

Chapter 3

The Diseases: Diagnosis, Treatment, and Scientific Background

“While it is important to keep the perspective that the vast majority of elderly people do not demerit, from the neurologist’s perspective these numbers of patients [with dementia] are staggering. ”

—Stuart A. Schneck, M.D.
American Academy of Neurology
Annual Meeting, 1986

The question ‘Why study dementia?’ is coming to be answered very clearly. There are few issues receiving public attention today whose ramifications touch upon so many areas of human well-being. The large number of lives involved; the severity of the physical, psychological, and economic influences of the disease upon the victims and related persons; and the long duration of the illness and [their] poor prognosis establish [the] dementia(s) as a fundamental problem in our society.”

—Mary L.M. Gilhooly and James E. Birren,
in *The Dementias: Policy and Management*,
M.L.M. Gilhooly, S.H. Zarit, and J.E. Birren (eds.)
(Englewood Cliffs, NJ: Prentice-Hall, 1986)

“The attitude of ‘(nothing can be done)’ results in nothing being done, and the functional ability of the patients is adversely affected.”

—James A. Greene, Jan Asp, and Nancy Crane,
Journal of the Tennessee Medical Association,
September 1985, vol. 559, p. 5.59

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The Diseases: Diagnosis, Treatment, and Scientific Background

Dementing disorders exact a staggering toll on patients and their families. Many of the worst problems are caused by the behavioral and intellectual effects of the diseases, which rob patients of their autonomy and exert emotionally wrenching pressures on family and friends. The larger issues related to caring for patients are covered elsewhere in this assessment; this chapter provides clinical and scientific background on the diseases themselves. The clinical and scientific information is intended to introduce other sections of the report, and is not followed by policy issues and options because these are found in other, more policy-oriented chapters.

Over 70 disorders can cause dementia. This chapter describes the clinical and scientific back-

ground on some of these disorders. Medical management of the various disorders causing dementia depends on the characteristics of individual patients. Treatment is quite effective for a few disorders, and several behavioral symptoms common to many of the most prevalent diseases frequently respond to medication. Symptoms of dementia are often made worse by acute medical illnesses and drugs, and prompt medical attention can reduce excess disability caused by poor health and medications. No cure is available, however, for the vast majority of dementing conditions, and the symptoms of intellectual decline frequently continue to worsen despite the best medical efforts.

DIAGNOSIS

Once the symptoms of dementia have been identified, the search for a specific cause commences. In the hands of experienced and capable physicians, the diagnostic process is highly efficient and conveys relevant information about the putative causes, possible treatments, and probable course of the disease in a given patient. The accuracy of detecting dementia has improved to over 90 percent at specialized centers in recent years (163). Yet diagnostic error is higher for identifying the specific diseases causing dementia and detection of the symptoms remains poor among some physicians. Many physicians are now apt to make the diagnosis of Alzheimer's disease, for example, any time a patient has notable intellectual or memory impairment. This contrasts markedly with medical practices common until recent years, when Alzheimer's disease was underdiagnosed because of ageism, different medical terminology, and errant theories of the causes of the disease (228). Many patients now in nursing homes were evaluated during the periods of underdiagnosis, and their records retain outdated diagnostic labels

such as "(cerebral atherosclerosis" or "chronic brain syndrome."

The diagnosis of a disease that causes dementia usually begins with identification of mental decline, either from querying patients or others who know them. Detecting early dementia can be difficult, but:

... dementia should be suspected whenever mental changes of insidious onset emerge without sufficient situational stress and gradually interfere with the daily living activities. . . . Dementia can be reversible or irreversible, precipitously progressive or indolent, bristling with multiple cognitive deficits, or characterized almost exclusively by disturbances of affect, motivation, and personality (218).

Problems in Diagnosis

Inaccurate diagnosis can arise from several sources. The errors may stem from atypical presentation of the disease, denial or misunderstanding by the patient or family, or physician error.

Symptoms may be mild and ill defined, or the disease may have progressed so far that any number of diseases could have caused the patient to lose most mental functions (84). The patient may not experience memory loss, or may exhibit bizarre behavior that is ascribed to depression or schizophrenia (163,289). The history may be inaccurate, due to inadvertent or deliberate reporting errors by the patient or the family. The patient or family may wish to deny the presence of any problems, or they may have identified the wrong ones. No family members maybe available to give a medical history. The onset of most dementing illnesses is not sudden, but patients and families may not notice a problem until a cataclysmic event or new source of stress dramatically highlights a loss of mental function. Finally, tests may be misinterpreted, the proper tests may not be ordered, or the symptoms of dementia may be missed by the health professionals who care for the patient.

Several factors predisposing to diagnostic error have been identified:

- ageism (neglect caused by expectations that a patient is "just senile");
- failure to use strict diagnostic criteria;
- insufficient time devoted to obtaining a history or examining patients;
- absence of a policy of searching for remediable causes of confusion;
- inadequate recourse to special tests; and
- incompatibility between the diagnostician and the patient (due to cultural, educational, or ethnic background (125)),

Some error is due to lack of knowledge, and this can be addressed by improved education. Other errors are due to failure to apply what is known. This can be due to the pressure of time, the clinical complexities of a particular case, lack of access to diagnostic technologies, or physician disinterest. Discovery of effective medical treatments for the common dementing conditions, especially Alzheimer's disease and multi-infarct dementia, would give physicians a major reason to find the correct diagnosis, likely reducing the diagnostic error rate in routine practice.

The problems of misdiagnosis that arise from patients and their families can be addressed by

public education and family support groups, but this type of problem will never be eliminated completely. Self-help groups, media attention, and accurate dissemination of scientific and medical information from laboratories into the general society are the major policy initiatives that could reduce this form of diagnostic error.

Misdiagnosis by physicians can be reduced through improved education during professional training, continuing medical education, and rapid dissemination of scientific data in medical journals and books. The Federal Government has taken the lead in sponsoring basic and clinical biomedical research, and also supports many extremely useful information dissemination mechanisms through the National Library of Medicine and the National Institutes of Health (NIH). The Federal Government generally has not had a role in assuring the incorporation of new information in the curricula of health professional programs (see ch. 9).

Clinical diagnosis is only as reliable as the process used to make it. Beginning with a patient's history of mental change, a diagnostic algorithm is then followed to identify possible specific causes. The breadth and adequacy of these procedures depends on the knowledge of the supervising physician, the availability of diagnostic tests, and the quality of the tests. The diagnostician's knowledge is related to the availability of current medical information, active continued reading of the medical literature about diagnostic options, and the person's educational background. The availability of diagnostic tests depends on a groundwork of basic and clinical science, marketing, and local access to people trained to perform the tests, whereas quality is linked to the limitations of the test itself (how well it works at best), the competence of those who perform it, and the accuracy with which results can be interpreted.

Many factors that influence the diagnosis of dementing conditions have been changing in recent years as a result of the greatly heightened interest in studying dementia. A consensus development conference of diagnosis of dementia will be held at NIH July 6-8, 1987.

Diagnostic practices among specialized groups at major medical centers are often quite differ-

ent from those in other services at the same institutions, as well as from practices that prevail in community hospitals and private clinics. Most of the published data come from centers of expertise and reflect high standards for evaluation; the actual care of patients in most communities is generally less thorough. The degree of diagnostic error is difficult to determine, however, because most studies are conducted at academic medical centers specialized in the care of dementia. Yet many persons with dementia reside in nursing homes, where they receive less thorough diagnostic evaluation. The most serious problem of diagnosis in nursing homes is widely believed to be underdiagnosis or failure to even recognize symptoms of dementia (274).

Failure to detect dementia among patients ranges from 4 to 60 percent in recent studies (125). These errors are, by and large, most frequent among patients known to have confusion or behavioral change. Even more troubling is the failure to notice that a patient is confused; examining physicians missed 79 percent of the cognitive deficits at a university hospital in a recent preliminary study (207). Another report found that errors in initial diagnosis affected therapy in 41 percent of the patients referred to a specialized hospital service for dementia (145). Great improvements are thus possible in the sensitivity of detecting mental impairment and identifying its specific cause even without technological advances.

Diagnostic uncertainty complicates clinical research by mixing patients with different diagnoses. A drug or diagnostic procedure maybe tested on patients with disparate diseases. Those with different illnesses or in different stages may respond but be undetected because they are lost among a large group of patients who show no effect. This can mask a benefit or danger. For a response to be detected, therefore, a drug or test must either be highly effective in a small group of patients or effective in most patients. Patient heterogeneity is thus the bane of efficient clinical testing. It does not preclude it, but it makes tests significantly less sensitive to small or moderate effects.

There is no clear way around this problem in clinical research on dementia. The standard for approving clinical protocols for mentally incompe -

tent patients requires that the experimental procedure either pose minimal risk or promise direct patient benefit (45 CFR 1983 ed. 46). Neither condition clearly holds for most investigational work, but it is unlikely that the regulations for research on human subjects will be altered. Such changes would require, at a minimum, extensive public review before being implemented. (Consent of dementia patients to participate in clinical research is dealt with more fully in ch. 5.)

The Diagnostic Process

The possibility of treating some reversible syndromes that masquerade as irreversible dementia provides a strong incentive for accurate diagnosis. Families wanting to know about possible genetic risks, furthermore, cannot be advised until a specific disease has been identified. The process followed in obtaining a clinical diagnosis centers on cultivating several different sources of potentially useful information: in the patient's medical and behavioral history, physical signs, laboratory tests, psychological tests, and brain imaging technologies.

The process of diagnosis also includes investigating other illnesses. One recent study of persons with dementia in the community found that 30 percent had medical conditions that contributed to the patient's mental deterioration, and that removal of some medications and correction of metabolic abnormalities actually improved the function of most (181). Thus broad inspection of a patient's possible medical problems is important.

Diagnosis is the function that both physicians and families regard as the doctor's strength. Families regard diagnosis as the doctor's function, above patient education, emotional support, or assistance in obtaining health and social services. Physicians concur in finding diagnosis less difficult to provide than counseling, coordination of care, or other services (113). The diagnostic process is thus generally directed by a physician with the assistance of family members or others familiar with the patient's history.

Patient History

The specific mental and physical changes reported by patients or those who know them well

are extremely important in determining the possible causes of dementia. The age at which intellectual changes began, the exact functions lost, and the rate of change are all quite helpful in sorting among the various disorders. The type, frequency, and severity of mood swings, personality changes, and catastrophic emotional reactions are also useful. A history of mental decline at specific times with some recovery after each episode strongly suggests multi-infarct dementia, for example. Medication frequently causes symptoms of dementia in older patients, and examiners should find out what medication a patient is taking. Dementia pugilistic (brain damage induced by repeated head trauma) is immediately suspected in former boxers, and a history of alcoholism may suggest a detailed search for alcohol-related damage to the brain.

The patient history is taken, if possible, from the patient. This cannot be done for many individuals with moderate or severe dementia. In such cases, a history must be taken from family or friends, and corroboration by several sources is often helpful in deciding fine points about the course of the illness. The resort to secondary sources is common for pediatricians, pathologists, and veterinarians, but is unusual for many physicians who specialize in other areas. The added complexities of surrogate informants often necessitate finding corroboration for important points, especially if there is a conflict of interest between the patient and the informant (see ch. 5).

The history will include the main reason medical help is sought, information volunteered by the patient or informant, and answers to questions posed by the interviewer. Specific questions are asked to elicit certain points helpful in distinguishing among the different disorders that might explain the symptoms. Abnormal involuntary movements combined with a history of a similar illness in other family members, for example, can be quite informative for Huntington's disease. An insidious onset with early deterioration of memory for recent events is typical of Alzheimer's disease, while early disturbance of a patient's gait with only a mild memory deficit inclines a physician toward a diagnosis of normal pressure hydrocephalus.

The history of the illness becomes the first, and in many cases the most important, step in determining the diagnosis. It often indicates which tests will be performed to rule out or suggest specific diseases, and also alerts the diagnostician to look for specific physical symptoms in the subsequent examination of the patient.

Physical Examination

The physical examination consists of a battery of tests of body functions to detect signs of dysfunction or other findings associated with particular diseases. For a patient with dementia, the exam has two main emphases: signs of damage to the nervous system, and evidence of diseases of other organs that could affect mental function.

Testing of several organ systems, such as the cardiovascular system, the lungs, and digestive organs, is done by an algorithm that physicians, nurses, and physician assistants learn during their professional education and progressively refine during their practice. Diseases of many organs other than the brain can induce confusion, loss of memory, and strange behavior, especially in older individuals (68) (see table 3-1), and such causes must be eliminated before a firm diagnosis of brain disease can be made. The general physical examination can, for example, identify signs of heart failure or thyroid dysfunction, which in elderly individuals can involve symptoms that resemble dementia.

