SCIENTIFIC SECTION

REVIEW ARTICLE

A rational approach to dementia

ALLAN H. ROPPER, MD

Dementia is a common problem facing all medical practitioners and it frequently results in hospitalization and death. This review provides a framework for dealing with dementia in clinical practice that is based on both traditional concepts and recent advances in the understanding of the problem. Distinguishing at the bedside between dementia and other disorders of intellect is emphasized. The main causes of dementia and their clinical characteristics are reviewed and a rational approach to definitive diagnosis is developed. Simple, effective symptomatic forms of therapy are described.

La démence est un problème que doivent fréquemment affronter tous les médecins et elle entraîne souvent l'hospitalisation et la mort. Cette revue offre un mode structuré de faire face à la démence en pratique clinique qui s'appuie aussi bien sur les notions traditionnelles que sur les progrès récents dans la connaissance de ce problème. On insiste sur les façons de distinguer, au chevet du malade, entre la démence et les autres dérèglements de l'intellect. Les principales causes de la démence et leurs caractéristiques cliniques sont passées en revue et une approche rationnelle à son diagnostic définitif est élaborée. On décrit des formes simples et efficaces de traitement symptomatique.

Dementia, the symptom complex of progressive mental deterioration, is one of the most ubiquitous problems facing physicians. In Europe conservative estimates indicate that up to 15% of persons over 65 years of age are afflicted.[1] If the same is true in the United States, 1 million persons in that country have some form of dementia, and approximately half have Alzheimer's disease.[2] Dementia is associated with a diminished life expectancy,[3,4] and some authors consider it to be one of the five leading causes of death in the United States and attribute to it almost 100 000 deaths a year in persons over the age of 65 years.[5]

The medical care of most persons with dementia is undoubtedly primarily in the hands of general practitioners rather than neurologists. Because of the gradual onset of dementia, its complexity and the assumption that senescence and deterioration are untreatable, dementia is probably often undiagnosed in its early stages and its symptoms go untreated. The current emphasis on "curable dementia" has also obscured the relatively simple, conservative help that the physician can offer the incurably demented patient and his or her family. In several careful studies of patients with dementia definite causes were found in nearly all cases, and the dementia proved to be treatable in 15%[6] to 30%[7] of patients. Because the patient populations were selected, this estimate may be slightly optimistic, however.

A rational approach to dementia depends on understanding the clinical states of the disordered mind and the associated neuropathologic abnormalities. The following is a review of the clinical phenomena that constitute dementia, as well as other states that should be distinguished from it. A list of the commonest causal diseases and their clinical and laboratory features is followed by a discussion of useful ways of treating the symptoms based on recent experience in the field.

Reprint requests to: Dr. Allan H. Ropper, Department of neurology, Massachusetts General Hospital, Fruit Street, Boston, MA 02114, USA

Syndromes to be distinguished from dementia

Dementia can be defined as a general deterioration of mental function; the process must be sustained and represent a clear decline from previous functioning. The following states should be distinguished from dementia (Table I):

Senescent forgetfulness

Senescent forgetfulness,[8] which some consider a benign concomitant of ageing, is common and is not usually pathologic or

Table I—Conditions to be differentiated from dementia

Common
Senescent forgetfulness
Confusion due to reversible metabolic derangement
Aphasia
Depression
Unusual
Schizophrenia
Hysterical pseudodementia
Ganser's syndrome
Mental retardation

progressive. The forgotten items or events belong to the remote past or are a small part of a larger recalled experience and may be available to the mind at other times. Senescent forgetfulness does not seem to be associated with the functional disability or reduced life expectancy of dementia, but in individual cases it may be hard to distinguish between the two conditions, and there may prove to be some organic basis for both.

Whether the many elderly people who cannot recall or perform tasks as well as they could formerly have mild dementia is unresolved. It is probably best to accept benign senescent forgetfulness as a syndrome, recognizing that it becomes a problem only when it causes functional disability or is the harbinger of progressive dementia.

Confusion and delirium

The term confusion is imprecise but denotes clouding of the senses, various degrees of disorientation and inability to think clearly. Minimally confused individuals may be roughly oriented and able to carry on a simple conversation; close questioning and observation may be necessary to uncover their confusion. Severely confused persons are unable to care for themselves or to follow the simplest commands because registration of immediate events is impaired. Confusion can be thought of as the mildest level of depression of consciousness. It is a major component of the dementia syndrome, although it can also result from a toxic or metabolic encephalopathy.

When a demented individual undergoes stress from a new environment, another illness or a medication, he or she may become more confused; however, the dementia is separate from the confusion. The state of well compensated dementia with superimposed confusion has been called beclouded dementia[9] and is the most common cause of confusion in a general medical service. The term "sundowning", meaning the appearance of confusion at night, also applies to this state.[10] Careful enquiry into the premorbid capacities of such persons reveals limited adaptability to new situations, frequent forgetfulness and behavioural changes such as periodic depression or anxiety. Autopsy will reveal Alzheimer's senile plaques and neurofibrillary tangles in the hippocampal cortex of many such individuals. The physical stress that produces beclouded dementia may be minor — a hip fracture, a minor surgical procedure under local anesthesia, a mild respiratory or gastrointestinal tract infection, or even emotional stress, such as grief, personal disappointment or enforced relocation.[11] Thus, the onset of confusion in a demented but mentally functioning person should prompt a search for a cryptic illness. Acute confusion may persist after the stress is removed, but 50% of the persons who are affected enough to require hospital admission will recover within several weeks or months.[12] Of the rest, some will remain confused, with mental deterioration, so that they are indistinguishable from the chronically demented.

Delirium is an acute, florid, reversible form of confusion. Its classic signs — agitation, hallucinations, motor hyperactivity and inattention — are easy to recognize. The delirious individual — for example, with delirium tremens — is alert, tremulous, agitated, at the mercy of external stimuli and autonomically overactive. Occasionally a quiet period supervenes. This toxic state is reversible and has no consistent neuropathological features.

Aphasia

Aphasia may cause difficulty in the differential diagnosis of dementia.[13-15] Except in rare cases of dementia, speech is not lost but is deranged as part of the impairment of all cognitive functions; nonverbal memory, facility with nonverbal tasks, spatial orientation and general behaviour are all affected. In contrast, the person with aphasia due to focal cerebral disease, such as a stroke, has difficulty only with language and language-related behaviour. The speech of a person with jargon aphasia, which results from lesions in Wernicke's area, may sound to the uninitiated ear like that of a delirious or demented person: it is voluble, fluent, effortless and articulate, but meaningless. Elements of normal speech may be amusingly combined to form nonsense words or neologisms. Substitution of words that have similar sounds or similar meanings may occur. All these features are the result of a long-standing lesion in the perisylvian region of the dominant hemisphere[16] or the thalamus.[17] The sudden onset and isolated nature of the deficit distinguish Wernicke's aphasia from dementia even when no other neurologic signs are present. Accompanying focal cerebral deficits, such as hemiparesis, hemisensory deficit or visual field loss, further distinguish aphasia from delirium and dementia.

There is a characteristic gradual impairment of language elements in many chronic dementias. Palilalia[18] and echolalia,[19] in which the patient repeats verbatim the syllables and words heard, are manifestations of bilateral or diffuse cerebral disease; hence, they are not aphasias but are frequently seen in severe dementia. Rare cases of dementia begin with an aphasia indistinguishable from that caused by stroke, but the onset is generally gradual.[20]

Abulia and amphigory

Two other nonaphasic disorders of language, abulia and amphigory, can occur with dementia. Abulia is a type of dementia in which all actions are performed in a delayed and laconic manner.[9] Questions are answered correctly, but only after a long pause, during which the patient seems preoccupied. For example, patients will count with long pauses between strings of numbers, always resuming at the correct place. When memory can be tested it is found to be normal. The state is caused by hydrocephalus, multiple bilateral lacunar strokes or lesions in both frontal lobes.

