

## 2 Clinical stages of Alzheimer's disease

Barry Reisberg and Emile H. Franssen

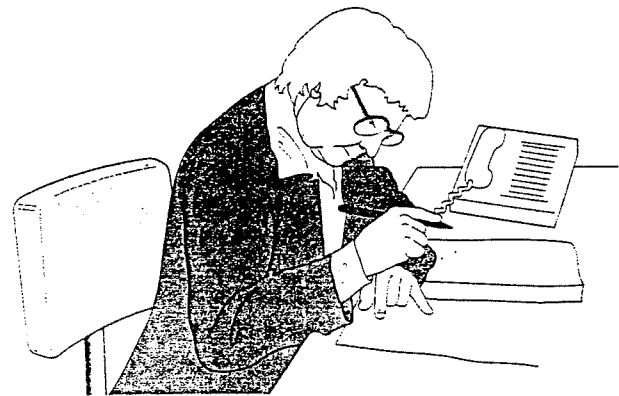
Alzheimer's disease (AD) is a characteristic process with readily identifiable clinical stages. These clinical stages exist in a continuum with normal aging processes. The clinical stages of AD can be described in alternative ways. For example, they can be described globally or they can be described in terms of constituent elements, referred to as clinical axes. One of these clinical axes, functioning and self-care, is particularly useful in describing the progression of AD. However, many conditions, particularly in aged persons, can interfere with functioning apart from AD. For these and other reasons, functioning changes alone do not adequately describe the progress of AD. However, the combination of global changes and their functional concomitants can provide a clear map of the progress of AD. This clinical map is enriched by noting the common behavioral concomitants of the stages. However, the behavioral and mood manifestations of AD are much more diverse than the cognitive and functional features of the disease progression.

Globally, seven major stages from normality to most severe AD are identifiable<sup>2</sup>. Functionally, 16 stages and substages corresponding to the global stages are recognizable<sup>3</sup>. These global and functional clinical stages and substages of aging and AD are summarized as follows.

### Stage 1: Normal

At any age, persons may potentially be free of objective or subjective symptoms of cognition and func-

tional decline and also free of associated behavioral and mood changes. We call these mentally healthy persons at any age, stage 1, or normal (Figure 1).

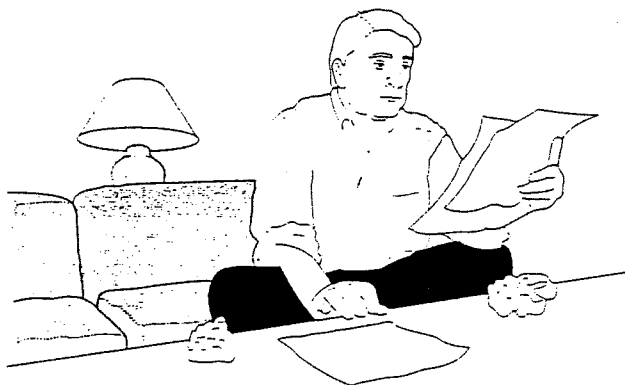


Copyright © 1999 Barry Reisberg, M.D.

Figure 1 Stage 1: Normal

### Stage 2: Normal aged forgetfulness

Half or more of the population of persons over the age of 65 experience subjective complaints of cognitive and/or functional difficulties. The nature of these subjective complaints is characteristic. Elderly persons with these symptoms believe they can no longer recall names as well as they could 5 or 10 years previously. They also frequently develop the conviction that they can no longer recall where they have placed things as well as previously (Figure 2). Subjectively experienced difficulties in concentra-



Copyright © 1999 Barry Reisberg, M.D.

**Figure 2 Stage 2: Normal aged subjective forgetfulness.** 'Why can't I remember where I put those papers? I used to remember where everything that I put away was located'

tion and in finding the correct word when speaking, are also common. Various terms have been suggested for this condition, but normal aged forgetfulness is probably the most satisfactory terminology. These symptoms, which by definition, are not notable to intimates or other external observers of the person with normal aged forgetfulness, are generally benign'. However, there is some recent evidence that persons with these symptoms do decline at greater rates than similarly aged persons and similarly healthy persons who are free of subjective complaints'.

