Retrogenesis theory in Alzheimer's disease: Evidence and clinical implications[*]

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Título: Teoría de la retrogénesis en la enfermedad de Alzheimer: Evidencia e implicaciones clínicas.
Resumen: La enfermedad de Alzheimer (EA) es una de las principales causas de muerte en el mundo. El bajo índice de natalidad, la mejora en las condiciones sanitarias y sociales y, como consecuencia, el aumento en la esperanza de vida, han hecho que el número de personas mayores de 65 años aumente cada vez más. Este aumento en la expectativa de vida ha llevado a que el número de casos nuevos de personas que presentan EA se haya incrementando de manera dramática en los últimos años. Diferentes estudios han demostrado que conforme va evolucionando la enfermedad de Alzheimer, se suele producir una regresión de las capacidades cognitivas, funcionales y físicas a estadios evolutivos previos del desarrollo. El presente artículo tiene como objetivo realizar una revisión de la evidencia que apoya el concepto de retro-génesis en la Enfermedad de Alzheimer, a la luz de la teoría del desarrollo evolutivo de Piaget. Se examinará la teoría de la retro-génesis tanto desde una perspectiva clínica, cognitiva, funcional, neurológica y neuropatológica. Finalmente, se discutirá las implicaciones que la teoría de la retro-génesis puede tener en la creación e implementación de programa de rehabilitación para personas con demencia.
Palabras clave: Enfermedad de Alzhimer; retro-génesis; rehabilitación.

Abstract: Alzheimer's disease (AD) is a one of the top leading causes of death in the world. In the United States alone, over 4.5 million Americans had Alzheimer's in the year 2000. The annual number of new cases is increasing dramatically every year as people begin to reach older ages in which the prevalence of AD is higher and as people survive longer with the disease. Anecdotal observations of individuals with AD from family members and/or caregivers indicate how suffers become "childlike" as the disease progresses. Recent research suggests that the progression of AD occurs in reverse order of normal human development. The present article reviews the evidence supporting this theory of retrogenesis. Cognitive, functional, neurologic and neuropathologic progression of AD will be examined and compared to developmental acquisition in each area. Potential implications of the retrogenesis theory on rehabilitation program development and implementation for individuals with dementia will be discussed.
Key words: Alzheimer's disease; retrogenesis theory; rehabilitation.

Introduction

According to 2002 census data, Alzheimer's disease (AD) ranks as the eighth leading cause of death in the United States and caused 59000 deaths in that year alone (Centers for Disease Control and Prevention, 2005). Over 4.5 million Americans were estimated to be suffering with this disease in the year 2000, a two-fold increase from the 1980 estimates (Herbert, *et al.*, 2003). Herbert and colleagues (2003) were able to predict the prevalence of AD in 2050; they report that 13.2 to 16 million Americans will have the disease if current population trends continue and no preventive treatments for Alzheimer's disease emerge. The annual number of new cases will begin to climb sharply around the year 2040, when all the baby boomers will be over 65. Two factors contribute to this change: (1) an increase in the number and proportion of people who survive to the oldest ages where AD is more frequent, and (2) an increase in survival rates of people with the disease.

However, AD is *not* a normal part of aging. It is a slow disease, starting with mild memory problems and ending

with severe brain damage. Although the progression of the disease varies from person to person, patients with AD live an average of 5 years after diagnosis, but can live for up to 20 years (Larson, *et al.*, 2004). The term dementia refers a loss of intellectual capacity that interferes with everyday functioning as result of a specific disease or condition (Weiner, 2003). Alzheimer's disease is the most common form of dementia, accounting for 50 to 70% of all forms of dementia (Launer & Hofman, 2000). The cognitive and functional impact of the disease is often referred to as dementia of the Alzheimer's type, or DAT.

Family members and caregivers of individuals suffering from DAT often observed that these individuals tended to become "childlike" as the disease progressed (Arango & Rogers, 2003). Current research has been focused on elucidating this process of "returning to childhood" that has been anecdotally documented to occur in patients with dementia of the Alzheimer's type and vascular dementia. This research suggests that degenerative mechanisms reverse the order of acquisition in normal human development. The process is known as retrogenesis (Reisberg, *et al.*, 1999a) and involves functional, behavioral, cognitive, and neurologic degeneration, as well as to the neuropathologic changes that occur in AD.