The term amphigory was coined by Fisher[21] to denote an incessant, nonsensical speech with normal language in an alert patient. Responses take the form of a prolonged discourse lasting from minutes to hours, with shifts from subject to subject, like the babbling of a 2- or 3-year-old child. The following is an example from one patient: "It kind of seems to me that I'm staying at home minding my own business without you throwing at me. Is this a boy? No, the hair is too long. It doesn't make any difference. It's there, and it's for them to take out. They've got the gong anyway." Amphigory has occurred following medial temporal lobe damage, with centrally placed tumours, occasionally in advanced Alzheimer's disease and in a few cases without evident neuropathologic changes.[21]

Psychiatric disorders

Psychiatric disorders are the main problems confounding the differential diagnosis of dementia.[22] Depression, mild or severe, is the biggest problem because intellectual impairment may appear to result from this disorder.[23] Speech is slow and there may be a paucity of ideas and little spontaneity. When depression is severe the individual becomes hypokinetic and virtually mute. Some observers have found an impairment of short-term memory associated with depression that improves as the depression lifts.[24]

Guidelines exist for distinguishing depression from dementia. With a depressive illness the history is more precise and the date of onset more certain; for example, mental deterioration of recent onset with rapid progression is more characteristic of depression than dementia.[25] Bedside examination of a depressed patient will show that orientation, memory and other intellectual functions are normal, but these findings may require persistence by the examiner. Somatic symptoms, such as anorexia, weight loss, insomnia and headache, are typical of early depression but not of dementia.[26] The depressive mood is pervasive in depression and less labile than in dementia. Finally, spontaneous complaints from the patient of "trouble remembering" or "losing my mind" are much more often related to depression than to dementia.[26] Twelve of 22 patients in one series[27] and 15 of 106 in another[6] who were thought to be demented were ultimately found to be depressed. This error is made more frequently in general practice than is generally recognized, and the distinction of these conditions deserves special emphasis since depression responds to specific treatment.

Schizophrenia is occasionally misconstrued as dementia because of the characteristic illogical thinking and inability to communicate meaningful ideas.[28] Schizophrenia nearly always occurs before a patient is 40 years old and can be clearly dated by family or friends. A bland, unemotional mood is seen in some cases of schizophrenia but only in advanced cases of dementia. The "word-salad" characteristic of schizophrenia, which is another source of diagnostic confusion, is not encountered in acutely psychotic patients but in those who are chronically ill and confined to hospital. Their language is often filled with rhymes, peculiar tangential associations or the addition of a fixed nonsense syllable to the end of each word.[14]

Hysterical pseudodementia probably does exist but is rarely encountered in general medical practice.[25,29] Isolated hysterical amnesia generally occurs in psychopathic persons, sometimes after a recent crime, who state that they do not know their own names or recall recent events. Complete loss of memory and identity in a patient who otherwise behaves normally occurs only in this condition. In a related condition, Ganser's syndrome,[30] patients act as though insane, but in a transparently absurd way, giving senseless answers in a way that they believe an insane person would. For example, while clearly aware of the question, they might make errors in simple arithmetic by one or two digits or answer that it is 9 am when an adjacent window shows it to be dark outside.

Mental retardation can be distinguished from dementia on the basis of age, affect and progression. The retarded person has an immature affect, a small and specialized fund of information related to his or her home environment and an inability to calculate or to comprehend tasks, such as reciting digits in the reverse order from that given.

Behavioural characteristics of dementia

Several attitudes have been suggested in the psychiatric literature as signs of early dementia:[25] for example, expressing too much satisfaction from trivial accomplishments; struggling too hard to perform at a level that would previously have required little effort; referring to notes, guides and calendars too freely; expressing disinterest in a topic and stating that sons or daughters keep up with it; and indicating a subsequent return to a question but neglecting to return. Several authors have suggested that the inability to maintain an appropriate threshold for frustration, to employ psychologic defence mechanisms and to express needs and drives is indicative of dementia.[31] Organic brain syndrome, a term used by some interchangeably with dementia, as defined in the American Psychiatric Association's "Diagnostic and Statistical Manual of Mental Disorders",[32] includes impairment of orientation, memory, judgement and intellectual functions, such as comprehension, calculation, knowledge and learning; lability and shallowness of affect are added as diagnostic criteria. As the disease progresses, self-absorption increases; then, when the individual recognizes his or her failing powers, anxiety and annoyance may occur. Later the personality disintegrates and the qualities that constitute a personality recede. Persons at the end of this recession appear remarkably similar. They are apathetic and unconcerned about social responsibilities and others' opinions of them. Defects of memory and orientation make functioning difficult in all but the most familiar situations. It is at this point in the primary dementing diseases, such as Alzheimer's disease, that neurologic signs appear.

Neurologic signs in dementia

The shuffling, graceless gait and the bent, slouching posture of persons with dementia are familiar to anyone who has observed the inhabitants of an institution for the aged. The most characteristic gait in dementia is the *marche à petits pas*, in which the person has a flexed stance with a slightly widened base, and advances with slow, small steps. This occurs with Alzheimer's disease, multiple lacunar strokes and, occasionally, hydrocephalus. As dementia progresses, the gait becomes stooped and shuffling, and the associated arm-swinging is lost; the hands are held cupped, with the thumb adducted. At the end the patient cannot move his or her legs, is bedridden and assumes a flexed or cradled posture — "paraplegia in flexion" — with hips and knees flexed toward the abdomen, and the heels resting on the posterior thighs.[33]

Medial frontal lobe damage or hydrocephalus can lead to a gait difficulty in which the patient, despite good leg strength, will not take a step, even when supported on both sides and coaxed. The patient will sometimes be able to imitate the walking movement while lying down. This gait apraxia is a common presentation of normal-pressure hydrocephalus.[34] The patient frequently sits with the hips flexed so that the knees are high in the air and the feet are off the ground. This may progress to the flexed or cradled posture.

A tonic foot response can interfere with the normal gait.[35] The "magnetic foot", an unusual apraxia, results from frontal lobe damage; the patient seems unable to lift one foot in order to step.

Paratonia is a resistance to the passive movement of a limb in all directions that worsens as the patient is urged to relax; the impression is that the patient is fighting against the examiner's movement. The resistance can be overcome by slow and continuous movement of the limb. Paratonia differs from spasticity in that the resistance is in all directions and seems proportional to the examiner's effort. Paratonic rigidity has been attributed to an inability to rapidly shift muscle tone, which is perhaps metaphorically similar to the inability to shift the mental set.

A number of well known "reflexes" characterize the diffuse cerebral diseases, particularly dementia. In the grasp reflex,[36] contact with the patient's palm elicits grasping; in an exaggerated form this becomes a searching movement of the entire forearm. The demented patient's frequent clutching and picking at the bedsheets is a reflection of this. In the tonic foot response[35] the toes turn downward when the sole is stimulated by nonpainful pressure. Direct pressure rather than stroking elicits the response best, and movement of the stimulus may cause the foot to follow it. Interference with the Babinski sign can be avoided if the lateral rather than the plantar aspect of the sole is stroked.

Sucking,[37] snouting, mouthing, puckering[38] and rooting are all variations of the primitive response to stroking or percussing of the oral region.[39] When these reactions are prominent they can be elicited by simply approaching the patient's mouth with an object in full view. The palmomental reflex,[40] which is seldom seen in normal adults, increases with age and is common in dementia; it is elicited by a quick scratch of the palm, preferably over the hypothenar eminence. In response, the corner of the chin, ipsilaterally, bilaterally or contralaterally, twitches upward. This reaction is subtle and brief, so the examiner's eye must be fixed on the patient's chin. Other reactions, including the corneomandibular,[41] nuchocephalic[42] and glabellar tapping[43] reflexes, are nonspecific and less frequently seen with dementia. The accurate elicitation of three or four of the primitive reflexes takes less than 30 seconds.

That these grasping and perioral reactions are primitive is not as informative as their origin. Much of the work in this area has been speculative and philosophic, centering on the release of lower levels of function from higher levels or on ontogenetic features. It should be kept in mind that bilateral, relatively widespread and diffuse cerebral lesions that impinge on the corticospinal system precede these reflexes, and that the reflexes may be the outstanding physical signs in diffuse structural brain diseases such as cause dementia.