### Stage 3: Mild cognitive impairment

Persons at this stage manifest deficits which are subtle, but which are noted by persons who are closely associated with the stage 3 subject. The subtle deficits may become manifest in diverse ways. For example, the person with mild cognitive impairment (MCI) may noticeably repeat queries. The capacity to perform executive functions also becomes compromised. Commonly, for persons who are still working, job performance may decline. For those who must master new job skills, decrements in these capacities may become evident. For example, the MCI subject may be unable to master new computer skills (Figure 3). MCI subjects who are not employed, but who plan complex social

events, such as dinner parties, may manifest declines in their ability to organize such events. Other MCI subjects may manifest concentration deficits. Many persons with these symptoms begin to experience anxiety, which may be overtly evident'.



Copyright © 1999 Barry Reisberg, M.D.

**Figure 3 Stage 3: Mild memory impairment.** In this stage, ability to perform complex occupational and social tasks is compromised and may be noticeable by colleagues. This is a 'border stage' which does not necessarily progress. When progression does occur, the true (potential) duration of this stage is probably 7 years; however, symptoms are commonly not observed until this stage has progressed at least midway through its temporal course

The prognosis for persons with these subtle symptoms of impairment is variable, even when a select subject group who are free of overt medical or psychological conditions which might account for, or contribute to, the impairments are studied. A substantial proportion of these persons will not decline, even when followed over the course of many years. However, in a majority of persons with stage 3 symptoms, overt decline will occur, and clear symptoms of dementia will become manifest over intervals of approximately 2 to 4 years'. In persons who are not called upon to perform complex occupational and/or social tasks, symptoms in this stage may not become evident to family members or friends of the MCI patient. Even when symptoms do become noticeable, MCI subjects are commonly midway or near the end of this stage before con-

cerns result in clinical consultation. Consequently, although progression to the next stage in MCI subjects commonly occurs in 2 to 3 years, the true duration of this stage, when it is a harbinger of subsequently manifest dementia, is probably approximately 7 years<sup>8</sup>.

Management of persons in this stage includes counseling regarding the desirability of continuing in a complex and demanding occupational role. Sometimes, a 'strategic withdrawal' in the form of retirement, may alleviate psychological stress and reduce both subjective and overtly manifest anxiety.

#### Stage 4: Mild Alzheimer's disease

Symptoms of impairment become evident in this stage. For example, seemingly major recent events, such as a recent holiday or a recent visit to a relative, may, or may not, be recalled. Similarly, overt mistakes in recalling the day of the week, month or season of the year may occur. Patients at this stage can still generally recall their correct current address. They can also generally correctly recall the weather conditions outside and very important current events, such as the name of a prominent head of state. Despite the overt deficits in cognition, persons at this stage can still potentially survive independently in community settings. However, functional capacities become compromised in the performance of instrumental (i.e. complex) activities of daily life. For example, there is a decreased capacity to manage personal finances. For the stage 4 patient who is living independently, this may become evident in the form of difficulties in paying rent and other bills. A spouse may note difficulties in writing the correct date and the correct amount in paying checks (Figure 4). The ability to independently market for food and groceries also becomes compromised in this stage. Persons who previously prepared meals for family members and/or guests begin to manifest decreased performance in these skills. Similarly, the ability to order food from a menu in a restaurant setting begins to be compromised. Frequently, this is manifest in the patient handing the menu to the spouse and saying 'you order'.



Copyright © 1999 Barry Reisberg, M.D.

**Figure 4 Stage 4: Mild Alzheimer's disease.** The diagnosis of Alzheimer's disease can be made with considerable accuracy in this stage. The most common functioning deficit in these patients is a **decreased ability to manage instrumental (complex) activities of daily life**. Examples of common deficits include decreased ability to manage finances, to prepare meals for guests, and to market for oneself and one's family. The stage 4 patient shown has difficulty writing the correct date and the correct amount on the check. Consequently, her husband has to supervise this activity. The mean duration of this stage is 2 years

The dominant mood at this stage is frequently what psychiatrists term a flattening of affect and withdrawal. In other words, the patient often seems less emotionally responsive than previously. This absence of emotional responsiveness is probably intimately related to the patient's denial of their deficit, which is often also notable at this stage. Although the patient is aware of their deficits, this awareness of decreased intellectual capacity is too painful for most persons and, hence, the psychological defense

mechanism known as denial, whereby the patient seeks to hide their deficit, even from themselves where possible, becomes operative. In this context, the flattening of affect occurs because the patient is fearful of revealing their deficits. Consequently, the patient withdraws from participation in activities such as conversations.

