ACCURACY OF DIAGNOSIS AND CONSEQUENCES OF MISDIAGNOSIS OF
DISORDERS CAUSING DEMENTIA

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I. DIAGNOSIS OF CLINICAL SYNDROME, DEMENTIA

This report addresses the issues of the medical and public health consequences of the misdiagnosis of dementia and of the disorders that produce dementia. It is critical in this regard to differentiate between the accuracy of diagnosis of the syndrome or symptom complex denoted by the term dementia and the accuracy of the diagnosis of the specific disorders that may present as dementia. It is now recognized that there are more than 70 such disorders, as shown in Tables 1 and 2. Alzheimer's disease is but 1 of these 70; its importance is that it alone accounts for more than half, perhaps nearer 60 percent, of all cases of dementia. Hence the accuracy of the diagnosis of Alzheimer's disease will be emphasized in this report.

A. Historical Perspective

1. Clinical and Mental Status: Changes Typical of Dementia

Interest in the accuracy of the diagnosis of dementia is a very recent phenomenon. During the first half of this century the chief medical concern about a dementing illness focused on neurosyphilis. After establishment of the serological test for syphilis, the discovery of arsenical therapy by Ehrlich, and the delineation of the late brain sequelae of this spirochetal infection and methods of treating it, physicians began to specialize in syphilology and a new medical specialty arose. But
other dementing illnesses were often lumped together under rubrics such as senility ("she's getting old, what do you expect") or cerebral arteriosclerosis ("it's just hardening of the arteries, the pipes get rigid you know"). From a public health point of view it seemed to make little difference. Demented patients who could not be cared for at home could be sent to state mental hospitals or to community "chronic hospitals," without regard to the diagnosis. The numbers were not overwhelming and medical and community concern was at a minimum. The low level of medical interest was reflected in the available English language textbooks of neurology and psychiatry (there was a somewhat greater interest in the phenomenology of dementia by European psychiatrists), which gave little space to dementing illnesses.

Several events have radically changed this situation. Life expectancy, which was about 49 years at the turn of the century, will approach 79 years by the year 2000. Life expectancy of those over 60 has increased dramatically, thereby greatly increasing the number of individuals at risk for dementia. At the same time, the advent of potent neuroleptics and antidepressants for the treatment of schizophrenia and depression has made it possible to begin to treat such patients in the community. When economic considerations prompted many state governments to empty out state mental hospitals insofar as possible, most of the beds occupied by dementia patients were also closed. As more governmental funds were applied to medical care with the advent of Medicare and
Medicaid, state regulatory agencies instituted strict regulations and eligibility criteria resulting in the closing of many "chronic" hospitals. Thus patients with dementia, increasing in total numbers at a time of hospital closings, became an increasing burden on the community and on families.

2. Differentiation of Dementia from Other Syndromes

In the 1950s, intensive clinical studies of the elderly with cognitive and behavioral impairment by foresighted physicians, such as Martin Roth in Great Britain, led to the delineation of the clinical syndromes involved. The results of such studies made it possible to begin to diagnose the specific disorders producing these symptom complexes. In the 1960s breakthroughs in three specific disorders awakened medical interest in the diagnosis of dementia: 1) the discovery by Gajdusek and colleagues—a discovery important enough to have led to a Nobel Prize—of latent virus as the cause of Creutzfeldt-Jakob disease previously thought to be a degenerative disorder; 2) the studies by Terry and Kidd of the ultrastructural changes in the Alzheimer brain and the prospective quantitative study by Blessed, Tomlinson, and Roth relating the degree of Alzheimer pathology to the degree of dementia in the elderly, which formed the basis for the recognition of Alzheimer’s as the most common form of dementia in the elderly; 3) and perhaps the most important of all from the diagnostic point of view, the delineation of "normal pressure hydrocephalus" by Adams and Hakim as a reversible cause of dementia. These advances were instru-
mental in focusing public attention upon the predominant form of dementia, Alzheimer's disease, and in creating recognition of the need for accurate differential diagnosis of the dementia syndrome in order to identify conditions that can be treated. A consensus statement on the importance of the diagnosis of reversible causes of dementia was developed by a work group sponsored by the National Institute on Aging (NIA; 1980) and criteria for the diagnosis of Alzheimer's were developed by a committee jointly sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhan et al., 1984).

8. Current Distinctions

1. Definition of Dementia

"Dementia" is the term used to describe the symptom complex of intellectual deterioration in the adult. This symptom complex may be caused by more than 70 disorders but the most important of these is Alzheimer's disease, which alone accounts for more than half of the cases. The term "dementia" had been used by physicians for many decades but in 1952 the American Psychiatric Association in the first edition of its Diagnostic and Statistical Manual (DSM) did not include this term but instead introduced a new diagnostic term, "chronic organic brain syndrome" (Amer. Psych. Assoc. Task Force, 1952). The definition of the latter term included the requirement that the condition be progressive
and irreversible. It becomes evident that many conditions that produced chronic symptoms of intellectual deterioration (for example, normal pressure hydrocephalus) were in fact reversible.

2. Advantages Based on Phenomenology and Clear Criteria

In 1980 the American Psychiatric Association dropped the invented label, chronic organic brain syndrome, and reintroduced "dementia," defined in terms of observable clinical criteria (Amer. Psych. Assoc. Task Force, 1980). The criteria were based upon clinical observation and judgement; no attempt was made to present specific operational criteria, such as scores on functional disability scales or mental status tests. Many clinicians who were not psychiatrists welcomed this approach and the DSM-III definition has been widely accepted.

3. Limitations

a. DSM-III. There are, however, limitations to the DSM-III diagnostic criteria. No definition exists of the degree of functional disability needed to qualify for the diagnosis of dementia and there is not as yet a consensus among workers in the field as to the appropriate scale to be used in these early cases. The definition stipulates impairment in memory and at least one other area of cognition. A small number of patients with dementing disorders have atypical presentations involving only a single area (e.g., language, visual perception, constructional ability, personality change, memory) for as long as 2 to 3 years, after which time more widespread involvement of cognitive
functions becomes evident (Katzman, 1985; Mesulam, 1982; Crystal et al., 1982; Pogacar and Williams, 1984). Adherence to DSM-III criteria would unduly delay diagnosis in such patients. Another problem is the exclusion criteria which tend to be recursive in DSM-III. Thus the DSM-III criteria for dementia require exclusion of such conditions as depression but the criteria for depression in DSM-III require exclusion of dementia. The extent to which this problem with definition contributes to the frequent misdiagnosis of these two conditions has not been adequately explored. Finally, there is lack of agreement with the decision made in the formulation of DSM-III to separate the amnestic syndrome from dementia. The most common cause of the amnestic syndrome in the United States is Korsakoff's psychosis which is related to thiamine deficiency and alcoholism. Patients with this disorder are included by many workers in their dementia series. Despite these limitations, however, experience indicates that diagnostic accuracy has been significantly advanced by the DSM-III definition of dementia.

b. Comparison of DSM-III with Alternative Criteria for Diagnosis of Dementia. Although the DSM-III criteria for diagnosis of dementia have had wide impact, several alternative diagnostic criteria have been proposed. Table 3 provides a direct comparison of these criteria. Included in this table are the DSM-III criteria (Amer Pscyh. Assoc. Task Force, 1980), the ADRDA/NINCDS criteria (McKhan et al., 1984), the NIA/AMA criteria
(NIA, 1980), and the recently published modification of DSM-III by Jorm and Henderson (1985). All the 1980 and later definitions require evidence of loss of intellectual ability in a patient who is awake and alert; the ADRDA/NINCDS and the NIA/AMA definitions do not require specific evidence of deterioration in social or occupational function but the ADRDA/NINCDS stipulates that the intellectual dysfunction be demonstrable on a formal mental status test. Two of the sets of criteria require demonstration of memory impairment and impairment of another area of cognition; Jorm and Henderson will accept either or both in this regard and hence would make it possible to include the Korsakoff syndrome as a dementing disorder. Neither the ADRDA/NINCDS nor the NIA/AMA criteria require exclusion of other DSM-III diagnoses and therefore simplify the diagnosis of coincidental dementia and depression.

Comparison of the more recent sets of diagnostic criteria for dementia with the 1952 DSM-I criteria for "chronic organic brain syndrome," its designation for the dementia syndrome, reveals very important differences. The DSM-I criteria (Amer. Psych. Assoc. Task Force, 1952) required the presence of irreversibility and chronicity, two criteria eliminated from current diagnostic approaches. The question of reversibility or irreversibility of dementia deserves comment. It has become evident that "irreversibility" is a term that may be appropriately applied to certain disorders but that its use reflects the state of
ignorance of the medical profession at a given date; a condition that may be irreversible in the spring of 1986 might become reversible at a later time. There are many precedents. At the turn of the century, general paresis, the form of dementia that occurred in neurosyphilis, was indeed irreversible. In the early 1900s the discovery that fever therapy would reverse many of the symptoms of this disorder was considered important enough to result in a Nobel prize; and when specific antibiotics were discovered, the entity essentially disappeared. The same story can be told for the dementia associated with pernicious anemia; when an intrinsic factor was discovered the dementia suddenly moved from the category of irreversible to reversible; today with tests for blood levels of vitamin B-12 and with treatment with parenteral B-12 available, this disorder is among the most reversible.

Herpes simplex encephalitis, one of the most common of the viral encephalitides, was, only a few years ago, one of the most devastating; it is now treatable with antiviral agents if diagnosed promptly enough and the symptoms are often reversible. Other major examples of dementias which can be reversed if diagnosed early enough include the dementia associated with normal pressure hydrocephalus and with intracranial masses, such as subdural hematomas. As research progresses, it might be anticipated (or hoped) that presently irreversible conditions, such as Alzheimer's disease, will become reversible. Moreover,
it is feasible to suppose that treatments will be discovered that might reverse symptoms of dementia before the underlying condition is treatable (an example is the effect of L-DOPA in reversing the motor symptoms of Parkinson's disease).

An important issue is the classification of confusional states associated with drug toxicity. In most instances such patients present acutely with some clouding of consciousness, and their condition is appropriately diagnosed as delirium. But at times an older individual may show the typical symptoms of dementia without any clouding of consciousness; moreover, the cognitive changes may come on insidiously and continue for months as use of an apparently innocuous medication continues. Although this scenario may occur with drugs with known anticholinergic properties, it is also seen as an idiosyncratic response to beta blockers used to treat hypertension, to digitalis-related medicines, or to diazepam-related sleep medicines. Elderly individuals sometimes do not metabolize drugs in the time course expected, and consequently blood concentrations build up over days or weeks and lead to chronic symptoms. A misdiagnosis of Alzheimer's disease may be made in individuals with such symptoms. Subsequent to the NIA/AMA task force on the reversible dementias, clinicians have been more aware of the possibility that drug toxicity may cause the symptoms of dementia. They are now more likely to recommend a therapeutic trial consisting of symptomatic elimination or replacement of each medication that might be at
fault. In addition, such a procedure will often reveal cases in which a medicine is not responsible by itself for the dementia symptoms, but has added to the cognitive impairment, an instance of a treatable "excess disability."

4. Problem Areas

a. Depression and Dementia. A most important diagnostic problem area is the differentiation of depression and dementia. The significance of the role of depression in the misdiagnosis of dementia was brought to the fore by the study of Ron et al. (1979). This study was of particular interest because it was carried out at Maudsley Hospital, the premiere psychiatric hospital in London. These investigators reported that on a 4-year follow-up, 31 percent of the patients who had been diagnosed between 1963 and 1972 as having "presenile dementia" were in fact misdiagnosed and that the most common misdiagnosis occurred in patients who were depressed and had associated memory complaints. Subsequent series (Table 4) appeared to confirm the frequency of misdiagnosis.

The relationship of depression and dementia is a complex one. Individuals with typical manic-depressive disorders (bipolar affective disorder) or recurrent depressions (unipolar affective disorder) may, with aging, develop memory and other cognitive changes in association with their affective disorder. Folstein and McHugh (1978) reported that aggressive treatment of the depression (often with electroconvulsive therapy) in such patients
resulted in improvement of cognition. These investigators found that a past history of depression, a subacute onset, and typical depressive vegetative signs and self-reports of depressed mood identified these patients. Rabins et al. (1984) have reported a 2-year follow-up of patients meeting these criteria showing continued improvement in memory and cognition, confirming the initial diagnosis of depression.

Depression presenting as dementia has been called "pseudodementia" by Kiloh (1961), a term that has been considered inappropriate by other authors (e.g., Reifler, 1982; Mahendra, 1983). Folstein and McHugh (1978) suggested that "dementia in depression" was a more appropriate term. Depression and dementia may coexist and in such patients treatment of depression may alleviate the affective symptoms without altering the dementing process (Reifler, 1982; Devanand and Nelson, 1985).

The relationship of dementia and depression may be even more complex. McCallister and Price (1982), Kral (1983), and Reding et al. (1985) have identified patients who initially met criteria for "pseudodementia" and later developed a frank dementia. There are several possible explanations. Perhaps dementia presents as depression in some patients, a conclusion endorsed by Reding et al. (1985). Or the diagnostic criteria for dementia used in their clinic were too strict—in favor of this possibility is the fact that a relatively insensitive mental status test, the Mental Status Questionnaire (MSQ), was in routine use. Or perhaps
the biological bases of depression and dementia are entwined in a manner not presently understood. The apparently complex relationship of depression and dementia has been explored in a useful editorial by Mahendra (1985) who points out the "considerable challenge to his [the diagnosticians'] prowess."