Table 3-1.-Examples of Diseased Brain States Caused By Failure of Organ Systems

Organ system	Symptoms and signs
Heart failure	Headache, confusion, stupor
Liver failure	Confusion, stupor, or coma; focal or generalized seizures, tremor
Kidney failure	Apathy, fatigue, confusion, stupor, generalized seizures, "dialysis dementia," "disequilibrium syndrome"
Endocrine	
Hypoglycemia	Episodic headaches, seizures, confusion, coma
Hyperglycemia	
Hypothyroidism	Apathy, psychosis, coma
Hyperthyroidism (apathetic)	
Cushing's syndrome (CS)	Apathy, psychosis, severe dementia, depression
Addison's disease (AD)	

SOURCE* Adapted from B.M. Coull, "Necrologic Aspects of Dementia," *Geriatric Medicine*, vol 1 C.K. Cassel and J.E. Walsh (eds.) (New York: Springer-Verlag, 1964)

Testing functions controlled by the brain and nerves—the neurological examination—is another important component. The examiner typically asks the patient to perform maneuvers or answer questions that are designed to elicit information about the health of specific parts of the brain or peripheral nerves. The examiner tests smell, vision, eye movement, muscle tone and power, touch, hearing, taste, and reflexes (both muscle reflexes and those that involve involuntary functions such as constriction of the pupils).

The neurological examination distinguishes signs of brain disease. Symptoms caused by damage to a particular anatomic location in the brain or spinal cord, for example, suggest stroke, tumor, or some other physically localized phenomenon. Multi-infarct dementia is suspected in a patient with dementia who also shows other localized brain damage and has high blood pressure or diabetes, while a patient without these findings is more likely to have Alzheimer's disease (48). Involuntary movements, rigidity of the limbs, and general slowness of speech and gait may induce a high suspicion of Parkinson's disease. Recent preliminary studies suggest that Alzheimer's disease may be correlated with specific tests of brain functions (217).

The characteristics of cognitive loss may also be useful in differentiating among possible explanations of mental change. A skillful examiner may be able to distinguish the patient with depression from one with a degenerative dementing condition, based on errors on the mental status examination due to lack of motivation or to inattention (favoring depression) versus those due to inability (thus implying brain disease).

Taken together, the history and physical examination permit an 80-percent diagnostic accuracy of dementing conditions (163), lower than the accuracy of detecting the symptoms of dementia, but well within the range of many other types of disease.

Laboratory Tests

The diagnostician selects specific laboratory tests based on the clinical history and physical examination, which typically leave the physician with a list of possible explanations of the symptoms

and signs that range from the highly probable to the improbable. Tests that might reinforce suspicion of some diseases or eliminate others from consideration are then performed. These include measurements of the concentration of cells and chemicals in the blood that might yield clues of infection or disordered metabolism, measurements of electrical activity in the brain (electroencephalograms or other more sophisticated tests), and measurements of chemicals and cells in the fluid that surrounds the brain (the cerebrospinal fluid [CSF]).

A large number of white blood cells in the blood combined with fever, for example, can indicate an ongoing infection. Abnormal blood concentrations of hormones, vitamins, electrolytes, or chemicals normally filtered by the kidneys can uncover diseases of the liver, kidney, or endocrine glands or exposure to heavy metals. Abnormal concentrations of chemicals in the urine may disclose poor kidney function or exposure to toxins or drugs.

Several lists have been developed of tests to distinguish among different conditions causing symptoms of dementia (see table 3-2); most include several blood tests and at least one brain imaging technique (discussed later in this section). No single standard protocol exists, however, because of both the variation among patients and disagreement about the usefulness of some tests.

The utility of any one type of test may be uncertain, and its use may then vary from place to place. Tests also vary in expense, risk, and discomfort for the patient. Obtaining a sample of cerebrospinal fluid, for example, requires entering the sac that encloses the spinal column in a procedure called lumbar puncture. Tests of CSF can reveal syphilis of the nervous system, evidence of bleeding, or ongoing infection (323). The test is relatively expensive (\$381 in one study), carries a small risk for the patient, often causes discomfort, and picks up relatively a few diseases compared with the number of patients tested (17, 130). Several authors have concluded that lumbar puncture should not be done unless a brain infection is suspected or the patient is under age 55 (17,130,201); other authors include the procedure in their recommendations (84,314,323). The debate about performing the lumbar puncture on all pa-

Table 3=2-Selected Laboratory Tests To Diagnose Specific Diseases and Search for Reversible Cause of Dementia

Test	Diseases suggested by test results
Blood count	Pernicious anemia, infection
Sedimentation rate	Immune disorders
Electrolytes, glucose, calcium, liver, and renal function tests	Clue to metabolic etiologies, liver disease, kidney disease
Urinalysis	Kidney disease
Syphilis serology (VDRL, etc.)	Syphilis
Vitamin B ₁₂ , vitamin B ₆ , vitamin B ₁₂ , folate	Vitamin deficiencies, pernicious anemia
Thyroid and adrenal function tests (TSH, T ₄ , T ₃ , resin uptake, cortisol)	Hype- or hypothyroidism; Cushing's disease, Addison's disease
CT or MRI	Normal pressure hydrocephalus, stroke, vascular disease, tumor
Lumbar puncture	Syphilis, cryptococcus, brain hemorrhage, other infection of the brain
EEG	Seizure disorder, transmissible dementia
Special Studies (When Appropriate): RISA study	Hydrocephalus, when other studies or history suggest possibility of that disease
Toxic screen including heavy metals	Environmental or occupational exposure; poisoning

SOURCES: Adapted from P.V. Rabins, "Reversible Dementia and the Misdiagnosis of Dementia," *Hospital and Community Psychiatry* 34: 830-835, 1983; and K.L. Tyler and H.R. Tyler, "Differentiating Organic Dementia," *Geriatrics* 39:38-52, March 1984.

tients with dementia thus continues, and different articles about diagnostic procedures include the test, exclude it, or list it as optional (5,30)84,165) 171,253,314). Lumbar puncture could rapidly become routine if a specific CSF test for Alzheimer's disease became available. Several of the promising new tests do require CSF samples at present. Physicians may thus be unsure of the proper course of testing, and their uncertainty will not diminish until more studies indicate the appropriateness or lack of utility of lumbar puncture.

Similar uncertainties are associated with many other diagnostic tests. A consensus on essential versus nonessential tests can only result from clinical trials that demonstrate a particular test's utility. The need for practicing physicians to know what tests to perform is one of the important drives behind clinical research. The rate at which diagnostic and treatment controversies are resolved depends, therefore, on continued funding of clinical research.

Investigators hold great hope for significant advances in the laboratory diagnosis of disorders causing dementia. Many researchers are now attempting to identify biological markers of Alzheimer's disease, for example, that would vastly simplify its diagnosis (308). Alzheimer's disease can now only be confirmed if tissue from the patient's brain can be directly inspected under the microscope, so clinical diagnosis proceeds by elimination of other possible explanations of demen-

tia in a patient with a history of symptoms applicable to several disorders. Specific tests of blood, CSF, and other more accessible tissues that could reliably identify patients with Alzheimer's disease or its subtypes would be highly desirable.

The search for specific laboratory markers is promising, but there is no evidence yet that it will be successful. One group recently found a soluble protein that is found at much higher levels in brains of patients with Alzheimer's disease than in brains of controls (336). Another group reports loss of an enzyme in patients with Alzheimer's disease (77). Some scientists have found biochemical aberrations in the blood cells of patients with Alzheimer's disease, but the diagnostic usefulness of the findings has not been established (32).

Cells grown in culture after removal from patients with Alzheimer's disease have demonstrated abnormalities of glucose metabolism (292). Irregularities that might be detected in the chemistry of CSF have also been found (111,313); but their presence has either not been confirmed by later investigators or cannot be detected by routine methods early enough in the illness to be diagnostically useful. Recent studies have demonstrated chemical imbalances that might be detected relatively early in the disease (99), but diagnostic tests based on these findings have not yet been devised. If a protein can be found in spinal fluid or blood that is not associated with other diseases, its detection would permit a specific diagnostic test for

Alzheimer's disease. That would revolutionize the diagnosis of dementias in general.

For those cases of Alzheimer's disease that clearly run in families, it may be possible to develop a direct test of DNA analogous to that under development for Huntington's disease (126,325, 326). An association of Alzheimer's disease with an unusual gene for an immunological blood protein (C4) has been shown in one study (234), but its specificity to Alzheimer's disease and its diagnostic importance have not been established. Other genetic tests either are nonspecific or have not yielded consistent results to different investigators (308).

Several scientific groups are developing antibodies against abnormal brain proteins found in those with Alzheimer's disease (83,123,321)336,342), but, again, the antibodies have yet not been used as diagnostic tools, either alone or in combination with brain imaging techniques.

psychological Tests

Psychological tests are used to screen for the presence of dementia (e.g., to distinguish depression from dementia), to follow up on initial findings, and to differentiate among the disorders causing dementia (e.g., to distinguish Huntington's from Alzheimer's disease). Short screening tests, called mental status tests, can be used by physicians, nurses, or other health professionals to estimate changes in global intellectual performance (33,74,90,97,124,128,158, 162,169,170,204,243, 24-4,260) 261,269)270,302,3 19); they are discussed at some length in chapter 8, and only their role in diagnosis will be covered here.

Different tests either measure specific mental functions or briefly survey those functions deemed most likely to be diagnostically decisive. Most of the tests developed over the past two decades have focused on questions and tasks that can be performed at the bedside in a relatively short time. The two tests most commonly used correlate well with each other among patients with Alzheimer's disease, and a formula to convert scores has been developed (307). Screening tests are judged most likely to be useful in routine practice, but generally are not sensitive to detection of mild dementia, and cannot differentiate among

patients with severe dementia. They are thus useful mainly for preliminary identification of symptoms, and can be followed up by more elaborate and specific tests.

More extensive tests of mental functions can be used to refine analysis of the clinical features. Extensive psychological testing can take several days and involve batteries of specific tests. Their use varies from place to place, but a panel of experts recently listed a number of specific tests found useful in the clinical diagnosis of Alzheimer's disease and dementia (212, table 2 and pp. 941-942).

Psychological tests are used primarily to confirm diagnoses that are already suspected, but they sometimes serve to distinguish among different diseases (224). The tests are intended to assess the functions performed by different parts of the brain (e.g., memory, calculation, knowledge of place and time, attention, understanding, and language use). These must be used carefully, because they can be influenced by a patient's educational background or socioeconomic status, but they are often successful in separating impairments of memory, for example, from those influencing perception or language. In addition, they are important in distinguishing disease from the effects of aging.

Psychological tests are essential to track the effects of experimental treatments, to trace the rate of deterioration of mental function, and to study subtypes of heterogeneous disorders like Alzheimer's disease. They are also useful for following the stages of illness in a group of patients and in the care of an individual over time.

Variations on psychological tests may help identify need for service or measure fair payment to caregivers, but their use for these purposes introduces complexities such as examiners' vulnerability to deliberately being fooled. The tribulations of using psychological tests for assessment of the type and amount of care a patient needs are dealt with in chapter 8.

Finally, psychological tests are important for indicating not only what is wrong, but also what functions are preserved. Knowledge of spared functions can assist family members or other caregivers in dealing with a patient.

Brain Imaging

All commentators agree that brain imaging is an essential component in the diagnosis of dementia, but the technique used depends on local availability and rapidly changing medical standards. Several methods for directly assessing the anatomy of the brain have been developed in the last two decades. The most powerful new technologies use computer analysis to create images of the brain. The differences among the techniques stem from the type of measurement used to generate data for the computer.

CT Scanning.—Computerized axial tomographic (CT) scanning is an extension of traditional X-ray diagnostic testing. CT scanning uses the same type of energy, X-radiation, as used for chest or skeletal x-rays, but the computer processes the information in a way that permits analysis of the internal anatomy of the head, including the brain. CT scanning machines are available in most major hospitals and many other clinical centers now, and the procedure is routinely used in most investigations of dementia. It can be useful by specifically detecting some causes of dementia, such as tumors or enlarged ventricles suggesting hydrocephalus or strokes in some locations of the brain. CT has also been used to study Alzheimer's disease and assess patient prognosis (161,80,85). Applied to Alzheimer's disease, CT scanning has been more helpful to date in establishing averages for Alzheimer patients compared with normal individuals than in differentiating Alzheimer's disease from other dementias.

PET Scanning.—Positron emission tomography (PET) relies on computer analysis similar to that used in CT scanning, but the machine detects positrons (electrons that have a positive rather than a negative electric charge) rather than X-rays. PET scanning works by injecting chemicals that radiate positrons. By using carefully chosen positron-emitting chemicals, the technique allows investigation of the brain in action—analysis of the physiology of the brain displayed in three-dimensional splendor. Injection of chemicals that closely resemble glucose, for example, reveals how fast the “cellular fuel” is taken into cells. That technique provides a rough measure of how actively nerve cells are firing in particular anatomic re-

gions, which in turn gives clues about the functions of large groups of nerve cells in the brain.

Several different causes of dementia reveal distinctive features in the PET scanner. Patients with Huntington's disease, for example, show lower glucose intake in the caudate nucleus, a group of cells known to be lost during the course of the disease (133,177). Several studies of Alzheimer's disease have also shown characteristic abnormalities in specific regions of the cerebral temporal cortex (55 and others cited therein, 75,76,86,92,98,102, 208,227).

The PET scanner is a fascinating and highly useful research tool, but it has several drawbacks that will prevent it from becoming a part of routine diagnosis soon. The major constraint is its dependence on availability of a nearby cyclotron (atom smasher). The chemicals that emit positrons must be made in such a machine, and they release positrons only for a relatively short time (minutes to hours). Cyclotrons are not available in most communities, and they are extremely expensive to construct. The combination of time and expense involved in setting up a PET scanning facility thus precludes its general applicability.