In the absence of complicating medical pathology, the diagnosis of AD can be made with considerable certainty from the beginning of this stage. Studies indicate that the duration of this stage of mild AD is a mean of approximately 2 years.

### Stage 5: Moderate Alzheimer's disease

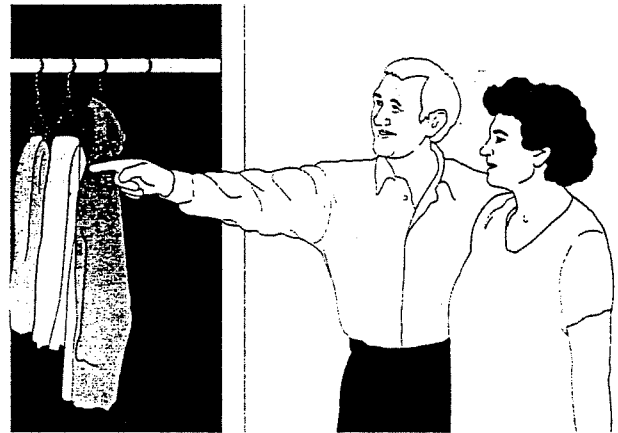
At this stage, deficits are of sufficient magnitude as to prevent independent, catastrophe-free, community survival. Patients can no longer manage on their own in the community. If they are ostensibly alone in the community then there is generally someone who is assisting in providing adequate and proper food, as well as assuring that the rent and utilities are paid and the patient's finances are taken care of. For those who are not properly watched and/or supervised, predatory strangers may become a problem. Very common reactions for persons at this stage who are not given adequate support are behavioral problems such as anger and suspiciousness.

Cognitively, persons at this stage frequently cannot recall such major events and aspects of their current lives as the name of the current president, the weather conditions of the day, or their correct current address. Characteristically, some of these important aspects of current life are recalled, but not others. Also, the information is loosely held, so, for example, the patient may recall their correct address on certain occasions, but not others.

Remote memory also suffers to the extent that persons may not recall the names of some of the schools which they attended for many years, and from which they graduated. Orientation may be compromised to the extent that the correct year may not be recalled. Calculation deficits are of such magnitude

that an educated person has difficulty counting backward from 20 by 2s.

Functionally, persons at this stage have incipient difficulties with basic activities of daily life. The characteristic deficit of this type is decreased ability to independently choose proper clothing (Figure 5). This stage lasts an average of approximately 1.5 years.

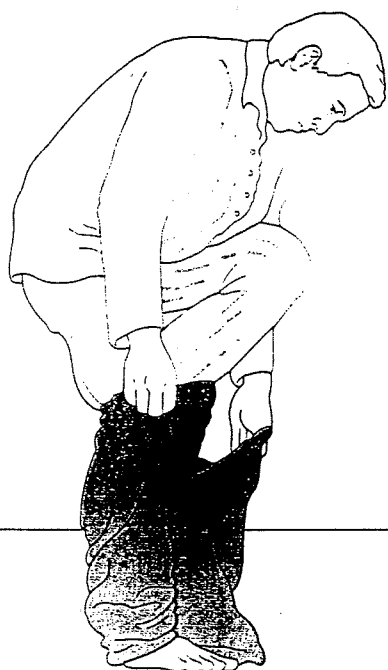


Copyright © 1999 Barry Reisberg, M.D.

**Figure 5 Stage 5: Moderate Alzheimer's disease.** In this stage, deficits are of sufficient magnitude as to prevent catastrophe-free, independent community survival. The characteristic functional change in this stage is **incipient deficits in basic activities of daily life**. This is manifest in a **decrement in the ability to choose proper clothing to wear** for the weather conditions and/or for the daily circumstances (occasions). Some patients begin to wear the same clothing day after day unless reminded to change. The spouse or other caregiver begins to counsel regarding the choice of clothing. The mean duration of this stage is 1.5 years