Clearly we are faced with a limitation in our understanding of the relationships between these two conditions, a limitation that hinders our ability to make accurate diagnoses and may lead to significant errors in predictions.

b. Normal Age Changes and Dementia. The definition of the boundary between normal changes and dementia is the most difficult and perhaps insurmountable aspect of the diagnosis of dementia. On the one hand, changes in memory often accompany normal aging, an aspect which has been extensively studied by psychologists (see review by Katzman and Terry, 1983). On the other hand, the onset of certain of the dementias, particularly Alzheimer's disease, is very insidious. At the time of the first clinical examination, family members may disagree among themselves whether the first changes occurred 6 months or 3 years earlier. Kral (Kral and Muller, 1966; Kral, 1978) used the term "benign senescent forgetfulness" to describe individuals with memory changes who were still functional, but there is evidence that such memory changes are not always benign. In patients with mild cognitive changes one cannot make an exact diagnosis even with the very best neuropsychological tests available; only the likelihood of
developing dementia can be estimated. In a prospective study of 488 volunteers, age 75 to 85 years, who were nondemented on initial examination, approximately 50 developed an unequivocal dementia over a 3-year period (R. Katzman et al., unpublished: "Bronx Aging Study"). Extensive neuropsychological tests had been carried out annually; the best predictor of dementia was the score on the Blessed mental status test. Subjects who initially made 0 to 2 errors (out of 33 possible errors) on this mental status examination developed dementia at a rate of less than 1 percent per year; those who made 5 to 8 errors developed dementia at a rate over 10 percent per year. But only one-third of those who made 5 to 8 errors have developed dementia as yet. The latter subset of subjects may be best described as an "at risk" group.

c. Dementia and Delirium. Delirium is a traditional medical term that was introduced as a diagnostic category by DSM-III. Delirium is a symptom complex used to describe global intellectual impairment associated with a clouded state of awareness. This syndrome was called "acute brain syndrome" in DSM-I. This phrase encompassed other terms, such as "acute confusional state," "toxic psychosis," and "metabolic encephalopathy." As indicated by these descriptions, delirium is often associated with metabolic or toxic conditions and most often is acute in onset and short in duration, but these features are not necessary criteria. Memory, orientation, and other cognitive areas are involved and mental status tests are abnormal, but the condition is differentiated from
dementia on the basis of a fluctuating level of awareness. Delirium can accompany a high fever, pneumonia, cardiac failure, alcohol intake, alcohol withdrawal, high doses of psychoactive medications, and liver or kidney failure—in fact a wide spectrum of systemic, metabolic, or toxic disorders. Although focal intracranial processes, such as stroke, usually present with focal features (e.g., hemiparesis), such disorders may also be accompanied by delirium. Thus delirium often represents a medical emergency and is most often diagnosed in emergency rooms; the treatment of the delirium is the treatment of the causative condition. Therefore in most instances delirium is easily differentiated from dementia.

There are two instances in which a diagnostic problem may arise. Although delirium can occur in a person at any age if the metabolic insult is sufficiently great, it occurs more often in older patients and in patients with preexisting dementia, perhaps because there is less "cerebral reserve." If delirium due to an intercurrent infection occurs in a patient with an undiagnosed dementia, for example, there may be temporary diagnostic difficulty until the two conditions are sorted out. A second situation in which there is diagnostic difficulty occurs when the delirium is due to chronic exposure to a toxic source; for example, an older patient does not metabolize adequately a sleeping medication, the level of which then builds up, leading to a persistent daytime confusional state. In such situations delirium is not
short lived if the patient takes the medication on a regular basis. In this particular instance it is not critical whether the label is delirium or dementia as long as the physician recognizes the cause and takes the patient off the precipitating medicine.

**d. Validity of Diagnostic Series.** When is the diagnosis of dementia to be considered correct? The difficulty in differentiating dementia and depression raises the question of what criteria for the validity of the diagnosis of dementia can be used. In the extensive literature on the diagnosis of dementia three implicit criteria have been employed. The first might be called the "authoritative opinion": a patient is referred to an academic center where an extensive examination is carried out and, often after a group discussion, a diagnosis is made. If this diagnosis differs from that of the referring or primary care physician, an error in the latter's diagnosis is assumed. Thus the initial series of Marsden and Harrison (1972), Garcia et al. (1984), and others are based upon a thorough, but one-time evaluation. The problem with this approach has been demonstrated by the work of Reding et al. (1984), described above, who found that half of the patients reported by Garcia et al. as examples of "pseudodementia" later developed frank dementia.

A second approach is to base diagnosis on a 1- to many-year follow-up. The majority of dementing illnesses progress. As a dementia progresses and cognitive loss becomes more evident, there is less uncertainty of diagnosis. If after several years
cognitive impairment has not progressed or has improved, then the
diagnosis of dementia can be questioned. This follow-up strategy
was used, for example, by Reding et al. (1984, 1985), Lijtmaer et
al. (1976), and others. Diagnosis by follow-up is clearly valid
in terms of the question of whether dementia is or is not present
when the cognitive state has clearly gotten significantly better
or worse. However, this approach must be used cautiously in
patients whose deficit has remained static, because a subset of
Alzheimer patients have periods of 2 years or more during which
their disease does not progress, a so-called plateau.

The greatest validity would be achieved if the clinical
diagnoses were compared to predicted cerebral biopsy or autopsy
diagnoses. Such comparisons are at present only available for a
subset of dementia patients who have met research diagnostic
criteria for Alzheimer's disease.

5. Tools/Technologies/Strategies to Improve Diagnosis of Dementia

The DSM-III diagnosis of dementia requires evidence of both
cognitive and functional loss, although cognitive loss alone
satisfies other criteria (see Table 3). Both forms of
impairment may become readily apparent when the history is first
taken. Intellectual changes involving several areas of cognition
may be described, including repetitiousness, forgetting names and
appointments, losing a chain of thought, difficulty in finding the
right word, losing one's way, and losing objects. These symptoms
are experienced occasionally by normal individuals but are
exaggerated in dementia. Functional impairment may present as poor performance on the job or as difficulty in managing the household or withdrawal from hobbies or social activities; the most sensitive indicator of change in cognitive performance is often difficulty coping with fiscal affairs, such as the checkbook or tax form.

However, such symptoms may not be readily apparent early in the course of a dementia. Social conversation may be normal. The physician may not become aware of impairment during the usual course of history taking. However, impairment will become evident if specific probing of mental status is undertaken. Medical students are taught to do a mental status examination. This is reinforced during specialty training of neurologists, psychiatrists, and geriatricians. In practice many primary care physicians do not routinely carry out an adequate mental status examination and specialists may put it aside if another complaint appears dominant. For example, McCartney and Palmateer (1985) found that mental status examination had been carried out on only 4 of 165 patients over the age of 65 admitted to the general medical services of a major teaching hospital. As a consequence 50 patients with cognitive impairment were missed. Other instances of significant underdiagnosis of cognitive impairment have been found not only in general medical settings but also on neurology (Folstein et al., 1985), psychiatry (Hoffman, 1982), and rehabilitation services (Garcia et al., 1984), where such mistakes
might not have been anticipated.

Thus the mental status examination remains the key to the diagnosis of dementia. The mental status examination as currently used was developed over decades of experience. Mayer-Gross (1931) and coworkers (Mayer-Gross and Guttman, 1937) and other European psychiatrists were interested in identifying aspects of examination that distinguished generalized affections of the brain (that is, dementia and delirium) from local disorders (e.g., aphasias or language disorders produced by strokes or tumors localized to the temporal lobe of the dominant hemisphere). After Mayer-Gross migrated to Great Britain in the 1930s, several of his British students (Roth among them) began to formulate specific test items to formalize the mental status examination; a large number of individual items were subsequently examined in terms of their specificity (Shapiro et al., 1956) and following these studies items were combined to develop effective instruments. The two mental status tests now in widest use are the information-concentration-orientation test of Blessed et al. (1968) and the Mini-Mental State (MMS) examination of Folstein et al. (1975). The test of Blessed et al. is the most sensitive (two test items, the memory phrase and the months of the year backward, are harder than items on other tests) and therefore of greatest use in very early cases; it has the added advantage that it has been validated in two autopsy series, with the error score on the test correlating with a quantitative measure of pathology, that is the number
of neuritic plaques per microscopic field in cases of Alzheimer's disease (Blessed et al., 1968; Katzman et al., 1983). The Blessed et al. test, however, is entirely verbal and measures recent and past memory, orientation, and concentration. The Mini-Mental State examination of Folstein et al. is broader in that it also tests language, writing, and drawing. These two tests have been brought together in a combined instrument that is being systematically tested. The Mental Status Questionnaire (Kahn et al., 1960) is contained within this combined test and can be scored separately. This combined test may be useful as a public health tool; it is, however, inappropriate to use this test with individuals who are mentally retarded or who have had a poor educational background. Also the tests are not appropriate for persons who are not fluent in English and for persons with different cultural backgrounds. Alternative tests need to be developed for such groups.

The use of other diagnostic tools in the differentiation of dementia and the differential diagnosis of dementia and depression has been suggested. Thus Ron et al. (1979) in their retrospective follow-up study found that both slowing on the EEG and neuropsychological test scores (the difference between WAIS verbal and performance scores) helped differentiate patients with presenile dementia from patients whose cognitive impairment was attributed to depression. The dexamethasone test has not been found useful in differentiating dementia and depression (Carnes et
al., 1983; Baldin et al., 1983; McKeith, 1984; Katona and Aldridge, 1985).

Some physicians implicitly use the presence of atrophy on CT scan as a criterion of whether a patient is demented. Such use of CT is inappropriate. Dementia is a clinical syndrome that can be present in patients without atrophy on CT. Although cerebral atrophy is a common characteristic of Alzheimer's disease, some Alzheimer patients do not have evidence of atrophy on CT; conversely, many individuals during normal aging show a moderate degree of atrophy; consequently, the Alzheimer process and normal aging overlap in this regard, although group differences are real. However, in patients under age 60 significant atrophy on CT may be a useful indicator of a dementing process.

6. Misdiagnosis of Dementia

a. Diagnostic Errors in General Medical Settings. UNDERDIAGNOSIS of cognitive impairment occurs in general medical settings in situations where the cognitive impairment is not the presenting complaint. Cognitive impairment (both dementia and delirium) was found in more than one-fourth of the general medical inpatients at the Johns Hopkins Medical Institutions but had not been recognized by staff in a majority of these patients (Knights and Folstein, 1977); similar results were found on neurology service (DePaulo and Folstein, 1978) and in a rehabilitation hospital (Garcia et al., 1984) (Table 4). Underdiagnosis in these series occurs because of the failure by the physicians to carry
out systematic mental status examinations.

b. Diagnostic Errors in Specialized Medical Settings. Under-diagnosis also occurs in the setting of specialized dementia clinics—Kral (1983) reported a 4- to 18-year follow-up of 22 patients with an initial diagnosis of pseudodementia. Twenty of these 22 patients had gone on to develop a progressive dementia of the Alzheimer's type. It might be argued that the diagnostic criteria (pre-DSM-III) initially used in this study were inadequate. Reding et al. (1985) reported similar results in a 2-year follow-up of a series of patients in whom diagnoses had been based on the DSM-III criteria. Thirty-one of the 225 subjects referred to their dementia clinic were initially diagnosed as having depression rather than dementia. On follow-up, however, 16 of the patients diagnosed as depressed and nondemented went on to develop frank dementia. The diagnoses in these 16 patients included Alzheimer-type dementia, multi-infarct state, Parkinson's disease, progressive supranuclear palsy, and spinocerebellar disorders.

In contrast, OVERDIAGNOSIS of dementia in patients referred to dementia clinics or referral practices has been reported to range from 10 to 50 percent (Garcia et al., 1981). An example is the report of Hoffman (1982) which indicates the diagnosis of dementia was changed in 40 percent of the patients admitted to a medical-psychiatric inpatient service and that in two-thirds of
those with an altered diagnosis, a reversible condition was found. It is important, however, to note whether the report of misdiagnosis is based simply upon a single evaluation—no matter how complete—or upon follow-up since there is a significant error rate in the former group. It is also important to recognize that the nature of the patient referrals in these reports leads automatically to over- rather than underdiagnosis errors because the patient had been referred because of suspected dementia.

Examples of overdiagnosis reported in series in which follow-up ascertainment has been used are shown in Table 4. It is striking that the rate of overdiagnosis has fallen dramatically in the two most recent series, both begun after DSM-III criteria became available.

