Alzheimer's Disease:

A Status Report For 2002

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Table of Contents

Tables

Figures

Executive Summary

- Alzheimer's disease is the most common cause of dementia (general mental deterioration) and occurs primarily in the elderly. It results from loss of nerve cell function in certain brain regions and leads to gradual and increasingly severe memory loss. Its victims lose the ability to function independently.
- Alzheimer's disease is defined as significant dementia with severe memory loss in combination with specific brain lesions observed after death. It was first described by the German physician Alois Alzheimer in 1907.
- Ninety percent of Alzheimer's disease occurs in people who are over 65 years of age. The number of new cases doubles in each decade of life after age 65. Epidemiologists estimate that perhaps half of those older than 85 may have Alzheimer's disease. It is estimated that about 5 million people in the U.S. and 15 million worldwide currently have Alzheimer's disease.
- The brains of persons who suffer from Alzheimer's disease undergo many changes, some of which can also be caused by other conditions. Neuritic plaques, accumulations of protein outside nerve cells, for example, occur only in Alzheimer's disease, while neurofibrillary tangles, which are twisted protein fibers that usually occur inside nerve cells, may also occur in other brain diseases. The amount of such lesions is not always highly correlated with the degree of dementia.

- Other changes to the brains of Alzheimer's disease victims include damage to the hippocampus—a brain area involved with memory processing, various blood vessel disorders, and deficiencies of neurotransmitters (chemicals which allow neurons to communicate with each other). None of these occur exclusively in Alzheimer's disease.
- Alzheimer's disease is currently diagnosed by neuropsychological testing; imaging tests such as PET scans may become more important in the future.
- The so-called amyloid cascade hypothesis is currently the most widely held explanation of the causes of Alzheimer's disease. Basically, it assumes that the beta-amyloid protein deposits are toxic to the brain. This theory is not universally accepted, however.
- Other things that have been suggested to be causal agents include: neurofibrillary tangles, inflammation, free radicals, and faulty brain metabolism. It is likely that many factors interact to contribute to the disease and ultimately lead to dementia.
- Known risk factors for Alzheimer's disease include increasing age, four different genes (three of which are mutations), and environmental factors such as head injury. Very poor education is strongly associated with an increased risk of Alzheimer's disease. Toxic substances have been considered possible causes, but there are no good data supporting this view.
- Alzheimer's disease may progress steadily or patients may remain stable for a year or more.
- Currently, the three main modes of treatment for Alzheimer's disease patients are behavioral treatments, replenishment of deficient neurotransmitters, and prevention of nerve cell damage.
- A number of pharmaceutical agents are undergoing intense scrutiny to determine which would be helpful in the prevention or treatment of Alzheimer's disease.

Introduction

Alzheimer's disease results from the loss of nerve cell function in certain areas of the brain, leading to gradual but increasingly severe memory loss and an inability to function independently. It is the most common cause of general mental deterioration (dementia) and occurs primarily in the elderly. As the size of the elderly population increases, the incidence of Alzheimer's disease is expected to rise as well.

There are two major types of Alzheimer's disease. The very common "late onset" Alzheimer's disease affects mostly the elderly and is also called sporadic Alzheimer's disease. "Early onset" Alzheimer's disease—also called familial Alzheimer's disease—is much less common, is likely to run in families, and affects mostly middle-aged people.

The causes of Alzheimer's disease are not known, although many theories exist. The most popular one assumes that certain abnormal protein deposits in the brain contribute to the disease. Several risk factors predispose persons to the disease, but the most important are:

- ✓ age
- ✓ certain genes
- ✓ severe head injury.

Risk factors may make a person more susceptible to a disease but do not assure that he or she will develop it:

- ✓ Women are often thought to be more frequently affected by Alzheimer's than men, but some recent studies contradict this assumption.
- ✓ Race and ethnic background do not affect the risk of developing the disease.
- ✓ Lack of adequate education seems to be associated with an increased risk of developing dementia.

Most experienced physicians can accurately diagnose "probable" Alzheimer's disease during a patient's lifetime. Diagnosis proceeds by exclusion of other diseases, conditions, or drugs that may cause or mimic dementia. A firm diagnosis can only be made after death by the detection of specific changes in the brain, however.

Alzheimer's disease cannot as yet be prevented or cured, but modern treatment may improve symptoms and slow progression in many patients. Treatment focuses mostly on replenishing brain levels of certain chemicals called neurotransmitters and on treating behavioral disturbances. Drugs approved for treatment of Alzheimer's disease are:

- ✓ acetylcholinesterase inhibitors to raise the levels of the neurotransmitter acetylcholine

- ✓ psychiatric medication to reduce behavioral disturbances such as depression, anxiety, insomnia, and agitation

Some treatments—such as vitamin E, estrogen, and NSAIDs—are considered promising but have not yet been firmly validated by scientific studies. These and other potentially promising approaches are under intense study.

Persons may live 5 to 20 years after diagnosis depending on their general health and the care they receive. Alzheimer's disease is not a direct cause of death—patients die of other causes.

This report will summarize the current status of Alzheimer's disease research, diagnosis, and treatment. Generally accepted information in the following areas will be summarized:

- ✓ Definition
- ✓ History
- ✓ Incidence
- ✓ Observed changes
- ✓ Diagnosis
- ✓ Possible causes
- ✓ Known and suspected risk factors
- ✓ Progression
- ✓ Treatment

Definition

Alzheimer's disease is an irreversible overall (global) decline in mental abilities in an alert person in concert with specific brain pathology (lesions). Memory loss is a major feature. In the early stages of the disease, a patient may also display odd behavior such as the pathological jealousy that Alzheimer described in his first patient. Orientation or language problems may occur. Ultimately all abilities are lost and the patient enters a chronic vegetative state.