### Stage 6: Moderately severe Alzheimer's disease

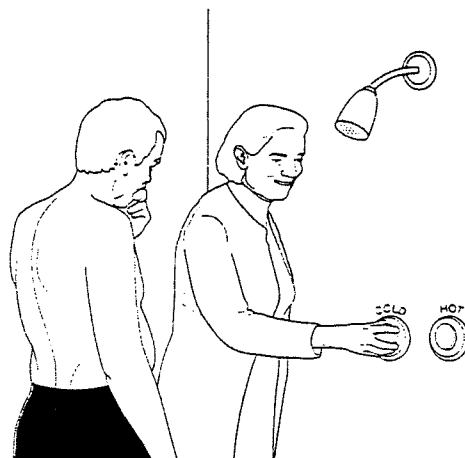
At this stage, the ability to perform basic activities of daily life becomes compromised. Functionally, five successive substages are identifiable. Initially, in stage 6a, patients, in addition to having lost the ability to choose their clothing without assistance, begin to require assistance in putting on their clothing properly. Unless supervised, patients may put their clothing on backward, they may have difficulty putting their arm in the correct sleeve, or they may



Copyright © 1999 Barry Reisberg, M.D.

**Figure 6 Stage 6a: Moderately severe Alzheimer's disease.** In the stage of moderately severe Alzheimer's disease, the cognitive deficits are of sufficient magnitude as to interfere with the ability to carry out basic activities of daily life. Generally, the earliest such deficit noted in this stage is decreased ability to put on clothing correctly without assistance. The total duration of the stage of moderately severe AD (stage 6a through 6e) is approximately 2.5 years

dress themselves in the wrong sequence. For example, patients may put their street clothes on over their night clothes (Figure 6). At approximately the same point in the evolution of AD, but generally just a little later in the temporal sequence, patients lose the ability to bathe independently without assistance (stage 6b). Characteristically, the earliest and most common deficit in bathing is difficulty adjusting the temperature of the bath water (Figure 7). Initially, once the spouse adjusts the temperature of the bath water, the patient can still potentially otherwise bathe independently. Subsequently, as this stage evolves, additional deficits in bathing independently as well as in dressing independently

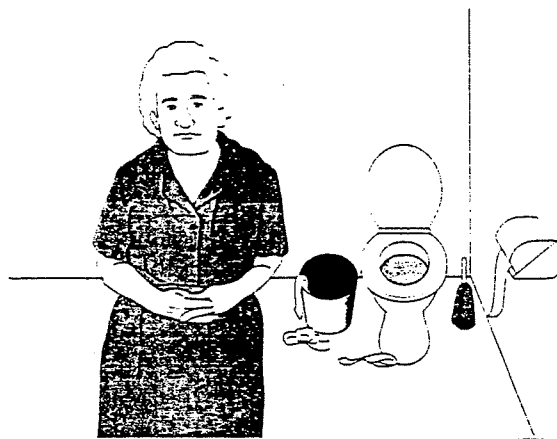


Copyright © 1999 Barry Reisberg, M.D.

**Figure 7 Stage 6b: Moderately severe Alzheimer's disease.** Requires assistance adjusting the temperature of the bath water. At approximately the same time as Alzheimer's patients begin to lose the ability to put on their clothing properly without assistance, but generally just a little bit later in the disease course, patients begin to require assistance in handling the mechanics of bathing. Difficulty adjusting the temperature of the bath water is the classical earliest deficit in bathing capacity in Alzheimer's disease

occur. In this 6b substage, patients generally develop deficits in other modalities of daily hygiene such as properly brushing their teeth independently. With the further evolution of AD, patients lose the ability to manage independently the mechanics of toileting correctly (stage 6c). Unless supervised, patients may place the toilet tissue in the wrong place (Figure 8). Many patients will forget to flush the toilet properly. As the disease evolves in this stage, patients subsequently become incontinent. Generally, urinary incontinence occurs first (stage 6d), then fecal incontinence occurs (stage 6e). The incontinence can be treated, or even initially prevented entirely in many cases, by frequent toileting (Figure 9). Subsequently, strategies for managing incontinence, including appropriate bedding, absorbent undergarments, etc., become necessary.

In this sixth stage cognitive deficits are generally so severe that persons will display little or no knowledge when queried regarding such major aspects of their current life circumstances as their current address or the weather conditions of the day. Recall



Copyright © 1999 Barry Reisberg, M.D.