In addition to these reflexes a number of nonreflexive signs are seen in dementia. Motor impersistence, or the inability to maintain a simple posture, such as keeping the eyes closed or protruding the tongue, is common in dementia as well as with lesions of the right parietal lobe.[44,45] Perseveration, the converse of impersistence, may also be seen, but it is not specific to diffuse brain disease since children and fatigued adults will also perseverate unknowingly. Perseveration of answers sometimes impedes the mental status examination but can be overcome by slower questioning, which presumably allows the damaged nervous system to "wind down". The inability to imitate sequential movements is a feature of dementia due to frontal lobe disease.

Bilateral pyramidal tract disease above the pons leads to pseudobulbar palsy. In this condition the patient's expressionless stare is accompanied by brief losses of emotional control, with stereotyped facial movements that simulate a wide grinning smile or an exaggerated frowning cry.[46] Facial reflexes, especially an exaggerated jaw reflex, are important signs of pseudobulbar palsy. Excessive salivation, dysarthria and swallowing difficulty are present in most cases. Another nonreflexive sign is sensory extinction, in which the patient reports only one of two stimuli simultaneously presented, such as touches on the face and arm; this phenomenon can be demonstrated in many elderly but nondemented persons.[47]

Certain signs are not expected in uncomplicated dementia. For example, asterixis suggests a metabolic encephalopathy. Agitation, sleepiness or difficulty in focusing attention on the examination suggests a metabolic derangement.

In the patient suspected of having dementia the physician should attempt to elicit the signs characteristic of diffuse, bilateral cerebral damage and to document specific features such as loss of memory and inability to perform daily tasks. This can be done by asking the patient to recall phrases and brief stories, tie shoes, dial a telephone and handle a fork and knife. The ease with which the mental set is changed and the complexity of available speech can be tested during the interview. Restricted vocabulary, clichés, exclamations and perseveration are common in early dementia. Impatience or other disagreeable behaviour may appear. With these observations in mind one can make a bedside assessment of the presence of dementia and its severity.

Diseases presenting mainly as dementia (Table II)

Structural diseases

Alzheimer's disease: The most common primary dementing process was described by Alzheimer in 1907.[48] It is a process clinically similar to Pick's disease,[49] which is considerably less common in North America, and debate continues as to whether the two are clinically separable.[50] The sexes are approximately equally affected; a small female preponderance has been reported in some series of cases.[51] Familial occurrence of both disorders has been reported.[52,53] In most series Alzheimer-type abnormalities are synonymous with the main form of both senile and presenile dementia.[54] The epithet "presenile dementia" should therefore no longer be used. The brain in these cases is small and light, with striking cortical thinning and some loss of white matter. Loss of neurons and of dendritic branching in the remaining nerve cells accounts for the diminished cortical size[55,56] and for the characteristic sulcal widening and ventricular enlargement seen on the computed tomographic (CT) scan. The pathological hallmarks of Alzheimer's disease are neurofibrillary tangles, which are intraneuronal accumulations of paired helical filaments similar in structure to normal neurofilaments,[57] and neuritic plaques, which are amyloid cores surrounded by degenerating neural processes.[58] The pathological features of Alzheimer's disease are emphasized because the number of plaques and tangles has been correlated with the severity of the dementia.[3,59] Whether it is these changes, neuronal loss or some other alteration that accounts for dementia is unclear. Computerized cell counting has recently been employed and may establish the number of remaining neurons as the ultimate arbiter of the severity of dementia.

The work of Crapper, Krishnan and Dalton[60] on the role of aluminum in the neurofibrillary change is noteworthy, but the most provocative development in recent years has been the transmission to animals, from the brains of patients with familial Alzheimer's disease, of a progressive neurologic illness suggestive of a slow virus infection.[61] The now confirmed finding of reduced activity of choline acetyltransferase in the brains of persons with Alzheimer's disease may be of more direct significance than pathologic change in the cortex.[62] There have been several attempts to reverse the cholinergic defect chemically.

The diagnosis of Alzheimer's disease is made by recognizing the typical clinical pattern and excluding the diseases that are to be mentioned. The average duration of illness is 2 to 5 years, sometimes longer, and periods of stability are not unusual. Its presentation may be pleomorphic, but impairment of memory is prominent. Paranoia, slovenliness or a Korsakoff's pure memory disorder may signal the onset of disease.

Creutzfeldt–Jakob disease: The experiments of Gibbs and associates[63] became a milestone in the history of dementia by demonstrating a slow virus infection in Creutzfeldt–Jakob disease, which had been thought to be degenerative. Since that time, human-to-human transmission has been reported.[64,65] This disease becomes apparent in patients between 40 and 60 years of age, and the sexes are equally affected. Several instances of familial occurrence[66] and one instance of husband and wife being affected[67] have been reported.

The main clinical characteristics include gait disturbance, rigidity, poor coordination, myoclonus[68,69] and a more rapid evolution than other dementias, usually a matter of months. By the time dementia supervenes cerebellar or brainstem signs or myoclonus has appeared. The appearance of myoclonus in rapidly advancing dementia is particularly suggestive of this disease. Progressive slowing of the electroencephalogram (EEG) rhythm and periodic sharp waves are also characteristic.[70] A variant occurs with hemianopia at the outset.

The histopathological pattern in Creutzfeldt–Jakob disease, a spongy change in the cortex, accounts for the name "spongiform encephalopathy". Although virus-like particles have been demonstrated by electron microscopy[71] they have not been characterized further or isolated.

Wilson's disease: This is a protean disease resulting from an autosomal recessive abnormality of copper metabolism.[72] Consanguinity in the ancestry of affected persons is common. The mental changes are variable, but psychiatric aberration is often the initial symptom,[73] and it is followed by other clinical signs, including spasticity, rigidity, a prominent pseudobulbar syndrome with dysarthria and dysphagia, and the Kayser–Fleischer ring. This greenish ring, which is the only pathognomonic sign of Wilson's disease, is at the limbus of the cornea, is generally more prominent at the superior and inferior margins and, even if incomplete, is nearly always present in patients with symptomatic neurologic disease. A history of cirrhosis or hemolytic anemia, both of which may be intermittently symptomatic, are clues to Wilson's disease as a cause of mental deterioration. Loss of intellect does not usually appear without other neurologic signs, and the value of routine copper screening in demented patients is unproven. Nevertheless, the illness responds readily to D-penicillamine therapy. Determination of the serum concentrations of copper and ceruloplasmin (both of which are low, though early in the disease the level of copper may be normal) and the copper content of a 24-hour urine sample (which is high)[74] is thus justified in younger patients or in those with dementia and a movement disorder. The CT scan shows dilatation of the frontal horns of the lateral ventricles due to atrophy of the caudate nucleus and low density in the basal ganglia, putamen and globus pallidus.[75]

Huntington's disease: Mental changes appear after the onset of the characteristic movement disorder in Huntington's disease. In rare cases, however, dementia is the prevailing symptom or appears before chorea or athetosis. The illness can begin in persons as young as 20 years of age, but usually appears in those 30 to 50 years old. Inheritance is via an autosomal dominant gene; hence, as in other kinds of dementia

Table II—Diseases that can present mainly as dementia

Structural
- Alzheimer's disease
- Creutzfeld–Jakob disease
- Wilson's disease
- Hydrocephalus
- Multiple bilateral lacunar strokes
- Subdural hematoma
- Cerebro-basal ganglionic degenerations (e.g., Parkinson's disease, Huntington's disease)
- Cerebral tumours
- Neurosyphilis
- Metabolic dysmyelination and demyelination Korsakoff–Wernicke's disease

Metabolic
- Hypothyroidism
- Vitamin B_{12} deficiency
- Chronic drug intoxication
- Alcoholism

a family history must be sought.[53] There is a loss of neurons in the caudate nucleus, putamen and cortex, with subsequent gliotic scarring. This loss of caudate substance, as in Wilson's disease, is sometimes visualized by CT scanning.[75] Interestingly, levodopa provokes the chorea in patients with Huntington's disease.[76]

Hydrocephalus: Low- or normal-pressure hydrocephalus classically presents with a triad of gait difficulty, incontinence and progressive dementia[77] and is caused by a known or postulated insult to the arachnoid membrane, such that cerebrospinal fluid absorption is impeded. Through dynamic compensation the ventricles enlarge but the overall pressure within the system remains normal or slightly elevated; this process differs from other structural causes of dementia in that ventricular enlargement is the cause and not the result of a loss of cerebral tissue. Gait impairment is the most consistent part of the syndrome and can assume several forms, including spasticity, ataxia, *marche à petits pas* and the apparent sticking of the feet to the floor.[78] Stretching of the corticospinal fibres as they are draped over the enlarging ventricles and encroachment on the frontal lobes have been postulated as causes of the gait disturbances.[79] The dementia in this process resembles abulia and never produces focal deficits. Its rate of onset varies considerably, but is usually a matter of months.

