sometimes she got lost in her own apartment.

The woman's five-year decline into full-blown dementia and death, along with autopsy results, were described by her physician in a 1907 medical journal. Though insightful, his report was hardly revolutionary. The physician, a German psychiatric neurologist named Alois Alzheimer, had little reason to suspect that his name would someday become a household word.

But in a modern world with an unprecedented and still-growing number of elderly people, the syndrome he so carefully documented in a handful of prematurely senile patients has mushroomed into a global health crisis, affecting as many as 4 million individuals in the United States alone. Alzheimer's disease, asserts T. Franklin Williams, director of the National Institute on Aging in Bethesda, Md., "is by far the most threatening epidemic that we have in our nation."



Randy Fletcher

Recent estimates suggest the disorder may affect almost half of the U.S. population aged 85 and older. It costs the nation nearly $90 billion each year and takes an immense emotional toll on its victims and their family members. Eight of the institutes and divisions within the National Institutes of Health now sponsor or conduct research on the debilitating disease.

Yet after more than a decade of intensive research, scientists for the most part remain puzzled as ever. Indeed, to diagnose Alzheimer's, doctors today rely upon essentially the same behavioral and biological hallmarks described by Alzheimer himself more than 80 years ago: a progressive dementia including severe loss of memory; and the accumulation in brain tissue of protein deposits called amyloid plaques, recognizable only upon autopsy.

Scientists have amassed an immense amount of information — "too *many* clues," in the words of one Alzheimer's specialist — about the biochemistry behind these classic symptoms. The accumulating knowledge hints that investigators may eventually solve the Alzheimer's riddle, perhaps by the end of the century, some say.

But daunting hurdles remain, according to Alzheimer researchers who gathered recently at the National Institutes of Health to pool their findings. Scientists at the meeting proposed causes ranging from mitochondrial mutations to unidentified, blood-borne agents, and potential cures ranging from simple aspirin to overlapping doses of potent, synthetically produced brain chemicals.

Faced with a plethora of possibilities, researchers admit they simply don't know what's at the root of the disease. And with no clear idea about the fundamental differences between Alzheimer's disease and normal aging — nor any reliable animal model upon which to try novel treatments — they say they remain hobbled in their attempts to develop effective treatments or preventive measures. Standard treatment today is limited to antidepressants and other drugs that target secondary symptoms of the disease.

"In order to prevent a disease, we generally need to understand its cause. And we certainly don't know the cause of Alzheimer's," says Leon Thal, a neuroscientist at the University of California, San Diego.

Until recently, experimental treatments for Alzheimer's have focused on the most prominent biological deficit associated with the disease: the death of nerve cells that secrete the neurotransmitter acetylcholine in the brain. These so-called cholinergic neurons constitute some of the main lines of communication between the forebrain and the hippocampus, two brain areas responsible for higher cognitive functions and memory.

Early attempts to maintain acetylcholine levels by providing two of the compound's raw ingredients — choline and lecithin — had essentially no effect in Alzheimer's patients. More recently, researchers have focused on such drugs as physostigmine and tetrahydroaminoacridine (THA), which help prevent acetylcholine breakdown and thus may help patients make the most of the limited acetylcholine supplies they still possess.

So far, about 125 Alzheimer's patients have received physostigmine, with mixed results. New analogs of the drug — which remain active in the body longer than the two hours typical of the original form — may prove somewhat more effective, researchers say.

THA, which stirred controversy in 1987 when the Food and Drug Administration called into question the methodology used by the drug's primary investigator (SN: 11/7/87, p.292), remains "interesting and promising" despite some evidence that it may cause short-term liver toxicity, says Thal. A three-year, multicenter U.S. trial of the drug is scheduled for completion later this year.

But attempts to alleviate Alzheimer's symptoms by manipulating the cholinergic system are hampered by scientists'

incomplete understanding of how the complex system operates. Moreover, says Israel Hanin of Loyola University in Chicago, "it's increasingly clear that the cholinergic system itself is not the Lone Ranger of Alzheimer's disease, and that other neurotransmitter systems are involved."