The observed brain lesions are abnormal structural changes in certain areas of the brain that may interfere with normal function. Alzheimer patients almost always have significant amounts of these lesions. However, normal elderly persons also may have these lesions to some degree without developing dementia—even if they live well beyond age 85.[1,2]

Therefore, the role the lesions play in the dementia is not fully understood. It was recently proposed to distinguish the brain lesions from the dementia until this issue is resolved, calling the former

Alzheimer *disease* (the lesions) and the latter Alzheimer *dementia* (the mental deterioration).[3] This implies that a person could have a normal lifespan and not become demented even if he or she has some of these lesions. Keeping this important fact in mind, we will adhere to common usage and refer to the disease plus dementia as "*Alzheimer's disease.*"

History

In 1907 Alois Alzheimer, a German physician, described a middle-aged woman who was pathologically jealous and soon became demented. After death at age 51, her brain showed lesions which Alzheimer had often observed in older people. He attributed her disease to premature aging.

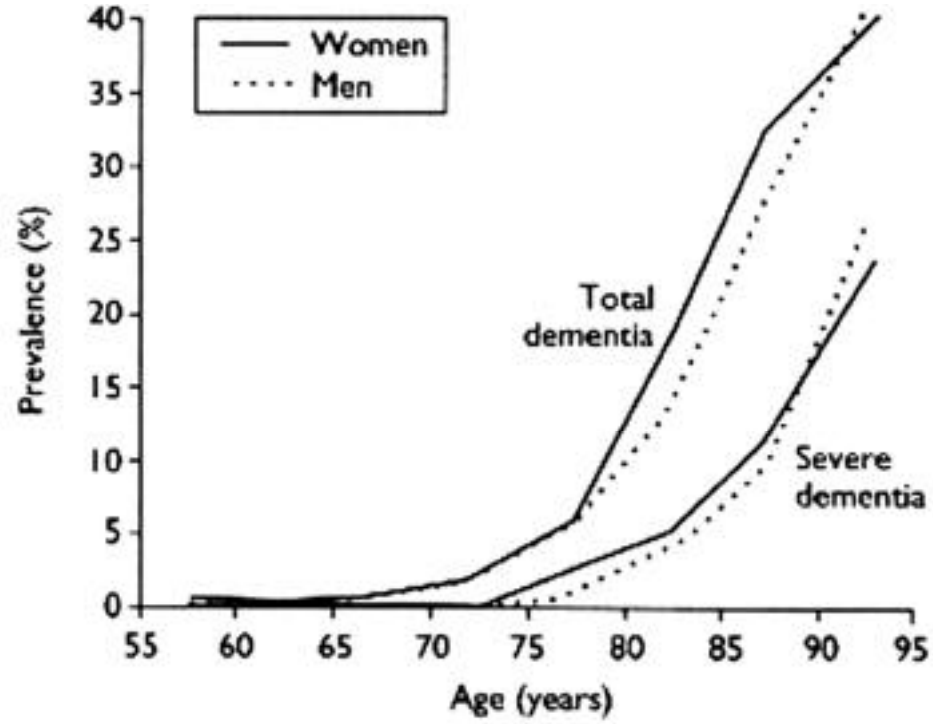
Before the 1970s, the common dementia of old age was called *senile dementia* and was thought to be caused by vascular disease. Only a rare premature dementia, which correlated with specific lesions, was then called Alzheimer's disease. However these types of lesions also occur in most senile dementia brains, and the mental deterioration is very similar. Today, both types of dementia are thought to be variations of the same disease*: early* and *late onset* Alzheimer's disease. Early onset Alzheimer's disease runs in families and is therefore also called *familial Alzheimer's disease.* The common late onset disease is also called *sporadic Alzheimer's disease.*

Incidence and Prevalence

Many types of dementia exist, but Alzheimer's disease is by far the most common. It is estimated that about 5 million persons in the U.S. and about 15 million people worldwide have Alzheimer's disease. *Multiple-Infarct Dementia* (resulting from many small strokes in the brain), dementia associated with Parkinson's disease, and other less common types of dementia are also well known (Fig. 1).[4] The characteristics of different types of dementia may easily overlap, particularly in the elderly.

Alzheimer's disease is a disease of the elderly—except for the familial form, which represents less than 10% of all Alzheimer cases. The most dramatic increase in incidence occurs above age 65: The number of new cases roughly doubles each decade beyond that. Whether the increase in incidence slows down beyond age 90 is not known and is

Figure 1: The increase of Alzheimer's disease and other types of dementia with age



difficult to assess independently of other illnesses. As the size of the aging population increases, the incidence of dementia is expected to continue to increase as well.

Epidemiologists estimate that up to 50% of persons over 85 may have Alzheimer's disease. Estimates should be confirmed by autopsy, but this is not always possible. One recent large autopsy-controlled study showed that about 33% of all tested persons who died over age 85 had significant Alzheimer-type lesions, but only half of them (16%) had been severely demented during life.[1] These numbers confirm that lesions need not lead to dementia during a "normal" lifespan; they also shed doubt on other, higher estimates of Alzheimer's disease in persons over 85. This study was performed in Finland, a country with high living standards and a high level of health care.

Different racial or ethnic groups do not have significantly differing amounts of the brain lesions typical for Alzheimer's disease. However, race and ethnicity are sometimes associated with different socioeconomic factors, which may influence whether a person lives long enough to develop dementia. A typical socioeconomic factor is education, and

very poor education is more strongly associated with dementia than good education.[4]

Pathology: Observed Changes in the Brain

The brains of Alzheimer's disease patients undergo many changes. We do not fully understand how these changes contribute to the disease or how they may work together. The most prominent changes are the brain lesions discovered by Alzheimer.