**Figure 8 Stage 6c: Moderately severe Alzheimer's disease.** Requires assistance with cleanliness in toileting. After Alzheimer's patients lose the ability to dress and bathe without assistance, they lose the ability to independently maintain cleanliness in toileting



Copyright © 1999 Barry Reisberg, M.D.

**Figure 10 Stage 6: Moderately severe Alzheimer's disease.** In this stage the patient's cognitive deficits are generally of such magnitude that the patient may at times confuse their wife with their mother or otherwise misidentify or be uncertain of the identity of close family members. At the end of this stage, speech ability overtly breaks down



Copyright © 1999 Barry Reisberg, M.D.

**Figure 9—Stage 6d and 6e: Moderately severe Alzheimer's disease.** Requires assistance to maintain continence. After Alzheimer's patients lose the ability to dress, bathe and toilet without assistance, they develop incontinence. Generally, urinary incontinence precedes fecal incontinence. Strategies to prevent episodes of incontinence include taking the patient to the restroom and supervision of toileting

of current events is generally deficient to the extent that the patient cannot name the current national head of state or other, similarly prominent newsworthy figures. Persons at this sixth stage will most often not be able to recall the names of any of the schools which they attended. They may, or may

not, recall such basic life events as the names of their parents, their former occupation and the country in which they were born. They still have some knowledge of their own names; however, patients in this stage begin to confuse their spouse with their deceased parent and otherwise mistake the identity of persons, even close family members, in their own environment (Figure 10). Calculation ability is frequently so severely compromised at this stage that even well-educated patients have difficulty counting backward consecutively from 10 by 1s.

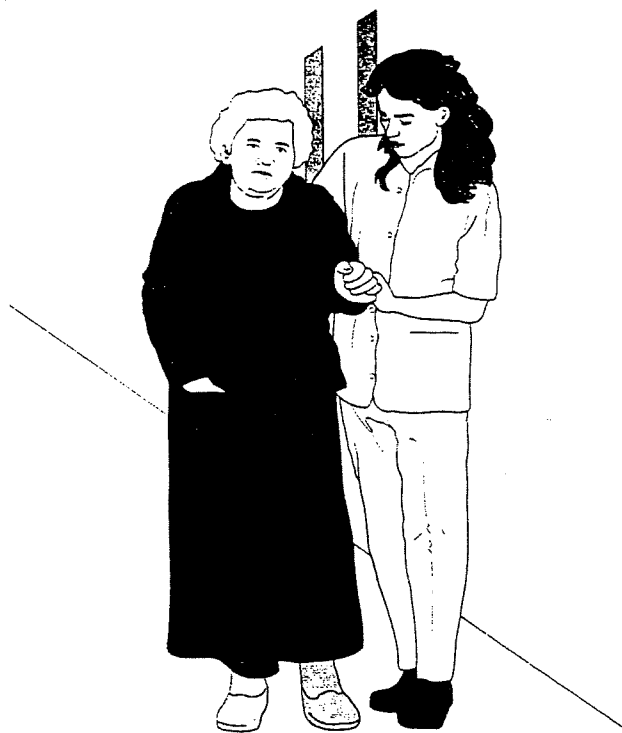
Emotional changes generally become most overt and disturbing in this sixth stage of AD. Although these emotional changes may, in part, have a neurochemical basis, they are also clearly related to the patient's psychological reaction to their circumstances. For example, because of their cognitive deficits, patients can no longer channel their energies into productive activities. Consequently, unless appropriate direction is provided, patients begin to fidget, to pace, to move objects around and place items where they may not belong, or to manifest other forms of purposeless or inappropriate activities. Because of the patient's fear, frustration and shame regarding their circumstances, as well as other factors, patients frequently develop verbal

outbursts, and threatening, or even violent, behavior may occur. Because patients can no longer survive independently, they commonly develop a fear of being left alone. Treatment of these and other behavioral and psychological symptoms which occur at this stage, as well as at other stages of AD, involves counseling regarding appropriate activities and the psychological impact of the illness upon the patient, as well as pharmacological interventions<sup>4,12</sup>.

The mean duration of this sixth stage of AD is approximately 2.5 years<sup>8</sup>. As this stage comes to an end, the patient, who is doubly incontinent and needs assistance with dressing and bathing, begins to manifest overt breakdown in the ability to articulate speech. Stuttering (verbigeration), neologisms, and/or an increased paucity of speech, become manifest.