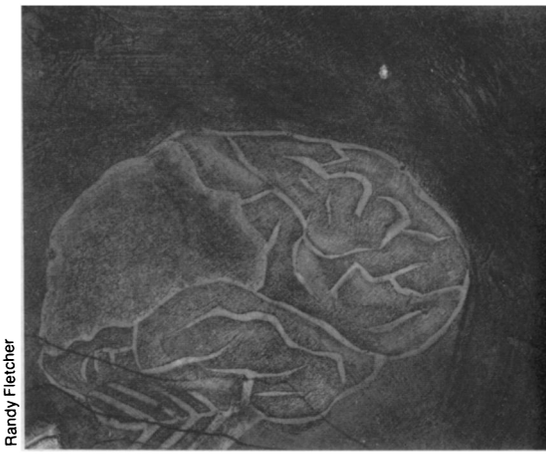
A handful of Alzheimer researchers have begun exploring the potential roles of other neurotransmitter systems, including the noradrenergic and serotonergic networks in the brain. Others, however, suspect that the real heart of the disease lies beyond the brain and that neuronal death represents a secondary or even tertiary "side effect" of a more fundamental dysfunction. Several intriguing theories along these lines are today drawing research attention.

Mitochondrial mischief: Some researchers propose that at least some cases of Alzheimer's may result from an inherited defect in mitochondria, the oxygen-dependent energy factories in cells. Mitochondria contain proteins essential to normal metabolism, and an inherited defect in these proteins could lead to the production of toxic, metabolic by-products or oxidizing "free radicals" that could damage neurons in the brain. Even if the mitochondrial defect were found in all cells, the resulting metabolic inefficiency might affect neurons more than it would other cells, since neurons require extraordinarily large amounts of oxygen.

The evidence for mitochondrial involvement in Alzheimer's is sketchy but provocative. Mitochondria within the protein plaques deposited on and around neurons in Alzheimer brains appear abnormal in photomicrographs, and evidence indicates they process oxygen with less than their usual amount of vigor in these patients.

Even more compelling, genetic analysis of mitochondria in the blood platelets of Alzheimer's patients reveals DNA mutations that appear capable of disrupting normal mitochondrial metabolism. W. Davis Parker Jr. of the University of Colorado Health Sciences Center in Denver says he has found "heavy hits," or mutations, in the mitochondrial DNA of five of the six living Alzheimer's patients he examined. He suggests that Alzheimer's, which in most cases seems to lack a hereditary pattern, might be inherited through mitochondrial DNA, which comes only from the mother. (Most genes are inherited through the DNA in cell nuclei, which comes from both parents.) Scientists have tentatively linked other "late onset" diseases to mitochondrial defects, he notes. And because of their complex inheritance pattern, maternally derived traits can give the appearance of arising sporadically in the population.

If Alzheimer's results from mitochondrial malfeasance, researchers might possibly treat or prevent it with drugs such as co-enzyme Q and deprenyl, which can suppress oxidative damage, Parker suggests. Others note that a synthetic version of a naturally occurring substance called acetyl-L-carnitine appears promising in its ability to both enhance cholinergic function and prevent oxidative damage.



Randy Fletcher

Membrane defects: Noting that "neurons are mostly membranes," Richard J. Wurtman of the Massachusetts Institute of Technology in Cambridge calls the study of membranes "the wave of the future" in Alzheimer's research. Membranes are mostly lipids, he says, and some of the latest thinking suggests the disease might result from abnormalities in certain membrane lipids.

Jay W. Pettegrew, a neuroscientist at the University of Pittsburgh, uses nuclear magnetic resonance spectroscopy to examine debris from cell-membrane breakdown in the brains of living Alzheimer's patients. The noninvasive technique allows him to detect, over time, any evolving changes in the types of lipid metabolites in the brain.