Some of the advantages of “functional imaging” available using the PET scanner might be developed for other imaging techniques, however. The special chemicals used in PET scanning might well have functional analogs that could be detected using brain scanning machinery available in major hospitals or adapted for magnetic resonance scanners, which are becoming more widely available..

SPECT Scanning.—Single photon emission computed tomography (SPECT) is another method for indirectly measuring physiological activity. It has been called the “poor man's PET scan” because it may eventually be able to perform many of the functions now only available through PET—although with diminished precision and resolution (163). The technique uses radiation detection machines available in hospitals with nuclear medicine departments, SPECT is likely to be useful in detecting strokes, hemorrhage, and areas of poor blood circulation to the brain (60).

A few studies have shown diminished blood flow to the lateral regions of the cerebral hemispheres

in Alzheimer's disease similar to the pattern found with PET (288). Patients with multi-infarct dementia and Pick's disease have also been studied (59, 146,322). One study used SPECT to detect the binding of specific chemicals known to be lost in Alzheimer's disease and was able to distinguish Alzheimer patients from controls (147). It is not yet clear whether SPECT will be widely useful in the diagnosis of dementia. Although less expensive than PET scanning, SPECT is nonetheless costly and may not prove more useful than other diagnostic procedures (163).

MRI Scanning.—Magnetic resonance imaging (MRI) is a new technology for making images of the brain and other parts of the body (315). The technique depends on detection of a phenomenon called nuclear magnetic resonance (NMR), and is also sometimes called NMR scanning. The nuclei of some atoms in the body are composed of odd numbers of nuclear particles. (Most atoms are stable only with an even number of nuclear particles.) Such nuclei can be detected by sending weak energy signals through very strong magnetic fields. The MRI machine consists of a set of powerful magnets and a source of energy in the same general range used for broadcasting radio. The radio signal is affected in predictable ways by the number of odd-numbered nuclei in its path,

The most common element with an odd number of nuclei is hydrogen, and water is the molecule most frequently associated with hydrogen in the body. In its usual application, therefore, MRI produces a map of the water content of various tissues in the body. (It can also be used for other, more specialized purposes, but they are not relevant to this discussion.)

MRI has several advantages and disadvantages. The biggest advantage is that it does not involve high-energy radiation such as X-rays, and its potential adverse effects are thus judged to be minimal. MRI also gives better images of the difference between the white and gray matter of the brain than CT scanning (differentiating cell-rich from cell-poor areas). The disadvantages include its current exclusion from use in patients who have artificial heart valves or limb prostheses that might be affected by the strong magnetic fields. MRI machines are also more expensive than CT

scanners, are available only at a few large hospitals, and are being acquired at a slower rate than CT scanners (299)315).

Magnetic resonance imaging can, in principle, be used for most of the same purposes as CT scanning, with the added benefit of higher resolution and ability to better differentiate subregions in the brain. For detecting strokes, and perhaps tumors, MRI maybe more sensitive (103). Preliminary studies report that MRI can distinguish dementia caused by Alzheimer's disease from multi-infarct dementia (20). MRI could theoretically supplant CT scanning in assessing the fluid-filled cavities in the brain and in measuring brain tissue density. One study compared the cost-effectiveness of CT scanning to MRI scanning in evaluating dementia. It found that MRI was significantly more expensive, but not a great deal more sensitive at picking up surgically correctable lesions in the brain (normal pressure hydrocephalus, blood clots, and tumors) (291). The validity of the study's results depends crucially on two factors: the prevalence of such surgically correctable causes of dementia (for which there are widely divergent estimates) and whether applications of MRI not included in the study are important. Many MRI studies are being performed to detect vascular dementia, for example, but the benefits of such use were not assessed in the study. Omitting this analysis is justified in the absence of a widely accepted treatment for vascular dementias. Consensus on optimally effective treatment of vascular dementia would likely enhance the importance of MRI as a diagnostic tool.

Finally, MRI might be useful in the future for functional imaging of a type possible now only with the PET scanner. This would presuppose the development of chemicals containing nuclei that could both be detected by the MRI machine and be used in cellular metabolism. Such developments would permit the great benefits of PET scanning without the prohibitive cost and constraints of proximity to a cyclotron.

Examination of Brain Tissue

A final diagnosis of Alzheimer's disease, Pick's disease, and many other disorders causing dementia can be made only if tissue from a patient's brain

is directly examined under the microscope. Tissue can be obtained either at autopsy or by taking a sample of the brain of a living patient (a biopsy). (The characteristics that define the microscopic appearance of brain tissue for each disease are described in the next section.)

Brain biopsy is not a routine clinical practice because of its invasiveness and high cost. It can be performed specifically for diagnostic purposes when entering the skull for some other reason. Although recent studies suggest that the risk of biopsy is relatively low—with complications of less than 5 percent (231) and mortality under 1 percent (163)—it requires a major operation, and its findings do not usually influence therapy. A major breakthrough in treatment, however, might well provide incentive for more frequent biopsy diagnosis (163). For now, biopsy is restricted to research centers and hospitals engaged in implanting drug delivery devices. The low frequency of biopsy means that the specific disease causing dementia in a particular patient is often uncertain until death. Indeed, uncertainty often prevails even after death because many patients are not autopsied. (The autopsy rate in the United States is now 14 percent, down from 50 percent at the turn of the century (211,215)).

Determining Which Tests To Use

The serious problem of misdiagnosis of irreversible dementia has led to several multidisciplinary conferences on the diagnostic approach to be followed. The National Institute on Aging (NIA) held a conference in December 1983 (166), and the

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) cosponsored a widely reported conference (212). The American Medical Association (AMA) also recently reviewed the diagnosis of dementia, although the AMA document does not prescribe a diagnostic protocol (5). All of these are in addition to a large number of diagnostic strategies promulgated in textbooks of neurology and psychiatry. Different physicians and other health professionals use the terms "Alzheimer's disease," "dementia," and "multi-infarct dementia" in different ways. The greatest confusion arises in defining Alzheimer's disease, because the diagnosis can be made only by excluding other illnesses (26).

These conferences have not yet yielded a uniform diagnostic approach, and any such algorithm would be expected to change rapidly as more is discovered about the different diseases. For now, the criteria promulgated at the NIA and NINCDS-ADRDA conferences appear to be the best available for Alzheimer's disease, combined with the American Psychiatric Association's Diagnostic and Statistical Manual criteria for the presence of dementia and specific diagnosis of multi-infarct dementia (7) (see table 3-3).

Lists of criteria, however, do not specify the tests to be performed, so the performance and interpretation of tests will probably remain varied among physicians. In one study of laboratory tests used in the diagnosis of dementia, the cost per patient depended primarily on the strategy used

Table 3-3.—Diagnostic Criteria for Dementia

Criterion	DSM-III	ADRDA/NINCDS	NIA/AMA
Memory deficit	+	+	+
Loss of intellectual function confirmed by mental status test.	+	+	+
Impaired social or work functions		+	
Impairment of additional cognitive functions (language, construction, personality, etc.)	+	+ / -	+
State of consciousness not impaired (alert and awake).	+	+	+
Evidence of brain damage (organic cause).	+		

KEY: + - Required for diagnosis.

+ / - - Suggestive of but not required for diagnosis.

DSM-III = *Diagnostic and Statistical Manual of Mental Disorders*, 3d ed.

ADRDA/NINCDS = Alzheimer's Disease and Related Disorders Association, Inc./National Institute of Neurological and Communicative Disorders and Stroke.

NIA/AMA - National Institute on Aging/American Medical Association.

SOURCES: American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 3d ed. (Washington, DC: 1980); G. McKhann, D. Drachman, M. Folstein, et al., "Clinical Diagnosis of Alzheimer's Disease," *Neurology* 34:939-944, 1984; National Institute on Aging, Task Force Report, "Senility Reconsidered. Treatment Possibilities for Mental Impairment in the Elderly," *Journal of the American Medical Association* 244:259-263, 1980.

to order tests. There were tradeoffs—some minor problems would be missed by the less costly strategies. The range of costs per patient was large, from \$153.92 to \$1,109.50 [182]. The optimal diagnostic algorithm for dementia is likely to be as elusive as for other syndromes. Diagnostic processes will defy unanimity and become established

slowly through large numbers of clinical investigations, medical textbooks, journal articles, and health professional conferences. Rigorous studies of comparative costs and benefits of different diagnostic approaches will, however, permit both greater certainty of diagnosis and more efficient delivery of care.

CHARACTERISTICS OF SPECIFIC DISEASES

This section describes briefly some of the major disorders that cause dementia, emphasizing those that are most common or have yielded most to scientific inquiry. Alzheimer's disease, which accounts for the majority of cases of dementia among the U.S. population, is the focus of most discussion because so little is known about its cause, prevention, or treatment. This discussion is followed by descriptions of multi-infarct dementia (the second most common cause of dementia) and other disorders that are scientifically or clinically instructive. The final part of this section considers disorders that may provide important scientific insights, present prospects for future research, or threaten to grow in magnitude and thus act as new sources of demand for long-term care.

Alzheimer's Disease

Alzheimer's disease refers to the disease process occurring in a patient who shows both the clinical symptoms of dementia and the characteristic microscopic changes in the brain. The clinical diagnosis is made on the basis of finding typical symptoms that progress over time and by eliminating other possible diagnoses that could explain those symptoms. (The symptoms have been described in the preceding section, and also in chs. 2 and 8.) Symptoms are only part of the picture, however; the definitive diagnosis of Alzheimer's disease requires biopsy or autopsy examination of brain tissue.

Microscopic Changes

Alois Alzheimer first noted microscopic changes that occurred in the brain of a woman patient with clinical dementia in 1906, and the following

year he reported this first case of the disease that bears his name (2). The findings he described are still those used to make the diagnosis of Alzheimer's disease, although the microscopic features that define the disease continue to be refined (193).

The significance of the abnormal findings in Alzheimer's disease can best be understood by describing some aspects of the organization of the human brain. The brain is organized differently from other organs in several ways. It consists of at least 10 billion nerve cells, with 10 times as many "supporting" cells. The nerve cells are connected to each other, each connecting with hundreds or thousands of other nerve cells. Scientists have made significant progress in understanding the complex organization of the brain over the past decade, although what they do not know still overwhelms what they do. The relationship between disrupted brain cell organization and certain disorders is becoming clearer, and Alzheimer's disease is one such disorder.

Anatomy of Abnormal Changes.—Death of nerve cells occurs in several locations in brains of patients with Alzheimer's disease. Pathologists have long noted a loss of cells from parts of the brain called the cerebral cortex (constituting the outer layers of nerve cells covering the brain) and the hippocampus (a large, curved aggregation of nerve cells near the underside of the brain). The abnormal microscopic findings are found both within nerve cells and between cells (near specialized junctions with other cells). The locations of the microscopic abnormalities appear to correspond roughly to the distribution of cells that use the chemical acetylcholine for cell-to-cell communication (see following discussion).

More recently, investigators have found that nerve cells are lost from a number of brain regions in Alzheimer's disease. Loss of nerve cells from one group, called the nucleus basalis of Meynert (10,279,329), is thought to be especially relevant. These cells are believed to be part of a "circuit" of nerve cells that communicate with one another and are involved in the physiological processes that perform memory and other complex brain functions (70). The loss of the nerve cells in the nucleus basalis is increasingly believed to be an important feature of Alzheimer's disease.

The nerve cells of the nucleus basalis connect to the two areas where the microscopic changes, Alois Alzheimer originally noted, take place: the cerebral cortex and the hippocampus. The parts of the hippocampus that are destroyed in Alzheimer's disease are those generally thought to be involved in memory (149). Some researchers have even suggested that symptoms of the disease could be explained by the lesions in the hippocampus alone (13), although there is disagreement on this point (62). Recent advances in identifying specific hippocampal cells lost in Alzheimer's disease may further elucidate their role in causing symptoms (199).

Types of Microscopic Changes.—Two patterns of microscopic change are generally used to make the diagnosis of Alzheimer's disease. The first consists of an aggregation of abnormal filamentous proteins in nerve cells called neurofibrillary tangles (220), which do not dissolve in solvents that dissolve most other proteins (65,285), although they have recently been dissolved in special solvents (151,284,285). Neurofibrillary tangles are not the same as normal fiberlike proteins found in nerve cells (150), although they share some features with proteins involved in maintaining the cell's shape (174). Neurofibrillary tangles are not found exclusively in Alzheimer's disease, but are also found in several other diseases, and the relationship of tangles to other microscopic abnormalities typical of some other diseases is not yet clear (114).

The second type of change is found in the area between cells, near the points of contact at which a nerve cell receives signals from other cells. These

abnormal clusters of proteins and associated components are called senile plaques or neuritic plaques.

Neurofibrillary tangles and senile plaques look quite different under the microscope, and their relation to one another is uncertain. Some studies suggest that they may be aggregates of similar types of protein (168), but preliminary characterizations of the protein components suggest significant biochemical differences (285). It also appears that the disease processes that have been known for years to affect the cortex and hippocampus are quite similar to those that affect cells in the nucleus basalis (279), suggesting that analogous processes may be taking place in many different parts of the brain.

Several other changes in the brain are often found in Alzheimer's disease, called granulovacuolar bodies, Lewy bodies, and Hirano bodies (248), but these are not generally used to identify patients with Alzheimer's disease, and may even suggest involvement of another disease (e.g., Parkinson's).