Brain lesions

When brain specimens are examined under a microscope, two types of lesions are prominent in Alzheimer's disease patients: *Neuritic plaques* (also called amyloid plaques) and *neurofibrillary tangles*. Both lesions are abnormal protein deposits in areas where they *may* interfere with normal functioning.

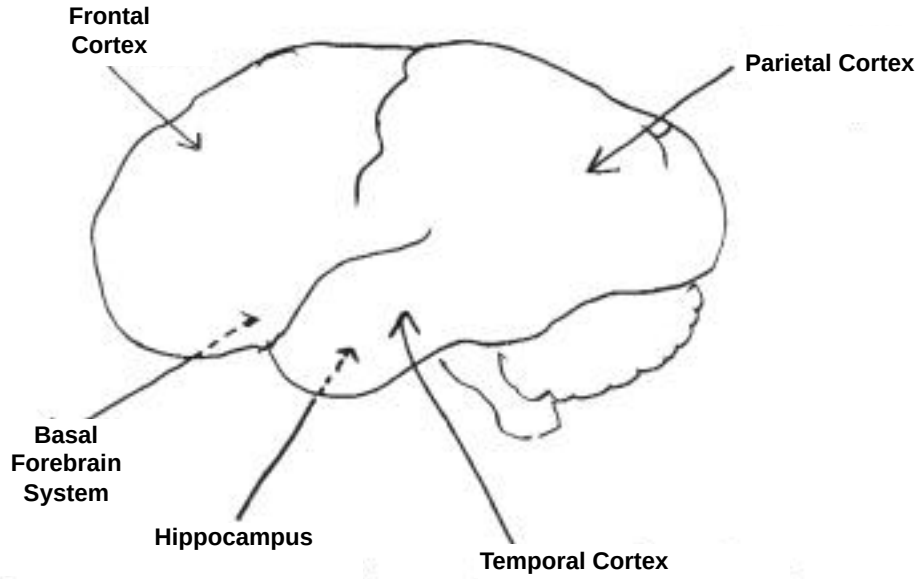
Neuritic plaques

Neuritic plaques, also called amyloid plaques, are dense aggregations of protein, called beta-amyloid, surrounded by degenerated nerve endings. The beta-amyloid is found outside the nerve cells (neurons). It results from abnormal breakdown of a normal tissue protein called amyloid precursor protein (APP). In early stages of the disease, so-called diffuse plaques seem to precede the amyloid plaques.[5] They consist of normal APP and may develop in response to brain trauma such as head injuries, deficient oxygen (hypoxia), or reduced circulation (ischemia). These diffuse plaques are still reversible. However, if they are not cleared away by normal body processes, they may eventually form beta-amyloid peptides that aggregate into insoluble amyloid plaques. Genetic predisposition, aging, and other factors may enhance formation of these plaques. Amyloid plaques eventually become "burned out" plaques that no longer show degenerated nerve endings.[5]

Neurofibrillary tangles

Neurofibrillary tangles are twisted protein fibers usually found inside the neurons. They appear to be degenerated proteins, of which a

Figure 2: The major areas of the brain affected by Alzheimer's disease



protein called *tau* is the major component. Tau, a normal cell protein, is probably involved in cell structure and function. Something apparently goes wrong with the processes by which cells normally process this protein, resulting in the characteristic tangles.

Neuritic plaques occur only in brains affected by Alzheimer's disease, while neurofibrillary tangles may also occur in other brain diseases as well as in normal, older, brains. They are both almost always found in Alzheimer's disease brains, usually in amounts larger than in brains from non-demented persons. However, more lesions do not necessarily result in more dementia. In fact, the correlation between the number of lesions and the degree of dementia is quite poor. Thus, even though all Alzheimer patients have significant amounts of lesions, the more demented patients don't always have more than the less demented, and some healthy people can have as many as the demented persons have. The lesions are most commonly found in the hippocampus, the frontal lobes, and the temporal lobes, brain areas which are associated with memory and reasoning abilities (Fig. 2).

Loss of nerve cells and brain shrinkage

Replacement of adult human nerve cells (neurons) is a rare event. When a neuron dies, it is effectively lost forever. Neuron loss, however,

is not always a bad thing because our brains contain masses of redundant neurons at birth and some cell death is part of normal development. Neuron loss during aging also does not necessarily lead to mental decline. A normal brain can to some extent compensate for dying neurons by increasing the contact points (synapses) between other neurons. Consequently, serious mental deterioration only occurs when neuron loss exceeds the compensatory reserve of the brain.

In Alzheimer's disease, a significant loss of neuron function occurs. This could be due to neuron death, to neuron shrinkage, or both. The loss of synapses is quite large and correlates well with the degree of the disease. Brains do shrink in Alzheimer's disease, but not much more than during normal aging. Thus, premature shrinkage is usually only a clinically significant event in the relatively younger group of Alzheimer's disease patients.