Radionuclide cisternography is most helpful in the diagnosis and preoperative evaluation of normal-pressure hydrocephalus.[80,81] Carefully selected patients will improve after shunt drainage of the ventricular cavities. Several criteria for selection have been suggested, including the classic triad of symptoms and the characteristic radiologic features,[82] but, despite sporadic reports of success, the implantation of a shunt in a patient with enlarged ventricles due to Alzheimer's disease is not justified. The clinical response to the removal of cerebrospinal fluid by repeated lumbar puncture has been useful in our experience as a predictor of shunt success but still requires confirmation.[83]

Vascular dementia: Because there is no correlation between dementia and the severity of arteriosclerotic change in the cerebral blood vessels,[84] the common attribution of senile dementia to a reduction in cerebral blood flow is no longer tenable.[85] Although several laboratories have established a relation between reduced cerebral blood flow and dementia, it is probable that reduced flow and metabolism reflect a loss of cerebral mass and not the reverse. Dementia will, however, occur after multiple bilateral lacunar strokes of the type seen in patients with long-standing hypertension. These strokes result in multiple small white-matter cavitations. When they are widespread in the hemispheres they give rise to a pseudobulbar state, a short-stepped, halting gait (which has been described as sputtering, since the patient shuffles before initiating a series of steps), Babinski's signs and a decline in intellectual function. The clinical course is punctuated by multiple minor, acute strokes, and the diagnosis of lacunar dementia should not be made without this history. To the extent that this type of dementia is subcortical, it has been reported to differ clinically from Alzheimer's cortical dementia.[11] Although amnesia is prominent in Alzheimer's disease, it is patchy or minor in lacunar dementia. Focal neurologic signs appear early in arteriosclerosis and late, if at all, in Alzheimer's disease. Multiple large-vessel occlusions can cause a patient to appear demented as a result of the combination of several focal deficits in higher cerebral function. Caution is still advised before attributing dementia to strokes, since up to 40% of persons over 65 years of age who show no evidence of intellectual deterioration prove at autopsy to have cerebral infarctions.[86] In three series only 8 of 84,[6] 5 of 60[7] and 72 of 258 patients[27] were thought to have dementia due to vascular disease. Further deterioration can be avoided in multiple infarct dementia by assiduous control of hypertension.

Subdural hematoma: A subdural collection of blood is notoriously difficult to detect in the elderly.[87] Alterations in the level of consciousness are a far more common consequence than dementia,[88] and a clear history of head trauma is infrequently obtained. A moderate headache that worsens with coughing should prompt investigation for a subdural hematoma. The cerebrospinal fluid is commonly xanthochromic and under normal or slightly increased pressure. Lumbar puncture, however, is not recommended for making the diagnosis. Studies of the reversibility of dementia after drainage of a subdural hematoma have not been done, but anecdotal evidence suggests that, in the patient who presents with dementia on this unusual basis, the dementia does improve.

Cerebrostriatal–cerebellar degenerations: These are a group of degenerative nervous disorders, including Parkinson's disease, in which dementia as a secondary phenomenon is associated with other neurologic symptoms corresponding to an affected subsystem of the brain. The dementia is presumably due to cortical cell loss. Parkinsonian symptoms, especially rigidity, are very common in most of the cerebrostriatal disorders, and the diagnosis becomes evident as the illness progresses. In the striatonigral degeneration described by Adams, Van Bogaert and Vander Eecken[89] dementia is notably absent. Loss of intellect has been reported at times in the spinocerebellar degenerations, such as Friedreich's ataxia. Sometimes it is only the family members without ataxia in whom dementia develops, although the syndrome tends to be consistent within a given family.[90] Clinically related to these diseases is progressive supranuclear palsy, in which there is mild dementia, progressive loss of vertical eye movement and rigidity. Patients frequently complain of difficulty walking or of stumbling because of defects in eye movement. The onset is in middle life. Severe rigidity eventually develops and the patient becomes confined to bed in approximately 5 years. The cortex is normal, but cell loss and neurofibrillary tangles appear in the basal ganglia, cerebellum and brainstem;[91] the subcortical nature of the dementia has been pointed out by several authors.[92]

Cerebral tumours: Strategically placed mass lesions in the cerebrum, particularly damage to the frontal lobes,[93] third ventricle,[94] thalamus,[95] temporal lobes[96] or corpus callosum, can produce dementia, causing memory disturbance and affective lability. The clinical aspects of the dementing syndrome probably do not allow localization of the tumour, except for abulia, which frequently occurs with frontal tumours. Fortuitously placed masses may also produce hydrocephalus by blocking the flow of cerebrospinal fluid. Because behavioural changes occur early with gliomas and the associated focal signs may be subtle, investigation for a brain tumour is justified in all persons with dementia of recent onset.

Neurosyphilis: Once the leading cause of admission to mental institutions, general paresis of the insane is now uncommon. Alterations in conduct and intellectual function and mood swings constitute the earliest symptoms.[97] An Argyll Robertson pupil or other pupillary abnormality accompanies the dementia in most cases. Serologic and cerebrospinal fluid tests for syphilis are virtually always positive, except for the exceptional seronegative case.[98] Mild lymphocytic pleocytosis and either an elevated gamma globulin concentration or a first-zone colloidal gold reaction are relatively consistent abnormalities of the cerebrospinal fluid in untreated cases. General paresis is a chronic meningomyelitis and involves the frontal and temporal lobes most severely. Cortical atrophy and ventricular enlargement are common, so that the CT scan appears similar to that in Alzheimer's disease. Although penicillin will cure the treponemal infection it has a variable effect on the dementia.

Metabolic dysmyelinating diseases: Inherited errors of lipid metabolism generally cause mental retardation in childhood, but cases with onset in the teens or 20s have occurred. Adult metachromatic leukodystrophy[99] and Kufs' disease,[100] the adult form of amaurotic idiocy, are seen infrequently; progressive dementia is a prominent and early feature. Diffuse white-matter disease frequently produces a combination of spasticity and abulia. Because these disorders are rare, the use of elaborate tests for their identification is not justified in the routine evaluation of dementia unless a CT scan shows diffuse white-matter lesions.

Demyelinative disease: Schilder's disease is the prototype of a group of progressive and widespread demyelinative diseases of the cerebral hemispheres that cause dementia. Widespread cerebral multiple sclerosis produces a similar picture,[101] with pseudobulbar signs and abulia, but the other features of multiple sclerosis usually accompany the illness. In Schilder's disease dementia may be the initial symptom. Prolonged conduction of the visual evoked response, reflecting demyelination in the optic nerve, may assist in the diagnosis.

Korsakoff's dementia: In alcohol-related Korsakoff's syndrome the memory deteriorates far more than other mental functions. In one large series 236 of 245 patients had had one or more bouts of Wernicke's encephalopathy.[102] The diagnosis of alcoholic Korsakoff's syndrome should not be considered without a history of at least one episode of confusion, ophthalmoplegia and nystagmus. The two syndromes blend imperceptibly as the confusion of one gives way to the memory loss of the other. Petechial thalamic lesions that somehow are related to a lack of thiamin are the cause of the dementia. It has recently been suggested that an inherited abnormality in transketolase, a thiamin-requiring enzyme, predisposes a person to the disease.[103] In one series of alcoholics the recovery of memory was reported to be complete in 21% and slight or absent in 54%.[102]

A selective amnestic dementia may also result from temporal lobe disease, including that generally caused by early or recovered herpetic encephalitis,[104] bilateral temporal infarction from cardiac arrest,[105] trauma, basilar meningitis[106] and tumours involving the walls of the third ventricle and the adjacent portions of the medial temporal lobes.