### Stage 7: Severe Alzheimer's disease

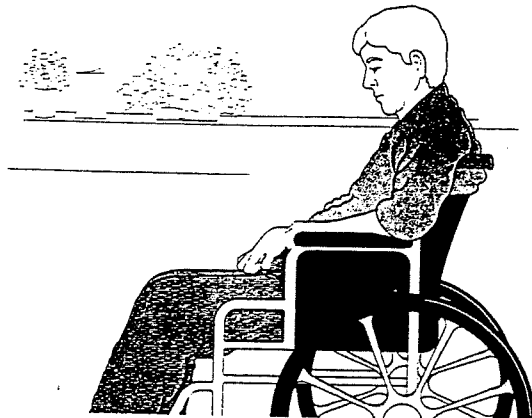
At this stage, AD patients require continuous assistance with basic activities of daily life for survival. Six consecutive functional substages can be identified over the course of this final seventh stage. Early in this stage, speech has become so circumscribed, as to be limited to approximately a half dozen intelligible words or fewer in the course of an intensive contact and attempt at an interview with numerous queries (stage 7a). As this stage progresses, speech becomes even more limited to, at most, a single intelligible word (stage 7b). Once speech is lost, the ability to ambulate independently (without assistance), is invariably lost (stage 7c, Figure 11). However, ambulatory ability is readily compromised at the end of the sixth stage and in the early portion of the seventh stage by concomitant physical disability, poor care, medication side-effects or other factors. Conversely, superb care provided in the early seventh stage, and particularly in stage 7b, can postpone the onset of loss of ambulation, potentially for many years. However, under ordinary circumstances, stage 7a has a mean duration of approximately 1 year, and stage 7b has a mean duration of approximately 1.5 years<sup>6,13</sup>. In patients who remain alive, stage 7c lasts approximately 1 year<sup>6,13</sup>, after which patients lose the ability not only to ambulate independently, but also to sit up inde-



Copyright © 1999 Barry Reisberg, M.D.

**Figure 11 Stage 7: Severe Alzheimer's disease.** Early in the course of this final stage of AD speech ability is limited to only a few words. Later, all intelligible speech is essentially lost, with speech limited to, at most, a single intelligible word. Subsequently, **ambulatory ability is lost and the patient requires assistance in walking**. Each substage of this final seventh stage lasts an average of 1–1.5 years

pendently (stage 7d). At this point in the evolution of AD, patients will fall over when seated unless there are arm rests to hold the patient up in the chair (Figure 12). This 7d substage lasts approximately 1 year<sup>6,13</sup>. Patients who survive subsequently lose the ability to smile (stage 7e). At this substage only grimacing facial movements are observed in place of smiles. This 7e substage lasts a mean of approximately 1.5 years<sup>6,13</sup>. It is followed in survivors, by a final 7f substage, in which AD patients additionally lose the ability to hold up their head independently.

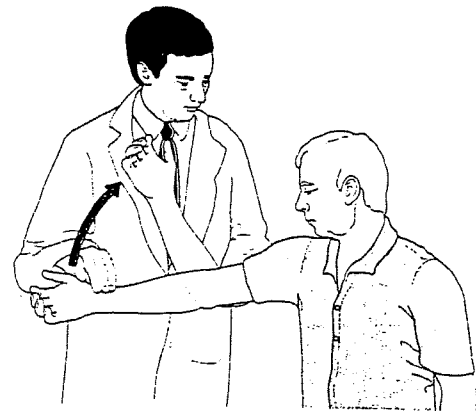


Copyright © 1999 Barry Reisberg, M.D.

**Figure 12 Stage 7d: Severe Alzheimer's disease.** Without armrests on the chair, the patients would fall over. In the latter portion of the final stage of AD, patients become immobile to the extent that they require support to sit up without falling. With the advance of this stage, patients lose the ability to smile and, ultimately, to hold up their head without assistance, unless their neck becomes contracted and immobile. Patients can survive in this final 7f substage indefinitely; however, most patients succumb during the course of stage 7

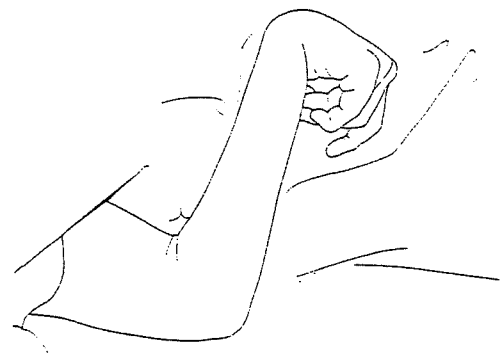
With appropriate care and life support, patients can survive in this final substage of AD for a period of years.