C. Summary—Dementia

Dementia represents a symptom complex that may be caused by many disorders. Criteria for the diagnosis of this symptom complex have been well specified in the American Psychiatric Association's Diagnostic and Statistical Manual, third revision (1980). Failure to determine whether or not dementia is present is a greater source of misdiagnosis than are errors in the differential diagnoses of the individual conditions that produce dementia. Typically the presence of dementia is overlooked in patients who present in acute or chronic hospitals with other principal complaints because of the failure to carry out a systematic mental status examination. On the other hand, dementia
is often overdiagnosed in older patients who complain of—or whose families complain of—beginning memory impairment. In a significant number of cases a treatable depression has been misdiagnosed as dementia under these circumstances. Although this situation has improved with the availability of DSM-III criteria for dementia and depression, serious problems remain in differentiating early dementia from depression in patients who show both mild cognitive impairments and depressive symptoms. Nor has the borderline between memory changes that occur in normal aging and beginning impairment in dementia been adequately defined. Very likely the latter boundary can only be established on a probability basis and a cohort of patients "at risk" for dementia identified.
II. ACCURACY OF DIFFERENTIAL DIAGNOSIS OF DEMENTING DISORDERS

A. Diseases that Present as Dementia

1. Clinical and Pathological Series

A number of published studies have reported the frequency of various disorders in patients presenting with the dementia syndrome. Several of these clinical series are summarized in Table 5; pathological series are in Table 6. Diagnoses on more than 700 clinical cases and 1100 pathological cases are presented in these tables. In both clinical and pathological series, Alzheimer's disease (or a synonymous diagnosis, such as degenerative dementia) accounts for over half of the cases. The clinical and pathological series diverge, however, in several aspects: clinical series report cases of toxic and metabolic dementias; these causes are not associated with diagnostic histological changes and hence are not included in the pathological series. Pathological series include a much higher percentage of vascular dementia than do most clinical series. This probably represents the sampling biases inherent in clinical series in which patients had been evaluated in a geriatric or dementia clinic or in a geriatric hospital. Thus patients who develop overt strokes may have been treated in an acute hospital and not sent to a dementia referral center. In support of this assumption is the fact that clinical studies based upon community sampling include a higher proportion of cases of vascular dementia (Folstein et al., 1985; R. Katzman et al., unpublished: "Bronx Aging Study").
Not all disorders that have been reported to present as dementia (Hasse, 1977; Katzman, 1984, 1986) appear in published series. This reflects both the relative infrequency of some of the disorders and the sampling bias that has occurred. Thus both factors may explain why dementia pugilistica (punch drunk syndrome) is not included in any of the published series. Series are gathered over years and therefore newly discovered entities—such as AIDS virus encephalopathy, which may become the third most common cause of dementia within the next 3 years—are not yet found in available series.

2. Age vs Frequency of Disorders that Produce Dementia

An important factor that must be taken into account in regard to the relative frequency of disorders that produce dementia is that of age. This factor will significantly impact the public health consequences of misdiagnosis. The incidence and prevalence of Alzheimer's disease increase exponentially with age at least to age 85. The incidence and prevalence of stroke also increase with age in an exponential fashion (Kurtzke, 1969; Katzman, 1983). In contrast, other disorders that produce dementia may be age-independent or peak during middle age (Table 6). Huntington's disease is one obvious example. An important reversible dementia that peaks in middle age is "normal pressure hydrocephalus" (perhaps better called "adult communicating hydrocephalus"). In a review, Katzman (1977) noted most reported cases were in individuals in their 50s and 60s. An autopsy series of dementia
patients reported by Jellinger (1976) confirmed that the majority of hydrocephalus cases were under age 70, accounting for 5 percent of dementia cases under age 70 and only 0.3 percent of cases over the age of 70. But these "treatable" conditions do occur in persons whose first symptoms occur past the age of 75, as shown in the Bronx Aging Study (described above) in which one case of hydrocephalus and one of brain tumor (glioma) were among the first 35 cases of dementia to develop.

B. Components of Diagnostic Workup

1. Current Workup: Technical Limits; Risks, Benefits, Costs

   a. Clinical Evaluation. The clinical evaluation—that is, the history, mental status, and physical and neurological examination—is central to the diagnosis of dementia and to the differential diagnosis of dementing illness. There is considerable variation as to how this clinical examination is carried out. Thus at one extreme, in a dementia clinic associated with a geriatric evaluation clinic and supported in part by a state grant, each patient is seen by an internist, neurologist, and psychiatrist; mental status tests and a neuropsychological battery are administered by a neuropsychologist; a nurse practitioner visits the home; a CT scan, blood tests, and other procedures needed are carried out; and a diagnosis is made at a consensus conference. At the other extreme, some patient families report that they have been told that their relative has Alzheimer's by a busy practitioner, based apparently upon a 10-minute examination
and a CT scan. There is evidence that the first type of evaluation can result in a high level of accuracy in diagnosis, as shown by the autopsy follow-up of Larson et al. (1985) described below. The cost of such an evaluation in one specialized clinic which accepts Medicare reimbursement is $644 for the clinical and psychiatric evaluations and $718 for the laboratory tests, for a total of $1362.

It is important to point out the impact of current federal policy on the workup of a dementia patient. The combination of a complete history, physical and neurological examination with, for example, a mental status examination (at a minimum the combined Blessed and MMS), and a discussion of the problem with the family will take at least 1 hour and 15 minutes by a very experienced physician. Current Medicare reimbursement does not provide reimbursement for the additional time spent on a dementia patient, time that is almost certainly the most cost-effective part of the entire workup.

b. CT Scan. The CT scan is universally accepted as an essential component of the diagnostic workup. The CT scan is required for the diagnosis of hydrocephalus and mass lesions in the brain, including brain tumors and subdural hematomas. Dementia secondary to hydrocephalus and subdural hematoma can be arrested and sometimes reversed by prompt intervention; occasional benign brain tumors (e.g., pituitary adenomas, meningiomas) can be removed and symptoms arrested or reversed; other brain tumors,
such as astrocytomas and microgliomas (primary brain reticulum cell sarcomas) may be usefully treated. Typical patterns of atrophy are sometimes diagnostic of Huntington's disease and Pick's disease. The CT scan of Biswanger's disease is also characteristic (Rosenberg et al., 1979). Although generalized cortical atrophy is not in itself diagnostic of Alzheimer's, the loss of tissue measured by combining cortical atrophy and ventricular enlargement is a useful adjunct in diagnosis (Gado et al., 1982). The cost of a noncontrast CT scan varies from about $225 to about $450 in different localities and with scanners of different resolution; in our estimates we use a figure of $341. The advantages of high-resolution scans include their capacity for identifying many vascular lesions, infarcts, and white matter changes that are missed on lower resolution scans.

c. Blood Tests—Systemic and Metabolic Disorders. Although systemic and metabolic disorders account for only 1 percent of patients presenting with symptoms of dementia, their identification is critical because progression of cognitive impairment can be arrested and sometimes function restored by treatment. Automated analytical systems make it possible to obtain 18 to 20 blood chemistries for less than $10, and a complete blood count adds only a few dollars. Unfortunately, tests of thyroid function, serum B-12 and folate levels, and syphilis are not included in available automated runs and their addition increases the cost to about $80. HLT-VIII antibody tests would increase the
costs further. A modest federal effort to reward development of automation of these tests would be a cost-effective expenditure.

d. Chest X Ray and EKG. These are traditional parts of the routine annual examination and are included in most lists of workup for dementia. There are no studies justifying their cost effectiveness as part of the dementia workup, but information as to whether there is a tumor or infection in the lung or whether there has been a silent myocardial infarct is often useful. The cost for these two procedures varies; current Medicare reimbursement levels in California are $84 and $53 for chest X ray and EKG, respectively.

e. EEG. The electroencephalogram reflects the activity of the cerebral cortex and might be assumed to be a useful diagnostic tool. In patients with Alzheimer's and other forms of dementia, the typical 8- to 12-Hertz occipital alpha rhythm may slow in frequency and disappear and the slower 4- to 7-Hertz theta rhythm become predominant. Ron et al. (1979) found that the EEG did help discriminate between dementia and depression. The EEG is of specific use in a small subset of patients in whom cognitive impairment is the expression of seizure activity, particularly temporal lobe seizures, and in patients with Creutzfeldt-Jakob disease, who may develop a striking periodic rhythm. Although such patients constitute less than 1 percent of dementia patients, the condition is treatable and would justify the cost. The cost of an EEG varies from $100 to $160.
f. Neuropsychological Evaluation. The neuropsychological evaluation is not universally recommended as an essential part of the dementia workup and its cost effectiveness has not been determined. Many investigators, however, find neuropsychological testing to be very useful in confirming the presence of dementia and in identifying in a semiquantitative fashion the kinds of impaired function. It is valuable in distinguishing between dementia and depression (e.g., Ron et al., 1979) and between so-called cortical dementia (e.g., Alzheimer's) and subcortical dementias (e.g., progressive supranuclear palsy) (Cummings and Benson, 1984). Additionally, neuropsychological evaluation provides a precise way to follow changes in cognition. Neuropsychological evaluations often take a number of hours and hence are labor-intensive. Costs range up to $500. Medicare reimbursement, however, is limited to about $200.

The tests listed above constitute the core of the dementia workup. These tests are essentially risk-free; the small amount of X-ray exposure resulting from the CT and chest X-ray will have little effect in the older patient being tested. Several other tests--described below--may be needed in special circumstances.

g. Lumbar Puncture. Lumbar puncture (LP) with analysis of the cerebrospinal fluid (CSF) has been traditionally included in the routine dementia workup and is needed to diagnose such treatable causes of dementia as neurosyphilis and chronic fungal meningitis. Infectious etiologies of dementia, however, have been
found to be uncommon. In a retrospective study of the results of lumbar puncture in 402 patients, hospitalized in two major teaching hospitals for the evaluation of dementia, 4 patients with central nervous system infections were found, 2 with fungus infections (due to Cryptococcus), 1 with tuberculosis, and 1 with Staphylococcus infection (Becker et al., 1985). In all these patients there was a subacute onset of a change in mental status and all had either fever or signs of meningeal irritation (that is, a stiff neck). The authors concluded that in the absence of such signs, "LP and CSF analysis should not be part of the routine evaluation of patients with dementia." A new category of patients in whom LP is needed are those with cognitive changes who have AIDS, because the dementia in AIDS can be due either to coincident opportunistic infections or to primary AIDS virus infection; the presence of the virus can now be demonstrated in CSF. The risk of an LP includes that of the post-LP headache which, however, is less frequent in older patients. Post-LP infection is a theoretical risk but is not seen in routine practice. The cost of CSF analysis is about $70.

h. Tests of CSF Circulation. In patients in whom the CT scan suggests the presence of hydrocephalus, special procedures, such as isotope cisternography or infusion test, may be necessary before surgical shunting.

In patients with suspected vascular dementia a search for etiologies, such as carotid artery or cardiac sources of
embolization, is often carried out. Although this is accepted and rational practice, its diagnostic value has not been adequately studied (see, for example, Postiglione et al., 1985).

There are several tests which measure functions that are altered in dementia but which are not diagnostic; these tests can be considered to be of research interest but have no proven value in the clinical diagnosis of dementia. These include measurements of cerebral blood flow with the xenon inhalation technique and measurements of evoked potentials.

2. Cerebral Biopsy

At the present time, and in the absence of specific biochemical markers, the definitive diagnosis of Alzheimer's disease, Pick's disease, and Creutzfeldt-Jakob disease depends upon confirmation by microscopic examination of the presence of characteristic changes in neurons of the cerebral cortex—in the case of Alzheimer's disease, the presence of abnormal foci of degenerating nerve endings, termed a neuritic plaque, and the presence of neurofibrillary tangles, abnormal nerve cells containing accumulations of submicroscopic fibrils; in the case of Pick's disease, abnormal inclusions in neurons, termed Pick bodies; in the case of Creutzfeldt-Jakob disease, by the spongy appearance of the cortex resulting from a particular pattern of nerve cell drop out and gliosis. Thus, during life one can only achieve a definitive diagnosis for these conditions by the use of cerebral biopsy, that is, by the surgical removal of a small piece
of cerebral cortex with subsequent histological examination supplemented by electron microscopic examination and by biochemical and virological studies. In addition to its critical role in diagnosis, cerebral biopsy has played a central role in advancing the understanding of these diseases. The classical electron microscopic studies of Alzheimer's by Terry (1963; Terry et al., 1964) and Kidd (1964) depended upon the availability of brain biopsy; the recent studies of Bowen et al. (1982) demonstrating the involvement of the cholinergic system during the first year of symptoms in Alzheimer's disease depended upon the availability of biopsy specimens; the demonstration that Creutzfeldt-Jakob disease is transmissible to chimpanzees primarily, but not exclusively, involved implantation of biopsy specimens into chimpanzee brain. Yet the cerebral biopsy procedure is used in much fewer than 1 percent of dementia patients in the United States, although it is used more commonly in Great Britain. Is this conservative approach justified by the risks of biopsy? How frequently do biopsies give unequivocal answers?

There are two surgical approaches to brain biopsy: 1) open surgery with removal of a piece of cerebral cortex under direct visualization; if the presentation is that of a diffuse disease, the biopsy is carried out in the right frontal lobe (in right-handed patients) as there is no apparent neurological defect that results from removal of a small amount of cortex in this "silent" area; 2) needle biopsy under stereotaxic or CT guidance. In the
first procedure about a cubic centimeter block of tissue is removed; in the second a small core of tissue the diameter of a needle is removed. In practice, the first procedure is used when disease of the cerebral cortex, such as the dementias, is present because this procedure preserves the architecture of the cortex which may be important in diagnosis; in addition, the gram of tissue usually removed makes it possible to carry out special staining procedures needed for diagnosis of dementias and illnesses (such as silver or thioflavine stains for neurofibrillary tangles); also this amount of tissue permits biochemical analysis (for example, for markers of the cholinergic system) and immunohistochemistry to be carried out, thus increasing the chance of specific diagnosis. In practice, the second procedure is used if a lesion is deep to the cortex, particularly if it is a suspected tumor or inflammatory lesion. Needle biopsies have been used extensively to confirm the diagnosis of herpes encephalitis which affects the medial temporal region. This is the only condition which regularly presents with mental status changes in which needle biopsy is performed.