So far, Pettegrew has noted that the Alzheimer's patients have higher brain levels of lipid metabolites called phosphomonoesters (PMEs) than do people suffering from other kinds of dementia. Interestingly, PME levels increase in the brain of developing fetuses just before an event called programmable cell death – a genetically determined, large-scale massacre of extraneous nerve cells. Alzheimer's might represent a replay of this early genetic program, Pettegrew suggests.

Moreover, he says he's "intrigued" that the three-dimensional structures of PMEs closely resemble those of certain neurotransmitters, suggesting PMEs could trigger their own signals in the brain. "They look the same," he says, "but do they act the same?" If PMEs do cause damage by binding to neurotransmitter receptors in the brain, then perhaps specific receptor blockers, such as those currently under investigation in stroke patients (SN: 11/4/89, p.292), may prove useful against Alzheimer's disease, Pettegrew says.

Protein problems: Dennis Selkoe of Harvard University proposes another way in which membrane abnormalities could play a role in Alzheimer's. He focuses on beta amyloid, the primary protein that accumulates in Alzheimer brains. Beta amyloid, he notes, is actually a snippet of protein cleaved from a much

Desperately seeking subjects

As basic research yields experimental Alzheimer's drugs with small but noticeable benefits, pharmacologists confront a growing dilemma over how best to design safety and efficacy trials. These studies require populations of otherwise-healthy patients who definitely have Alzheimer's. But a sure diagnosis of Alzheimer's comes only after a patient has died. And in the United States, most people with probable Alzheimer's already take numerous medications that may interact with experimental drugs in unpredictable ways.

Elderly Americans are "on too many drugs with too many side effects already," says Jay W. Pettegrew of the University of Pittsburgh. If researchers try to evaluate experimental Alzheimer's drugs on top of an already complicated mix of medications, Pettegrew says, "this is going to get real messy real quickly."

Despite that inherent messiness, researchers have begun safety trials of several powerful drugs in novel combinations. They are pairing such drugs as physostigmine, deprenyl, desipramine, clonidine, guanfacine and yohimbine – each of which carries its own poorly understood risks, including potential ill effects on the heart. In some cases, improvements in cognitive function have been demonstrated in small numbers of patients.

But with scientists still uncertain about the effects these drugs have individually, some wonder whether combining them in humans may be a dangerous act of therapeutic desperation. Researchers should think twice before they "concoct a cocktail and throw it at elderly patients," says John Growdon of Massachusetts General Hospital in Boston.

Elkan Gamzu of Cambridge NeuroScience Research, Inc., a pharmaceutical company in Cambridge, Mass., wonders whether trials of drugs with relatively little potential are stealing too many patients from studies of more promising drugs. Among drug companies, he says, "there is a great competition for the healthy Alzheimer's patient." – *R. Weiss*

larger protein called amyloid precursor protein (APP), which sticks out from cell membranes. Normally, APP's cleavage site remains well protected, buried within the lipid matrix of a cell membrane. One way for APP to lose a beta amyloid fragment might be for the membrane to leave that key cleavage site exposed to enzyme activity, perhaps because of a structural defect in the membrane.

Moreover, with the recent detection of amyloid deposits not just in the brain but in many parts of Alzheimer patients' bodies (SN: 9/23/89, p.197), Selkoe proposes that the beta amyloid associated with Alzheimer's may originate somewhere else in the body, with the protein deposits later accumulating in the blood vessels, brain and elsewhere. He points to evidence of a similar genesis for other, apparently related diseases called amyloidoses, all of which involve the production of abnormal protein fragments and their deposition in tissues.

Therapeutic approaches worth investigating for such a mechanism include drugs that block the APP-cleaving enzyme or antibody-like substances that could "mop up" the amyloid protein fragments before they begin to accumulate in the brain.

Immune reactions: At some point in Alzheimer's disease, the immune system gets involved. But scientists remain uncertain whether the disease is itself an immune disorder or whether the immune system joins the fray late in the biochemical process.