With the advent of the seventh stage of AD, certain physical and neurological changes become increasingly evident. One of these changes is physical rigidity. Evident rigidity upon examination of the passive range of motion of major joints, such as the elbow, is present in the great majority of patients, throughout the course of the seventh stage (Figure 13)<sup>14,15</sup>. In many patients, this rigidity appears to be a precursor to the appearance of overt physical deformities in the form of contractures. Contractures are irreversible deformities which prevent the passive or active range of motion of joints (Figure 14). In the early seventh stage (7a and 7b), approximately 40% of AD patients manifest these deformities<sup>16</sup>. Later in the seventh stage, in immobile patients (from stage 7d to 7f), nearly all AD patients manifest contractures in multiple extremities and joints<sup>16</sup>.



Copyright © 1999 Barry Reisberg, M.D.

**Figure 13 In the final stages of AD patients manifest increasing rigidity.** Rigidity is evident to the examiner in the stage 7 patient upon passive range of motion of major joints such as the elbow



Copyright © 1999 Barry Reisberg, M.D.

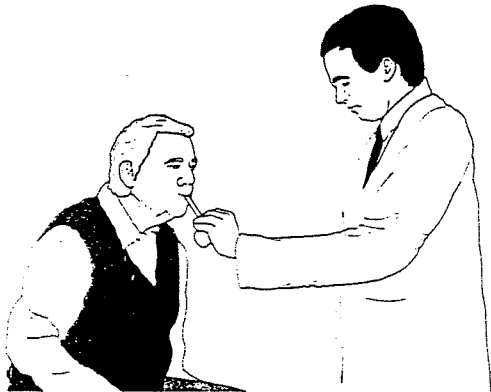
**Figure 14 Contractures of the elbow, wrists and fingers.** Development of joint deformities known as contractures, is an increasing problem in the stage 7 Alzheimer's disease. A contracture is a joint deformity which makes full range of movement of a joint impossible without producing severe pain. Approximately 40% of patients in stage 7a and 7b manifest these deformities to the extent that they cannot move a major joint more than half way. In the immobile Alzheimer's patient (stages 7d to 7f), approximately 95% of patients manifest these deformities which are usually present in many joints

Neurological reflex changes also become evident in the stage 7 AD patient. Particularly notable is the emergence of so-called 'infantile', 'primitive' or 'developmental' reflexes which are present in the



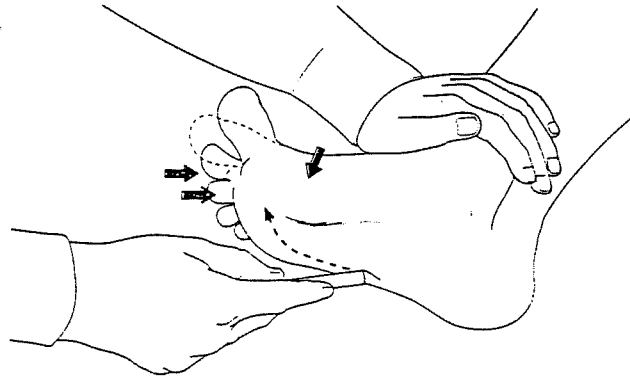
infant but which disappear in the toddler. These reflexes, including the grasp reflex, sucking reflex (Figure 15), and the Babinski plantar extensor reflex (Figure 16), generally begin to re-emerge in the latter part of the sixth stage and are usually present in the stage 7 AD patient<sup>7</sup>. Because of the much greater physical size and strength of the AD patient in comparison with an infant, these reflexes can be very strong and can impact both positively and negatively on the care provided to the AD patient<sup>8</sup>.

AD patients commonly die during the course of the seventh stage. The mean point of demise is when patients lose the ability to ambulate and to sit up



Copyright © 1999 Barry Reisberg, M.D.