Nonstructural and metabolic dementia

The nonstructural dementias are, in fact, reversible encephalopathies. The excess or lack of a factor changes the metabolic milieu of cerebral neurons enough to cause dysfunction without permanent structural change. As in metabolic encephalopathies, such as azotemia and hepatic failure, some degree of diminished alertness or confusion accounts for the poor intellectual performance.

The three most common causes of cryptic nonstructural dementias are hypothyroidism,[107] vitamin B_{12} deficiency[108] and chronic drug intoxication. A number of observers have related folate deficiency to dementia in the absence of vitamin B_{12} deficiency,[109] but many neurologists dispute that point. Mental abnormalities accompany vitamin B_{12} deficiency fairly regularly, but the deficiency is seldom the only finding. Long-term ingestion of drugs, especially bromides, barbiturates and alcohol, can cause a dementing syndrome; the history of ingestion is usually available. Routine screening for drug ingestion should be undertaken if there is a suspicious history since drug ingestion accounts for 5% to 10% of the dementias.[110]

Alcoholic dementia refers to recent dementia in persons who habitually ingest large amounts of alcohol and have no history of head trauma, vascular disease or (hepatic) encephalopathy. Alcoholic dementia can be distinguished from Korsakoff's and Alzheimer's dementias by the relatively nonprogressive course, the considerable constructional difficulty and the prominent behavioural disturbances, in addition to amnesia.[111] The role of alcohol is presumptive, but the cortical atrophy demonstrated by CT brain scanning may reverse with abstinence.[111] An altogether different syndrome of chronic and pure auditory hallucinosis also occurs in alcoholics and should be distinguished from alcoholic dementia, Korsakoff's syndrome and schizophrenia.

The clinical features of Marchiafava–Bignami disease, an alcohol-related degeneration of the corpus callosum, are variable. Some persons have a dementia that slowly evolves over 3 to 6 years, with abulia, prominent release reflexes, paratonia and a slow, hesitant and somewhat wide-based gait, similar to that of persons with bilateral frontal lobe disease or hydrocephalus. Perhaps the most notable

For Rx summary see page 1259 ⟶

feature is a tendency for the syndrome to remit.[112]

Laboratory investigation of dementia

If the diagnosis or cause of dementia is uncertain, observation of the patient in the hospital and laboratory testing (Table III) may be required.

The first-rank tests for unclassified dementia should include a complete blood count, a serologic test for syphilis, measurement of the serum concentrations of thyroxine, urea nitrogen, vitamin B_{12} and liver enzymes, drug screening, electroencephalography, CT scanning of the brain and lumbar puncture, with the injection of radiolabelled material if appropriate. Other tests that offer marginal contributions or are indicated only in specific circumstances are cerebral angiography, pneumoencephalography, measurement of the serum copper and ceruloplasmin concentrations and of the copper content of a 24-hour urine sample, leukocyte or urine assay for leukodystrophy enzyme abnormalities, skull roentgenography and brain biopsy.[113] Psychologic testing may be of value even if the bedside examination is careful.[26] One should not, however, depend on formal psychologic testing to distinguish between depression and dementia. The recent development of brief mental status examinations for the diagnosis of organic brain syndrome may prove helpful.[114]

Table III—Basic investigations in dementia

Routine
Complete blood count
Serologic test for syphilis
Measurement of serum concentrations of
Thyroxine
Urea nitrogen
Vitamin B_{12}
Liver enzymes
Drug screening
Electroencephalography
Computerized tomography of the brain
Lumbar puncture
Indicated in specific circumstances
Cerebral angiography
Pneumoencephalography
Measurement of serum copper and ceruloplasmin concentrations and copper content of a 24-hour urine sample
Leukocyte or urine assay for leukodystrophy enzyme abnormalities
Skull roentgenography
Study of cerebrospinal fluid flow by instillation of radiolabelled material via lumbar puncture
Repeated lumbar puncture to drain cerebrospinal fluid
Brain biopsy

The present cost of the first-rank tests at the Massachusetts General Hospital is US$415.00, excluding the costs of hospital care. The tests may take 3 or 4 days. The blood tests and the electroencephalography are done on the day of admission, the CT scanning is done on the second day and the lumbar puncture is done on the evening of the second day or the following morning. On the third and fourth days scanning of the cerebrospinal fluid flow is performed along with any additional tests that are necessary. Observation of the patient over this period informs the physician of the patient's adaptability to new situations, day-to-day memory function and behavioural manageability. In a well organized clinic and with prior planning of the tests it is possible to carry out the investigation on an outpatient basis.

Electroencephalography

This procedure is helpful in determining whether the dementia has an organic cause. Focal lesions will also cause electroencephalographic abnormalities, but a normal tracing by no means excludes organic disease. In unusual circumstances the procedure offers a specific diagnosis, such as when the periodic sharp-wave complexes of Creutzfeldt-Jakob disease appear.[70] In Alzheimer's disease the EEG shows a reduction or absence of α-waves and their replacement by low- to medium-voltage θ- and δ-waves.[115] In arteriosclerotic dementia due to cortical infarcts there is a tendency for focal electroencephalographic abnormalities to occur.[116] Lacunar infarctions may cause some slowing of the waves but generally no focal changes. Normal-pressure hydrocephalus causes nonspecific abnormalities in about half the cases.[117] Except for large-vessel vascular disease, tumours are the most common cause of focal electroencephalographic abnormalities.

CT scanning

Noninvasive, high-resolution CT scanning has replaced pneumoencephalography as the preferred radiologic procedure in the investigation of dementia. Cerebral atrophy and ventricular enlargement are shown to great advantage in the scan, and there is a close correlation between CT and anatomic dimensions.[118] If there is a possibility of a tumour or infarction CT scanning should be done early on, as such a finding will preclude other tests. However, there is only a limited correlation between CT-demonstrated ventricular enlargement and sulcal widening, and the clinical severity of dementia.

Normal-pressure hydrocephalus causes ventricular enlargement with little or no cortical atrophy. The absence of marked cortical atrophy or the presence of ventricular enlargement out of proportion to sulcal widening are indications to proceed to radionuclide cisternography.[119] Intermediate ratios of atrophy to ventricular enlargement are common in elderly persons, especially those with Alzheimer's disease. The cisternogram is then helpful in determining which patients might benefit from shunt drainage of the cerebrospinal fluid. The CT scan occasionally shows dilatation of the frontal horns of the ventricles, which suggests Huntington's or Wilson's disease.[75]

Radionuclide cisternography

This procedure provides a way of assessing the flow of cerebrospinal fluid. It is done by injecting a radioactive pharmaceutical into the lumbar subarachnoid space during lumbar puncture. Arachnoiditis has been reported to occur rarely after the procedure when the older radioactive preparations are used, but otherwise the procedure is without known risks. Under normal conditions the isotope reaches the basal cisterns at 1 hour and appears over the hemispheres at 12 hours. At 24 hours all of the isotope should be concentrated over the hemispheres and centred near the sagittal sinus. Since the cerebrospinal fluid flows from the choroid plexus of the lateral ventricles outward to absorptive sites at the arachnoid villi, the isotope should not enter the ventricles to any great extent. In normal-pressure hydrocephalus and other communicating forms of hydrocephalus the flow pattern is disordered, so that the isotope flows into the ventricles in the first 24 hours and remains there for up to 3 days. In Alzheimer's disease the isotope enters the ventricles transiently at 4 to 12 hours and then clears by 36 hours. Except in one series,[120] no benefit from shunt drainage has been described when the isotope transiently appears in the ventricles and subsequently clears. Cisternography should be done in most demented patients for whom a specific diagnosis cannot be made by the first-rank tests.

Treatment of dementia

Specific therapy for symptomatic dementia should be instituted immediately. For most patients with atrophic dementia the physician can do much to keep the patient well compensated and ease the family's burden. The physician should avoid assuming that the demented patient is oblivious to his or her plight, since psychiatrists and laymen have repeatedly observed the contrary.[121,122]

The obvious physical needs of the patient should be met by a team consisting of a physician, a social worker and a visiting nurse. This will greatly reduce the frequency of admission to hospital. An adequate diet can be ensured with a meals-on-wheels program or if the family or friends leave prepared meals in the refrigerator and then call twice a day to remind the patient to eat.