Neurofibrillary tangles and senile plaques are not found exclusively in the brains of patients with Alzheimer's disease. Both are found in most people as they age (33). One investigator found plaques or tangles in almost three-fourths of patients age 55 to 64 who did not have dementia (318). That may confuse those trying to understand the difference between normal aging and Alzheimer's disease, but the confusion is warranted only in a minority of cases. In most patients with this type of dementia, the plaques and tangles are found in dramatically increased numbers and their profusion is concentrated in the regions of the hippocampus and certain parts of the cerebral cortex (247,248). In aging patients who do not have dementia, the plaques and tangles are much less frequent and are dispersed. Physicians do occasionally encounter patients in whom there are mild symptoms of dementia combined with autopsy findings showing an intermediate number and distribution of plaques and tangles. It is difficult to be certain whether these individuals had Alzheimer's disease, but such patients are exceptions, rather than the norm.



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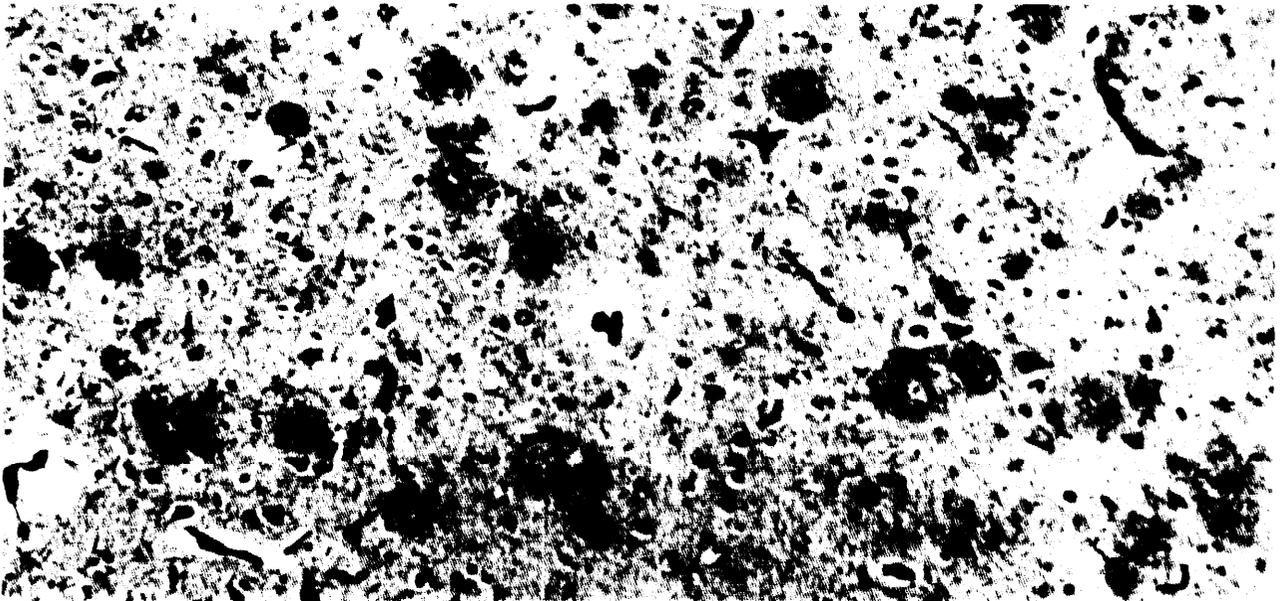


Photo credit: Office of Technology Assessment

Microscopic appearance of senile plaques, taken of brain tissue from the cerebral cortex of a 60-year-old woman with Alzheimer's disease of over 10 years' duration. The photo is taken at 100x magnification of tissue stained with a silver-containing dye that binds to the abnormal material associated with senile plaques. The plaques are dark areas dispersed throughout the photograph.

Heterogeneity of Alzheimer's Disease

Alzheimer's disease is primarily defined by its clinical symptoms and microscopic changes. It is quite likely, however, that this combination of clinical and microscopic findings actually refers to a **group** of disorders, each with possibly different causes.

Researchers in recent years have increasingly focused on identifying subtypes of patients with clinically diagnosed Alzheimer's disease. A consensus is beginning to form that there are several types (35,118,205,286). Several different findings have been suggested as defining important subtypes:

- familial aggregation (presence of many cases in one family);
- disturbance of reading, writing, and speaking ability;
- age at onset of symptoms;
- presence of uncontrollable abnormal movements; and
- severe personality disorders and psychoses.

Patients showing the brain changes typical of Alzheimer's disease can have a wide variety of symptoms (232). Investigators have found younger patients to have more severe cognitive deterioration (205), more severe behavioral disruption (14), and more severe disturbance of language use (56). Several other features differentiate early from late-onset cases. Younger patients have poorer results on psychological tests (190). They also show degeneration of additional groups of brain cells (36) and more "circuits" of nerve cells (272). PET scanning devices have been reported to detect differences between patients who develop the disease at younger ages and those who first show symptoms when older (175).

These differences may be due to the illness lasting longer for patients with younger age of onset (investigators could be measuring *duration* rather than finding real biological differences). The most recent studies have attempted to assess that issue and have concluded that there are differences in the disease process itself, rather than merely in stage of illness when patients are studied. Other variants may be due to atypical presentations

whose cause and relationship to more typical cases are unclear (289). Despite all the suggestions that there may be distinct subtypes of Alzheimer's disease, no single way of defining such groups has emerged, and conflicts between the different studies of subgroups must be resolved before the categories are widely accepted (156).

The diagnosis of Alzheimer's disease may thus be refined over the next several decades, as subtypes are better defined and their characteristics are codified into diagnostic practice. In the meantime, it is likely that work being done on patients with Alzheimer's disease is focused on a diverse group of disorders with different causes. The treatment and prevention of the illness will likely depend on identifying specific causes and characteristics that differ for the various subgroups. This dependence of new treatments and preventive strategies on understanding the etiology and biological processes of the disease reinforces the importance of finding the cause or causes of Alzheimer's disease.

Possible Causes of Alzheimer's Disease

Scientists have not identified a cause of Alzheimer's disease. But various hypotheses have been supported by different amounts and quality of supporting data. There is substantial evidence for some ideas (e.g., the loss of some chemicals used in nerve cell communication and the existence of familial clustering), while others are primarily working hypotheses. (For an overview about the possible causes, see ref. 338, or one of the books on the topic written for the lay audience: see refs. 57a,141,191). A recent scientific review is also available in *Neuroscience* (246).

The possible causes of Alzheimer's disease can be roughly divided into several groups. The groups overlap extensively, and one cause does not preclude others. They may even be directly linked. The disruption of nerve cell circuits often cited as a potential cause does not explain why the nerve cells die. Complete understanding of the etiology will thus need to elucidate the sequence of events that lead to the expression of disease, and is likely to involve many steps. The loss of specific nerve cells is not, for example, incompatible with the

role of genetic factors, infectious agents, or environmental exposures that might explain why the cells die. One way of grouping possible causes is:

- genetic factors (e.g., familial aggregation, association with Down's syndrome, and altered DNA-binding proteins);
- exaggerated aging (i.e., the severe form of a normal process—discussed in ch. 2);
- environmental factors (e.g., metal exposures, head trauma, viruses, and other infectious agents);
- immunologic factors (e.g., special susceptibility to infectious agents or proclivity for reacting against one's own brain cells);
- disrupted nerve cell "circuits" (including loss of specific populations of nerve cells and disruption of communication between certain groups of brain cells), which is a causal hypothesis that would require a *further* explanation for cell death; and
- intrinsic metabolic factors (e.g., disruption of biochemical pathways in brain cells or in different types of cells throughout the body, disturbance of protein transport in nerve cells, and changes in cell membranes), which would also require a further explanation of why certain factors were lost.

Genetic Factors.—One of the questions about Alzheimer's disease most often asked of physicians and other health professionals is: Is it genetic? This is a common fear among relatives of affected patients. Unfortunately, the answer is not simple.

Clearly in some families Alzheimer's disease appears in a way that looks very much like a genetic trait. When a pattern suggests an inherited trait, the disease is called "familial Alzheimer's disease." The largest such family discovered so far, spanning seven generations, was reported in 1983 (233), and more than 100 smaller families had been reported in various medical journals (63,64,296).

In familial Alzheimer's disease, the children of an affected parent have been found to have a 50-50 chance of having the putative gene that leads to the disease (although a person carrying the disease gene may die before showing symptoms). The chances of eventually developing the disease are high if a person carries the gene and lives past age 85. This pattern of inheritance is called "au-

tosomal dominant" transmission by medical geneticists, and it suggests that the presence of a single gene confers predisposition to Alzheimer's disease in such families.

Although there is no longer any doubt that some families are affected by Alzheimer's disease in a way that suggests a single gene trait, substantial disagreement exists on how many cases of Alzheimer's disease can be traced to genetic factors and whether there is only one genetic form. Some researchers have found that early onset cases (beginning before age 65) are more likely to be familial than late-onset (337), but this has not been confirmed by all investigators (56).

If genetic and nonfamilial forms exist, what can families be told about their genetic risks? One physician who has studied families with Alzheimer's disease extensively has developed a way to calculate risks (141, app. C) and suggests that a case is most likely to be genetic if it begins before age 65 and if there are two or more immediate relatives also affected (139). If the case is of the genetic form, then the risk to the patient's children depends on the age at which the disease began—later onset means lower risk to children. Some investigators have suggested that disturbance of language function might predict familial occurrence (38,40)96), but others have reported just the opposite (171). One group has constructed a mathematical model based on preliminary clinical studies. The model suggests that a single gene may predispose to Alzheimer's disease among patients with a specific set of clinical symptoms (41,42). The model also suggests that all such cases may be genetic, and account for 78 percent of all cases of Alzheimer's disease.

Many if not most people who develop Alzheimer's disease do not have relatives who are also affected. This evidence has been offered to suggest that fewer than a third of cases are genetic, but the data cannot be so simply interpreted. Most studies exclude investigation of cases over a certain age (often 69 or 79) because of the unreliable nature of medical information available about very old individuals. Yet such exclusion can unduly diminish the reported number of cases in relatives, particularly since Alzheimer's disease becomes increasingly common with age and is highly

prevalent only among those over 80. Any age cut-off thus precludes investigation of the group most likely to be informative. A definitive answer about the prevalence of familial versus nonfamilial Alzheimer's disease thus awaits rigorous study of large families with longitudinal investigation of all patients into advanced old age.

Because of these uncertainties, the relative number of genetic and nonfamilial cases of Alzheimer's disease is difficult to estimate. Recent studies have shown familial rates as low as 25 percent (142), but most show higher familial prevalence (40,96, 140)312). One statistical analysis of patients with Alzheimer's disease estimated that over half of all cases may be of the genetic form (40,96), but this has not been uniformly accepted (258). Some confusion over the conflicting studies is due to the unusual genetic characteristics of Alzheimer's disease in affected families: Because of its late manifestation this trait should appear in only about one-third of predisposed individuals (39). when life expectancy is age 70 to 75, two-thirds of the people carrying the postulated Alzheimer's gene will die before they show symptoms, and only one-third would develop the disease. The child of an affected patient would thus stand a one in six chance of developing Alzheimer's disease. Yet life expectancy is rapidly increasing, especially among older age groups in the United States, and so the relative prevalence of the familial form of Alzheimer's disease may well increase.

In addition to the confusion caused by the delayed onset of Alzheimer's disease in affected families, many other uncertainties surround the prevalence and special characteristics of the genetic form of Alzheimer's disease. Some of these uncertainties are due to different scientists studying relatively small groups of patients that differ from one medical center to another. Other differences arise from varying measurement techniques for assessing the type, severity, and clinical characteristics of dementia in the studies. There may even be more than one genetic form of Alzheimer's disease (308).

The presence or absence of a single gene that predisposes people to developing Alzheimer's disease does not imply that other factors do not also play a role. The delay in onset of the disease caused

by the postulated gene is difficult to explain, although this is also true of another genetic disease, Huntington's disease (discussed later). Other factors, including all other possible causes discussed in this section, could also play a role in the genetic form of Alzheimer's disease.

Uncertainty about the familial form of Alzheimer's disease should be resolved as soon as possible because of the importance of such information in counseling families. Some families are clearly affected by a familial form of the disease, and others are clearly affected by a form that is not primarily genetic. Many families, however, do not have enough information about their relatives to be sure whether the disease is genetic or not, and it is these people who most need guidance.

Environmental Factors.—Several scientists have attempted to identify personal or dietary habits, drug use, environmental toxins, or infectious agents that might cause Alzheimer's disease. Epidemiologic surveys of large numbers of patients have looked at many factors. One factor found by many studies is association with previous trauma to the head (100,143,223,340 citing 3)4). The age of the mother at birth of the affected patient, higher prevalence of thyroid disease, and risk of Down's syndrome in relatives have been reported by a few studies but not most; even the association with head trauma is not found in all studies (4,266).

The association of Alzheimer's disease with prior head trauma may simply be due to the family member's being more likely to remember a head injury for a patient with Alzheimer's disease than if the patient did not later develop the disease. Careful analysis of the data suggests this is unlikely, however (101,264). There are other reasons to suspect that the association of Alzheimer's disease with head trauma may be more than mere coincidence. First, the association has been uncovered in three independent studies that did not have other findings in common. Second, there have been several reports of individuals with severe head trauma who have subsequently (after years) developed Alzheimer's disease (reviewed in ref. 277). Third, the pathological changes that take place in Alzheimer's disease resemble those that have long been known to take place in boxers

who live to old age. Most boxers sustain repeated and severe head trauma as part of their sport; the knockout is, after all, a form of concussion in which the brain temporarily fails to function normally because of acute trauma.