Needle biopsies were seldom carried out for diagnostic purposes in subjects with symptoms of diffuse cerebral disease prior to the availability of antibiotics. Cerebral biopsy, however, came into use, particularly in Europe, in the late 1950s and early 1960s. We have been able to identify 10 series (Table 7) with diagnostic and/or risk data encompassing 551 patients.
A majority of the patients reported were children in whom diagnoses of recessive metabolic disorder (such as Tay-Sachs disease) was sought. Because most of the recessive metabolic disorders can now be diagnosed using skin cultures or other peripheral tissues, such biopsies are not so common today. There are 4 series which focus on adult patients with symptoms of dementia and include 132 cases.

a. Diagnostic Accuracy. In the five general series (encompassing 419 patients, predominantly children), cerebral biopsy yielded a specific diagnosis in 40.0 percent; 34.5 percent of the biopsies were abnormal but not diagnostic, and 25.5 percent were normal (Antunes, 1963; Blackwood and Cumings, 1966; Eadie, 1964; Groves and Möller, 1966; all summarized by Blackwood, 1971, and by Kaufman and Catalano, 1979). Autopsy data were reported in 46 cases. In the autopsied cases all specific diagnoses were confirmed (26 cases); 2 of 4 cases reported as normal on biopsy were found to be normal at autopsy; in 1 case there was an active meningoencephalitis that had been missed; in the other case, cerebellar atrophy. The significant problem was the 16 cases in which biopsies were abnormal but not specific. At autopsy, 4 continued to show nonspecific findings, and there was 1 case of white matter disease (Schilder's). Tumors were present in 5 cases; all of these cases were pre-CT scan and probably would be diagnosed by imaging. But here were also 4 cases with diffuse diseases not diagnosed on biopsy, including 2 cases of lipidoses
and 2 cases of Creutzfeldt-Jakob disease. Hence, in terms of specific diffuse diseases, there were no false positives but 5 of 46, or about 11 percent, false negatives and another 10 percent without specific diagnoses even at autopsy.

Directly pertinent to the question of the usefulness of cerebral biopsy in patients with dementia are the four series that concentrated upon such cases. Green et al. (1952) reported the results of biopsies of 15 patients with presenile dementias. There were 7 cases of Alzheimer's, 1 case of Pick's, and 7 cases showing nonspecific changes. In the series of 59 biopsies in patients with presenile dementia reported by Smith et al. (1966), there were 34 cases of Alzheimer's, 1 combined case of Alzheimer's and Pick's, 2 Pick's, 2 vascular, 2 chronic meningoencephalitis, and 1 Creutzfeldt-Jakob. Seventeen (29 percent) biopsy cases showed no specific changes. Bowen et al. (1982) reported 36 brain biopsy samples; Alzheimer's accounted for 23, Creutzfeldt-Jakob for 1, vascular disease for 2, leukodystrophy for 1, and microglioma for 1. Eight cases had no diagnostic changes. A 23-case series of Katzman and associates (Coblentz et al. (1973), Kaplan et al. (1985), Crystal et al. (1982), and Koto et al. (1977)) included 11 Alzheimer's, 1 Pick's, 2 microinfarcts, 1 normal pressure hydrocephalus with meningeal thickening, 2 Creutzfeldt-Jakob, 1 chronic meningitis, 1 vasculitis, and 4 nonspecific. We are aware of eight autopsies; six confirmed specific diagnoses. One of the cases that had nonspecific changes on biopsy turned out
to have motor neuron disease on autopsy; the other had a lacunar state. Thus in the earlier series of Green et al. (1952) and Smith et al. (1966), 24 of 74 biopsies were nonspecific and failed to provide diagnosis. In contrast, in the series of Bowen et al. and Katzman et al. the number of nondiagnostic biopsies fell to 21 percent. This may be attributed in part to the improved diagnosis of subcortical diseases by use of modern imaging methods and in part to improved understanding of diseases that produce dementia. Specifically the changes in the brain characteristic of Creutzfeldt-Jakob disease were not yet appreciated at the time of the Green et al. and Smith et al. series, nor had the syndromes of normal pressure hydrocephalus and of multi-infarct dementia been defined at the time of the Green et al. and Smith et al. series. Overall, however, in these four series 73 percent of the biopsies gave a specific diagnosis.

b. Risks of Biopsy. Risk data are not available for the important biopsy series of Bowen et al. Data are, however, available for six series that include 437 cases. These data are heavily skewed by the Blackwood and Cumings series of 178 biopsies; these authors state: "There has been no evidence at all that the patients have suffered in any way. There was neither immediate clinical deterioration nor was there post-operative death in any case. There was no evidence of post-operative epilepsy or haemorrhage, or infection." Perhaps this salutary experience explains why biopsies are more readily carried out in
Great Britain. In the remaining 259 cases (series of Green et al.; Groves and Møller; Smith et al.; Kaufman and Catalano; and Katzman) (Table 7) there were three postoperative deaths (two associated with postoperative hemorrhage, one a cardiac arrest in a 15-month-old who also underwent ventriculography), and there were 10 instances of morbidity—none resulting in permanent neurological deficit. In the entire 437 cases the overall mortality was 0.75 percent and morbidity 2 percent. If one considers only the three dementia series included there was one death in 96 biopsies, or about a 1 percent mortality rate, and three instances of postoperative morbidity, a 3 percent rate. If in fact there has been no morbidity in the Bowen series then these percentages would be reduced by about one-third.

An additional risk not to be found in these statistics is that of spreading infection of the latent virus disorder, Creutzfeldt-Jakob disease. Instances of spread by improperly sterilized instruments which are used in subsequent brain operations has been documented (Bernoulli et al., 1977). However, the parameters for adequate chemical as well as heat sterilization have now been established and are used in most neurosurgical operating rooms (Traub et al., 1974; Gajdusek et al., 1977; ANA, 1986).

c. Role of Biopsy. Cerebral biopsy has played a critical role in advancing knowledge of dementias. The classical description of the ultrastructural changes in Alzheimer's disease in the early 1960s by Terry (1963) and by Kidd (1964) required the availability
of fresh tissue obtained at cerebral autopsy. The extensive biochemical studies of Bowen and colleagues that have established the changes in the acetylcholine and other neurotransmitter systems early in the course of Alzheimer's required biopsy tissue. In the immediate future, Alzheimer biopsy material may be needed for the adequate study of the molecular biology of the disease and for determining what genes are expressed in the diseased brain, information that will be necessary for an understanding of pathogenesis and that may help in determining etiology. In addition, cerebral biopsy has led to the delineation of the pathology characteristic of several unusual but important disorders that present with dementia.

The use of cerebral biopsy for diagnosis has been more controversial. One concern is that 20 to 25 percent of the biopsies will not produce a specific diagnosis. In most instances when an autopsy has been carried out in patients with nonspecific diagnoses, unusual disorders have been found which reflect the selected nature of patients being referred for this procedure. Although the numbers are small in these series, there was no instance of a case in which the biopsy was nondiagnostic and the autopsy showed Alzheimer's. In our experience, histological changes on biopsy are often dramatic, even in early cases. Thus the procedure does have significant diagnostic usefulness. One could raise the issue of whether this would be a cost-effective approach. A second concern is the risk; this has been extraordi-
narily variable between series and undoubtedly increases in relationship to the degree of cognitive impairment of the patient. In our own series two of the three instances of postoperative morbidity were due to bleeding at the operative site resulting in subdural hematomas. In both instances the patients had advanced dementia and large ventricles and were being considered for ventricular shunts; as indications have changed they would no longer be considered as suitable candidates for ventricular shunting. Nor would they have been considered to be suitable candidates for diagnostic biopsy alone. The third instance of postoperative morbidity was a prolonged bout of asceptic meningitis in a patient with isolated primary cerebral vasculitis. The three deaths that were reported in the series of 437 biopsies were all from the 1960s or earlier. It seems reasonable in the absence of larger recent series to assume a mortality of about 0.5 percent. Under these circumstances it is likely that diagnostic biopsies at present will be used sparsely in the United States and reserved for cases that are difficult to diagnose. The situation will change radically if a therapy with efficacy but significant side effects were developed (an example would be a drug that had to be administered by intraventricular cannula); then the risk of biopsy would be quite reasonable. Until that occurs Biemond's criteria (1966) still hold: when the patient has a progressive disorder with dementia and "all other possible diagnostic methods have already been tried and failed to provide sufficient
diagnostic certainty; the general condition of the patient permits it..." Biemond also recommended that "modern diagnostic possibilities are exploited to the fullest in the examination of the material obtained."

3. Limits of Autopsy Certainty

Alzheimer was both a psychiatrist and anatomist and his description of the case that proved to be the prototype of Alzheimer's disease included both a description of symptoms and of changes in brain tissue. A 1984 NIA conference on diagnosis of dementia emphasized that Alzheimer's is truly a clinical pathological diagnosis dependent upon the presence during life of dementia and upon the typical pathology—silver staining neurofibrillary tangles and neuritic plaques—at biopsy or autopsy (Khachaturian, 1985). In most autopsied cases the pathological changes are so evident that there would be full agreement among pathologists concerning the diagnosis. However, in a few cases pathological changes are very mild. This creates uncertainty because the brains of nondemented elderly (Tomlinson, 1977; Ulrich, 1985) may show a few neurofibrillary tangles in the hippocampus or amygdala or an occasional neuritic plaque in the cerebral cortex. The NIA conference (Khatchaturian, 1985) recommended specific autopsy criteria for the diagnosis of Alzheimer's disease. Samples for microscopy should be stained with the Bielschowsky silver technique, thioflavin S method (with ultraviolet illumination), or the Congo red technique (polarized
light), as these methods are highly sensitive. To compensate for an inadequate history and to assure a separation greater than 95 percent of Alzheimer's disease from normal aging changes, the panel recommended that the diagnosis be made if the number of neuritic plaques exceed 15 per 1 mm of microscopic field in patients older than 75, exceed 10 in patients between 65 and 74 years old, exceed 8 in patients between the ages of 50 and 64, and exceed 2 in patients under 50. In addition, neurofibrillary tangles anywhere in the neocortex should not be present in patients under 75. The report (p. 1103) states "In the presence of a positive clinical history of AD these criteria should be revised downwards, although to what extent remains to be determined by future research. One suggestion was that one might only need 50 percent as many lesions in neocortical samples to retain a high confidence for the histological diagnosis."

Another limitation of autopsy accuracy occurs due to a small percentage of cases—perhaps about 5 percent in the typical series—in which there is an absence of pathological change in the brains of patients known to be demented during life. Such cases are represented in 4 percent of autopsies of the Tomlinson (1977) series, 11 percent of the Sulkava et al. (1983) series, and 6 percent of the Terry et al. (R. Terry, personal communication, 1985) series. In the latter series, 6 of 101 autopsies of quite elderly (average age 85) nursing home patients belonged in this category. The traditional neuropathological studies were
supplemented with quantitative counts of nerve cells remaining in
cerebral cortex and with measurements of markers of the
cholinergic system and the somatostatin system. All were within
limits of normal relative to age-matched brains. Such cases may
represent neurodegenerative disorders whose pathology cannot be
demonstrated by the typical stains (which, in the case of the
Terry et al. series, include H & E, silver, and thioflavin
stains) or biochemical measurements. However, it is also possible
that at least some of these cases represent metabolic or toxic
dementias that were potentially reversible and were not diagnosed
during life. Thus the existence of such cases reflects the
limitations of current diagnostic accuracy.

4. New Technologies

a. MRI. Magnetic resonance imaging (MRI) was approved for
reimbursement by Medicare on January 1, 1986. MRI images are
spectacular in the amount of anatomic detail that can be
visualized. It is possible that MRI will eventually replace CT as
the primary imaging technique but there is not yet sufficient
experience to warrant this change.

MRI may be especially effective in diagnosis of multi-infarct
dementia, lacunar states, and Binswanger's disease, all forms of
vascular dementia, because it is so sensitive to alterations in
tissue structure produced by vascular lesions. In fact, the
current problem is that vascular and white matter changes are seen
in some asymptomatic persons and limits of normal have yet to be
defined. MRI correlation with autopsy findings is needed. The vascular etiology of dementia may become an MRI diagnosis. The current cost of an MRI is about $700.

b. Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT). The development of PET using a fluorine-18-labeled cogen of glucose has made it possible to examine brain metabolism in specific brain regions during life. This dramatic new technology has been used to examine Alzheimer patients at different stages of their disease. There is evidence that memory changes may precede measurable metabolic changes (Cutler et al., 1984, 1985). However, it has been found that in relatively early cases an asymmetric but bilateral reduction in metabolism in parietal cortex is present (Friedland et al., 1985a,b); later there is a dramatic reduction in metabolism throughout the cerebral hemispheres. Experience is still too limited to know how useful the biparietal pattern may be in diagnosis. The potential usefulness of PET as a clinical diagnostic tool is limited by the short half-life of positron-emitting isotopes (about 90 minutes for fluorine 18) and the need for a local cyclotron with a team of physicists and radiochemists.