Emphasis should be placed on maintaining a stable and familiar environment. A schedule of daily events, with fixed times for walking, eating and visiting, should be constructed by the physician in consultation with the family. This simple approach ensures the participation and enthusiasm of most families and will extend by years the nominal independence of the demented individual. Advantage should be taken of the remaining cognitive abilities. Reading may have a far more calming effect than drugs. Signs reminding the patient which room he or she is in should be placed in the home. Clocks and calendars that clearly display the year will prevent the anxiety that results from disorientation. Major changes should be avoided. Trips merely for the sake of a change generally end as fiascos when the patient finds himself or herself in unfamiliar surroundings. Likewise, when the patient must finally be transferred to a nursing home familiar objects from home should be taken along and old friends should be encouraged to visit. A soft light in the evening will allay the fears and behavioural outbursts that occur at night.

When to institute nursing home care or guardianship is a difficult decision for the physician, but some general suggestions can be offered. Family involvement is a special feature of senile dementia and it is not true that families want to rid themselves of elderly relatives. In fact, most families hold on to elderly people far too long and do not take advantage of the available facilities.[123] Day care in the geriatric branch of a community hospital may provide a solution for families who cannot remain at home during the day but are able to care for the elderly individual at night and on weekends.[124] Several psychogeriatric wards, modelled after British prototypes, exist in the United States and have provided useful short-term hospitalization for mentally disturbed geriatric patients, often allowing discharge without transfer to a chronic care facility.[125]

The suggestion for transfer to a custodial facility will generally come from the family, but the physician should be familiar with, and inform the family about, available institutions. A physician's approval of the institution and the care it will provide, and an offer to look in on the patient, can allay the fears and avoid future feelings of guilt of the family. Several kinds of nonpharmacologic inpatient treatment can improve the condition of some demented patients; these have been reviewed in the literature.[126,127]

Severe depression associated with dementia may be treated with drugs such as amitriptyline,[128] but unnecessary medications, especially sedatives, should be avoided. Even small doses of psychotropic drugs will cause side effects that are more distressing than the behavioural symptoms for which they were prescribed. Severe anxiety and insomnia are best treated with diazepam and diphenhydramine, and the patient should be observed for increased confusion. Since demented patients are generally calmest in the morning, awakening in a delirious or confused state indicates side effects from bedtime medication. Unmanageable psychosis or agitation may respond to therapy with a phenothiazine or haloperidol, although neither drug has an advantage over the other. The long-term use of phenothiazines is discouraged since extrapyramidal side effects are dangerous in these patients. The addition of antiparkinsonian drugs is also discouraged, since they can often produce a confusional or psychotic state.

The use of drugs to increase the cerebral blood flow has no justification in theory or in fact. Similarly, intramuscular administration of procaine, oral administration of ribonucleic acid or vitamin E, and hyperbaric oxygen therapy[129] have all been in vogue at one time or other but are currently of no proven benefit.[130]

Because reduced concentrations of cholinergic enzymes in brain tissue have been found, several trials of anticholinesterase drugs[131] or dietary precursors of acetylcholine[132,133] have been conducted. They have shown variable benefit in reducing the memory deficit in Alzheimer's disease.

Dementia, then, is a disorder that can be rationally diagnosed and treated.

References

1. Neilsen J: Geronto-psychiatric period-prevalence investigation in a geographically delimited population. *Acta Psychiatr Scand* 38: 307, 1963
2. Tomlinson BE, Blessed G, Roth M: Observations on the brains of demented old people. *J Neurol Sci* 11: 205, 1970
3. Peck A, Wolloch L, Rodstein M: Mortality of the aged with chronic brain syndrome. *J Am Geriatr Soc* 21: 264, 1973
4. Kay DWK: Outcome and cause of death in mental disorders of old age: a long term follow-up of functional and organic psychoses. *Acta Psychiatr Scand* 38: 249, 1962
5. Katzman R: The prevalence and malignancy of Alzheimer disease. *Arch Neurol* 33: 217, 1976
6. Marsden CD, Harrison MJG: Outcome of investigation of patients with presenile dementia. *Br Med J* 2: 249, 1972

7. FREEMON FR: Evaluation of patients with progressive intellectual deterioration. *Arch Neurol* 33: 658, 1976
8. KRAL VA: Senescent forgetfulness: benign and malignant. *Can Med Assoc J* 86: 257, 1962
9. ADAMS RD, VICTOR M: *Principles of Neurology*, 1st ed, McGraw, New York, 1977, pp 271-80
10. STERJILEVICH SM: La turbulence nocturne du vieillard psychotique. *Encephale* 51: 238, 1962
11. KRAL V: Psychiatric problems, in *Practical Geriatrics; Guidelines for General Practice*, VON HAHN HP (ed), Karger, Basel, 1975, p 259
12. Idem: Stress reactions in old age. *Laval Med* 38: 561, 1967
13. CHÉDRU F, GESCHWIND N: Disorders of higher cortical function in acute confusional states. *Cortex* 8: 395, 1972
14. GESCHWIND N: Non-aphasic disorders of speech. *Int J Neurol* 4: 207, 1964
15. WEINSTEIN EA, KAHN RL: Nonaphasic misnaming (paraphasia) in organic brain disease. *Arch Neurol Psychiatry* 67: 72, 1952
16. BENSON D, GESCHWIND N: The aphasias and related disturbances, in *Clinical Neurology*, 3rd ed, BAKER AB, BAKER LH (eds), Har-Row, Hagerstown, Md, 1977, p 8
17. MOHR JP, WATTERS WC, DUNCAN GW: Thalamic hemorrhage and aphasia. *Brain Lang* 2: 3, 1975
18. ALAJOUANINE T, CASTAIGNE P, SABOURAUD O, et al: Palilalie paroxystique et vocalisations itératives au cours de crises épileptiques par lésion intéressant l'aire mortice supplémentaire. *Rev Neurol* 101: 685, 1959
19. STENGEL E: A clinical and psychological study of echo-reactions. *J Ment Sci* 93: 598, 1947
20. HORENSTEIN S: Amnestic, agnosic, apractic, and aphasic features in dementing illness, in *Dementia*, 2nd ed (Contemporary Neurology series), WELLS CE (ed), Davis, Philadelphia, 1971, p 35
21. FISHER CM: Nonsense speech — amphigory. *Trans Am Neurol Assoc* 95: 238, 1970
22. ALEXANDER DA: 'Senile dementia': a changing perspective. *Br J Psychiatry* 121: 207, 1972
23. KLERMAN GL: An overview of depression, in *Comprehensive Textbook of Psychiatry*, 2nd ed, FREEDMAN AM, KAPLAN HI, SADOCK BJ (eds), Williams & Wilkins, Baltimore, 1975, p 1003
24. STERNBERG DE, JARVIK ME: Memory functions in depression. *Arch Gen Psychiatry* 33: 219, 1976
25. WELLS CE: Dementia: definitions and description, in *Dementia*, 2nd ed, op cit, p 1
26. KILOH LG: Pseudo-dementia. *Acta Psychiatr Scand* 37: 336, 1961