Many boxers who live to old age develop a clinical syndrome called dementia pugilistic (boxer's dementia) that includes tangles in the cerebral cortex and elsewhere (66,72). Dementia pugilistic has traditionally been classified separately from Alzheimer's disease because its cause is known, additional anatomical changes characteristic of previous trauma are usually absent in Alzheimer's disease, and the distribution of neurofibrillary tangles is not identical to that found in Alzheimer's disease. The evidence is equivocal at present, and the concept of head trauma causing Alzheimer's disease is controversial (277), but investigators are now reexamining the association to see if head trauma might not be a cause of Alzheimer's disease.

Viruses or other transmissible dementia agents have also been suggested as causes of Alzheimer's disease. Several disorders that cause dementia are known to be caused by viruses or unusual agents. The hypothesis that Alzheimer's disease might be caused by infection is based on such clinical associations, combined with additional scientific evidence. Plaques from patients with Alzheimer's disease are sometimes similar to those found in the animal disease scrapie, which is known to be infectious (268). Some patients also develop microscopic plaques in a part of the brain often affected in kuru, a transmissible human dementia (106,250).

The relationship between Alzheimer's disease and transmissible dementia is puzzling. Kuru is just one of several dementing conditions caused by an unusual group of slow-acting infectious agents unlike conventional viruses, bacteria, or other known microbes. Kuru was discovered on the island of New Guinea, where it was propagated by ritual cannibalism of those who died (106). Creutzfeldt-Jakob disease and Gerstmann-Strassler syndrome are two other dementing conditions caused by similar agents. The scientific work that elucidated the infectious cause and unusual characteristics of the agents causing kuru and Creutzfeldt-Jakob disease earned the 1976

Nobel Prize for Physiology and Medicine for D. Carleton Gajdusek.

Subsequent work has noted several associations between the microscopic plaques and protein constituents thought to be part of the infectious agents that cause these diseases—scrapie, Creutzfeldt-Jakob disease, Gerstmann-Strassler syndrome, and kuru (107,251,252,294). A gene whose expression is increased in mice infected with scrapie also binds to senile plaques of patients with Alzheimer's disease, providing another tantalizing association of unknown significance (332). Familial Alzheimer's disease was initially reported to be infectious, transmitted to primates, but these reports have not been replicated despite numerous attempts (44,120). Finally, some have questioned the evidence for the chemical similarity of Alzheimer's disease changes and the plaques associated with the unusual infectious disease scrapie (268). The hypothesis that unusual infectious agents cause Alzheimer's disease thus remains an intriguing but unconfirmed speculation.

It is also possible that a virus that acts in an unconventional way in some patients, causing a slow and insidious disease, may also cause Alzheimer's disease. The evidence for this is based primarily on knowledge that several other diseases believed to be caused by viruses can also cause dementia (e.g., progressive multifocal leukoencephalopathy and subacute sclerosing panencephalitis). On the other hand, no viruses have ever been consistently associated with Alzheimer's disease, despite extensive searches, and no immune reaction is found in the brains of patients with Alzheimer's disease comparable to that found in other viral dementias.

In summary, the possibility of a viral cause of Alzheimer's disease cannot be either ruled out or definitely confirmed by existing studies.

Several groups of scientists have found that the abnormal protein aggregations that make up plaques and tangles are also associated with high concentrations of aluminum and silicon. The elevation of silicon concentrations was first described in 1972 (11,235), and several groups found high aluminum content beginning in 1976 (71,241). The findings are not disputed, but their interpretation is not yet clear. Both aluminum and silicon are

very common elements in the Earth's crust, and high exposure levels to dust containing both silicon and aluminum is normal. Recent studies have noted the association of aluminosilicates in damaged areas of the brain, and researchers postulate that these deposits are causing the alterations (50,51). Other studies show an association of several neurological diseases with aluminum deposition and trace mineral content in water supplies (234).

Many Alzheimer's disease researchers interpret the presence of aluminum and silicon as a result of cell death, rather than its cause. Their explanation is that the nerve cells die, or for some other reason insoluble abnormal protein aggregates begin to form in nerve cells and near nerve terminals. Aluminum and silicon, highly prone to forming insoluble complexes, then deposit on the protein moieties and are thereby concentrated. This explanation relegates the role of aluminum and silicon to a secondary and relatively unimportant function rather than serving as primary toxins. More work must be done, however, to determine whether silicon and aluminum deposition is a cause or a consequence of Alzheimer's disease.

Other metals may also play a role, particularly if absent from the diet. A disease process that resembles Alzheimer's disease in some respects is found in Guam, some islands in Japan, and a few other Pacific islands. This disease has clinical and microscopic overlap with Parkinson's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), and Alzheimer's disease. The factor common to each of these regions is a deficiency of calcium and magnesium in the water supply (107, 239).

Immunologic Factors. -Defects in the immune system have also been proposed as working hypotheses in explaining Alzheimer's disease. The involvement of the immune system theoretically could be independent of other factors, or could also involve infectious agents, genetic predisposition, or environmental toxins. Nerve cells share many surface features with cells of the immune system, and so might be affected by similar mechanisms (104,105). One study showed that the immune function of one type of cell-so-ailed T8+ suppressor lymphocytes-is lower in patients with Alzheimer's disease than in control pa-

tients (293). Another showed diminished production of interleukin-1, a substance that stimulates immune cells, associated with Alzheimer's disease (167). Antibodies of a particular type, called IgG, are specifically increased in some patients with Alzheimer's disease (57,58,88,136). And a gene that controls a blood protein involved in immune function, factor C4B, has been associated with Alzheimer's disease (234). However, the significance of these findings is not clear. Several investigators have failed to find any significant decline in immune function or specific lymphocyte function that is predictive of Alzheimer's disease (136,155, 185)304).

Disrupted Nerve Cell Circuits. -Researchers in the last decade have correlated Alzheimer's disease with loss of specific groups of nerve cells and disrupted communication between nerve cells. Studies of the loss of cells in the nucleus basalis and hippocampus, noted earlier, are good examples of this work, but the story does not stop with the loss of nerve cells. Discovery of effects in the nucleus basalis and hippocampus was preceded by the work of several investigators who were studying cell -to-cell communication in the brains of patients who had died with Alzheimer's disease or other disorders. Investigators in the United Kingdom noted that there was a dearth of protein that makes the chemical acetylcholine in some parts of the brains of patients with Alzheimer's disease (reviewed in 16).

The relative absence of acetylcholine suggested that the cells using it to communicate with other cells might be dying off. Other evidence suggested that such a defect might explain the loss of memory in Alzheimer's disease (16)69), and researchers found that the cells lost from the nucleus basalis were a major source of acetylcholine for the cerebral cortex (69,329,330). Others were able to confirm that the nucleus basalis cells did indeed make acetylcholine (226), and transport it to the cortex (209). Taken together, the different studies began to present a coherent picture: Nerve cells that use acetylcholine were lost from the nucleus basalis and other areas, reducing the amount of acetylcholine released to cells in the cortex and hippocampus, and disrupting memory processes.

The story is not so simple, however, because nerve cells that use acetylcholine are not the only

ones lost in Alzheimer's disease (245)295)) and cell loss is not strictly correlated with the use of acetylcholine as a chemical transmitter (219). Several other regions of the brain suffer loss of nerve cells (193). Nerve cells that use the chemicals serotonin (73), somatostatin (78,116,178,272,287) and corticotropin-releasing factor (22,81,93,303) are also lost.

These discoveries represent a major advance in the understanding of Alzheimer's disease, but there are lingering complexities, and much is left unexplained (246). Some cell groups lost in Alzheimer's disease also die off in other disorders. Groups of cells that die off in some patients remain healthy in others (36,272), and different patients show contrasting patterns of cell loss and chemical defects (70,78). Some of the abnormal changes of Alzheimer's disease can also be induced in nerve cells grown in tissue culture by adding two chemicals—aspartate and glutamate—that are believed to be naturally used to communicate between cells (79), and these chemicals are found diminished in brain regions of patients dying with Alzheimer's disease (238,281). That finding suggests that cell communication involving these two chemicals may cause cell death in the brain, in addition to cells that use acetylcholine to communicate. Despite such evidence that other factors may be involved, the loss of acetylcholine does appear to be a consistent finding, affecting all subgroups (99). Some subgroups may have other defects in addition to the loss of cells that use acetylcholine.

Scientists do not appear near a complete explanation of why Alzheimer's disease occurs in some people and not others, or why only some cells die. Even if nerve cell circuits are involved, this provides only an intermediate explanation, and does not suggest an ultimate cause. Many questions remain unanswered. Are certain nerve cells genetically programmed to die in some people? Are they killed by viruses or toxins? Do they have specific biochemical or metabolic aberrations? Or are they mistakenly killed by the body's own immune defenses?

Intrinsic Metabolic Factors. -Several investigators have reported disrupted biochemical pathways and other metabolic abnormalities in patients with Alzheimer's disease. Enzymes are proteins

that facilitate chemical reactions. Some researchers have found abnormal function of specific enzymes involved in sugar metabolism in brain cells (28,32,280), in patients' cells grown in tissue culture (293), and in red blood cells (29).

Others have found abnormalities of proteins that affect DNA or RNA, the genetic material of all cells. One group found that patients with Alzheimer's disease had less RNA in their brains at autopsy, and they traced the defect to more rapid degradation of RNA. The amount of a protein that slows RNA degradation was abnormally low, and so release from normal inhibition led to accelerated decay of RNA (278). That defect would make it difficult for cells to produce normal amounts of protein, and it might explain other biochemical abnormalities or cause cells to be vulnerable to insults. The specific metabolic features of RNA metabolism in Alzheimer's disease are still under study, and the results are not completely consistent from report to report (306). Other investigators have found slowed repair of DNA (189), increased sensitivity to damage of DNA (283), or changes in the proteins that stick to DNA (that might regulate which genes are turned on and off) (213)324).

Another focus of study has been the cell membrane—the thin layer of material that separates cells from one another and from body fluids. The cell membrane includes elements that determine its electrical properties (and the ability to transmit nerve cell impulses) and that allow other cells and proteins to recognize the cell from its exterior. Abnormalities of cell membranes could, therefore, have profound disrupting effects in nerve cell communication and recognition. Several researchers have produced preliminary evidence of such membrane changes (339,345).

Nerve cells need contact with other nerve cells or muscle cells in order to survive. The exact requirements for nerve cell survival are not known, but likely include “trophic factors” carried back to the nerve cell. One hypothesis suggests that trophic factors specific to particular nerve cell populations are lost in Alzheimer's disease, leading to loss of the nerve cells (8,9). Replacing the trophic factors might lead to partial clinical recovery or growth of new cells to replace those that are lost. This possibility of nerve cell regrowth has been

supported by finding that some cells in certain regions of the brain do proliferate in Alzheimer's disease, but do not find their normal attachments (109). Recent studies of a protein called nerve growth factor (NGF) suggest that it may promote growth and sustenance of nerve cells that use acetylcholine in the nucleus basalis, and preliminary studies show improvement of learning-impaired rats in response to administration of NGF (reviewed in 198).

Some investigators have suggested that the nerve cells that die off in Alzheimer's disease do so because they cannot adequately move important structural proteins over long distances through the thin threadlike projections of the cell that conduct electrical impulses (107,121). These theories are based, in part, on the nature and location of abnormal protein aggregates (plaques and tangles) in the brain. Others interpret the location and composition of abnormal protein condensation as suggesting that proteins related to plaques and tangles accumulate around small blood vessels and impede the flow of oxygen and nutrients to nerve cells (112). That interpretation is supported by many reports of reduced metabolism in certain parts of the cortex of patients with Alzheimer's disease, but this condition could also be found if cells died from other causes. Finally, the abnormal protein aggregates in tangles share some features with proteins that are involved in maintaining the cell's shape (174).

Summary .-Many different causes of Alzheimer's disease have been postulated, and others may be suggested. It appears likely that genetic factors are important in some cases. Infectious agents, head trauma, immune dysfunction, toxins, and metabolic aberrations may also be involved and are being investigated vigorously. Research on Alzheimer's disease has become a priority only in the last decade, and the effort to track down a cause can succeed only with further work. That additional work will require substantial and sustained research support from Congress (see ch. 13).

Issues in Treatment of Alzheimer's Disease

No fully effective treatments or means of preventing Alzheimer's disease has been found. Al-

though a few drugs can marginally alleviate some of the symptoms, the most effective way to manage patients is by adapting the environment to patient needs rather than prescribing a specific medical treatment. Medical options are limited, but much can be done to reduce the adverse impact of Alzheimer's disease on patients, families, and others (328).

A physician who makes a diagnosis of Alzheimer's disease must also make several related determinations. The health and safety of patients, their families, and those who come in contact with patients can be influenced by these considerations. Several issues commonly confronted are whether the patient:

- should continue to drive,
- can retain his or her job (especially difficult for those in highly skilled positions that involve substantial responsibility for others or affect public safety),
- can make decisions about financial and legal matters, and
- is eligible for special disability or health programs.