SPECT, however, has been touted as a "poor man's PET." SPECT cannot be used at present for metabolic measures but it can be used to measure truly regional blood flow accurately using iodine-123-labeled compounds that are commercially available. SPECT equipment is within the range of capital expenditures that most
hospitals can make; moreover, there are many nuclear medicine specialists capable of using SPECT whose skills are underutilized because CT and MRI have displaced isotope scanning in many instances (for example, the brain scan is no longer used). Hence there is great interest on the part of such specialists in this new technique. Nevertheless, there is need for great caution. The sensitivity and specificity of SPECT measurements of blood flow in the diagnosis of dementia has not been determined. This is a matter of public health interest because the total expenditure for SPECT might be very large at a time when justification of its use is in doubt.

c. Biological Markers. The identification of a specific biological marker of Alzheimer's disease that can be used clinically would be a most important advance in the diagnosis of this disorder. This area has recently attracted the attention of many sophisticated laboratories. Two major types of markers are being investigated: 1) cerebrospinal fluid changes reflecting altered brain neurotransmitters or abnormal proteins; 2) peripheral markers, reflecting changes in skin or blood cells. The first is straightforward conceptually, but so far disappointing. The second approach is based on the assumption that systemic changes occur in Alzheimer's disease, changes that have not been demonstrated pathologically or biochemically. A number of very reputable investigators have claimed success in finding such peripheral markers, but most attempts have not yet
been replicated and there is no consensus yet as to their potential usefulness as diagnostic markers. Specifically, none of the changes reported have been shown to differentiate normal patients from Alzheimer patients early in the course of the disease. Nor is it certain whether any proposed marker distinguishes Alzheimer's disease from other brain disorders.

Markers reflecting brain changes. Thal (1985) and Thienhaus et al. (1985) have recently reviewed the extensive data available on cerebrospinal fluid (CSF) changes in dementia. The enzyme acetylcholinesterase is decreased in cerebral cortex; some investigators have found it decreased in CSF, others have not. Thal suggests that the apparent decline in some studies may be a dilutional effect secondary to ventricular enlargement. But even if this is not the explanation, decreases in the dopamine metabolite HVA, which have been found to be consistent in a subgroup of patients and appear to be related to the severity of dementia, are also found in other disorders, notably Parkinson's disease. The neuropeptide somatostatin is markedly reduced in the cerebral cortex in Alzheimer's disease; in CSF it has been found to be decreased in some patients but not in others. Norepinephrine is often decreased in the brain of Alzheimer patients but is increased in the CSF (Raskind et al., 1984). At present, changes in neurotransmitters or their metabolites in the CSF do not appear to be likely diagnostic markers.

An interesting area still to be explored is whether one or
more of the abnormal brain proteins associated with Alzheimer's disease can be found in CSF or serum. Proteins of interest include paired helical filament protein, amyloid protein, and Alzheimer-specific nucleus basalis antigen (Wolozin et al., 1986). At present none of the antibodies to these proteins have served to identify the minute quantities of these abnormal proteins that may escape from the brain. Nonetheless, the effort certainly seems worthwhile.

Peripheral markers. Possible changes in peripheral cholinergic markers have interested a number of investigators. There have been reports of changes in red blood cell and plasma choline and in fluxes in Alzheimer patients, but others have either not been able to confirm these changes or have found statistical changes that are not useful as diagnostic tests (Hanin et al., 1984; Greenwald et al., 1985; Blass et al., 1985). Changes in pseudo-cholinesterase and in red cell acetylcholinesterase that sometimes occur are not diagnostic (Smith et al., 1982; Chipperfield et al., 1981; Perry et al., 1982). One group of investigators found that sodium-lithium countertransport rates in red cells were elevated in Alzheimer's, but the number of subjects was small and this finding has not been replicated (Diamond et al., 1983). The susceptibility of persons with Down's syndrome to Alzheimer's disease has led many workers to seek evidence of abnormal chromosomes in lymphocytes from Alzheimer patients. Although several investigators have reported increased chromosomal fragmen-
tation or aneuploidy in cultured cells, others have not been able to confirm this (Mark and Brun, 1973; Martin et al., 1981; Sulkava et al., 1979; Nordenson et al., 1980; Ward et al., 1979). Cook-Deegan and Austin (1983) found that the DNA content in noncultured lymphocytes was not altered in familial or sporadic Alzheimer's, making chromosomal aberration unlikely.

The most intriguing work at the present is represented by reports of alteration of function of cultured Alzheimer fibroblasts. Changes reported to occur include increased CO production (Sims et al., 1985), increased superoxide dismutase (Thienhaus et al., 1984), altered calcium uptake (Peterson et al., 1985), altered intracellular calcium, and reduced DNA repair (Robison et al., 1985). Some of these reported changes are quite striking—for example, W. G. Bradley and coworkers (Robison et al., 1985) found no overlap between the rates of DNA repair obtained in Alzheimer as compared to control cultures; a change in DNA repair was also reported by Li and Kaminskas (1985). All of these reports are preliminary and one can point to possible methodological flaws (for example, some of the Alzheimer patients may have received neuroleptics whereas controls have not; some of the Alzheimer patients may have become cachetic and the controls not; additional control groups are needed, including cells from patients with other neurological diseases; some of the studies have used fibroblasts from the NIA repository, cells obtained from highly selected families who may be atypical). Nevertheless, the
changes reported are sufficiently dramatic to warrant a high priority pursuit of these findings. If one of these changes turns out to be specific for Alzheimer patients it would not only be an important diagnostic marker but might also provide a clue as to etiology.

Another important approach is the search for genetic markers for Alzheimer’s disease. Based upon studies of families in which Alzheimer’s disease has appeared for several generations, it is assumed that a dominant autosomal gene predisposing to this disorder is present. Several groups are now attempting to use the sophisticated methodology currently available for locating genes (employing RFLPs, restriction fragment length polymorphisms), methodology that was so successful in locating the Huntington gene, to study Alzheimer's disease. This approach may not work if several genes produce Alzheimer's disease; moreover, it may be quite difficult because of the late age of onset of Alzheimer's, creating uncertainty as to which living members of a family are really free of disease. The use of subtraction libraries containing DNA and cDNA clones may provide alternate approaches to the molecular genetics of Alzheimer's disease.

C. Diagnostic Criteria

Specific criteria that have been developed in the past decade for the diagnosis of Alzheimer's disease and multi-infarct dementia have contributed to an improvement in diagnostic accuracy. Two widely used sets of criteria for the diagnosis of
Alzheimer's disease are compared in Table 8: the DSM-III criteria for the diagnosis of "primary degenerative dementia" (PDD) (which are similar to those suggested by Eis dorfer and Cohen, 1980), and the ADRDA-MINCDS criteria for the probable, possible, and definite diagnoses of Alzheimer's disease. The introduction of the term "primary degenerative dementia" by the DSM-III was somewhat of an anomaly since elsewhere in that manual specific and simple terms, such as "dementia," had been substituted for cumbersome phrases, such as "chronic organic brain syndrome." DSM-III states that PDD is intended to include Alzheimer's disease, Pick's disease, and dementias with nonspecific brain changes (the latter group referred to in this report as the "5 percent problem"). In fact, it has turned out that many investigators have used the DSM-III criteria to identify the typical case of Alzheimer's disease for research purposes; autopsy studies have shown that more than 90 percent of patients who meet DSM-III criteria for PDD have Alzheimer's disease. Most clinicians hope that in the next edition of its diagnostic and statistical manual, the American Psychiatric Association will drop the term "primary degenerative dementia" and use the term Alzheimer's disease. DSM-III criteria for PDD include the DSM-III criteria for dementia with "an insidious onset with uniformly progressive deterioration course...exclusion of all other specific causes of dementia by history, physical examination, and laboratory tests" (DSM-III, p. 126). The ADRDA/MINCDS criteria for probable Alzheimer's are
similar to the DSM-III criteria but are more detailed; the ADRDA/NINCDS also allows for more variation in course, recognizing, for example, that the course is not always progressive and that plateaus may occur. Both sets of criteria are restrictive, however. Karasu (1986) noted: "Essentially DSM-III is a research oriented instrument, which requires that there be a minimum of false-positive diagnoses in order to obtain a homogeneous sample and to keep any distortion or dilution of statistical data at the lowest possible level." This it succeeds in doing with its criteria for PDD/Alzheimer's. Karasu continues: "In contrast, clinical practice must insist on a minimum of false-negative diagnoses."

This latter statement is appropriately applied to the DSM-III criteria for Alzheimer's disease because there are many patients with autopsy- or biopsy-proven Alzheimer's disease who do not meet the criteria. For example, some patients will present with impairment of only one area of cognition (e.g., memory, language, or right parietal lobe deficit) (Katzman, 1985; Crystal et al., 1982). Not infrequently an Alzheimer patient may have a coexistent disorder that by itself may produce dementia (e.g., hypothyroidism), but treatment is found not to slow the progression of the cognitive loss. The report of the ADRDA/NINCDS committee on the diagnosis of Alzheimer's disease recommended that patients with an atypical course, findings, or coexistent disease be diagnosed as "POSSIBLE ALZHEIMER" (McKhann et al., 1984).
Because the designation of possible Alzheimer's is so recent, there are as yet no follow-up reports on its validity. This same report reserved the designation of "DEFINITE ALZHEIMER" for cases with biopsy or autopsy confirmation. The ADRDA/NINCDS report used the term "PROBABLE ALZHEIMER" for patients who meet criteria similar to those of DSM-III.

DSM-III also included criteria for the diagnosis of multi-infarct dementia. These criteria include the presence of dementia, "a stepwise deteriorating course [i.e., not uniformly progressive] with 'patchy' distribution of deficits early in the course...focal neurological signs and symptoms...evidence...of significant cerebrovascular disease" (DSM-III, p. 128). Relatively few patients are found to meet these criteria exactly. It has been found that scoring systems, introduced by Hachinski (1978) and modified by Rosen et al. (1980), have been of much greater utility for diagnostic purposes. However, these "ischemic scores" have so far only been validated retrospectively and a prospective autopsy series needs to be carried out. A defect of these scoring systems is that patients with pure multi-infarct dementia as well as patients with combined multi-infarct dementia and Alzheimer's disease will score similarly. Also, clinicians now find that evidence of infarct or lacunes (a lacune is a small hole in the brain—less than 15 mm in diameter—resulting from destruction of a small region of brain tissue due to the occlusion of a small artery deep in the white matter or adjacent nuclei
(gray matter), a region where there is inadequate collateral circulation and many small arteries are "end arteries") on CT scan is helpful in the diagnosis and MRI may provide specific laboratory confirmation of multi-infarct dementia, although not differentiating patients with multi-infarct dementia and Alzheimer's. New criteria taking into account these techniques need to be formulated. At present the accuracy of the diagnosis of multi-infarct dementia cannot be determined.

D. Diagnostic Errors: Current Status

There is every indication that the current workup combined with the use of specific diagnostic criteria has greatly improved the clinical differential diagnosis of dementing disorders in the middle or later stages of these disorders. Larson et al. (1985) reported confirmation of specific clinical diagnoses by autopsy data obtained during a retrospective study of 200 patients with suspected dementia who had been referred to a specialized geriatric outpatient evaluation clinic. Each patient underwent an intensive evaluation including the diagnostic workup described above, and a consensus diagnosis was obtained on each. There were 37 deaths and 17 autopsies. Fifteen patients diagnosed clinically as Alzheimer's had the diagnosis confirmed; 3 of the 15 patients had pathological evidence of Parkinson's disease in addition to Alzheimer's and the coexistence of Alzheimer's and Parkinson's disease had been recognized in two of these patients during life. Correct diagnoses were also made in the remaining 2 patients, 1
with changes consistent with alcoholism, the other with Parkinson's disease without Alzheimer's. These data are encouraging. Unfortunately the results cannot yet be generalized. These patients were evaluated after 3.5 years of symptoms, and they demonstrated scores on the MMSE in the moderately impaired range. Hence the data may not be applicable to the early diagnosis of mildly impaired patients. Moreover there is an evident selection bias in this sample. There was a paucity of patients with diagnoses seen in other series; specifically, only 1 percent of the cases had multi-infarct dementia, there were no cases of normal pressure hydrocephalus or brain tumor, and no indication of cases of Creutzfeldt-Jakob disease or Huntington's chorea, all of which are present in prospective series and in large autopsy series. Perhaps diagnoses of such conditions had been made by other physicians, reducing the likelihood of the families of patients with predominantly neurological conditions seeking the services of this clinic.

There are additional autopsy data in regard to the accuracy of the diagnosis of Alzheimer's disease or "primary degenerative dementia" (DSM-III equivalent of Alzheimer's) in patients who meet research diagnostic criteria. In three prospective series, such patients have been followed to autopsy; in the Berg (Berg et al., 1984) series 6 of 6 diagnoses were confirmed at autopsy, in the Raskind (personal communication) series, 13 of 14 diagnoses were confirmed, and in the Sulkava et al. (1983) series, 22 of 27 were
found to have Alzheimer's. The missed diagnoses include
Creutzfeldt-Jakob disease and Parkinson's disease, as well as two
instances of subcortical gliosis and two without specific changes.
If generally applicable, this experience would indicate that
clinical diagnoses carried out under these optimal conditions
approaches a 90 percent level of accuracy, a level of accuracy
that probably exceeds that reached by physicians for most
diseases. This 90 percent level of diagnostic accuracy is
particularly striking when compared to that reported by Jellinger
(1976) from the Neurological Institute of the University of
Vienna. Jellinger had obtained 1009 autopsies in patients who had
been found to be demented during life. Clinical diagnoses of
these patients during life included presenile (163 cases) and
senile (286 cases) dementia and cerebral atherosclerosis (560
cases); when compared to the pathological diagnoses, 45.3 percent
of the clinical diagnoses of presenile dementia (including patho-
logically Alzheimer's and combined Alzheimer's and multi-infarct
dementia cases) were correct, 77.6 percent of the diagnoses of
senile dementia were correct and 49.9 percent of the diagnoses of
cerebral atherosclerosis were correct (here accepting combined
Alzheimer's and multi-infarct dementia cases as correct diagnoses)
so that overall accuracy was 65.3 percent. One can speculate that
the availability of specific criteria and increasing clinical
awareness of the differential diagnosis of dementia has greatly
improved diagnostic accuracy.