This process of retrogenesis is so robust that the stages of AD can be translated into corresponding developmental ages (DAs). This is important because an awareness of a patient's current developmental age can assist in providing appropriate management and care. As Alzheimer's disease continues to affect a growing percentage of the population, this

line of research also naturally extends to the development of innovative interventions to prevent decline and improve cognitive, social and behavioral outcomes in these patients. For example, an intergenerational program that pairs individuals with AD and preschool-aged children with similar DAs could be implemented that meets the developmental needs of both parties involved so that young children and the older adults with dementia can benefit from the interaction. After examining the stages of AD and providing evidence to support the retrogenesis phenomenon in the progression of Alzheimer's disease, we will discuss potential implications of this retrogenesis theory for rehabilitation professionals with a specific emphasis on involving young children in rehabilitation programs and designing activities that are appropriate to the developmental age of the older adult with AD.

General Stages of Alzheimer's Disease

The development of Alzheimer's disease begins in the entorhinal cortex an area near the hippocampus. Next, it spreads to the hippocampus, which is essential to the formation of short-term and long-term memories. These affected regions begin to atrophy. The brain changes are thought start 10 to 20 years before any visible signs and symptoms appear. Forgetfulness, or problems with short term (working) memory, is the first visible sign of the underlying disease.

As the disease begins to affect the cerebral cortex, memory loss continues and changes in other cognitive abilities emerge. The clinical diagnosis of AD is usually made during this stage. Signs of mild AD can include: memory loss, confusion in unfamiliar places, difficulty with finances, impaired judgment, loss of spontaneity and sense of initiative, and mood and personality changes, including increased anxiety. In the brain, amyloid plaques and neurofibrillar tangles (the hallmarks of Alzheimer's disease) first damage areas of brain that control memory, language, and reasoning. Physical/functional abilities do not decline until later in the disease (Arango, 2004).

By this moderate stage AD, damage has spread further to the areas of the cerebral cortex that control language, reasoning, sensory processing, and conscious thought. Affected regions continue to atrophy and signs and symptoms of the disease become more pronounced and widespread. Behavior problems, such as wandering and agitation, can occur. More intensive supervision and care become necessary. Symptoms of this stage can include enhanced memory loss and language problems, shortened attention span, difficulties recognizing familiar faces, language problems, difficulty organizing thoughts and thinking logically, occurrence of repetitive statements or movement, presence of hallucinations or delu-

sions, appearance of suspiciousness or paranoia, irritability, loss of impulse control, and perceptual-motor problems (Arango & Fernandez, 2003; Arango & Rogers, 2002).

In the last stage of AD, known as severe AD, plaques and tangles are widespread throughout the brain and areas of the brain have atrophied further. Patients cannot recognize familiar loved ones and are unable to communicate. Symptoms during this stage can include: weight loss, seizures, skin infections, difficulty swallowing, groaning, moaning, or grunting, somnolence, and urinary and fecal incontinence. At the end, patients may be in bed much or all of the time. It is common for most people with AD to die from other illnesses.

Cognitive Retrogenesis

Ajuriaguerra and Tissot (1968) were the first researchers to take an empirical approach to the study of retrogenesis. They observed that the decline of certain capacities in dementia appeared to reverse Piaget's developmental stages. Jean Piaget's theory of intellectual development (1952) identified four major stages and emphasized the interactive relationship between internal operations and the environment in the acquisition of knowledge. Cognition and behavior development in children and loss in people with DAT we found to be remarkably similar (Matteson, Linton, and Barnes, 1996) (see Table 1). Patients with dementia of the Alzheimer's type do indeed appear to "go backwards" through the sensorimotor, preoperational, concrete operational, and formal operational stages defined by Piaget.