Damage to the hippocampus

The *hippocampus* is an area of the brain involved in memory processing (Fig. 2). Alzheimer's disease affects memory in particular. Plaques and tangles tend to aggregate in the hippocampus, and imaging studies have shown that the degree of Alzheimer's disease correlates well with damage to the hippocampus.[6] Damage to the hippocampus from other causes—even without amyloid plaques or tangles—mimics Alzheimer's disease so well that even an experienced physician cannot tell the difference.[7]

Blood vessel disorders

Vascular disease due to atherosclerosis often co-exists with Alzheimer's disease, particularly in older people, and may well contribute to it.[8-14] Many older people have some degree of atherosclerosis, so it is difficult to decide on its role in Alzheimer's disease. One type of dementia, pure *vascular dementia* such as Multiple-Infarct Dementia (MID) results from many strokes (infarctions) in brain tissue and follows a different clinical course from Alzheimer's disease.[8] Another type of vascular disease, *vascular amyloidosis*, also has clinical and pathological characteristics different from those of Alzheimer's disease.[15] Vascular dementia and Alzheimer's disease may occur together in older persons and lead to so-called "mixed dementia."

Neurotransmitter deficiencies

Neurotransmitters are substances that transmit information between neurons. Neurons that secrete or receive the neurotransmitter *acetyl* -

choline are involved in memory processing. The brains of Alzheimer's disease patients have abnormally low levels of several neurotransmitters, especially acetylcholine. This may be due to the fact that those cells that produce or process the acetylcholine are no longer functioning. Death of these "cholinergic" cells is gradual. Medication that increases levels of acetylcholine may be helpful—at least in the earlier stages of the disease.

Diagnosis

During life, diagnosis is clinical and proceeds by excluding other causes of dementia. After death, significant plaques and tangles confirm the diagnosis.[16]

Neuropsychological testing

Physicians have many tools with which they can differentiate Alzheimer's disease from other types of dementia. The *Mini-Mental State Examination* (MMSE) exists in many translations and is a widely-used screening test.[17,18] The MMSE uses a score from 0-30 to test cognitive function—the higher the score, the better the function (Table 1).[50] The *Global deterioration scale* ranks or *stages* the ability to perform daily activities in, such as getting dressed; the higher the stage, the worse the ability (Table 1). Other standard tests, such as the *Alzheimer's Disease Assessment Scale* (ADAS[18]), *the Clinical Dementia Rating* (CDR[19]), and the *Clinicians Interview-Based Impression of Change* (CIBIC[20]) are used for specific diagnosis and also for the evaluation of drugs in clinical trials. Most clinics dealing with dementia use their own combination of standard tests. A single comprehensive and universally accepted testing procedure does not yet exist.

Experienced clinicians can detect even subtle or atypical forms of Alzheimer's disease. Clinical diagnosis, which is ultimately confirmed postmortem, is 85%-100% accurate today. There are attempts to identify the disease earlier so that patients can be treated earlier. Several tests are also being developed to detect *mild cognitive impairment* (MCI), which may precede Alzheimer's disease.

Conditions that mimic Alzheimer's disease

In addition to excluding other major dementing disorders, such as multiple infarct (stroke) dementia and Parkinson's disease dementia, physicians must make sure that the dementia is not caused by reversible

Table 1: Mild, moderate, and severe Alzheimer's disease as measured with the MMSE and Global deterioration scale.

		Measure		
Stage	Duration, yr	Global Deterioration Scale,* score	Mini Mental State Exam,† score	Global autonomy
Mild	2–3	3–4	26–18	Independent living
Moderate	2	5	17–10	Supervision required
Severe	2–3	6–7	9–0	Total dependence

*Scale measures progressive need for assistance in daily activities (e.g., choosing clothes, dressing); scores range from 1–2 (normal) through 6–7 (severe dysfunction).[2]

†This 22-item scale measures cognitive function; scores range from 30 (excellent function) to 0 (severe dysfunction).[3]

factors such as medications. Older persons may use several drugs simultaneously, and they tend to eliminate these drugs more slowly than do younger adults.

Depression may mimic dementia, but depression is also very common in Alzheimer patients.[21] Physicians usually treat the depression first and then see whether the patient is still demented.

Delirium often results in transient demented behavior. Several reversible brain disorders such as encephalitis can lead to delirium. Non-prescription drugs, such as antihistamines, can cause deliri-

um that mimics dementia.[20]

Parkinson's disease patients also sometimes develop dementia, and at postmortem their brains usually show a different type of brain lesion, lesions which demonstrate abnormal components called *Lewy bodies*.[22] There may be a link between the two diseases, since about half of these patients also have enough plaques and tangles to justify the diagnosis of Alzheimer's disease.

Imaging and laboratory tests

Imaging methods and laboratory tests may eventually help better distinguish Alzheimer's disease from other dementia and detect it at earlier stages.[6,23-25] Reduced metabolic activity and circulation in sensitive areas of the brain, such as the hippocampus, have been demonstrated with PET scans and other imaging methods. At present, however, neither imaging nor laboratory tests are sensitive enough to provide an advantage over clinical diagnostic accuracy, which is about 90-99%.

Possible Causes

The causes of the observed changes in Alzheimer brains is not yet known. However, research is intense and many theories exist. The *amyloid cascade hypothesis* is currently the most popular.

The Amyloid Cascade Hypothesis

Because amyloid (neuritic) plaques are so predominant in Alzheimer's disease, many researchers speculate that amyloid or the amyloid plaques have a major role in causing the disease.[26] Several arguments support this hypothesis:

- ✓ Brains of old Alzheimer's disease patients usually have more plaques than brains of old non-demented persons.
- ✓ Genetic mutations associated with early onset Alzheimer's disease (familial) in one way or another affect the major protein (beta-amyloid) found in the plaques.
- ✓ Beta-amyloid protein was found to be toxic to cells in some—but not all—laboratory studies.

The theory supposes that beta-amyloid or the plaques are toxic to neurons. In order to test the amyloid cascade hypothesis, scientists engineered mouse strains that carry the mutant human gene for the protein (amyloid precursor protein) that gives rise to beta-amyloid. These mice produce enormous amounts of amyloid, and some of them develop

learning disabilities. These mice are used to develop and test possible treatments, such as a vaccine against amyloid deposition.