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E. Summary—Differential Diagnosis

Subsequent to a diagnosis of dementia the responsibility of the physician is to identify which of the 70-plus conditions that may cause dementia is present. There is now a consensus that an adequate differential diagnosis requires a careful and thorough clinical evaluation, CT scan, and blood tests; in special circumstances a variety of other procedures, including lumbar puncture, electroencephalogram, and other tests, may be needed. On the other hand, there are other procedures which are interesting from a research perspective but whose diagnostic use has not yet been justified, procedures such as measurement of cerebral blood flow and positron emission tomography.

A major thrust of this work is to identify those conditions which may be treatable, such as normal pressure hydrocephalus, and those conditions which are potentially reversible, such as dementia secondary to drug intoxication or metabolic derangements. The clinical workup of the patient may cost close to $1000; however, the diagnostic workup is cost-effective (before consideration of the enormous impact on patient and family) if the result is identification of those cases with treatable and reversible causes.

Cerebral biopsy can provide a specific and definitive diagnosis in about three-quarters of the cases in which it is carried out. Because no specific diagnosis is reached after intensive microscopic study of the tissue in one-quarter of the
cases and because a 1 percent serious postoperative complication rate has been reported, this procedure is not widely used. Nevertheless, it can be a useful test in determining the diagnosis in cases in which significant diagnostic uncertainty exists. As potent medications for treatment of Alzheimer’s disease are discovered and precise diagnosis is needed, cerebral biopsy may need to be used more frequently in the future.

The most important conditions that produce dementia are Alzheimer’s disease, which accounts for more than one-half of the cases, and vascular or multi-infarct dementia, which accounts for another 10 to 20 percent of the cases. Specific clinical criteria have proved to be useful in improving the diagnoses of these conditions; thus, autopsy studies have shown a 90 percent clinical diagnostic accuracy in cases in which DSM-III criteria are met. There are, however, many patients with Alzheimer’s disease who do not meet these diagnostic criteria. Also, it is difficult at our present state of knowledge to correctly identify patients who have both Alzheimer’s disease and another dementing condition, particularly multi-infarct dementia or Parkinson’s disease. In each of these situations a peripheral marker for Alzheimer’s disease would be very useful. The search for such markers should have a high priority.
III. PROGNOSIS AND PROGNOSTIC ACCURACY

That the course of dementing illnesses is progressive and malignant, leading to early death, has been recognized for more than three decades, and formed part of the argument for differentiating dementing illness from other behavioral afflictions of the elderly (Roth, 1955; Katzman, 1976; Wang, 1978).

A. Estimates of Life Expectancy and Mortality

Wang (1978) compared the duration of disease and survival reported in several pathological series in the 1960s to survival anticipated from life tables: patients with senile dementia (mean age of onset 71.3 years) survived on the average 6.0 years, half of the expected survival of 11.1 years; patients with presenile dementia (mean age of onset 53.8 years) survived 6.9 years against an expected survival (based on the life statistics of an age- and sex-matched group) of 22.3 years; and patients with vascular dementia (mean age of onset 66.8 years) survived 3.8 years with an expected survival of 13.4 years. In the most recently published series, Barclay et al. (1985a,b) reported a mean survival time in Alzheimer patients of 8.1 years and 6.7 years in patients with multi-infarct dementia. Life expectancy in males is particularly affected. Barclay et al. found that at 5 years after diagnosis of Alzheimer's disease the actual survival relative to the anticipated survival of an age- and sex-matched group is about 60 percent in females and about 25 percent in males. This low rate of survival of males with dementia may in part account for
mortality differences between Alzheimer and multi-infarct patients because there is a higher proportion of males in the multi-infarct dementia group. The fact that mean survival was increased in Barclay's 1985 series as compared to Wang's 1960s series is consistent with the improved life expectancy of the elderly and better care for dementia patients, a phenomenon that Gruenberg has termed "the failures of success" (1977, 1978).

B. Predictors of Mortality

It is evident from these studies that dementia is a predictor of death and this has been confirmed in a variety of reports. Nielsen et al. (1977), who carried out a 15-year follow-up of the entire population of a Danish island, found that those with severe dementia at the beginning of the study were all dead within 5 years, and that survival was significantly shorter for both males and females with dementia. Similar results were obtained in a study of a large (500-bed) nursing home by Peck et al. (1978). In the same nursing home, Vitaliano et al. (1981), using a dichotomous (branching, two-choice) model, found that the presence of dementia, age over 80, and being male predicted mortality. In the Vitaliano study, functional status (also treated dichotomously) was not a predictor of death; T. Brown et al. (unpublished) found, on the contrary, that the Blessed et al. functional scale was the best predictor of mortality. Additional studies using sensitive functional scales are needed in this regard.

Bronchopneumonia was the major cause of death in dementia
patients in the nursing home study, an observation previously noted by Kay (1962). Peck noted (Peck et al., 1978; p. 307) that "Inability to communicate one's medical and nursing needs diminishes the prospect of being treated adequately by others, professionals and nonprofessionals."

C. Functional Decline

1. Course

Alzheimer's disease is characterized by progressive cognitive and functional decline. The disease may progress from a point where there are only mild cognitive deficits in a still functioning individual to the stage where the patient becomes mute, incontinent, and must be dressed, bathed, and fed. The decline is more or less continuous although quite variable between individuals. This variability must be emphasized. An early edition of Merritt's *A Textbook of Neurology* (1973) describes the course of the disorder as between 1 and 20 years. We have documented individuals with autopsy-proven Alzheimer's who have gone from mild forgetfulness to inability to give their name in 1 year and individuals with autopsy-proven Alzheimer's and mild dementia who showed no change on mental status scores over a 2-year period. In most individuals cognition and function decline together, but there are again significant individual differences; for example, one occasionally finds patients whose measured cognitive impairment is so great that they cannot give their own name yet are able to care for most activities of daily living without help.
2. Stages

Despite the variability in rate of progression and in individual cognitive functional components, it is sometimes convenient to characterize "stages" of the disorder. The most commonly used classifications are the Clinical Dementia Rating (CDR) devised at Washington University (Hughes et al., 1982) and the Global Deterioration Scale (GDS) devised by Reisberg et al. (1983).

Are there predictors (other than age and sex) of the rate of functional decline and of mortality? The data available from longitudinal studies are scanty. Information from the Duke longitudinal study suggested that changes in EEG occipital domain frequency, the WAIS deterioration quotient, and neurological changes were predictive (Wang, 1978). Berg et al. (1984) did not find EEG predictive, nor were changes on the CT scan or visual evoked responses predictive; the best predictors in their study were WAIS subtest scores, especially the digit symbol subtest, and an aphasia battery. Both Chui et al. (1985) and Mayeux (Mayeux et al., 1985) found that the presence of myoclonus and extrapyramidal signs unrelated to medication indicated poor prognosis.

Reisberg et al. (1983) reported a follow-up study of 41 community-residing Alzheimer patients. Although the numbers are small, the data may be of some practical use. Six patients died and six patients were institutionalized over an average 2-year period. Patients with only subtle clinical evidence of a decrement in cognitive performance (Global Deterioration Scale
Scores of 2 and 3) could be expected to be alive and residing in the community over a 2-year period. Patients who had begun to show functional deficits in such areas as shopping and handling their own financial affairs had a "guarded" prognosis: more than one-quarter of such patients either died or required institutionalization.

Although there is a paucity of information regarding the course and prognosis of Alzheimer's disease, longitudinal data concerning other dementias are almost nonexistent. Barclay et al. (1985a,b) found that patients with Alzheimer's disease and patients with multi-infarct dementia had comparable progression of behavioral and cognitive impairment and need for home care or institutionalization. This is in accord with findings in the Bronx Aging Study and in our own experience. We reviewed the extensive literature available on the results of placement of shunts in patients with normal pressure hydrocephalus (Katzman, 1977). Approximately 55 percent of patients showed significant improvement after surgery but this was in part offset by a 40 percent complication rate. As far as we are aware, there has been no long-term follow-up of such patients. Even more striking is the lack of data concerning patients with other forms of "reversible" dementia. We have already described evidence suggesting that some of the patients diagnosed as having pseudo-dementia later presented with a frank dementia presumably of the Alzheimer type. Larson et al. (1984) diagnosed reversible
dementias in 15 of 107 dementia patients. Eleven of these 15 showed initial improvement when treated. But only 3 patients with potentially reversible dementia became completely normal; their diagnoses included subdural hematoma, medication toxicity, and rheumatoid vasculitis. Particularly discouraging was the finding that 8 of the 15 patients with reversible dementia followed for more than 2 years developed progressive deterioration consistent with an Alzheimer-type dementia. The initial diagnoses of these patients included hypothyroidism (3), subdural hematoma (1), and medication toxicity (4). Thus it appears that patients with subclinical Alzheimer's may be more likely to develop excess disability with coincident metabolic or intracranial processes. However, even if improvement is short-lived, diagnosis and treatment are certainly desirable.

3. Excess Disability

Yesavage (1985) has emphasized the importance of excess disability that may occur when a patient with Alzheimer's or multi-infarct dementia has a concurrent depression, infection, or other medical condition. Larson et al. (1984) in their follow-up of 107 dementia patients noted 5 patients with the diagnosis of irreversible dementias who improved cognitively when coexistent diseases including congestive heart failure, depression, anemia, and Parkinson's disease were treated. These 5 patients remained demented but improved cognition was measurable on the Mini-Mental State examination and the dementia rating scale. Removal of
excess disability is important in improving function but there is no evidence that it alters the overall course of these disorders.

D. Predictors of Institutionalization

In considering predictors of institutionalization, one must distinguish between patients who live essentially alone in society—a significant proportion of the elderly—and those who live with family, one of whom acts as caregiver. The isolated patient may quickly reach a point where he or she cannot cope with such exigencies as shopping for food and requires help either from a companion or attendant or by being placed in a nonmedical facility, such as a board and care unit. Dementia patients with caregivers often remain at home until quite late stages of the disorder. The caregiver of a dementia patient is often a husband, wife, sister, daughter, or occasionally a friend or son. The high level of devotion that characterizes home care is suggested by the title of the standard manual, aptly titled The 36-Hour Day (Mace and Rabins, 1981). The predictors of nursing home placement in such circumstances are not the degree of cognitive impairment but the behavioral changes that result from the impairment and, more so, the ability of the family or other caregivers to cope. Thus in a study of 14 married male patients with Alzheimer's disease, the items most closely associated with nursing home placement were incontinence of bladder and bowel, inability to speak coherently, and inability to bathe and groom oneself (Hutton et al., 1985).
IV. PUBLIC HEALTH CONSEQUENCES OF MISDIAGNOSIS

A. Misdiagnosis of Dementia Syndrome

There is little doubt that the most dramatic impact of misdiagnosis occurs when a reversible cause of dementia is ignored. Consider the following 1985 misdiagnosis (case observed by one of the authors) that occurred in a Veterans' Administration (VA) medical center that serves as a teaching hospital for a major university. A 65-year-old World War II veteran was readmitted to the alcohol unit of the VA because he could no longer be cared for at a room and care facility. The patient, a single male, had been a successful university administrator elsewhere and had served as dean for student admissions; during an administrative upheaval in 1971 he had resigned in protest anticipating that he could obtain a similar job elsewhere. When the expectation was not met he was employed in temporary capacities, became depressed and admittedly alcoholic, depending in part on help from his family. He did not, however, develop such complications of alcoholism as cirrhosis or delirium tremens. He had been admitted to the VA 6 months earlier because of increasing memory problems and some difficulty in walking; his symptoms were attributed to his alcoholism and he was placed in a board and care unit. He quit drinking at this time but symptoms progressed; when readmitted it was found he could no longer walk without assistance and was sometimes incontinent. Admission to the VA skilled nursing facility was arranged. A neurological consultant, called just before transfer to the
nursing facility, noted the coincidence of gait apraxia, incontinence, and a dementia characterized primarily by partial disorientation and impairment of recent memory but intact language function. Review of the CT scan showed large ventricles which had been interpreted as indicative of atrophy. A diagnosis of normal pressure hydrocephalus was made and confirmed with isotope cisternography. Following a ventricular shunt to drain away the excess spinal fluid, gait promptly returned to normal, incontinence disappeared, and mental status examination became normal, although the patient felt that his memory was not intact. Because of the years of dependency, plans for discharge to his board and care facility have been arranged. The impact of the correct diagnosis in this case on the patient and upon the VA health system is evident. If one assumes only a 5-year period of life in the community rather than in a skilled nursing facility, more than $100,000 will have been saved. If the diagnosis had been made at the first admission, additional savings of several thousands of dollars would have been made. These dollars hardly reflect the untold hours of nursing care that an incontinent patient would have needed. Dementias as truly reversible as in this patient probably only constitute 3 percent of dementia patients but the existence of such cases fully justifies, in monetary terms alone, a full diagnostic workup of every dementia patient. However, much of the impact of misdiagnosis on the individual, family, and society occurs in less dramatic fashion. Let us consider several
of the consequences of such misdiagnosis.

