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# The Evolution of the Diagnosis of Dementia: Past, Present, and Future

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It is perhaps surprising to note the improvement in differential diagnosis of dementing illnesses that has occurred in the past several years. Less than a decade ago a number of retrospective studies had reported a 30%–50% error rate in diagnosis of dementia [4, 17], whereas in the past 2 years the error rate has been reduced to 15%–20% [20]. A significant achievement; but an important gap yet to be closed.

The apparent delay in the development of an adequate differential diagnosis had its roots, perhaps, in the fact that this topic has not always been the favorite enterprise of neurologists. In the 1885 edition of Gowers' *Diseases of the Nervous System* (a text 1356 pages long), only 16 lines are spent on "senile dementia" and only one page on general paresis. Of course, many of the degenerative diseases of the brain had not yet been discovered. But lack of interest persisted. In the 1951 edition of Walshe's text (*Diseases of the Nervous System*), there is still no description of the differential diagnosis of dementia, no description of Alzheimer's disease, no description of dementia as associated with subacute combined degeneration, and only three pages on general paresis. Merritt's and Brain's texts began a more systematic coverage of these diseases. It is only in the past decade that this topic has become fully accepted and adequately described in the majority of neurological texts. One can only speculate on the cause of this lack of interest. Had dementia simply been abandoned to psychiatrists (most of whom – with notable exceptions – were themselves not interested), was dementia simply considered to be part of normal aging, or had the localizationist interests of neurologists become so great that generalized affections of the brain had to be ignored?

Our current understanding of the clinical entity, dementia, can be traced back to the pioneering work of Roth in recognizing that mental illness in the elderly was due to multiple and separable disorders, one of which was dementia, and that differentiating such disorders was critical toward understanding prognosis. Alzheimer's disease accounts for 50%–55% of the cases of dementia; vascular disease for another 20%–25%. However, the clinician must also consider over 60 additional disorders which may cause dementia [5, 9–11]. The latest addition to this list has been AIDS;

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the HTLV III virus has been identified in brains of patients who manifest dementia and pyramidal tract signs [7, 19].

There is now a generally accepted formal definition of dementia contained in the 1980 edition of the *Diagnostic and Statistical Manual of the American Psychiatric Association* (DSM III) [1]. The definitions in DSM III of dementia, depression, and amnestic syndrome have played a role in improving diagnostic accuracy. Dementia, as defined in DSM III, requires the presence of both intellectual decline and impaired functioning; a critical aspect of the definition is that memory plus other areas of cognition must be altered; and the patient must be alert, without a fluctuating level of awareness.

Particular emphasis has been paid by a number of authors to "pseudodementia," that is, depression presenting as memory and related problems [3, 24]; in fact, in several of the retrospective series, this has been the major source of diagnostic error [4, 17]. It is our experience that using DSM III diagnoses for dementias and depression and recognizing that older individuals with unipolar or bipolar depressions may have secondary memory deficits (dementia in depression) permits the interested clinician to separate these syndromes with accuracy.

## Diagnostic Workup

A consensus has also developed in the United States as to the diagnostic procedures appropriate for the diagnosis of dementia. The presence of dementia is established by history and mental status examination; neuropsychologic evaluation may be needed. The differential diagnosis of the sixty or more disorders that may be presented as dementia requires the history, physical and neurologic examination, and the following special procedures: CT; EEG; X-ray of the chest; and electrocardiogram. A blood count, biochemical screen, serologic test for syphilis, thyroid function tests, and vitamin $B_{12}$ level are obtained where possible. With the availability of automated tests, these procedures have often been carried out before the dementia patient is referred to a neurologist. The yield today from the blood tests is small, perhaps providing a diagnosis in 1%–2% of the cases; but for that 1%–2%, these tests are very important since many of the conditions are treatable. Often a spinal tap and a neuropsychological evaluation is useful. Special procedures useful in evaluation of patients with suspected normal pressure hydrocephalus include monitoring of intracranial pressure, infusion tests, and isotope cisternography.

## The Mental Status Test: Neuropsychological Evaluation

A development that occurred in parallel with the characterization of the dementia syndrome was the development of formal mental status tests. There is a direct line from Mayer-Gross' observations on the *Symptoms of organic brain disease* published in 1931 [13] and the 1937 Mayer-Gross and Guttman *Schema for the examination of organic cases* [14] to the three tests most widely used in current dementia research – the Folstein et al. mini mental status; the Blessed et al. orientation information concentration test; and the Mattis dementia rating scale [2, 12, 22]. All three of these

added advantages of absence of artifact due to bone and better visualization of white matter changes. Visualization of anatomic landmarks is greatly enhanced, especially if scan time is increased. Hence, MRI may replace CT scan in the differential diagnosis of dementia if experience bears out its potentialities.

*MRI and Vascular Dementia.* MRI has a particular role to play in the diagnosis of vascular dementia since it is capable of identifying a high proportion of old infarct and lacunes. Tomlinson et al. [22] demonstrated that dementia occurs with multiple strokes when more than 50–100 g of cerebral hemisphere is destroyed. It should become possible to estimate the volume of tissue destroyed on MRI. If this turns out to be clinically feasible, then multi-infarct dementia will become an MRI diagnosis.