In studies of Alzheimer brains, researchers have noted that microglial cells —"housekeeping" cells within the brain— often contain bits of neuronal debris. But do they themselves start the trouble by imprudently gobbling up innocent neurons, or are the microglial cells simply cleaning up another troublemaker's mess?

Whatever starts it, once microglial cells consume these neuronal tidbits they can produce a molecule called HLA that attracts white blood cells called T-lymphocytes and stirs them into a hyperactive state. This finding, along with controversial evidence that Alzheimer's patients harbor antibodies against their own brain tissue, leaves many researchers looking at the immune system as a key participant in the pathology.

"Our hypothesis is that there is a specific immune response against yet-to-be-identified antigens in Alzheimer's disease brains," says Felicia Gaskin, a behavioral neurobiologist at the University of Virginia in Charlottesville. It remains unclear whether those antigens are infectious particles such as viruses or are the patient's own proteins triggering an autoimmune response, she and others say. For that matter, any of several immune-cell stimulants may trigger Alzheimer's, says Joseph Rogers of the Institute for Biogerontology Research in Sun City, Ariz. "I think all you need are a few activated lymphocytes wandering into the brain... and away you go."

Henry M. Wisniewski of the New York State Institute for Basic Research in Developmental Disabilities, in Staten Island, also blames the immune system for many of the problems in the disease. But he suggests that immune-system scavenger cells in the brain may directly contribute to the Alzheimer's scenario by overproducing beta amyloid themselves.

On the other hand, says William R. Markesbery of the University of Kentucky in Lexington, perhaps researchers should blame the immune system not for overactivity but instead for loafing on the job when it ought to be disposing of the accumulating bits of beta amyloid. "Amyloid deposition may represent a failure of the sanitation department," he says.

Whatever its role in the disease, the immune system clearly becomes activated at some point, triggering an inflammatory process that would best be shut down, says Patrick L. McGeer of the

Alzheimer's Medicines in Development

DRUG	COMPANY	U.S. DEVELOPMENT STATUS
BMY 21502	Bristol-Myers Squibb (New York, NY)	Phase I
Capoten Captopril	Bristol-Myers Squibb (New York, NY)	Phase II
SQ 29 852	Bristol-Myers Squibb (New York, NY)	Phase II
DuP 996	Du Pont (Wilmington, DE)	Phase I
HOE 427	Hoechst-Roussel (Somerville, NJ)	Phase I/II
HP 029	Hoechst-Roussel (Somerville, NJ)	Phase II
HP 128	Hoechst-Roussel (Somerville, NJ)	Phase II
Sabeluzole	Janssen Pharmaceutica (Piscataway, NJ)	Phase I
Nimotop® Nimodipine	Miles Inc. (Elkhart, IN)	Phase III
Guanfacine	A.H. Robins (Richmond, VA)	Phase II
Zacopride	A.H. Robins (Richmond, VA)	Phase II
Milacemide	G.D. Searle (Chicago, IL)	Phase II
Alcar Acetyl-L-Carnitine	Sigma-Tau (Gaithersburg, MD)	Phase II
Oxiracetam	SmithKline Beecham (Philadelphia, PA)	Phase II/III
Avan Idebenone	TAP Pharmaceuticals (N. Chicago, IL)	Phase II
Cognex® Tacrine	Warner-Lambert (Morris Plains, NJ)	Phase III

Phase I — Safety testing and pharmacological profiling in humans.

Phase II — Efficacy testing in humans.

Phase III — Extensive clinical trials in humans.

Pharmaceutical Manufacturers Assoc.

Rescuing neurons with NGF

Within the past year, researchers have gained the ability to mass-produce therapeutic quantities of nerve growth factor (NGF) — a naturally occurring substance that can enhance the growth and survival of cholinergic nerves. Along with about 16 other known growth factors that affect the nervous system, NGF may one day help rescue dying neurons in Alzheimer's patients, researchers say.