1. Failure to Recognize Dementia

The most significant misdiagnosis may be failure to recognize dementia on the part of physicians who are concerned about other patient complaints. An ample number of surveys indicate that cognitive impairment in the elderly often goes unrecognized. As these surveys have not followed such patients to diagnosis, the consequences of such failures have never been systematically investigated. The potential consequences which are documented only in individual anecdotes indicate that some reversible dementias may go undiagnosed. Individuals with unrecognized progressive dementias may continue to run businesses and fail to transfer responsibilities when cognitive impairment first impairs judgement. In individual instances bankruptcies and losses of millions of dollars have occurred. A question increasingly raised in legal fights over wills is whether the deceased had Alzheimer's disease and whether the person was competent when the will was written. Individuals with early dementia who have significant professional responsibilities may make errors affecting others (for example, a radiologist who misinterprets X rays). Families will be put under stress. A spouse, not recognizing the reason for a change in behavior or personality of the afflicted person, may separate or sue for divorce. Underdiagnosis of dementia is particularly important at present as automatic retirement is no longer required. Because the incidence
of dementia is so strongly age-related it becomes critical to ensure the competence of those employed in responsible positions. Some industries are beginning to recognize this; for example, the identification of impaired physicians (the impetus is fear of drug dependence) has now become an obligation of medical staffs in some states. But society has not yet dealt with the need for periodic examination, the use of sensitive mental status tests, and other approaches to this problem.

2. Normal Aging and Dementia

A very different set of consequences occurs if normal aging is misinterpreted as dementia (as occurs in up to 5 percent of some referral series). A person so diagnosed may seek early retirement. Family plans may revolve around the wrongful presumption of progressive disability. The effects are particularly devastating in families with prior experience with Alzheimer's disease who fear the incident as another example of familial Alzheimer's; yet this is a situation in which a misdiagnosis is more likely to occur.

In earlier decades senile dementia was viewed not as a disease but as a concomitant of advanced age. The common stereotype of an elderly individual included reduced mental capacity, leading to reduced expectations as well as reduced demands on the aging individual. But the boundary between normal and pathological aging is being redrawn as a consequence of our recognition of dementia as a disease. We now accept older
individuals in responsible roles, including that of political leadership. Mandatory retirement age even for airline pilots is disappearing. In this environment there is now a need to define more precisely the boundary between normal aging and dementia.

3. Depression and Dementia

The misdiagnosis of depression and dementia is an occurrence that has attracted particular medical attention. It is evident that if a patient with depression is inadequately treated then there will be unnecessary disability. However, there has been so much emphasis upon this possible misdiagnosis that most patients with both depressive and cognitive symptoms will at least receive a trial of antidepressant medication. Reding et al. (1985) have called attention to a small group of patients in whom Alzheimer's disease had been underdiagnosed, in whom a diagnosis of "pseudodementia" has been incorrectly given. The consequences of this misdiagnosis might be similar to that of the veteran described earlier but may not be as great as in other cases of failure to recognize dementia since a different form of behavioral impairment will have been recognized and a patient is unlikely to have been permitted to continue with significant responsibilities until a trial of therapy is concluded.

4. Delirium and Dementia

Jarvik (1980) has pointed out the importance of the diagnosis of delirium which, if the underlying disease is untreated, carries on the one hand a mortality of up to 40 percent and on the other
hand can often be completely alleviated if proper diagnosis and treatment are carried out.

There is little likelihood of delirium and dementia being confused with each other in younger patients, but in the very elderly delirium may be dismissed as a chronic dementia, resulting in inappropriate treatment. There are no adequate studies of the rate of such misdiagnosis although all physicians who treat the elderly are familiar with instances in which this has occurred. Physician education would appear to be the most important mechanism available to prevent this misdiagnosis from occurring.

II. Misdiagnosis of Dementing Disorders

1. Misdiagnosis of "Reversible and Treatable Conditions": Drugs, Metabolic Disorders, Nutritional Deficiency, Normal Pressure Hydrocephalus, Subdural Hematomas, Infections

The importance of such conditions was noted by the NIA task force on reversible dementias (1980). Such conditions may account for up to 15 percent of patients with dementia. Recently two studies of the outcome of treatment of "reversible" conditions have been published (Larson et al., 1984; Freemon and Rudd, 1982). Unfortunately only a minority of such persons return to normal; in the Larson et al. (1984) study the figure was just under 3 percent of the total dementia sample. However, two-thirds of the patients with such diagnoses improved in these two series. Thus one can estimate that dementia can be completely reversed in 3 percent of
patients and improved in an additional 8 percent of dementia patients.

2. Failure to Recognize Vascular Etiology

From a public health point of view, the failure to differentiate vascular dementia from Alzheimer's disease has little consequence at present because the course is approximately the same, although vascular dementia may have a marginally greater mortality if age and sex are taken into account. Nevertheless from a treatment point of view there may be important differences.

3. Misdiagnosis of "Nontreatable" Disorders: Impact of Failure to Recognize the Presence of Dementia and Impact of Failure to Diagnose Depression

Suppose a "nontreatable" dementia is present but there is misdiagnosis within this broad category. In the case of failure to diagnose Creutzfeldt-Jakob (CJ) disease there may be a minimal safety hazard for persons caring for the patient; but there are documented cases where corneal donation from undiagnosed CJ patients has led to later infection of the recipient. A similar safety hazard exists with postmortem use of CJ pituitary as a source of growth hormone. Although the course of CJ is usually much shorter (often in terms of months) than Alzheimer's disease, in instances where there have been proven misdiagnoses (for example, in one of the patients in Raskind's autopsy series of patients meeting diagnostic criteria for Alzheimer's), the course may be longer, that is, 2 or 3 years.
Both progressive supranuclear palsy (PSP) and Alzheimer's are irreversible and progressive degenerative diseases of the brain, but misdiagnosis of PSP as Alzheimer's may have several consequences for the family and patient because the presentation and prognosis of the two conditions are so different. The most significant cognitive symptoms in PSP are usually in memory and slowness of response; because of the slowness of the patient they appear to be much more impaired cognitively than they are. If the family mistakenly believes the patient has Alzheimer's, a condition in which the cognitive deficit reflects a loss of neurons involved in basic processes of understanding as well as memory, then they may not make the effort to communicate with the PSP patient who is in fact intact in many intellectual spheres. On the other hand the PSP patient may have rapid progression of motor deficit and become wheelchair-bound at a time in the course of the illness when the Alzheimer patient is still quite mobile. Thus correct early diagnosis would help with the family's ability to plan for the future.

4. Misdiagnosis as Function of Age of Patient

As previously noted in the very elderly, Alzheimer's and vascular dementia constitute a greater percentage of the population of dementia patients and the reversible dementias occupy a smaller niche. For example, normal pressure hydrocephalus accounts for 5 percent of cases of dementia in patients under 70 and less than 1.5 percent of cases after age 70.
(Jellinger, 1976). Nevertheless, that reversible normal pressure hydrocephalus occurs after age 70 is well documented. What is not known about this condition, or about the other reversible causes of dementia, is the proportion of cases in the very elderly in which proper diagnosis and treatment leads to significant clinical improvement.

5. Failure to Recognize Excess Disability

A number of gerontologists have recognized the role of intercurrent problems, physical illnesses, depression and anxiety, and environmental stresses in increasing the disability of patients with primary dementing illnesses (e.g., Brody et al., 1974; Yesavage, 1985). Larson et al. (1985) have documented cognitive improvement in patients with excess disability whose concurrent problems have been diagnosed and treated. The importance of such efforts needs further documentation and physicians need to be made aware of these findings.

C. Impact on Families

1. Limitation on Reimbursement as Function of Diagnosis

The limitation of reimbursement as a function of diagnosis has been of great concern to families and the Alzheimer's Disease and Related Disorders Association, in particular when the diagnosis of Alzheimer's has been considered to be a "psychiatric" diagnosis and therefore not entitled to the same reimbursement schedules as ordinary medical disorders. There is currently great interest on the part of lawmakers in rectifying this situation. If
successful, the reverse might occur and Alzheimer's become a favored diagnosis. There is no doubt that such fiscal impact of diagnosis will influence the choice of diagnosis by the physician who feels that the first obligation is to the welfare of the patient. The extent to which current "misdiagnoses" represents such concern by physicians needs to be documented.

2. Home Health and Nursing Home Care

Home health and nursing home care are often not covered by Medicare or insurance carriers if the diagnosis of Alzheimer's is the primary one. It is easier to obtain care for one's patient if a diagnosis of congestive heart failure or urinary tract infection is made. Consequently the physician and family may seek secondary diagnoses to justify needed care. Again the system needs to be rationalized if diagnostic terms are to have meaning and reasonable statistics are to be obtained.

D. Diagnostic Accuracy and Public Health Policy

1. Costs

In an earlier section we analyzed the costs of the diagnostic workup. Is this diagnostic workup cost-effective from a purely fiscal standpoint or must justification rest on the social and individual benefits that accrue from correct diagnosis? Suppose we assume that a comprehensive single physician workup will cost $1100 for most patients and then we add another $150 to cover the costs of additional tests needed on a fraction of the patients, a total of $1250. The cost of diagnostic workup on 100 patients
would be $125,000. This is the equivalent of the cost of five
person-years of nursing home care in most jurisdictions. Based
upon the conservative estimate that 3 of the 100 dementia patients
have fully reversible dementias and an additional 8 have a
treatable process that can be arrested, the cost of the workup on
the 100 patients would be offset if these 11 patients saved on the
average 5 1/2 months of nursing home care. Thus a complete
diagnostic workup is likely to be more than cost-effective on a
purely dollar basis. But studies confirming that this happens
would be difficult to design and have not been carried out.

2. Legislation and Diagnostic Criteria for Alzheimer's Disease

Because of the recognition of the social importance of
Alzheimer's disease and the public interest in this disorder, an
interest fostered by local chapters as well as the national
Alzheimer's Disease and Related Disorders Association, legislation
specifically designed to benefit the Alzheimer patient and family
members has been introduced in the Congress and in many state
legislatures. Insofar as such legislation provides support for
model clinics (such as the six California State-supported
Alzheimer Disease and Diagnostic and Treatment Centers) or for
specialized care facilities (for example, day care centers,
respite centers, or special "restraint-free" units for agitated
Alzheimer patients), the problem of diagnostic accuracy may not be
of critical importance. The professional and community consensus
is to serve patients with related disorders as well as those with
Alzheimer's and to base client selection on functional considerations. In part, this attitude is a consensus of the acknowledged diagnostic uncertainty that exists at present. If, however, legislation includes patient or family entitlement provisions and specifies "Alzheimer's disease" then our present diagnostic uncertainty would create significant problems, particularly in regard to patients with "possible" Alzheimer's disease and to patients with mixed Alzheimer's disease and depression, vascular dementia, or Parkinson's disease. Based upon the authors' clinical experience, about 40 percent of Alzheimer patients belong to these categories. Hence, at our current state of clinical knowledge it would be counterproductive to establish specific diagnostic criteria for Alzheimer's or other specific dementing disorders. It would be appropriate, however, to establish guidelines based on DSM-III for the clinical syndrome of "dementia." It would also be appropriate on the basis of our current knowledge to require a comprehensive differential diagnostic workup to ensure that resources for patients with progressive irreversible dementia are not spent on individuals with a treatable or reversible cause of dementia.

3. Workup at Nursing Home Centers

Nursing home costs account for the greater portion of the public expenditures for demented individuals. In our own studies, two-thirds of individuals in a large urban nursing home were demented and 55 percent of all the autopsies showed Alzheimer's
disease. But among the demented patients in nursing homes are some with undiagnosed treatable or reversible disorders: normal pressure hydrocephalus, brain tumors, drug toxicity, or metabolic disorders. If one accepts as a reasonable goal for every patient with dementia a thorough diagnostic workup at least once in the course of his or her disease, then one must acknowledge that this goal has not been met for the majority of patients admitted to nursing homes in the past. Although this situation is constantly improving with the growing interest in dementia, it is also evident that this progress has occurred unevenly, particularly in the "old-old" patient. This situation would be significantly helped if—by legislation or regulation—a thorough diagnostic workup were required for every nursing home patient with dementia, either before admission or during the first month after admission.

4. DRGs for Physician Care of Dementia

Medicare may move to an overall physician DRG reimbursement scheme. If this does occur, a dementia DRG that allows for a full diagnostic workup, patient care, and family counseling should be considered. Under present DRG categories for inpatients, dementia patients are admitted under the category of "neurological disorder, other"—a category that would prevent the needed diagnostic workup of the dementia patients, a workup which is more costly than that for patients with certain other neurological disorders.
V. SUMMARY OF RECOMMENDATIONS

A. Physician Education Regarding Accepted Guidelines

--Use of mental status test in general medical patients.
--Workup of patients with dementia.
--Diagnostic criteria.

B. Medicare Guidelines

--Explicit statement requiring adequate workup as a protection of patient rights.

C. Diagnostic Accuracy

--Monitoring of trends in accuracy of diagnoses.

D. Development of Specific Diagnostic Tests

--Support of research seeking to identify a biological marker for Alzheimer's disease that can serve as a specific diagnostic test.

E. Research Regarding Areas of Diagnostic Uncertainty

--Research into the consequences of failure to recognize dementia (such as occurs in general medical settings).
--Longitudinal studies of outcome and prognosis of dementia patients with diagnoses other than Alzheimer's or vascular dementia.
--Clinical pathological verification of usefulness of MRI in diagnosing vascular dementias.
--Research into differential diagnosis of multi-infarct dementia from mixed multi-infarct dementia and Alzheimer's.
References


Katzman, R., Brown, T., Fuld, P., et al., "Validation of a Short Orientation-Memory-Concentration Test of Cognitive Impairment," 


Kurtzke, J.F., Epidemiology of Cerebrovascular Disease (Berlin: Springer-Verlag, 1969).