Several researchers, however, are not convinced that beta-amyloid or amyloid plaques play a major role in the disease. They also provide strong arguments for their skepticism, the most important being the poor correlation between amount of amyloid and the degree of dementia.[27,28] These researchers suggest that amyloid could just as easily be a result or a marker of the disease, or even be protective in the early stages.[29-32]

Neurofibrillary tangles as neurotoxins

Neurofibrillary tangles have also been proposed to cause neuron damage in Alzheimer disease, particularly because the tangles correlate better to the dementia than the plaques. Also, genetic mutations for a protein (tau), found in these tangles, are associated with another type of dementia called *frontotemporal dementia*. This rarer dementia, however, is pathologically and clinically different from Alzheimer's disease.[33] As with amyloid plaques, the role of these tangles in neuron damage in Alzheimer's disease is not clear at present.

Inflammation

Inflammatory processes are a common feature in the Alzheimer brain. Inflammation is the body's cellular and biochemical response to damage, protective initially but potentially damaging to all tissues, including the brain. Small retrospective* studies have indicated that people taking non-steroid anti-inflammatory drugs (NSAIDs) are at less risk for developing Alzheimer's disease than persons not taking these drugs. However, another anti-inflammatory steroid drug, Prednisone, had no effect on the progression of Alzheimer's disease in a careful, large prospective* trial.[34] Thus, whether inflammation contributes to the disease is not yet clear at present.

Free radicals

Free radicals (or highly reactive oxygen molecules) are potentially destructive molecules that occur in normal metabolism. Although they do serve useful functions—for example, in fighting infection—excessive or prolonged exposure to free radicals is thought to contribute to many degenerative disorders. Such exposure could occur through inflammation, aging, or environmental agents. Reduced levels of free radical scavengers, natural chemicals that inactivate free radicals, are often observed in the serum of patients with Alzheimer's disease and are

* see glossary

thought to result from oxidative stress (excess free radical exposure). However, the exact role of free radicals in Alzheimer's disease is not clear and subject to intense research and debate.[35]

Faulty brain metabolism

The brain accounts for about 25% of the body's oxygen and energy utilization. Any failure to meet these needs could endanger neurons. Faulty energy metabolism is often observed in Alzheimer brains and may be a direct cause of the disease.[29,35-37] It is well known that anything that impairs brain metabolism, such as low oxygen or reduced cerebral circulation, (atherosclerosis, head injury, strokes, etc.) may cause symptoms of dementia. Therefore, treatment aimed at improving energy metabolism in the brain may help against mental decline in Alzheimer's disease.

Multiple causes

It is likely that many factors interact to contribute to the disease and ultimately lead to dementia. How this happens is not known, but researchers are accumulating much new data that may help solve the riddle. A *proposed* sequence of events ultimately leading to dementia is suggested below:

- ✓ Damage to the brain, due to combinations of genetic factors, environmental factors, and aging, including the deposit of amyloid plaques and neurofibrillary tangles.
- ✓ Damage to brain energy metabolism.
- ✓ Certain neurons become less efficient and production of neurotransmitters, particularly acetylcholine, declines.
- ✓ The affected neurons do not communicate efficiently with each other and deteriorate as synapses are lost.
- ✓ When enough functioning neurons are lost in crucial areas of the brain, dementia occurs. The greater the brain reserve of neurons and of synapses, the later the deterioration.

This model may help explain several observations: why neurotransmitter therapy helps in earlier stages of the disease, why loss of synapses is a consistent finding in Alzheimer's disease, and why many old people with significant lesions do not develop dementia. [35,38,39]

It is likely that many factors interact to contribute to the disease and ultimately lead to dementia

Known and Suspected Risk Factors

Risk factors are characteristics that are often observed in association with a given disease in large populations. When present, they indicate an increased chance that a disease will occur, and may provide clues about potential causes. Risk factors do not necessarily cause a disease and can be purely coincidental. Depending on the strength of association with the disease and upon further scientific proof, a risk factor may turn out to be a cause of the disease, a factor that worsens the disease, or merely the result of the disease.

Age

Age is not considered to cause the disease, since the majority of persons over the age of 85 do not (yet?) have the disease

The dramatic increase in Alzheimer's disease seen with aging (Fig.1) demonstrates that age is the most important risk factor. Up to 50% of people over the age of 85 have been estimated to have the disease, although that high estimate has not been confirmed in autopsy-controlled studies**.** However, aging by itself is not considered to cause the disease since a considerable number of persons over the age of 85 do not (yet?) exhibit symptoms of Alzheimer's disease. Of course, the disease may still manifest if these people grow even older, but this possibility has been difficult to test.[39] Many diseases become more prevalent with age, such as heart disease, diabetes, and cancer. This does not mean that aging causes these diseases but perhaps that the aging body is less able to cope with the "causes." Many researchers suspect that free radical damage plays a significant role in the effects of aging on Alzheimer's disease. Increased free radicals are associated with aging**.** They result from many types of brain injuries, including head injury and vascular problems, and may well contribute to neuron damage.

Genes

Four genes are established risk factors forAlzheimer's disease

Four genes are established risk factors for Alzheimer's disease (Table 2).[40] Three of them are mutations and are associated with familial, early onset disease. The fourth is a normal gene variation that is strongly associated with late onset disease. Possible roles for may other genes are being investigated.