These determinations are not purely medical, but they involve a medical evaluation and assessment of the severity of illness. Physicians who care for a patient with dementia are therefore involved in these complex and difficult considerations (282). Correct determinations require understanding of the particular patient, the patient's environment, the family structure, the availability of outside supports, and eligibility criteria for government programs.

These nonmedical considerations become a part of patient management, although they are not commonly considered medical treatment. Other issues raised by the treatment of those with Alzheimer's disease are more directly linked to medical care.

Quackery .-Diseases that are common, devastating, and incurable attract crank remedies. Hope and desperation conspire to create a market that is open ground for opportunism. Many diseases are subject to this phenomenon: cancer, acquired immune deficiency syndrome (AIDS), and arthritis, among others. Alzheimer's disease, and many other dementing disorders, are among the targets

for quackery. Bizarre treatments such as “chelation therapy” and “blue-green algae manna” have been promoted for those with Alzheimer’s disease in the absence of evidence of efficacy (52), and there will doubtless be more such remedies proposed in the future.

Distinguishing legitimate treatment from quackery can be difficult. Quackery implies a cynical intent to profit from what is known to be useless, or failure to gather evidence that questions the legitimacy of a practice. The way that numerous accepted medical treatments work is only poorly understood, and many start out as accidents; few important treatments were expected, and many are irrational in their origins. A few characteristics of quack remedies, however, distinguish them from standard medical practice. Potential patients and families should ask several questions before embarking on a treatment regimen:

- How is it advertised? Quack remedies are often purveyed through popular magazines and are notably absent from medical journals.
- How accessible is it? Quack remedies are generally costly, and available only through special outlets. In contrast to experimental clinical trials, the promoters are not associated with universities, major medical centers, or reputable practitioners.
- What is in the treatment? Elixirs and miracle potions will not specify what they contain, while clinical trials involve clearly defined components.
- Are the practitioners qualified? Those involved in clinical trials will be licensed to practice medicine, and are likely to have specialty certification as well. Those with legitimate qualifications are not threatened by prospective patients asking about them. Those who lack qualifications cannot provide patients with the information and are more likely to take offense.
- What is the rationale behind the treatment? This may be difficult for someone not expert in the field to judge, but those explaining clinical experiments will be able to cite support in the medical literature, while quacks may refer only to a popular journal or offer no rationale.

Ž What evidence supports the effectiveness of the treatment? For early clinical trials, there will be evidence from animal testing; quack remedies will refer only to anecdotes of successful use. Another difference between them is the elaborate data-gathering methods and analysis for clinical trials. Remedies that have been used for years on many patients and yet lack rigorous scientific data on effectiveness are highly suspect.

False Hope and Preliminary Data.—The same factors that encourage charlatans can also generate problems for the most careful, well-meaning investigator. Preliminary reports of small increments of medical progress can be greeted by the release of pent-up emotions, leading to unjustifiably high hopes that are dashed in bitter disappointment.

That phenomenon has happened at least twice for preliminary reports of Alzheimer’s disease treatments. One was a study on the use of naloxone, a drug that blocks the effect of heroin-like drugs, and the second a report on implantable drug pumps. Both were both picked up by the national press.

The story on naloxone resulted from a small clinical trial in a few patients that was published in a letter to the *New England Journal of Medicine* (259). The trial was carefully planned, but involved only seven patients. Such a small sample is common for treatments on the frontier of inquiry. The report was singled out by Margaret Heckler, then Secretary of Health and Human Services, at a press conference on the efforts of the Federal Government to address the problems of Alzheimer’s disease. It then was widely publicized. The Secretary had merely cited it as an example of promising research, but the preliminary nature of the data could not support the onslaught of public attention. Subsequent trials of the agent belied the initial optimism (298).

The other episode attracted even wider publicity. A group at Dartmouth Medical School implanted drug pumps in four patients with Alzheimer’s disease (diagnoses that were confirmed by biopsy at the time of insertion). The pumps were used to deliver a drug that simulates the ac-

tion of acetylcholine, based on the theory that the reduction in acetylcholine might be corrected by direct replacement of the drug. The primary interest in doing the study was to test the feasibility of using such pumps to deliver drugs for patients with Alzheimer's disease, not to cure the disease in the four initial patients. The investigators did, however, distribute questionnaires to the patients' families to find out if they could detect any changes in the patients. The families did not know which drugs were infused into the pumps, and the investigators alternated between using the drug and a harmless fluid. The preliminary drug pump study is being followed up by studies at 10 centers across the United States.

A few members of the national press heard about the initial experiment and asked permission to cover the story. The investigators wrote a short description in the medical journal *Neurosurgery* (131). They also held a press conference because of the interest the story had generated. Although one reason for the press conference was to note the preliminary nature of the data (the title of the paper started with the words "preliminary report"), it had the opposite effect, making reporters believe there was a big story to cover (242). Reports on the pump therapy eventually reached the public through 160 newspapers, many national magazines (including *Newsweek*, *McCalls*, *Forbes*, and *Family Circle*), and most of the national television news services (PBS, NBC, CBS, and Cable News Network) (242). One result was that the "2,600 persons—many desperately trying to stop the dementia consuming their loved ones—who contacted Dartmouth Hitchcock officials in the weeks following the news all had to be told the same thing: there is no new treatment at Dartmouth for Alzheimer's disease, only a research program; it is unproven, however good-looking in principle" (242).

The article in *Neurosurgery* contained only passing reference to the beneficial effects reported by families, but the television and news services talked mainly to enthusiastic family members and doctors. The press release distributed at the news conference referred to patient benefits in the opening sentences, and added qualifications only in the third paragraph (242). Neither the medical article nor the press release noted that the psy-

chological tests that had been given to the patients throughout the trial had failed to show significant improvements. Although it is standard practice to "spice up" stories in public relations work—and the Dartmouth press release is not atypical—the result in terms of the effects on the hospital, the investigators, and the families who heard about the work and yearned for good news was far from the benign, good publicity intended.

The bloating of preliminary research data, whether by reporters, investigators, or research subjects, has several untoward effects. The ensuing publicity can impede the conduct of the very research being reported, endangering the validity of results and making life difficult for investigators who must split their time between doing their work and fielding questions from the media. Other investigators doing similar work are often irritated by such episodes. Some of that irritation might be due to jealousy, but it can also stem from adverse effects on their work and suddenly having to temper the unrealistic hopes of their own patients. Finally, the hopes of those desperately looking for progress are dramatically lifted, then suddenly dropped and shattered.

Recently, the problem of constraining public expectations has taken a new twist. Stories about scientific advances in finding biological markers for diagnostic purposes have appeared in *Time*, *Newsweek*, business publications, and many newspapers, resulting in many physicians being asked to do the diagnostic tests, yet the tests are clearly stated in the articles to be in experimental stages of development.

Even more instructive is the intense publicity surrounding the publication of the lead article in the November 13, 1986, issue of the *New England Journal of Medicine* (302a). The article reports encouraging results from testing of the drug tetrahydroaminoacridine (THA, first discovered in 1909, but newly applied to treatment of Alzheimer's disease) on 17 subjects with the diagnosis of Alzheimer's disease. The Associated Press report about the article reads "Researcher Fears Hysteria Over Alzheimer's Drug Discovery" (130a). The researchers in this case have clearly anticipated that their drug trial would be widely reported, and that the public would demand quick action to

make the drug available. (THA is nonpatentable, raising yet another issue, because private firms state they are reluctant to manufacture it and push it through the expensive FDA approval procedure without any way to guarantee a profit.) Press hunger for new results is clear in this instance, where all the rules of careful reporting were followed. The study was carefully controlled, the results dispassionately displayed, and the steps leading to the trial were called a “triumph for the scientific method” in an accompanying editorial (78a). Yet many physicians learned of the story from their patients (the AP story was released on a Wednesday about the Thursday issue of the *Journal*, and most subscribers do not receive their copies until Friday or early the following week). People do in fact want to know the results of reliable studies as soon as they can, and the early news accounts of the THA article contain the important qualifiers, yet the scientists clearly anticipate widespread misunderstanding.

There is no simple way to prevent public relations disasters. Any institutional or regulatory solutions are likely to be worse than the problem. Reporters can work to be more objective, and investigators can be open but not unrealistic. The line between enthusiasm for work in progress and the creation of unjustified optimism is thin. Most researchers are working in this field, after all, just so they can contribute to the eradication of the blight of Alzheimer’s disease. Progress is welcomed and feeds the emotional drives of investigators as well as patients and their families. Further, it is important that such events not inhibit the reporting of preliminary results. Preliminary reports are efficient ways to test new approaches to treatment, and reporting them when preliminary results are known—whether successful or not—can save other investigators time and wasted effort. But physicians and other scientists can be careful in how the results are reported.

Many family members are grasping for straws. In research on dementia, many such straws are reported each month, but most are buried in medical journals. Both the reports cited here were covered not only in the medical literature (where their significance was likely to be understood), but also heralded at press conferences (where it was likely to be misunderstood). It is safe to report failures,

but success must be handled carefully. Perhaps the most important preventive measure is for clinical investigators to anticipate the publicity, think through how to handle it, and at times eschew it. A delicate balance must be struck between informing the public and the risk of misinforming it.

Medical Management.—Health professionals can manage Alzheimer’s disease in several ways. Some of their functions are:

- diagnosis of the disease causing dementia;
- the search for diseases of other organ systems that can be treated, which might improve the patient’s mental function;
- assessment of the type and severity of the disease or diseases;
- management of those aspects of the disorder that *can* be treated (e.g., behavioral problems amenable to treatment by medication or to family education on avoidance or management);
- referral to medical supports (e.g., participation in clinical trials can be therapeutic not only for medical benefits but also in providing a feeling of contributing to the ultimate conquest of Alzheimer’s disease);
- education of the patient and family about the disease (e.g., what to expect, genetic risks, drugs and foods to avoid); and
- referral to social and legal supports (e.g., family support groups, legal services, government programs).

The importance of family education, legal referral, and recommendation of family support groups is elaborated in several other chapters. The focus here is on management of the medical aspects of this dementing disease.

Some pharmaceutical agents have been reported to diminish the cognitive impairment of patients with Alzheimer’s disease. Only one, however, has been approved for clinical use by the U.S. Food and Drug Administration (FDA) (based on several clinical trials). Although patient improvement is consistent, it is minimal. The agent in question, a mix of different drugs, has been in clinical use for three decades; it is marketed under the trade name Hydergine. Hydergine has been used in Europe for treating dementia for over a decade, and is increasingly being used in the United States.

Its mechanism of action is unknown. Hydergine was once thought to improve blood flow, but it is now called a "metabolic enhancer." It alters the biochemistry of nerve cells in several ways, but the reason for mild mental improvement is not known (47,180,328).

Medical management of behavioral symptoms can improve mental function of the patient, simplify the patient's care, or both (135,265). Many patients develop depression, which can be treated by both education and antidepressant medications. Care must be taken to avoid those antidepressant agents that inhibit the action of acetylcholine, which can worsen the patient's dementia, and to use agents less likely to exacerbate dementia (83, 154,239).

Management of hallucinations, anxiety, sleep disorders, agitation, aggression, and wandering often includes changing the patient's habits, adapting the environment, educating the family, and administering drugs targeted specifically at the behavior in question. One physician has suggested that the guidelines for treatment should be to treat **disability not abnormality**, to reverse associated curable illnesses, to limit troublesome symptoms, and to maintain continued support (27).

Most physicians with extensive practice in treating dementia occasionally use medications to control patients' behavior, but the drugs are carefully monitored, and a different selection of agents is usually tried than for other kinds of patients. The drugs used to manage behavioral symptoms, for example, are chosen to minimize their untoward effects on intellectual functions (333). Older individuals in general, and patients with dementia in particular, are more likely to develop adverse side effects from drugs affecting behavior. Thus special care must be taken to prescribe those medications least likely to worsen the dementia and to induce unwanted side effects (328).

This careful approach to medications contrasts with the situation found in some nursing homes. One study reported a more than 300-fold variation among different long-term care facilities in the dose and frequency of medications used to control patients' behavior (256). Such large differences cannot be explained by variations in accepted medical practice, and the pattern of use

suggested that drugs were relied on in some facilities as substitutes for staff.

Difficulty in eating can be a major problem among dementia patients. It is not clear why patients with dementia have difficulty eating. They may forget how to eat, refuse to eat-expressing a wish to die-or lose their desire for food. One preliminary report of eating in a nursing home suggests that the cause may be difficulty in swallowing. That study found that of those who depended on caregivers to eat there was a strong correlation with poor mental function, but only a minority of those with very poor mental function had eating difficulties (290). This suggests that there may be a common factor linking eating difficulty to severity of dementia for a fraction of residents. If true, that common factor might also indicate that difficulty in swallowing is an organic symptom, and refusal to eat more involuntary than conscious.

For those experiencing eating difficulty, it is important to evaluate the cause of the difficulty. Is it confusion about how to eat, or tendency to gag or cough when swallowing? Training both family and institutional caregivers how to differentiate organic from voluntary refusal to eat, and how to deal with eating difficulty is the main avenue to treatment. Referral to a speech therapist may help to determine the nature of the eating difficulty, if ability to swallow is in question.