27. SIM M, SUSSMAN I: Alzheimer's disease: its natural history and differential diagnosis. *J Nerv Ment Dis* 135: 489, 1962
28. MAHER B: The language of schizophrenia: a review and interpretation. *Br J Psychiatry* 120: 3, 1972
29. LEWIS A: Amnesic syndromes: the psychopathological aspects. *Proc R Soc Med* 54: 955, 1961
30. GOLDIN S, MACDONALD JE: The Ganser state. *J Ment Sci* 101: 267, 1955
31. CHAPMAN LF, WOLFF HG: The cerebral hemispheres and the highest integrative functions of man. *Arch Neurol* 1: 357, 1959
32. American Psychiatric Association, committee on nomenclature and statistics: *Diagnostic and Statistical Manual of Mental Disorders,* 2nd ed, Am Psychiatr Assoc, Washington, 1968
33. DANIELS LE: Paraplegia in flexion. *Arch Neurol Psychiatry* 43: 736, 1940
34. MEYER JS, BARON DW: Aparaxia of gait: a clinico-pathological study. *Brain* 83: 261, 1960
35. GOLDSTEIN K: The tonic foot response to stimulation of the sole: its physiological significance and diagnostic value. *Brain* 61: 269, 1938
36. ADIE WJ, CRITCHLEY M: Forced grasping and groping. *Brain* 50: 142, 1927
37. BIEBER I: Grasping and sucking. *J Nerv Ment Dis* 91: 31, 1940
38. PILLERI G: Schippenzeichen von Darwin ("pursing of the lips") beim morbus Alzheimer. *Psychiatr Clin Neurol (Basel)* 152: 301, 1966
39. PAULSON GW, GOTTLIEB G: Developmental reflexes: the reappearance of foetal and neonatal reflexes in aged patients. *Brain* 91: 37, 1968
40. BLAKE JR, KUNKLE EC: The palmomental reflex: physiological and clinical analysis. *Arch Neurol Psychiatry* 65: 337, 1951
41. WARTENBERG R: Winking-jaw phenomenon. *Arch Neurol Psychiatry* 59: 734, 1948
42. JENKYN LR, WALSH DB, CULVER C, et al: The nuchocephalic reflex in diffuse cerebral disease (abstr). *Neurology (Minneap)* 24: 358, 1974
43. PEARCE J, AZIZ H, GALLAGHER JC: Primitive reflex activity in primary and symptomatic parkinsonism. *J Neurol Neurosurg Psychiatry* 31: 501, 1968
44. FISHER CM: Left hemiplegia and motor impersistence. *J Nerv Ment Dis* 123: 201, 1956
45. BEN-YISHAY Y, DILLER L, GERSTMAN L, et al: The relationship between impersistence, intellectual function, and outcome of rehabilitation in patients with left hemiplegia. *Neurology (Minneap)* 18: 852, 1968
46. ARING CD: Supranuclear (pseudobulbar) palsy. *Arch Intern Med* 115: 198, 1965
47. FINK M, GREEN M, BENDER MB: The face-hand test as a diagnostic sign of organic mental syndrome. *Neurology (Minneap)* 2: 46, 1952
48. ALZHEIMER A: Über eine eigenartige Erkrankung der Hirnrinde. *Allg Ztschr Psychiatrie* 64: 146, 1907
49. NEUMANN MA: Combined amyloid vascular changes and argyrophil plaques in the central nervous system. *J Neuropathol Exp Neurol* 19: 370, 1960
50. SJÖGREN T, SJÖGREN H, LINDGREN AGH: Morbus Alzheimer and morbus Pick: a genetic, clinical and patho-anatomical study. *Acta Psychiatr Neurol Scand* (suppl 82): 1, 1952
51. GOODMAN L: Alzheimer's disease: clinico-pathologic analysis of 23 cases with theory on pathogenesis. *J Nerv Ment Dis* 117: 97, 1953
52. FELDMAN RG, CHANDLER KA, LEVY LL, et al: Familial Alzheimer's disease. *Neurology* 13: 811, 1963
53. PRATT RTC: *The Genetics of Neurological Disorders* (Oxford monograph on medical genetics), Oxford, New York, 1977
54. TERRY RD: Dementia: a brief and selective review. *Arch Neurol* 33: 1, 1976
55. COLON EJ: The cerebral cortex in presenile dementia: a quantitative analysis. *Acta Neuropathol (Berl)* 23: 281, 1973
56. SCHEIBEL ME, LINDSAY RD, TOMIYASU U, et al: Progressive dendritic changes in aging human cortex. *Exp Neurol* 47: 392, 1975
57. WISNIESKI H, TERRY RD, HIRANO A: Neurofibrillary pathology. *J Neuropathol Exp Neurol* 29: 163, 1970
58. TERRY RD, GONATAS NK, WEISS M: Ultrastructural studies in Alzheimer's presenile dementia. *Am J Pathol* 44: 269, 1964
59. ROTH M, TOMLINSON BE, BLESSED G: Correlation between scores for dementia and counts of 'senile plaques' in cerebral gray matter of elderly subjects. *Nature (Lond)* 209: 109, 1966
60. CRAPPER DR, KRISHNAN SS, DALTON AJ: Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. *Science* 180: 511, 1973
61. TRAUB RD, GAJDUSEK DC, GIBBS CG: Transmissible virus dementia: the relation of transmissible spongiform encephalopathy to Creutzfeldt–Jakob disease, in *Aging and Dementia*, SMITH WL, KINSBOURNE M (eds), Spectrum Pub, New York, 1977, p 91
62. SMITH CM, SWASH M: Possible biochemical basis of memory disorder in Alzheimer disease. *Ann Neurol* 3: 471, 1978
63. GIBBS CJ, GAJDUSEK DC, ASHER DM, et al: Creutzfeldt–Jacob disease (spongiform encephalopathy): transmission to the chimpanzee. *Science* 161: 388, 1968
64. DUFFY P, WOLF J, COLLINS G, et al: Possible person-to-person transmission of Creutzfeldt–Jakob disease (C). *N Engl J Med* 290: 692, 1974
65. GAJDUSEK DC, GIBBS CJ JR, ASHER DM, et al: Precautions in medical care of, and in handling materials from, patients with transmissible virus dementia (Creutzfeldt–Jakob disease). *N Engl J Med* 297: 1253, 1977
66. MAY WW, ITABASHI HH, DEJONG RN: Creutzfeldt–Jakob disease. II: clinical, pathologic, and genetic study of a family. *Arch Neurol* 19: 137, 1968
67. JELLINGER K, STEITELBERGER F, HEISS WD, et al: Konjugale Form der subakuten spongiösen Enzephalopathie. *Wien Klin Wochenschr* 84: 245, 1972
68. ROOS R, GAJDUSEK DC, GIBBS CJ JR: The clinical characteristics of transmissible Creutzfeldt–Jakob disease. *Brain* 96: 1, 1973
69. FISHER CM: The clinical picture in Creutzfeldt–Jakob disease. *Trans Am Neurol Assoc* 85: 147, 1960
70. BURGER LJ, ROWAN AJ, GOLDENSOHN ES: Creutzfeldt–Jakob disease: an electroencephalographic study *Arch Neurol* 26: 428, 1972
71. VERNON ML, PUCILLO DA, HAMILTON R: Jakob–Creutzfeldt disease: virus-like particles in two brain biopsies (abstr). *Fed Proc* 29: 286, 1970
72. BEARN AG: Wilson's disease, in *The Metabolic Basis of Inherited Disease*, 3rd ed, STANBURY JB, WYNGAARDEN JB, FREDRICKSON DS (eds), McGraw, New York, 1972, p 1033
73. SCHEINBERG IH, STERNLIEB I, RICHMAN J: Psychiatric manifestations in patients with Wilson's disease. *Birth Defects* 4: 85, 1968
74. STERNLIEB I, SCHEINBERG IH: Penicillamine therapy for hepatolenticular degeneration. *JAMA* 189: 748, 1964
75. ROPPER AH, HATTEN HP JR, DAVIS KR: Computed tomography in Wilson disease: report of 2 cases. *Ann Neurol* 5: 102, 1979
76. Presymptomatic detection of Huntington's chorea (E). *Br Med J* 3: 540, 1972
77. ADAMS RD, FISHER CM, HAKIM S, et al: Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure: a treatable syndrome. *N Engl J Med* 273: 117, 1965
78. MESSERT B, BAKER NH: Syndrome of progressive spastic ataxia and apraxia associated with occult hydrocephalus. *Neurology (Minneap)* 16: 440, 1966
79. YAKOVLEV PI: Paraplegias of hydrocephalics (clinical note and interpretation). *Am J Ment Defic* 51: 561, 1947