Experiments indicate that NGF enhances memory in aged rats and some monkeys. Next, researchers plan to give NGF to aged monkeys whose cognitive skills have been carefully evaluated, and to note any resulting changes in memory or other mental parameters. If successful, these experiments may lead to the first therapeutic use of NGF in humans, investigators say.

The potent growth factor is not without its risks, however. In hamsters, NGF appears to boost production of APP — the precursor of the amyloid protein, that collects in the brains of Alzheimer's patients. And to be effective, the drug must be administered directly into the brain in regular doses, probably with the use of an implantable pump. This delivery system carries a small but constant risk of infection.

In the more distant future, some researchers say, Alzheimer's patients may benefit from transplants of genetically engineered cells that secrete growth factors such as NGF inside the brain.

— R. Weiss

University of British Columbia in Vancouver. Toward that end, he proposes a simple addition to the Alzheimer's armamentarium: aspirin.

McGeer cites his own anecdotal evidence that Alzheimer's rarely strikes rheumatoid arthritis patients, who typically take aspirin on a regular basis. "An aspirin a day keeps the gerontologist away," he suggests. Other researchers have reported observations that contradict McGeer's, and they note that even if aspirin had potential in Alzheimer's, it might not enter the brain in sufficient concentrations before reaching toxic levels in the blood.

Other theories on Alzheimer's genesis abound. Researchers still wonder, for example, whether aluminum – found in high concentrations in amyloid plaques – helps cause the syndrome or simply becomes concentrated in these protein deposits later in the disease.

And scientists have yet to understand the differences between familial Alzheimer's – the clearly inherited form accounting for an apparent minority of cases – and noninherited Alzheimer's, which appears unpredictably in the elderly and somewhat more frequently in women than in men.

Meanwhile, efforts to evaluate new therapies remain hampered by the lack of a clear biological marker allowing physicians to diagnose the disease before the patient's death, by the uncertain value of various cognitive tests used to measure improvements in patients' behavior and memory, and by the difficulty of finding enough study participants with Alzheimer's who are not already taking many other drugs (see box).

And, as with all diseases of the central nervous system, drug developers must wrestle with the problem of getting their product into the brain, past the membranous border patrol known as the blood-brain barrier. All told, says James Simpkins of the University of Florida in Gainesville, "Alzheimer's disease is probably more difficult to treat pharmaceutically than any other disease."

Nonetheless, asserts Williams of the National Institute on Aging, "the scientific base is there" to devise an effective treatment. With more than a dozen drugs already in clinical trials and with drug companies using automated methods capable of screening hundreds of compounds per week for potential nervous-system activity, "we can do it within the next five or 10 years if we want to," he declares.

Even a drug capable of delaying the onset of Alzheimer's by a decade or two would be a worthy goal, says Thal, who adds wryly: "That would allow us to die quietly and nicely from some other disease." □

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ble scientific publications reaching a general audience would avoid simplifying the human complexities of the disease by presenting as science such ludicrous, off-the-wall theories.

Member, Alcoholics Anonymous
Athens, Ga.

Ancestral anatomy

Although I am sure that within the anthropological community there are specific meanings associated with "modern" and "Asian," I was surprised to learn in reading "Migration evolves Down Under" (SN: 12/2/89, p.365) that there was a notable anatomical difference between "modern man" and "Asian man." As a person proud of my Japanese ancestry, I immediately checked under my bed for a stone hand-axe or flint-chipping implement, but was unable to locate any.

Seriously, I would like to know what the technical meanings are.

Kay Otani
Los Angeles, Calif.

No contrast was intended between "modern man" and "Asian man." The article reports on the argument that modern humans display significant anatomical differences from human ancestors whose remains have been found in Asia, the Near East and elsewhere, dating to more than 200,000 years ago and possessing some racially distinct features. According to the argument, environmental forces produced the changes in cranial shape and other skeletal features typical of modern humans, whether they live in Tokyo or Tulsa. – B. Bower