Incontinence of bowel and bladder is a significant problem for many of those with dementia. Half of all patients in nursing homes have urinary incontinence, and this group overlaps extensively with those suffering with dementia. The majority of those in nursing homes with urinary incontinence also have bowel incontinence (64 percent), and most showed severe mental impairment (57 percent). Despite the magnitude of the problem, fewer than 5 percent had a specific cause for the incontinence noted in their medical record (237). Many cases of incontinence can be either eliminated or compensated for using existing technologies, but require a careful evaluation of the cause of incontinence, use of appropriate drugs or devices, and staff training (237).

Many of the problems faced by those with dementia are probably susceptible to improvement

by using current technologies with more rigorous application of existing knowledge. One hope for improved care of dementia patients—not only in nursing homes, but also in hospitals, clinics, homes, and day care centers—is knowledge that will be developed in special teaching nursing homes. The National Institute on Aging, the Robert Wood Johnson Foundation, and the Veterans Administration are supporting a new movement to affiliate nursing homes with centers of medical excellence such as nursing and medical schools. These facilities will be much more involved in testing new methods of treatment and management, and will in the long run likely set new standards for care of the chronically ill.

Prospects for Research on Drugs and Devices.—Although only one minimally effective agent has been approved by FDA to be marketed for use in dementia, many other drugs and devices are under investigation. These are too numerous to describe here, and the list changes rapidly as new ideas or agents emerge.

One promising route to discovering new drugs has been the study of chemical imbalances in Alzheimer's disease. The acetylcholine hypothesis suggests numerous possible treatments, and many have been tried or are under investigation. The rationale behind these trials has been extensively reviewed (see 25,54,119,132)200,255,271)341). Many agents are also being tested in relation to other theories of causation, such as the silicon-aluminum hypothesis, the viral hypothesis, the improvement of membrane characteristics, and the correction of immune deficiency. Other agents being tested in the United States have been used in other countries with some reported success (216). Some experimental therapies are directed at chemical imbalances in the brain that involve chemicals other than acetylcholine. These include very short proteins (called neuropeptides), nicotine, and drugs that oppose the action of opiate drugs (117). Advances in therapy may arise from these numerous clinical trials, but existing reports of successful treatment are either preliminary, have not been replicated by other investigators, are inconsistent, or result in only minimal clinical improvement.

Novel ways to deliver drugs to the brain are also important in treatment research. Many chemicals that are active in the brain are digested before they reach the bloodstream or cannot get into the brain even if they enter the blood. Many investigators are developing drug pumps or altering drug structure in attempts to circumvent these problems.

Use of nerve cells themselves for treatment of Alzheimer's disease or other brain diseases is an especially intriguing possibility. The technique involves directly placing nerve cells in the brain, where they grow and can release chemicals that communicate with other brain cells. The method has been used successfully in several animal model diseases—most recently in primates (257) and cell growth can be confirmed and behavioral deficits corrected by the new cells (23,68,95,199). Nerve cells from one species can also grow in another; they appear to be protected from the immune system of the recipient, but they do not function as well (23).

Investigators hope that nerve cell implantation (sometimes called “brain transplants” in the popular press) can eventually benefit patients with Alzheimer's disease (as well as those with Parkinson's disease) (23), but such therapies will hinge on extensive animal testing and preliminary human trials and are unlikely to be available within the next decade. Many technical problems must be overcome, and the appropriate source of nerve cells is not at all clear. Use of human fetal cells would be ethically objectionable to many, and cells from other species do not work as well and might also be rejected by some recipients on moral grounds (95). A neutral source of tissue (e.g., from a source in the patient) may yet be found.

Implantation of patients' own cells has already been tried in Swedish patients suffering from Parkinson's disease (described later in this chapter), but it yielded no clinical benefit (23). The cells were taken from the core of the adrenal gland, which contains nerve-like cells. None of the barriers to development of this technique now appears insurmountable, although it will likely take many years of research before practical treatments are found.

Dementia Caused by Blood Vessel Disease

Diseases of the blood vessels cause more deaths in the United States than any other group of disorders. Coronary heart disease and stroke are the most prominent examples. In addition to causing death, blood vessel disease can cause many other clinical syndromes, including dementia.

Vascular disease is believed to be the second most common cause of dementia. In one large study, it accounted for 17 percent of cases, and was found in combination with Alzheimer's disease in an additional 18 percent (310). The prevalence of pure vascular dementia is, however, now a topic of clinical debate (221). Current methods of classifying patients are being questioned, and some clinicians are uncertain about the relationship between symptoms of dementia and brain cell loss due to vascular disease. Some investigators beginning clinical trials specifically for patients with multi-infarct dementia are noting difficulty in identifying sufficient numbers of patients (31a).

The prevalence of vascular dementia can be resolved only with further rigorous longitudinal studies. Some answers may be found in the ongoing Systemic Hypertension in the Elderly Project, whose primary sponsor is the National Heart, Lung, and Blood Institute. The National Institute on Aging is sponsoring an analysis of the data that will track the incidence of multi-infarct dementia in response to treatment of high blood pressure.

Detection of vascular dementia is important for several reasons. If dementia is caused by large strokes, further deterioration may be prevented using standard treatments for stroke. Finding vascular disease in the brain can also alert the physician to look for damage to the heart, kidneys, or other organs. Evaluation of patients with vascular dementia may also disclose preventable or treatable underlying risk factors such as hypertension or diabetes. And risk to other family members is different if the dementia is caused by blood vessel disease rather than by Alzheimer's disease. (The genetic aspects of vascular disease are more indirect, generally related to underlying causes such as blood lipids, diabetes, or hypertension. Relatives may benefit from detection of such risk

factors if they take action to reduce the chances of developing vascular disease themselves.)

The incidence of and mortality from stroke and heart disease have declined dramatically over the past two decades. Mortality from stroke decreased almost 50 percent from 1968 to 1982, for example (91). The decline is likely due to a combination of changing dietary patterns, other changes in personal habits, and improved medical care of the elderly—the major factors behind the parallel decline in mortality from heart disease (188). Most of the statistics on this decline are for large strokes, however, and do not yield direct information about vascular dementia. It is likely that this encouraging trend also pertains to vascular dementia, but that relationship has not been studied directly.

Dementia caused by blood vessel disease results from death of nerve cells in regions nourished by diseased vessels. The death of brain tissue due to poor delivery of blood is called ***cerebral infarction***. Dementia may ensue after a certain total mass of brain tissue has been destroyed (273). Such damage can be caused by one or a few large strokes, several smaller ones, or many microscopic ones. Dementia may also result from death of brain cells due to lack of oxygen reaching the brain (following a heart attack or heart failure, or for other reasons) (46)320). Large strokes are not usually difficult to differentiate from other dementing conditions because they affect many brain functions in addition to mental activity.

When cerebral infarcts are smaller, however, dementia may be the main symptom—making it difficult to distinguish from Alzheimer's disease or other dementias. The precise symptoms and physical findings depend on which parts of the brain die, and attempts are being made to define more specifically the characteristics of vascular dementia (89,152)221)225,344).

When there are multiple infarcts, the diagnosis is called multi-infarct dementia (MID). The number can range from a few to over a dozen. On average, individual infarcts are about a half inch in diameter (1 centimeter), and symptoms are commonly absent until 100 to 200 cubic centimeters of brain tissue have been destroyed (160)273), unless the patient has another dementing condition.

Multi-infarct dementia can be distinguished from Alzheimer's disease and most other disorders by its association with:

- a relatively abrupt onset;
- progression of dementia in "steps" rather than gradual deterioration;
- history of previous strokes;
- symptoms or physical findings that can be anatomically traced to loss of specific nerve cells; and
- presence of diabetes, high blood pressure, or cardiovascular disease affecting other organs.

Poor blood flow in the major arteries feeding the brain can be directly detected and correlated with dementia (317). Such poor blood flow typically precedes symptoms in patients with MID, but is found only after symptoms arise in Alzheimer's disease (267). Rigidity of blood vessels in the brain can be indirectly measured, and corroborates the association with MID compared with controls or those with Alzheimer's disease (157).

The special features of MID are measured in standardized questionnaires developed to differentiate it from other dementias (108,128)270), and these are used in research studies to classify patients with dementia.

Life expectancy is somewhat shorter for patients with MID than for those with Alzheimer's disease (15). Patients with MID also tend to be older and more frequently have abnormal electrocardiograms (indicating higher likelihood of heart disease) (48), although one recent study found a 5 to 6 percent prevalence of dementia among young stroke victims (under 65) (176).

If MID is associated with high blood pressure, diabetes, or disease in other organs, the associated conditions can be treated. Some believe MID should be treated like stroke, but the treatment of stroke is itself controversial and variable when the stroke is not caused by identifiable factors. As with Alzheimer's disease, treatment of MID awaits new discoveries.

In addition to multi-infarct dementia, dementia can arise from occlusion of blood vessels by debris in the blood stream (emboli) (reviewed in 159). These emboli can arise from diseased heart valves, damage to cells lining the heart, dislodging of clots

in large vessels, the release of fat from large bones, or large sudden infusions of air or other gases.

Death of cells due to loss of blood supply can also affect the white matter of the brain, rather than the cerebral cortex. The white matter contains relatively few nerve cell bodies; death of non-neural cells and nerve cell *processes* in these regions results in disconnection of different nerve cell groups rather than loss of nerve cells. This can nonetheless cause dementia. One name for this type of disease is Binswanger's disease, or subacute arteriosclerotic encephalopathy (236). Its prevalence may be higher than previously estimated—something newly discovered because MRI scanning makes its detection possible. One recent study described a number of patients with a disorder that is clinically difficult to distinguish from Binswanger's disease, but that appears to have a cause other than hypertension or arteriosclerosis (46). That new finding further demonstrates the uncertainty of classification and cause even among clinical subtypes of vascular dementia. Further studies employing MRI scanning may confirm that brain infarction is more common than previously believed, and should clarify the relationship between infarction and clinical symptoms of dementia (160).

Dementia can follow bleeding into the brain caused by diseased or malformed blood vessels. Blood vessels in the brain may also form balloon-like sacs, called aneurysms, that can disturb adjacent structures or rupture to cause bleeding. Both bleeding and aneurysm formation are relatively common, but patients presenting with just dementia only rarely have them. Finally, some very rare diseases of the brain's blood vessels, such as Moya-Moya disease or Takayasu's disease, can cause dementia.

Other Dementias

Parkinson% Disease

Parkinson's disease is a relatively common disorder, and some Parkinson's patients develop dementia. The prevalence of symptomatic dementia among Parkinson's patients is somewhat controversial (19). Some investigators have found a disproportionate fraction of patients with Parkinson's

disease exhibit symptoms of dementia (87,184,206), while others find that the **rate** of cognitive impairment has been inflated, and is actually no higher than the risk for the general population (45,183,305). Most neurologists now consider Parkinson's disease to be associated with dementia in a minority of patients even in those who do not have Alzheimer's disease or another dementia (148)245,300).

There is also a clear subset of patients whose brains show the changes of both Parkinson's and Alzheimer's diseases (34,186,276,331). That group of patients underscores the confusing relationship between the various disorders causing dementia. The dementia occurring in Guam and other Pacific islands combines features of Alzheimer's disease, Parkinson's disease, and other disorders, and is now thought to be historically (and probably causally) related to decreased calcium and increased levels of other minerals in local water supplies (107)240).

The primary symptoms of Parkinson's disease are involuntary movements, slowness, and rigidity. Speech is often slow, and movement is difficult to initiate. Most patients have a characteristic tremor (rapid shaking) of the fingers that is traditionally likened to pill-rolling.

Parkinson's disease is associated with loss of nerve cells located in the substantia nigra (black substance, so called because the cells contain dark pigment). whereas the cells lost in Alzheimer's disease are believed to use acetylcholine or other chemicals to communicate with other cells, those lost in Parkinson's disease use primarily dopamine. The work on the biochemistry of Parkinson's disease in fact predates that on Alzheimer's disease by over a decade, and Parkinson's disease serves as the model for researchers studying Alzheimer's disease (245). Drugs that partially replace the function of dopamine have been discovered, and these substantially reduce the abnormal movements in most patients with Parkinson's disease. The advent of such drugs was welcomed as a therapeutic revolution in neurology in the 1970s.

There are several different varieties of Parkinson's disease. The cause of classic Parkinson's disease is not known. Another type, postencephalitic Parkinsonism, has been linked to previous

brain infection with a virus. It is most often found among those who contracted brain infections during the influenza epidemic of 1918, but it can occur in others as well. One interesting feature of postencephalitic Parkinson's disease that distinguishes it from classic Parkinson's disease is the finding of neurofibrillary tangles in nerve cells of the substantia nigra. The tangles are similar to those found in other groups of cells in Alzheimer's disease.

Another interesting aspect of Parkinson's disease and its relation to dementia has emerged from an unfortunate experiment that began a few years ago in Stanford, CA. A former chemistry student began manufacturing a drug resembling heroin in his home. The process he used also yielded a side product that was ingested with the drug. This side product, called 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), caused him and others who took the drug to develop symptoms of Parkinson's disease. Administration of the drug to primates also induces a disease resembling Parkinson's disease, and the animals lose cells in the substantia nigra just as would a human patient with Parkinson's disease. The cells that die do not look like those found in classic Parkinson's disease, however, and the degree to which MPTP-induced Parkinson symptoms suggests the primary cause of classic Parkinson's disease remains unknown. MPTP-induced symptoms bear on the debate about whether Parkinson's disease can cause dementia in the absence of other diseases, because MPTP patients showed intellectual decline (301).