80. WOOD JH, BARTLETT D, JAMES AE, et al: Normal pressure hydrocephalus: diagnosis and patient selection for shunt surgery. *Neurology (Minneap)* 24: 517, 1974
81. BENSON DF, LEMAY M, PATTEN DH, et al: Diagnosis of normal-pressure hydrocephalus. *N Engl J Med* 283: 609, 1970
82. OJEMANN RG, FISHER CM, ADAMS RD, et al: Further experience with the syndrome of "normal" pressure hydrocephalus. *J Neurosurg* 31: 279, 1969
83. FISHER CM: Communicating hydrocephalus (C). *Lancet* 1: 37, 1978
84. BUTLER RN: Psychiatric aspects of cerebrovascular disease in the aged. *Res Publ Assoc Res Nerv Ment Dis* 41: 255, 1961
85. WELLS CE: Dementia reconsidered. *Arch Gen Psychiatry* 26: 385, 1972
86. TOMLINSON BE, BLESSED G, ROTH M: Observations on the brains of non-demented old people. *J Neurol Sci* 7: 331, 1968
87. STUTEVILLE P, WELCH K: Subdural hematoma in the elderly person. *JAMA* 168: 1445, 1958
88. MCKISSOCK W, RICHARDSON A, BLOOM WH: Subdural haematoma: a review of 389 cases. *Lancet* 1: 1365, 1960
89. ADAMS RD, VAN BOGAERT L, VANDER EECKEN H: Striato-nigral degeneration. *J Neuropathol Exp Neurol* 23: 584, 1964
90. CARTER HG, SUDAVAJNA C: Familial cerebello-olivary degeneration with late development of rigidity. *Neurology (Minneap)* 6: 876, 1956
91. STEELE JC, RICHARDSON JC, OLSZEWSKI J: Progressive supranuclear palsy: a heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Arch Neurol* 10: 333, 1964
92. ALBERT ML, FELDMAN RG, WILLIS AL: The "subcortical" dementia of progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 37: 121, 1974
93. FRAZIER CH: Tumor involving the frontal lobe alone: symptomatic review of 105 verified cases. *Arch Neurol Psychiatry* 35: 525, 1936
94. RIDDOCH G: Progressive dementia without headache or changes in the optic discs due to tumours of the third ventricle. *Brain* 59: 225, 1936
95. SMYTH GE, STERN K: Tumours of the thalamus: clinico-pathological study. *Brain* 61: 339, 1938
96. KOLODNY A: The symptomatology of tumours of the temporal lobe. *Brain* 51: 385, 1928
97. DEWHURST K: The neurosyphilitic psychoses today: a survey of 91 cases. *Br J Psychiatry* 115: 31, 1969
98. CH'IEN L, HATHAWAY M, ISRAEL CW: Seronegative dementia paralytica: report of a case. *J Neurol Neurosurg Psychiatry* 33: 376, 1970
99. HIROSE G, BASS NH: Metachromatic leukodystrophy in the adult. *Neurology (Minneap)* 22: 312, 1972
100. SCHNECK L, VOLK BW, SAIFER A: The gangliosidoses. *Am J Med* 46: 245, 1969
101. BERGIN JD: Rapidly progressive dementia in disseminated sclerosis. *J Neurol Neurosurg Psychiatry* 20: 285, 1957
102. VICTOR M, ADAMS RD, COLLINS GH: *The Wernicke-Korsakoff Syndrome: a Clinical and Pathological Study of 245 Patients, 82 with Post-mortem Examinations*, Davis, Philadelphia, 1971, p 16
103. BLASS JP, GIBSON GE: Abnormality of a thiamine-requiring enzyme in patients with Wernicke-Korsakoff syndrome. *N Engl J Med* 297: 1367, 1977
104. GASCON GG, GILLES F: Limbic dementia. *J Neurol Neurosurg Psychiatry* 36: 421, 1973
105. RICHARDSON JC, CHAMBERS RA, HEYWOOD PM: Encephalopathies of anoxia and hypoglycemia. *Arch Neurol* 1: 178, 1959
106. UTZ JP: Histoplasma and cryptococcus meningitis. *Res Publ Assoc Res Nerv Ment Dis* 44: 378, 1964
107. WHYBROW PC, PRANGE AJ JR, TREADWAY CR: Mental changes accompanying thyroid dysfunction. *Arch Gen Psychiatry* 20: 48, 1969
108. STRACHAN RW, HENDERSON JG: Psychiatric syndromes due to avitaminosis B_{12} with normal blood and bone marrow. *Q J Med* 34: 303, 1965
109. REYNOLDS EH, ROTHFIELD P, PINCUS JH: Neurological disease associated with folate deficiency. *Br Med J* 2: 398, 1973
110. WELLS CE (ed): Diagnostic evaluation and treatment in dementia, in *Dementia*, 2nd ed (Contemporary Neurology series), op cit, p 45
111. CARLEN PL, HOLGATE RC, WORTZMAN G, et al: Reversible cerebral atrophy in recently abstinent chronic alcoholics measured by computed tomography scans. *Science* 200: 1076, 1978
112. LEVENTHAL CM, BARINGER JR, ARNASON BG, et al: A case of Marchiafava–Bignami disease with clinical recovery. *Trans Am Neurol Assoc* 90: 87, 1965
113. SIM M, TURNER E, SMITH WT: Cerebral biopsy in the investigation of presenile dementia. I: Clinical aspects. *Br J Psychiatry* 112: 119, 1966
114. FOLSTEIN MF, FOLSTEIN SE, MCHUGH PR: "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189, 1975
115. LIDDEL DW: Investigation of EEG findings in presenile dementia. *J Neurol Neurosurg Psychiatry* 21: 173, 1958
116. FARBROT O: Electroencephalographic study in cases of cerebral vascular accidents (preliminary report). *Electroencephalogr Clin Neurophysiol* 6: 678, 1954
117. BROWN GL, GOLDENSOHN ES: The electroencephalogram in normal pressure hydrocephalus. *Arch Neurol* 29: 70, 1973
118. HUCKMAN MS, FOX J, TOPEL J: The validity of criteria for the evaluation of cerebral atrophy by computerized tomography. *Radiology* 116: 85, 1975
119. GADO MH, COLEMAN RE, LEEK KS, et al: Correlation between computerized transaxial tomography and radionuclide cisternography in dementia. *Neurology (Minneap)* 26: 555, 1976
120. APPENZELLER O, SALMON JH: Treatment of parenchymatous degeneration of the brain by ventriculo-atrial shunting of cerebrospinal fluid. *J Neurosurg* 26: 478, 1967
121. Death of a mind (E). *Lancet* 1: 1012, 1950
122. KAHN RL, ZARIT SH, HILBERT NM, et al: Memory complaint and impairment in the aged. *Arch Gen Psychiatry* 32: 1569, 1975
123. BEREZIN MA: The elderly person, in *The Harvard Guide to Modern Psychiatry*, NICHOLI AM JR (ed), Harvard U Pr, Cambridge, Mass, 1978, p 541
124. RATHBONE-MCCUAN E: Geriatric day care: a family perspective. *Gerontologist* 16: 517, 1976
125. PRINSLEY DM: Psychogeriatric ward for mentally disturbed elderly patients. *Br Med J* 3: 574, 1973
126. BOWER HM: Sensory stimulation and the treatment of senile dementia. *Med J Aust* 1: 1113, 1967
127. ANDERSON F (ed): *Practical Management of the Elderly*, 3rd ed, Lippincott, Philadelphia, 1976, pp 302-18
128. KRAL V: Depressions in the aged and their treatment. *Psych Dig* 33: 49, 1972
129. EISNER DA: Can hyperbaric oxygenation improve cognitive functioning in the organically impaired elderly? A critical review. *J Geriatr Psychiatry* 8: 173, 1975
130. KRAL V: Somatic therapies in old age, in *Practical Geriatrics*, op cit, p 283
131. PETERS BH, LEVIN HS: Memory enhancement after physostigmine treatment in the amnesic syndrome. *Arch Neurol* 34: 215, 1977
132. SMITH CM, SWASH M, EXTON-SMITH A, et al: Choline therapy in Alzheimer's disease (C). *Lancet* 2: 318, 1978
133. BOYD WD, GRAHAM-WHITE J, BLACKWOOD G, et al: Clinical effects of choline in Alzheimer senile dementia (C). *Lancet* 2: 711, 1977