Table 2: Genes in Alzheimer's disease

Gene	Chromosome	Frequency
Familial, Early Onset Type		
*PS*1	14	Common in early onset familial disease, not in the more usual later-onset patients
APP	21	Rare even in early onset familial disease, normal other patients
PS2	1	Very rare even in early onset familial disease
Later Onset Type		
APOE	19	*APOE4* increases the risk of Alzheimer's Dementia. *APOE2* appears to protect. *APOE3* to be neutral.

Many other genes have been proposed to be involved but have not been confirmed, e.g. abnormalities in mitochondrial DNA (mtDNA). See reference 30 for a continually updated internet listing of genes proposed to be biological risk factors for Alzheimer's Dementia.

All three mutations seen in early onset disease appear to increase deposition of amyloid plaques.[41-44] One gene apparently codes for an abnormal version of a precursor protein, which *may* increase deposition of plaques. The other two mutations—*presenilin 1* and *presenilin 2*—appear to code for enzymes that may cause faulty removal of precursor protein. These enzymes, however, have other important functions as well as their action on amyloid.

The only gene associated so far with late-onset Alzheimer's disease is the gene for *APOE4*. The *APOE* gene codes for *apolipoprotein E,* a normal cholesterol-transporting protein found in many tissues. APOE comes in three normal variations: APOE2, considered to be protective; APOE3, considered to be neutral; and APOE4, considered to increase the potential for developing Alzheimer's disease.[43,44] However, having genes for APOE4 does not guarantee that a person will develop the dis-

ease; the genes just increase a person's chances compared, for example, to genes for APOE2.

APOE genes and Alzheimer's disease

APOE comes in three normal variations: APOE2, considered protective; APOE3, considered neutral; and APOE4, considered to be harmful. Each person carries a set of two APOE genes and can have one of six possible combinations: APOE2 + APOE2, APOE2 + APOE3, APOE2 + APOE4, APOE3 + APOE3, APOE3 + APOE4, and APOE4 + APOE4. Persons with two APOE4 genes appear to be the most susceptible. Although even two APOE4 genes do not guarantee the disease, they do seem to make persons more susceptible to late onset Alzheimer's disease. Many diseases, including cardiovascular disease, have been linked to genes for APOE4. APOE may be thought of as an "aging" gene, since with age fewer people having the APOE4 gene survive than those with APOE2.

Women are thought to have a higher risk of developing Alzheimer's disease, but whether this is because more women live into the age of risk than men or because they have two X chromosomes (men have one X and one Y chromosome) is controversial.[45] Also, the higher incidence in women has been questioned in some recent studies.[1, 45] The role of hormones is uncertain at present.

Environmental influences

Head injury is clearly linked to Alzheimer's disease.[46] Patients with an APOE4 gene in addition to head injury may be at particular risk. Head injury by itself can cause brain damage, an accumulation of amyloid type proteins, and dementia.

Very poor or no education is strongly associated with Alzheimer's disease.[4,47] However, a university degree has no advantage over junior high school education. We do not know how lack of education affects the development of dementia. Perhaps poorly educated people simply do worse on the psychological tests and are not really more demented. On the other hand, the process of education and learning may stimulate the creation of new connections (synapses) between neurons, thus creating a greater brain reserve, which may, as discussed earlier, compensate for age-associated neuron loss.

Toxic agents such as aluminum have been considered to cause or contribute to Alzheimer's disease. None have yet been proven to do so.

Progression

Alzheimer's disease may progress steadily, but some patients remain stable for a year or more even without treatment.[48,49] Some may even improve. However, usually Alzheimer patients become increasingly unable to care for themselves so that their survival depends on other secondary illnesses and on the quality of care they receive. The severity of Alzheimer's disease is described as mild, moderate, or severe (Table 2[50]).

Alzheimer's disease is not a direct cause of death

Some memory loss and slowing in reaction time is normal in the aging process without leading to dementia. However *mild cognitive impairment* (MCI) is a recently defined condition with more than usual memory loss. It appears to precede Alzheimer's disease in some cases: each year, about 12-15% of persons with diagnosed MCI progress to Alzheimer's disease.[51]

Survival after diagnosis of Alzheimer's disease can range from one to twenty years. Under good socioeconomic conditions, mean survival without drugs is about 8 years.[52] Alzheimer patients usually die of other illnesses such as pneumonia.

Some memory loss and slowing in reaction time is normal in the aging process and does not always lead to dementia.

Treatment

Today there are three main modes of treatment:

- ✓ Behavioral treatments
- ✓ Replenishment of deficient neurotransmitters, particularly acetylcholine
- ✓ Slowing the progression of the disease by preventing neuron damage

About 90% of patients diagnosed with Alzheimer dementia develop abnormal behavior

Behavioral treatment

Odd or antisocial behavior is often more upsetting to the patient or to the caregivers than the dementia itself. About 90% of patients diagnosed with Alzheimer dementia develop abnormal behavior.[53,54] Both behavioral modification techniques and drugs are used. Frequent adjustment in treatment must be made to the remaining but usually declining abilities of the patient. Drugs used to treat psychiatric symptoms include the following:[53]

- ✓ Depression: Selective Serotonin Reuptake Inhibitors (SSRIs); other, newer antidepressants such as *buproprion*; or older tricyclic antidepressants.
- ✓ Psychosis, agitation, or aggression: *risperidone* (risperdol) and *olanzopine* (zyprexa).
- ✓ Anxiety/insomnia*: short-acting benzodiazepines (risk of dependency with prolonged use); occasionally, the antiepileptic medication *depakote.*

The physician uses these drugs carefully and slowly increases the dose to make sure the patient receives enough—but not too much. Since each patient is different, doses must be individualized. Surprisingly low doses of *risperdol,* for instance, can reduce behavioral tensions in a family when given to an Alzheimer's patient.