Piaget's developmental theory also assisted researchers in the assessment of residual cognitive capacities of older adults with dementia in the more severe stages. These patients often had severely impaired function and were previously considered "untestable". A Piagetian test battery (the Uzgiris and Hunt Ordinal Scales of Psychological Development - OSPD) that was originally designed to assess an infant's level of sensorimotor development from birth to age 2 was adapted for the AD population. There were five subscales in this new version of the OSPD: (1) visual pursuit and object permanence, i.e., tracking an object through an arc of 180 degrees, (2) means-ends, i.e., reaching out for an object, (3) causality, i.e., appropriately responding (e.g., with a smile) to an event, (4) spatial relations, i.e., glancing between two visually presented objects/persons, and (5) schemes, i.e., visually inspecting an object held in hands. The scale is hierarchical and the highest rated task performed is the raw score for each individual subscale. The sum of the subscales was the total score, ranging from 0 to 55. Cognitive decline using this measure was highly correlated with functional decline in later stages of AD (Auer, *et al.*, 1994).

Table 1: Piaget's Developmental Levels and Corresponding Stages of Alzheimer's Disease.

Piaget Developmental Level	Alzheimer's Disease Stage
1. *Sensorimotor Period (Birth – Age 2)*	*Severe stage AD*
Substage 1: Use of reflexes	Speech and motor dysfunction Few words spoken
Substage 2: Primary Circular Reaction (PCR)	Incontinence Unable to walk or eat
Substage 3: Secondary Circular Reaction (SCR)	
Substage 4: Coordination of SCRs	*Moderate stage AD*
Substage 5: Tertiary Circular Reactions (TCR)	Recent memory loss Remote memory preserved Unaware of surroundings
Substage 6: Invention of new means through deduction	Personal hygiene problems Agitation, wandering, obsessive symptoms Difficulty counting to 10
2. *Preoperational Period (Age 2-7)*	*Mild stage AD*
Stage 1: Preconceptual Stage	Difficulty choosing proper clothing Bathes only with coaxing
Stage 2: Perceptual or Intuitive Stage	Cannot subtract 3 repeatedly starting at 20
3. *Concrete Operational Stage (Age 7-12)*	*Early stage AD* Decreased ability to perform in job Increased difficulty in social interactions Deficit in memory and concentration Difficulty with counting up by 7
4. *Formal Operational Stage (Age 12+)*	*Preclinical* Normal forgetfulness - No impairment Possible subjective worry about memory loss

Adapted from Matteson, Linton & Barnes (1995).

Functional Retrogenesis

The Functional Assessment Staging (FAST) procedure describes 16 successive functional stages and substages of loss of capacity (Reisberg, 1988). As the disease progresses, individuals with AD lose the following sequence of abilities. First, they lose their ability to hold a job (FAST stage 3), and then become unable to manage their finances (FAST stage 4). They cannot select appropriate clothing for the occasion (FAST stage 5), put on clothes without help (FAST stage 6a), shower without help (FAST stage 6b), or toilet without help (FAST stage 6c). They become unable to control their urine (FAST stage 6d) and their bowels (FAST stage 6e). At later stages in the disease, they can only speak only five to six words (FAST stage 7a), then just one word (FAST stage 7b). They have lost all other abilities and are only able to walk (FAST stage 7c), then simply sit up (FAST stage 7d),

then only smile (FAST stage 7e), and finally only hold up one's head without assistance (FAST stage 7f).

It is readily apparent that the FAST progression in reverse describes the capacities that an infant gains over the course of human development. At one to three months, he/she can hold up his/her head without help. At two to four months he/she can smile. By six to ten months, he/she can sit up. By one year he/she can walk and speak one word. By 15 months, his/her vocabulary grows to five to six words. At age two or three, he/she learns to control his/her bowels and, at age three to four and a half, her urine. By age four, he/she can toilet unaided and shower unaided. At age five, he/she can dress herself. Between the ages of five and seven, she learns to select the proper clothes. At age eight to twelve, she begins to handle simple finances, and between ages 12 and 18 she holds her first job. The functional deterioration sequenced by a person with AD reverses the order of acquisition of the same functions in human development.