*Binswanger's Disease.* Rosen et al. [18] demonstrated that the CT picture of altered appearance of white matter was consistent with the pathologic demonstration of demyelination in hemispheral white matter in a patient with Binswanger's disease. This report has led to an increase in the number of patients diagnosed during life with this disorder. However, it is found that some elderly without the symptoms of Binswanger's disease show white matter attenuation; this has been termed the "leukoencephalopathy of normal aging." This phenomenon is accentuated on MRI. Adequate clinical pathologic studies have not been carried out. The need for correlation of clinical and anatomic features with the CT and MRI images, suggesting disease of white matter both in patients with symptoms and in normal elderly with abnormal white matter on scans, should be a high priority. A specific diagnosis based upon imaging may be possible; but if not, the nature of the white matter change in normal aging – a quite unexpected finding – needs to be defined.

## Ischemic Score

While awaiting such studies, a most useful instrument is the Hachinski ischemic score. First devised upon the basis of clinical experience, later confirmed on the basis of a retrospective pathologic study. We currently have the opportunity of investigating the usefulness of the ischemic score in a prospective study of the development of dementia in 488 initially nondemented 80-year-olds. To date, 26 subjects have developed Alzheimer's disease, and 11 vascular dementia. Both the original Hachinski scoring system and the Rosen modification separated patients with Alzheimer's disease from those with vascular dementia, but many of the scores were borderline. However, these ischemic scores do not take into account CT data; in our series, 10 of the 11 subjects who developed vascular dementia had positive CT scans. Kawas has proposed a new scoring system which utilizes items from the original 13-item Hachinski system and, in addition, gives weight to the CT scan findings (Table 1). This scoring system proved to discriminate between the subjects in our study who developed Alzheimer's disease and those with vascular dementia.

## Evoked Responses

Primary sensory systems remain intact in most dementing illnesses, with the obvious exceptions of subacute combined degeneration due to vitamin $B_{12}$ deficiency and multiple sclerosis. Event-related potentials that are generated in association cortex

**Table 1.** Comparison of ischemic scores

|  | Hachinski | Rosen | Kawas[a] |
|---|---|---|---|
| Abrupt onset | 2 | 2 | 2 |
| Stepwise deterioration | 1 | 1 | 1 |
| Fluctuating course | 2 |  |  |
| Nocturnal confusion | 1 |  |  |
| Relative preservation of personality | 1 | 1 |  |
| Depression | 1 |  |  |
| Somatic complaints | 1 | 1 |  |
| Emotional incontinence | 1 | 1 |  |
| History of hypertension | 1 | 1 |  |
| Associated arteriosclerosis | 1 |  |  |
| History of stroke | 2 | 2 | 2 |
| Focal neurologic symptoms | 2 | 2 | 2 |
| Focal neurologic signs | 1 | 1 | 2 |
| CT (or MRI) evidence: |  |  |  |
|  Definite infarct |  |  | 2 |
|  White matter change (Binswanger's) |  |  | 1 |

[a] C. Kawas and R. Katzman (to be published)

might be expected to be a sensitive indicator of early dementia. The potential that has proven of most interest has been the P300, a positive potential with a latency of 300 ms in young adults, produced in response to infrequent or unexpected stimuli. There is no doubt that P300 is altered in Alzheimer patients as a group, compared with age-matched normal subjects. However, as with so many tests, it is not yet useful in individual cases, both because of normal variations and because of difficulty in obtaining these potentials in all subjects. Current investigations are directed toward identification of stimulus parameters that might improve the sensitivity and selectivity of this procedure.

## Cerebral Blood Flow

CBF, determined by clearance of inhaled $\gamma$-emitting xenon, reflects the degree of dementia rather than the specific disease.

## Alzheimer's Disease

### Diagnostic Criteria and Peripheral Markers

A task force on Alzheimer's disease, established about 18 months ago by the U.S. Department of Health and Human Services, developed a new nomenclature with specific criteria for the diagnosis of Alzheimer's disease [15]. The term "definite Alzheimer's" is reserved for those instances in which there is histologic confirmation of the disorder. "Probable Alzheimer's" describes the patient whose clinical course and findings are characteristic: an insidious onset, continuous progression, and involvement of two or more areas of cognition in a patient who is otherwise healthy and

alert, and in whom other disorders that might produce dementia have been ruled out. These criteria are similar to previously described research diagnostic criteria. The term "possible Alzheimer's" then covers the approximately 40% of Alzheimer patients who also have an atypical course – for example, patients who present with primary loss of one area of cognition.

### Markers for Alzheimer's Disease

Perhaps the most important advance in the diagnosis of dementia would occur if a highly specific biochemical marker of this disease were found. Such a marker does not now exist. However, a variety of procedures other than cognitive measures will differentiate groups of Alzheimer patients from groups of normal subjects; e.g., atrophy on CT. Other inconsistent measures include P300 evoked response, degree of immunosuppression, CSF acetylcholinesterase, and choline uptake by red cells. Would a panel of such markers increase diagnostic accuracy? The authors doubt that it would, but this approach should be further explored.

## Dementias of Unknown Cause

Our knowledge of dementing disorders is not complete. In several autopsy series, about 5% of the cases reported to have had dementia during life do not have evidence of pathologic changes at postmortem. The clinical course often resembles that of Alzheimer's disease. To what extent do these cases represent dementias of systemic or metabolic origin not properly worked up during life? To what extent do they represent neurodegenerative diseases whose anatomic or biochemical pathology has not yet been recognized?

## Summary

Significant advances in the differential diagnosis of dementing illnesses have occurred in the last decade as clinical syndromes have been better defined, as the importance of clinical tools, including the mental status examination, has been appreciated, and as new technologies, especially the CT, have become available. A useful method of incorporating CT findings in the differential diagnosis of vascular dementia is described. Further advances are to be expected with the utilization of MRI. A major deficiency remaining is the lack of a specific peripheral marker of Alzheimer's disease.

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