**Figure 15 Sucking reflex.** 'Primitive' reflexes, also known as 'infantile' reflexes or 'developmental' reflexes, such as the sucking reflex, are evident in the stage 7 Alzheimer's patient



Copyright © 1999 Barry Reisberg, M.D.

**Figure 16 Babinski or plantar extensor reflex.** Another infantile reflex seen in the stage 7 Alzheimer's patient is the Babinski reflex. This abnormal response to stimulation of the sole of the foot is marked by dorsiflexion of the great toe and fanning of the other digits of the foot

independently (stages 7c and 7d). The most frequent proximate cause of death is pneumonia. Aspiration is one common cause of terminal pneumonia. Another common cause of demise in AD is infected decubital ulcerations. AD patients in the seventh stage appear to be more vulnerable to all of the common causes of mortality in the elderly including stroke, heart disease and cancer. Some patients in this final stage appear to succumb to no identifiable condition other than AD.

Illustrations featured in Chapter 2

Copyright © 1999 by Barry Reisberg, M.D.

## References

1. Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139: 1136-9
2. Reisberg B, Sclan SG, Franssen EH, et al. Clinical stages of normal aging and Alzheimer's disease: the GDS staging system. *Neurosci Res Commun* 1993;13 (Suppl 1):551-4
3. Reisberg B. Functional assessment staging (FAST). *Psychopharmacol Bull* 1988;24:653-9
4. Flicker C, Ferris SH, Reisberg B. A longitudinal study of cognitive function in elderly persons with subjective memory complaints. *J Am Geriatr Soc* 1993; 41:1029-32
5. Geerlings MI, Jonker C, Bouter LM, et al. Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. *Am J Psychiatry* 1999;156:531-7
6. Reisberg B, Kluger A. Assessing the progression of dementia: diagnostic considerations. In Salzman C,

- ed. *Clinical Geriatric Psychopharmacology*. Baltimore, 1998:432-62
7. Flicker C, Ferris SH, Reisberg B. Mild cognitive impairment in the elderly: predictors of dementia. *Neurology* 1991;41:1006-9
  8. Reisberg B, Ferris SH, Franssen E, et al. Mortality and temporal course of probable Alzheimer's disease: a five-year prospective study. *Int Psychogeriatr* 1996;8:291-311
  9. Reisberg B, Franssen E, Sclan SG, et al. Stage specific incidence of potentially remediable behavioral symptoms in aging and Alzheimer's disease: a study of 120 patients using the BEHAVE-AD. *Bull Clin Neurosci* 1989;54:95-112
  10. Finkel SI, Costa e Silva JC, Cohen GD, et al. Behavioral and psychological symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. *Am J Geriatr Psychiatry* 1998;6:97-100
  11. Reisberg B, Kenowsky S, Franssen EH, et al. President's Report: Towards a science of Alzheimer's disease management: a model based upon current knowledge of retrogenesis. *Int Psychogeriatr* 1999;11:7-23
  12. Katz I, Jeste D, Mintzer JE, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. *J Clin Psychiatry* 1999;60:107-15
  13. Bobinski M, Wegiel J, Tarnawski M, et al. Relationships between regional neuronal loss and neurofibrillary changes in the hippocampal formation and duration and severity of Alzheimer disease. *J Neuropath Exp Neurol* 1997;56:414-20
  14. Franssen EH, Reisberg B, Kluger A, et al. Cognition independent neurologic symptoms in normal aging and probable Alzheimer's disease. *Arch Neurol* 1991;48:148-54
  15. Franssen EH, Kluger A, Torossian CL, Reisberg B. The neurologic syndrome of severe Alzheimer's disease. Relationship to functional decline. *Arch Neurol* 1993;50:1029-39
  16. Souren LEM, Franssen EH, Reisberg B. Contractures and loss of function in patients with Alzheimer's disease. *J Am Geriatr Soc* 1995;43:650-5
  17. Franssen EH, Souren LEM, Torossian CL, Reisberg B. Utility of developmental reflexes in the differential diagnosis and prognosis of incontinence in Alzheimer's disease. *J Geriatr Psychiatry Neurol* 1997;10:22-8
  18. Souren LEM, Franssen EH, Reisberg B. Neuromotor changes in Alzheimer's disease: implications for patient care. *J Geriatr Psychiatry Neurol* 1997;10:93-8