Neurotransmitter therapy

In healthy brains, neurotransmitters are usually broken down by enzymes after use. For example, *acetylcholine esterase* breaks down acetylcholine. Drugs that inhibit this natural breakdown of neurotransmitters are used in raising deficient neurotransmitter levels in Alzheimer's disease.

Cholinesterase inhibitors are the mainstay of therapy

The mainstay of neurotransmitter therapy of Alzheimer's disease is *cholinesterase* inhibition, using drugs that prevent enzymatic breakdown of acetylcholine. Approved drugs for treatment of mild and moderate Alzheimer's disease in the United States are:

- ✓ *donepezil* (aricept)
- ✓ *rivastigmine* (exelon)
- ✓ *reminyl* (galantamine).

Recently published, rigorous, year-long, multicenter studies in both

* almost half of Alzheimer's disease patients have sleeping problems

Europe and the USA have shown a clear benefit with donepezil and a possible effect on slowing the progression of the illness.[48,49] Although less studied than donepezil, the other two drugs appear to have similar clinical benefits.[55] Since they are eliminated faster than donepezil, they must be given twice a day. They also need to be dosed carefully to avoid gastrointestinal side effects. *Tetrahydroaminoacridine* (THA; cognex) is now less used because of the risk of liver complications.

Antidepressant drugs that raise the neurotransmitter serotonin (SSRI) may improve the depressive symptoms of Alzheimer patients and those cognitive disorders that are due to depression. Other drugs that raise neurotransmitter levels have not yet been proven useful, although many have been studied.

Prevention of excess neurotransmitter action

Just as deficiencies of some neurotransmitters cause problems, excess levels of other neurotransmitters may be damaging. These types of neurotransmitters, such as glutamate, have the important function of exciting the neurons. However, excess levels may lead to over-stimulation and cell death. A drug that may prevent this type of action and delay loss of cognition, *Memantine* (an N-methyl-D-aspartate receptor antagonist), was recently approved in Europe, and an application for approval was recently filed with the FDA.[56]

Prevention of cellular damage

A major aim of research in treating Alzheimer's disease is to slow—hopefully even stop or reverse—the damage to and loss of neurons. Several studies are underway to test drugs that may benefit patients at different stages of the disease or help prevent it altogether. Some of these substances are well known, such as estrogen, whose effects on neurons are still not clear. Others are completely new substances that may prove to be useful. Some of the studies that are supported by the U.S. government are listed in Table 3.[57]

Anti-inflammatory drugs: Treatment with certain non-steroidal anti-inflammatory drugs (NSAIDs) appears to reduce the incidence and prevalence of Alzheimer's disease in retrospective epidemiological studies.[58] This led to the wide-spread use of low doses of ibuprofen or other relatively non-toxic non-steroidal anti-inflammatory agents to treat patients with established Alzheimer's disease. Clear evidence for a beneficial effect in patients with established disease does not yet exist. Ibuprofen and other NSAIDS may act on the inflammatory component of Alzheimer's disease. However, recent animal studies of

Table 3. Substances in current clinical trials sponsored by the U.S. Government (source: clinicaltrials.gov)

Substances under study	Effects being tested
Rofecoxib, Naproxen (NSAIDs—non-steroid anti-inflammatory drugs). Cyclophosphamide	Prevention of neurodegeneration due to inflammation + immune response
Vitamin E (antioxidant) and Donepezil (acetylcholine esterase inhibitor) examined in one study	Reduced conversion from MCI to Alzheimer's disease
Ginkgo biloba	Decreased incidence of dementia, slow cognitive decline, and functional disability
Estrogen	Preservation of cognitive function
CX516, a modulator for glutamate (neurotransmitter) receptors	Preservation of cognitive function
Statins (cholesterol-lowering agents), i.e. atorvastatin calcium	Preservation of cognitive function
Nefiracetam, drug that increases acetylcholine	Preservation of cognitive function
Rosiglitazone, an insulin-sensitizing compound	Effect on cognitive impairment in patients
Vaccines against against amyloid deposition: [one, AN-1792, **discontinued because of side effects**]	Prevention of dementia by interfering with plaque formation

ibuprofen indicate that this anti-inflammatory agent may have other important effects as well.[59]

Prednisone, an effective *steroid* medication against inflammation in the central nervous system, has been tested rigorously in patients with established Alzheimer's disease and proved not to be useful.[34] It is possible that anti-inflammatories such as NSAIDs only act in early stages before much damage has been done. Routine use of NSAIDs must be

done carefully, because side effects such as bleeding and kidney toxicity may occur, particularly with high doses and prolonged use.

Anti-oxidants may be beneficial; there is evidence of oxidative damage in Alzheimer's disease. Positive effects were reported in people regularly consuming vitamin C and vitamin E in a prospective study of a large population.[60] Vitamin E has also been reported to delay progression in Alzheimer's disease, but the statistics of that study have been questioned.[61] Stronger support for the use of vitamin E and C as preventive agents was recently published.[62] Both the acetylcholine esterase inhibitor donezepil and vitamin E are currently being tested in combination to see if they prevent MCI from progressing into AD (Table 3). Other anti-oxidants are being studied, including such unusual antioxidants as the curry spice curcumin.[63]

Hormone Replacement Therapy, notably with estrogens, has been associated with a reduced incidence of Alzheimer's disease in epidemiological studies. These results are hard to interpret, since those few American women who take post-menopausal hormone replacement comprise a highly self-selected group. They are usually well educated and health conscious, and these lifestyle factors, rather than the hormones, may actually reduce dementia. A prospective study of the effect of estrogen replacement in women with established Alzheimer's disease clearly did not find a benefit for the patients.[64] A subsequent small study using high doses of estrogen, however, claimed a benefit.[65] Estrogen is currently not recommended as a treatment of the disease because of conflicting evidence regarding its usefulness. A rigorous large prosepective trial to determine whether or not estrogen replacement reduces the incidence of Alzheimer's disease is underway.