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Table 1.--Disorders Presenting as Dementia

ALZHEIMER'S DISEASE
With or without vascular disease
With or without Parkinson's disease
With or without other dementing diseases

OTHER IRREVERSIBLE DEMENTIAS

Degenerative Diseases
Pick's disease
Huntington's disease
Progressive supranuclear palsy
Parkinson's disease
Cerebellar degenerations
Amyotrophic lateral sclerosis (ALS)
Parkinson-ALS-dementia complex of Guam and New Guinea
Rare genetic and metabolic diseases (Hallervorden-Spatz, Kuf's, Wilson's, late-onset metachromatic leukodystrophy, adrenoleukodystrophy)

Vascular Dementias
Multi-infarct dementia
Cortical microinfarcts
Lacunar dementia
Binswanger disease
Cerebral embolism by fat or air

Anoxic Dementia
Cardiac arrest
Cardiac failure (severe)
Carbon monoxide

Traumatic
Dementia pugilistica (boxer's dementia)
Head injuries (open or closed)

Infections
Aquired Immune Deficiency Syndrome (AIDS)
AIDS dementia
Opportunistic infections
Creutzfeldt-Jakob disease (subacute spongiform encephalopathy)
AIDS (primary or opportunistic infections)
Progressive multifocal leukoencephalopathy
Post-encephalitic dementia
Behcet's syndrome

(Tab continued)
TREATABLE DEMENTIAS

Infections
- Herpes encephalitis
- Fungal meningitis or encephalitis
- Bacterial meningitis or encephalitis
- Parasitic encephalitis
- Brain abscess
- Neurosyphilis (general paresis)

Normal Pressure Hydrocephalus (communicating hydrocephalus of adults)

Space-Occupying Lesions
- Chronic or acute subdural hematoma
- Primary brain tumor
- Metastatic tumors (carcinoma, leukemia, lymphoma, sarcoma)

Multiple Sclerosis (some cases)

Auto-immune Disorders
- Disseminated lupus erythematosus
- Vasculitis

Toxic Dementia
- Alcoholic dementia
- Metallic poisons (e.g., lead, mercury, arsenic, manganese)
- Organic poisons (e.g., solvents, some insecticides)

Other Disorders
- Epilepsy
- Concentration camp syndrome
- Whipple disease
- Heat stroke

Note: Many of these disorders produce dementia in a small percentage of patients (e.g., epilepsy, tumors).

__________________________

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### Table 2.—Reversible Causes of Dementia

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Depression, Sensory deprivation, Other psychoses</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>Sedatives, Hypnotics, Anti-anxiety agents, Anti-depressants, Anti-arrhythmics, Anti-hypertensives, Anti-convulsants, Digitalis and derivatives, Drugs with anti-cholinergic side effects, Others (mechanism unknown)</td>
</tr>
<tr>
<td><strong>Nutritional Disorders</strong></td>
<td>Pellagra (B-6 deficiency), Thiamine deficiency (Wernicke syndrome, acute phase treatable), Cobalamin deficiency (B-12) or pernicious anemia, Folate deficiency, Marchiafava-Bignami disease</td>
</tr>
<tr>
<td><strong>Metabolic Disorders</strong></td>
<td>Hyper- and hypo-thyroidism (thyroid hormones), Hypercalcemia (calcium), Hyper- and hypo-natremia (sodium), Hypoglycemia (glucose), Hyperlipidemia (lipids), Hypercapnia (carbon dioxide), Kidney failure, Liver failure, Cushing syndrome, Addison's disease, Hypopituitarism, Remote effect of carcinoma</td>
</tr>
</tbody>
</table>

**Note:** Most of these disorders produce dementia in only a small percentage of cases.

---

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<table>
<thead>
<tr>
<th>Criteria</th>
<th>DSM-III</th>
<th>ADRDA/ NINCDS</th>
<th>NIA/ AMA</th>
<th>Jorm &amp; Henderson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of intellectual abilities....................</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>--Confirmed on mental status tests...............</td>
<td></td>
<td>R</td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Impaired social or occupational function...</td>
<td>R</td>
<td></td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Memory impairment...................</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Impairment of additional area of cognition (e.g., language, construction, praxis or personality change)...</td>
<td>R</td>
<td>+</td>
<td>R</td>
<td>•</td>
</tr>
<tr>
<td>State of consciousness not clouded--alert, awake</td>
<td></td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Evidence of organic factor or absence of conditions other than organic mental syndrome........</td>
<td>R</td>
<td></td>
<td></td>
<td>R</td>
</tr>
</tbody>
</table>

Note: R = required, + = desirable/not required.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total N</th>
<th>Orig Diag</th>
<th>Outcome Diag</th>
<th>Misclassifica</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dem</td>
<td>Nondem</td>
<td>Dem</td>
<td>Nondem</td>
</tr>
<tr>
<td>Kendall, 1974</td>
<td>98</td>
<td>98</td>
<td>0</td>
<td>75</td>
<td>23</td>
</tr>
<tr>
<td>Ron et al., 1979</td>
<td>51</td>
<td>51</td>
<td>0</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>Smith &amp; Kiloh, 1981</td>
<td>200</td>
<td>200</td>
<td>0</td>
<td>164</td>
<td>36</td>
</tr>
<tr>
<td>Rabins, 1981</td>
<td>41</td>
<td>41</td>
<td>0</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>Reding et al., 1984</td>
<td>56</td>
<td>56</td>
<td>0</td>
<td>55</td>
<td>1</td>
</tr>
<tr>
<td>Larson et al., 1985</td>
<td>200</td>
<td>200</td>
<td>0</td>
<td>198</td>
<td>2</td>
</tr>
</tbody>
</table>

*Sources: Listed in first column.

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Table 5.—Disorders Producing Dementia: Diagnoses in Nine Clinical Series*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Group</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer</td>
<td>499</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Parkinson</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Vascular</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL ALZHEIMER</strong></td>
<td></td>
<td>517</td>
<td>65.9</td>
</tr>
<tr>
<td>Vascular (MID)*</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntington</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSP</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALS</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kufs</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-anoxic/CO</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-traumatic</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-encephalitic</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creutzfeldt-Jakob</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL &quot;OTHER IRREVERSIBLE&quot;</strong></td>
<td></td>
<td>134</td>
<td>17.1</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal infections</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subdural</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL &quot;TREATABLE&quot;</strong></td>
<td></td>
<td>82</td>
<td>10.5</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>21</td>
<td></td>
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</tr>
<tr>
<td>Metabolic</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium/PTH</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-12</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL &quot;REVERSIBLE&quot;</strong></td>
<td></td>
<td>37</td>
<td>4.7</td>
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<tr>
<td>Cause uncertain</td>
<td>14</td>
<td></td>
<td>1.8</td>
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<tr>
<td>Total N</td>
<td>784</td>
<td>784</td>
<td>100</td>
</tr>
</tbody>
</table>

*Multi-infarct dementia.

**SOURCES:** Series include Marsden and Harrison (1972), Freeman and Rudd (1982), Coblentz et al. (1973), Smith and Kiloh (1981), Rabins (1981), Delaney (1982), Garcia et al. (1981), and Larson et al. (1985).

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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>&lt; 70 Years of age</th>
<th>&gt; 70 Years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Alzheimer atrophy</td>
<td>73</td>
<td>44.8</td>
</tr>
<tr>
<td>Vascular</td>
<td>25</td>
<td>15.4</td>
</tr>
<tr>
<td>Mixed Vasc/Alzheimer</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Pick</td>
<td>15</td>
<td>9.2</td>
</tr>
<tr>
<td>Parkinson</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>Olivo-Ponto-Cerebellar</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>Wernicke encephalopathy</td>
<td>6</td>
<td>3.7</td>
</tr>
<tr>
<td>Post-anoxic</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Post-traumatic</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>9</td>
<td>5.5</td>
</tr>
<tr>
<td>Tumor</td>
<td>14</td>
<td>8.6</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob</td>
<td>5</td>
<td>3.1</td>
</tr>
<tr>
<td>Inflammatory (MS/general paresis)</td>
<td>9</td>
<td>5.5</td>
</tr>
<tr>
<td>Unclassified or normal</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Total N</strong></td>
<td>163</td>
<td></td>
</tr>
</tbody>
</table>

Table 7.--Diagnostic Cerebral Biopsies

<table>
<thead>
<tr>
<th>General series</th>
<th>Number of cases</th>
<th>Diagnostic</th>
<th>Abnormal but not diagnostic</th>
<th>Normal</th>
<th>Deaths</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antunes (1963)</td>
<td>28</td>
<td>15</td>
<td>6</td>
<td>7</td>
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<td></td>
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<tr>
<td>Eadie (1964)</td>
<td>50</td>
<td>15</td>
<td>14</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blackwood &amp; Cumings (1966)</td>
<td>178</td>
<td>77</td>
<td>66</td>
<td>35</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Groves &amp; Möller (1966)</td>
<td>117</td>
<td>44</td>
<td>37</td>
<td>36</td>
<td>1*</td>
<td>1**</td>
</tr>
<tr>
<td>Kaufman &amp; Catalano (1979)</td>
<td>46</td>
<td>17</td>
<td>22</td>
<td>7</td>
<td>1'</td>
<td>5''</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>419</strong></td>
<td><strong>168</strong></td>
<td><strong>145</strong></td>
<td><strong>106</strong></td>
<td><strong>40</strong></td>
<td><strong>34.5</strong></td>
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<table>
<thead>
<tr>
<th>Dementia series</th>
<th></th>
<th></th>
<th>No specific changes</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Green et al. (1952)</td>
<td>15</td>
<td>8</td>
<td>7</td>
<td>0</td>
<td>1''</td>
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<tr>
<td>Smith et al. (1966)</td>
<td>59</td>
<td>42</td>
<td>17</td>
<td>1'</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bowen et al. (1982)</td>
<td>36</td>
<td>28</td>
<td>8</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Katzman et al.</td>
<td>23</td>
<td>19</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(update &amp; series)</td>
<td><strong>Total</strong></td>
<td><strong>133</strong></td>
<td><strong>97</strong></td>
<td><strong>36</strong></td>
<td><strong>1</strong></td>
<td><strong>3</strong></td>
</tr>
<tr>
<td>%</td>
<td>73</td>
<td></td>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Cardiac arrest, 15 months.
**Hemiparesis, cleared.
'Aspiration.
''3 pneumonia, 1 pulmonary embolus, 1 focal epilepsy.
"Subdural hematoma with pneumonia.
**"Postoperative.
"Coblenz et al. (1973), Kaplan et al. (1985), Crystal et al. (1982), and Koto et al. (1977).
""No report.

**SOURCES:** Listed in first column.

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<table>
<thead>
<tr>
<th>Criteria</th>
<th>DSM-III/PPD</th>
<th>Alzheimer's probable</th>
<th>Alzheimer's possible</th>
<th>Alzheimer's definite</th>
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<tbody>
<tr>
<td>Dementia present on:</td>
<td></td>
<td>R</td>
<td>R</td>
<td>R</td>
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<tr>
<td>-clinical evaluation...</td>
<td>R</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>-mental status tests...</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive deficit in two or more areas</td>
<td>R</td>
<td>R</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Impairment of function</td>
<td>R</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Onset age 40 - 90</td>
<td>R</td>
<td>R</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Insidious onset</td>
<td>R</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Progressive course</td>
<td>R</td>
<td>R*</td>
<td>R*</td>
<td></td>
</tr>
<tr>
<td>Exclusive of systemic or brain disorders that may produce dementia</td>
<td>R</td>
<td>R</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Exclusive of depression and other psychiatric disorders</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tests:</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Normal LP</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>EEG normal or slowing</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>CT atrophy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Absence of focal motor or sensory changes</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Histological changes characteristic of Alzheimer's</td>
<td></td>
<td></td>
<td></td>
<td>R</td>
</tr>
</tbody>
</table>

Note: R = required, + = desirable/not required.
*Accepts plateaus.


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Congress of the United States
Office of Technology Assessment

LOSING A MILLION MINDS:
CONFRONTING THE TRAGEDY OF ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

Contractor Documents

Part 1:
Epidemiology, Diagnosis, and Basic Science

March 1987

The Epidemiology of Dementing Disorders, Peter S. Cross and Barry J. Gurland,
The Columbia University Center for Geriatrics, Gerontology and Long-Term Care,
New York, New York 10032

Accuracy of Diagnosis and Consequences of Misdiagnosis of Disorders Causing
Dementia, Robert Katzman, Bruce Lasker and Nanay Bernstein, School of
Medicine, University of California, La Jolla, California 92033

Basic Neuroscience and Disorders Causing Dementia, Donald L. Price, The Johns
Hopkins University School of Medicine, Baltimore, Maryland 21205-2182

These are contractor documents that were used in preparing OTA's final
Assessment Report. OTA makes these contractor documents available for the use
of readers desiring a more detailed or technical discussion of an issue than can
normally be accommodated in our final Report. As an OTA contractor documents,
they have not been reviewed or approved by the Technology Assessment Board.
The findings and conclusions expressed are those of the authors and do not
necessarily reflect the views of OTA, the Advisory Panel or the Technology
Assessment Board.