Progressive Supranuclear Palsy (PSP)

PSP is a disorder with several clinical similarities to Parkinson's disease. It was first described in 1904 (153). Half to two-thirds of the patients with PSP deteriorate intellectually (192). PSP was not clinically distinguished from Parkinson's disease until 1964 (297), and accounts for roughly 4 percent of patients with Parkinson's disease (343). It differs from Parkinson's disease in that patients lose the ability to gaze up or down, and it is usually not associated with a tremor. Recent reports have shown that the chemical imbalances in PSP, like Parkinson's disease, involve dopamine, but these same studies disagree on the extent to

which there are also Alzheimer-like changes in acetylcholine (169,276).

An interesting group of recent findings bears on the relationship among these disorders. The pathological changes of PSP are anatomically located in places characteristic of Parkinson's disease, but microscopically they more closely resemble the neurofibrillary tangles of Alzheimer's disease (although they can be distinguished on careful inspection). Further, investigators have found some suggestive, but not conclusive, chemical similarities in the tangles found in Alzheimer's disease, PSP, postencephalitic Parkinson's disease, and several other rare disorders (82). These similarities represent one more of the mysterious and poorly understood relationships among the various disorders causing dementia.

Huntington's Disease

Huntington's disease is a genetic disorder that causes uncontrollable twisting and writhing movements and also leads to dementia. Most patients with Huntington's disease do not develop symptoms until late middle age, and the symptoms may vary from person to person even in the same family. The movement disorder is thought to be caused by a loss of nerve cells in brain regions called the caudate nucleus and putamen.

Children of an affected parent have a 50-percent risk of developing the disease. The social and long-term care needs of these patients are similar to those for Alzheimer's patients (325,326). A group of investigators recently tracked the gene from parents to children in large families, including one extended family living near Lake Maracaibo in Venezuela. Molecular genetic techniques were used to map human chromosomes (37) and were applied to families with Huntington's disease (126). The disease-causing gene is located on chromosome number 4, and the test can be used in some families to predict whether particular individuals will develop Huntington's disease (326).

The test is not available for clinical use and is not useful in many families (e.g., because tracking the gene usually requires that DNA from an affected parent be available). Even in the best studied families, the test is not always accurate (because it does not detect the Huntington's gene

itself, but rather one close to it), and so interpretation must be cautious. Such care is important in Huntington's disease because test results are fraught with serious social, emotional, economic, and financial problems (21,173,197,325,326).

Current experience with the Huntington's disease test will be relevant to genetic risks of familial Alzheimer's disease if an analogous test can be developed for Alzheimer's and other dementing disorders. Problems in techniques, information dissemination, and privacy protection encountered by Huntington's families will likely prove true for those concerned with familial Alzheimer's disease as well. The work on Huntington's disease is thus an important pioneering effort.

Dementias Caused by Infection

Infection by bacteria, viruses, fungi, or unconventional agents can all cause dementia, but do so only rarely. Two infectious dementias—transmissible dementia and AIDS dementia—are of special note because of their prevalence and scientific interest.

Other infections can cause dementia, but only rarely. Longstanding syphilis, for example, was once among the most common causes of dementia, but it is now quite rare in the United States.

Transmissible Dementia.—The transmissible dementias caused by unusual infectious agents—Creutzfeldt-Jakob disease, Gerstmann-Strassler syndrome, and kuru—have already been discussed in describing possible infections caused by Alzheimer's disease above. Several interesting features were not mentioned there, however. Transmissible dementias characteristically kill patients much more rapidly than Alzheimer's disease does, although the transmissible dementias are also clinically heterogeneous.

Creutzfeldt-Jakob disease has become a concern among those receiving hormone therapy for congenital short stature because several young patients who were treated with human growth hormone recently died with Creutzfeldt-Jakob disease; an additional four patients are being investigated to see if they too have transmissible dementia (43,304). The dementing disease in these young patients is thought to be linked to con-

lamination of growth hormone by patients with Creutzfeldt-Jakob disease (110,172,309). Until mid-1985, growth hormone was only available from preparations purified from pooled human pituitary glands, but that supply has been terminated and a new source derived from genetically engineered bacteria has been approved. Current and future stocks of growth hormone should thus not be contaminated.

A related concern has emerged in connection with blood donations. Creutzfeldt-Jakob disease can be transmitted to animals from the blood of affected human patients (195). That finding has led one group to urge that patients with dementia refrain from donating blood, and that blood banks reject blood from dementia patients (202). The handling of tissues and fluids of patients with Creutzfeldt-Jakob disease and other transmissible dementias also requires special precautions (6).

The relationship between Alzheimer's disease and transmissible dementia has long been a topic of speculation. As with Alzheimer's disease, there is clustering of cases in some families (12,203). Familial cases of transmissible dementia can clearly infect primates (12,44,203). The microscopic changes of the transmissible dementias are quite different from those of Alzheimer's disease—loss of nerve cells, proliferation of nonnerve supporting cells, and a peculiar “spongy” appearance of defined brain regions under the microscope. In some patients, however, there is overlap of microscopic findings (64,203).

Attention has recently shifted from atypical transmissible dementias to infections caused by more conventional viruses as causes of Alzheimer's disease (195). Dementia caused by lingering brain infections with conventional viruses is also well known, but it was rare until recently except in patients whose immune systems were debilitated.

AIDS Dementia.—A most alarming cause of dementia has been recently identified in patients with acquired immune deficiency syndrome. AIDS is caused by a small virus that attacks and kills specific cells of the immune system, rendering the patient defenseless against microorganisms. The AIDS virus causes infectious dementia through two mechanisms: the immune dysfunction of AIDS

leads to brain infections by other organisms, and the AIDS virus also appears to cause dementia directly (24,144,229,230,246,262). Brains of patients who die with AIDS dementia—that directly caused by the AIDS virus—show clusters of immune cells in some areas, affecting primarily cells deep in the brain rather than in the cerebral cortex. AIDS dementia is now the most common cause of dementia caused by infection (161). A large fraction, probably most, of patients with AIDS develop dementia (245). The majority of such cases appear to be due to the AIDS virus itself, while a minority are caused by a variety of other organisms in addition to AIDS virus infection (230).

Researchers do not yet know whether the dementia also afflicts those who are infected by the virus and do not get full-blown AIDS (249). Dementia in such patients can precede other symptoms of AIDS, and at least some patients with this type of dementia do not fulfill all the criteria of AIDS (187,214). That is of concern for several reasons. Patients infected with AIDS virus who do not develop clinical AIDS far outnumber those who do. Those who succumb to AIDS invariably die under current therapies, but mortality rates among those who do not develop AIDS though infected with the virus are unknown. Children and infants infected with AIDS can also develop dementia and malformations of the brain (18). Investigations in this area are just beginning, and the magnitude of the problem of AIDS dementia will not be known until many more investigators are involved and more data accumulated.

Dementias caused by Toxins

Alcohol.—Alcohol is associated with over a dozen forms of brain disease. The diseases may be due to direct effects of alcohol, to nutritional factors, or to indirect effects of damage to the liver or other organs. The most common alcohol-related dementia is Wernicke-Korsakoff syndrome. Korsakoff's syndrome is not found only among chronic alcoholics, but alcoholism is by far its most common cause.

Wernicke's encephalopathy—the early, short-term part of the Wernicke-Korsakoff syndrome—is characterized by disorders of eye movement, abnormal gait, and global confusion. If left un-

treated, it can progress to coma or permanent neurological damage, and severe cases can be fatal even if treated. Eighty percent of those who develop Wernicke's encephalopathy go on to develop Korsakoff's syndrome (263) although some patients develop Korsakoff syndrome without ever showing Wernicke's encephalopathy. Korsakoff syndrome is characterized by loss of recent memory, often attended by disorientation to time and place and other mental symptoms. Some cases of Korsakoff syndrome have only memory loss, and represent a pure amnesia rather than dementia.

Wernicke-Korsakoff syndrome is related to deficiency of vitamin B-1 (thiamine), and the standard initial treatment is thiamine administration (122). The disease appears to be caused by poor nutritional intake in patients with a genetic predisposition to the disease (31). The chain of events leading to the syndrome is not fully understood, however, in part because animal models of thiamine deficiency are not exact duplicates of the human disease (122,263).

There is currently a debate in neurology and psychiatry about whether there is a dementia directly caused by long-term alcoholism, in the absence of nutritional problems or diseases of other organs (such as heart, liver, and endocrine glands) (49,115). Circumstantial evidence indicates that those who have a history of heavy drinking for 15 to 20 years develop a dementia that is distinct from either Alzheimer's disease or Wernicke-Korsakoff syndrome. Such patients typically show listlessness, poor judgment, carelessness, diminished attention, and slowing of thought processes. They do not usually have the language problems or difficulty drawing figures typical of Alzheimer's disease (115). The debate is about whether these changes are due to direct chronic toxicity of alcohol on the brain or to other factors.

Other Toxic Dementias.—Liver damage due to alcohol or severe liver disease can also cause dementia. The liver is responsible for clearing many toxins out of the body, and liver failure due to cirrhosis can cause accumulation of byproducts followed by dementia and even coma.

Chronic exposure to heavy metals (especially mercury and lead) at home or in the workplace can cause dementia. Many alcohol-related diseases

in addition to Korsakoff's syndrome and liver disease can induce dementia. Dementia can result from excess blood lipids, exposure to toxic chemicals, and severe nutritional deficiencies.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) is a relatively uncommon cause of dementia. Its importance lies not in its frequency, but in its potential for correction. The classic description of the findings is a combination of dementia with urinary incontinence, a slow and hesitant gait, and dilation of the fluid-filled spaces in the brain. Another symptom that suggests NPH is a history of bleeding in the brain or head trauma. In practice, NPH may lack some of these features or have characteristics of other dementing conditions (47).

Normal pressure hydrocephalus was first described in 1964 (210), and the condition began to be more widely noticed the following year (129). The treatment for NPH is to provide a surgically implanted conduit (shunting) for fluid to drain from the brain into another body cavity, usually the abdominal cavity (164). The efficacy of shunting varies widely, depending on severity, diagnostic accuracy, and duration of illness (success hinges on accurate detection and prompt treatment). Many studies find successful relief of symptoms in 40 percent of cases (127)164)291). When shunting works, it brings rapid clinical improvement.

One consideration in shunting for NPH is whether a sample of brain tissue should be taken for microscopic examination while inserting the shunt inside the skull. That procedure may permit a diagnosis of another dementia if the shunting procedure fails, but it does entail a slight added risk to the patient. A problem with current treatment for NPH is the high rate of major complications, estimated at 40 percent, and this emphasizes the need for careful selection of patients (164).

Down's syndrome

There are several interesting relationships between Alzheimer's disease and Down's syndrome. First, the number of individuals affected with Down's syndrome among relatives of patients with Alzheimer's disease is greater than expected (137,

138,140,141). But even more curious is the similarity in brain changes that occur with age in Down's syndrome.

Young individuals with Down's syndrome have a reduced number of cells in the nucleus basalis, and these cells may die off with age (53). Patients with Down's syndrome who survive into middle age frequently develop a dementia, and the microscopic and anatomic features of the findings in the brain are visually indistinguishable from those that occur in Alzheimer's disease (194)247,327,334, 335). There may be some differences, however, in the detailed chemical composition of tangles and plaques between Alzheimer's disease and Down's syndrome (179). The similarities between Alzheimer's disease and premature aging in Down's syndrome have led to speculations about causal links between the two diseases (94).

Down's syndrome is usually caused by the presence of an extra chromosome 21 in the patient's cells. More rarely, it is caused by chromosomal rearrangements or malformations that lead to excess of only part of chromosome 21. These findings have led to investigation of whether there is a chromosome defect in Alzheimer's disease as well, but results are mixed, and no aberration is consistent (reviewed in 327). Many investigators are studying Down's syndrome as a model of Alzheimer's disease in a relatively homogeneous population, assuming that the brain changes that occur are part of the syndrome and might provide clues to the origin of Alzheimer's disease.

Pick's Disease

Pick's disease is a rare dementing disorder clinically similar to Alzheimer's disease. The diagno-

sis of Pick's disease is, in fact, most often made on autopsy of a patient with clinically diagnosed Alzheimer's disease. The cause of Pick's disease is mysterious and uncertain, and it also can occur in families.

The distinction between Pick's and Alzheimer's diseases rests on the microscopic appearance of the brain. While someone with Alzheimer's disease has plaques and tangles, a patient with Pick's disease has pale and swollen nerve cells that contain globules of protein that are designated "Pick bodies." Recent evidence suggests biochemical similarities between Alzheimer tangles and plaques and Pick bodies (254). The intriguing relationship between these two dementing disorders is underscored by a newly described genetic disease that combines features of both (222).

Dementia without Detectable Brain changes

One final category of dementia is defined by the absence of any abnormal findings in the brain despite clear clinical symptoms. Such cases constituted a small fraction (2 of 50 patients) of those in a classic autopsy study of dementia (311), and cases continue to be reported—5 of 99 patients in a recent study (134). One 91-year-old man whose brain revealed no plaques at all (despite extensive search) but who suffered from dementia is of particular interest (13) since most persons his age without dementia would have a few plaques. This mysterious group of patients has been called the "5 percent problem" (163). The condition has also been called "simple atrophy" or "idiopathic dementia" because its cause and mechanism are unknown.

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