Vaccination against the amyloid protein of the amyloid plaque has been in the news lately.[66] It has been reported to reduce learning disorders in mice genetically engineered (transgenic) to have high levels of a mutant human amyloid precursor protein in their brains. However, trials in humans have been stopped because of the development of acute inflammatory disease of the brain in some of the patients.[67] Scientists are looking at other drugs and methods to stop amyloid deposition.

Statins, which inhibit cholesterol synthesis, have been reported to have some positive effect on Alzheimer's disease. Whether this is due to reducing the risk of vascular disease or to some other effect is not known.[68] There is no indication that cholesterol-rich or cholesterol-low diets have any effect on Alzheimer's disease.

Folic acid*:* An elevated blood level of homocysteine, a risk factor for vascular disease, also appears to be a risk factor for Alzheimer's dis-

ease.[69] Preventive treatment with folic acid to reduce blood homocysteine levels has therefore been recommended. However, very high levels of folic acid may mask vitamin B_{12} deficiency, and severe B_{12} deficiency itself can lead to irreversible neurological damage.

Hope for the Future

Research has made tremendous strides in the last twenty-five years and holds the promise of slowing or even preventing Alzheimer's disease. Twenty-five years ago, researchers still wondered whether this devastating disorder was an "inevitable consequence of aging." Therapies are now available that not only reduce the symptoms of Alzheimer's disease but may also slow its progression. Progress will, without a doubt, continue in this direction.

Glossary

Acetylcholine: a neurotransmitter that is involved in memory processing and found to be particularly low in Alzheimer's disease brains.

Amyloid cascade hypothesis: a popular theory assuming that beta-amyloid or amyloid plaques start the disease process.

APOE: apolipoprotein E, a cholesterol-transporting protein that also plays a role in brain metabolism. The gene coding for APOE4, a type of APOE, is associated with greater risk for Alzheimer's disease.

Beta-amyloid: a protein that is associated with some disorders including Alzheimer's disease where it is a component of abnormal plaques.

Delirium: severe but often reversible state of confusion and disorientation, often involving hallucinations; can be caused by drugs or by disease, including encephalitis.

Dementia: general mental deterioration with loss of learned abilities, of reasoning abilities, of memory, often with language problems and behavioral changes; usually the result of brain damage.

Epidemiology: the study of diseases in large populations.

Frontotemporal dementia: rare dementia associated with a faulty gene for the protein "tau"; affects the frontal lobe of the brain.

Hippocampus: part of the temporal lobe of the brain involved in memory processing.

Lesion: injured or disturbed tissue which may result in change or loss of normal functioning.

Multiple-Infarct Dementia (MID): follows a different course from Alzheimer's disease and results from many small strokes in brain tissue.

Neuritic plaques: abnormal protein deposits associated with neurons in Alzheimer's disease brains.

Neuron: nerve cell, an elongated cell with many branches and extensions called dendrites and axons.

Neurotransmitters: cell-produced chemicals that transmit information between neurons. If neurons do not secrete or receive neurotransmitters, information is not passed on. Neurons that secrete or receive acetylcholine, a major neurotransmitter, are involved in memory processing.

Oxygen free radicals: highly reactive and potentially destructive molecules; occur in normal metabolism and serve useful functions, as in the immune response. Excessive amounts can damage tissues.

Presenilin 1 and presenilin 2: mutant genes associated with early onset familial Alzheimer's disease; thought to play a role in deposition of amyloid plaques and to have other functions.

Prospective studies: usually well-planned studies that attempt to control for anything that might obscure the interpretation of the results.

Retrospective studies: unplanned studies done "after the fact," relying on records or recall.

Risk factor: a factor frequently correlated with certain diseases but not necessarily a cause. A risk factor can be a cause but also just a marker of a disease. People can have all the risks factors but not have the disease. People can have the disease but none of the risk factors.

Synapse: communication points between neurons. The area where den-

drites (branches of neurons) of one neuron connect with the axon (a very long branch of a neuron) of the other neuron. The neurotransmitters flow across the synapse from one neuron to the other.

Transgenic mice: mice genetically engineered to contain non-species i.e. human genes; used to test the effect of certain usually mutant genes on human disease for which the mice serve as a model.

Vascular amyloidosis: a brain blood vessel disease that is also associated with amyloid; this condition does not, apparently, relate to the amyloid plaques seen in Alzheimer's disease patients.

Vascular dementia: dementia due to cardiovascular disease, usually due to multiple strokes as in mutiple-infarct dementia.

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Tables and Figures

Table 1. Mild, moderate, and severe Alzheimer's disease as measured with the MMSE and Global deterioration scale; Serge Gauthier (Table 2). CAMJ, 2002' URL: http://www.cmaj.ca/cgi/content/full/166/5/616/T220. See References.

Table 3. Substances in current clinical trials sponsored by the U.S. Government (table compiled and adapted from data from http://www.clinicaltrials.gov)

Figure 1. The increase of Alzheimer's disease and other types of dementia with age. (Ott et al, 1995, see references); URL: http://bmj.com/cgi/content/full/310/6985/970/F2

Figure 2. The major areas of the brain affected by Alzheimer's disease (Brain diagram of A. Heinz booklet, Fig. 3.)