Each FAST stage can be heuristically translated into a corresponding developmental age (DA), or the age at which each ability is acquired (Reisberg, *et al.*, 1998). Due to individual differences, there is some variability in the precise temporal and ordinal sequence of acquisition of functional abilities in children. Coincidentally, the variability in the loss of these same functions in the person with AD is of similar magnitude (Sclan & Reisberg, 1992). In addition, the time it takes a child to acquire each ability or set of abilities is approximately the same amount of time needed for a person with Alzheimer's disease to lose the same capacity (Reisberg *et al.*, 2002).

The FAST was found to be strongly correlated with other measures of dementia, such as the Mini-Mental State Examination, however the final six to eight FAST stages produced floor effects using this measure (Reisberg, 1984). Post-mortem examination of the brains of individuals with AD showed that deterioration, as measured by the FAST, was strongly correlated with neuropathological changes, including hippocampal volume loss, cell loss, and neurofibrillary changes (Reisberg, 2002).

The Brief Cognitive Rating Scale (BCRS) is another instrument that describes sequences of progressive losses in Alzheimer's disease. Some of its subscales can be translated into developmental ages (DAs), for example the geometric figure drawing and the food preparation and self-feeding subscales (Reisberg, 1998). Many emotional changes in AD are also explainable, in part, on the basis of the corresponding DAs. Thus, if a developmental age can be obtained, that DA can be used to anticipate the loss of other abilities, as well as identify general management needs and activity preferences. These AD-DA correspondences have been found to be valid despite differences between AD patients and infants in physical size, life history, societal and self expectations, concurrent morbidity, and other factors (Reisberg, 2002).

Neurologic Retrogenesis

Studies have shown that "primitive reflexes" or "developmental reflexes" (such as the sucking reflex, the hand and foot grasp reflexes, the rooting reflex and the Babinski plantar extension reflex) that disappear in the first few years of life re-appear in people with advanced stage Alzheimer's disease. Interestingly, these reflexes appear to emerge at approximately the same point in the process of AD deterioration as might be anticipated by the corresponding DA. For example, Franssen and colleagues (1997) grouped AD patients according to their FAST stage score and then calculated the percentage of each group manifesting one or more of these developmental reflexes. Less than 1% of the normal or mildly impaired (FAST stages 1-3) individuals were found to have any of these reflexes. The developmental age at this stage corresponds to the period of adolescence to adulthood, in which the reflexes are not typically observed. Developmental reflexes were also uncommon (less than 5%) in

the mild to moderate AD group (FAST stages 4 – 5). In a similar vein, these developmental reflexes are highly unlikely to be observed in a group of five- to twelve-year-old children. However, in the severe stages of Alzheimer's disease (FAST stages 7a and 7b and stages 7c and 7d), 85% and 97% of each group respectively manifest at least one developmental reflex. Notably, these are the developmental stages in infancy of 12-15 months and newborn to 12 months in which the sucking reflex, the hand and foot grasp reflexes, the rooting reflex and the Babinski plantar extension reflex are much more likely to appear.

Neuropathologic Retrogenesis

In the study of brain development, the disappearance of primitive reflexes in infants has been related to the progressive myelination of neurons in the brain. The pattern of myelination in the pattern has also been related to the progression of neuropathologic losses observed in Alzheimer's disease. Specifically, areas of the brain that are the last to be myelinated are the most vulnerable to death and decreased glucose metabolism in AD (McGeer, *et al.*, 1990). Braak and Braak (1991) studied neurofibrillar pathology and noted that the stages of change in AD reverse the pattern and sequencing of myelination in normal development as measured by the Fleshing stages of progressive developmental myelination. Moreover, non-human primate research in this area has even shown that cognitive decline in a Rhesus monkey is correlated with increased myelin degeneration (Peters, *et al.*, 1996). This finding is consistent with the theory of retrogenesis and suggests a link between neuropathological deterioration in AD and progressively worsening cognitive and functional abilities. These changes as a group then correspond to a specific developmental age.

Implications of Retrogenesis and Developmental Age on AD Care

Humans of all ages have needs, including movement, socialization, love, and dignity. Unfortunately, these fundamental needs are not always well understood in persons with Alzheimer's disease. According to the studies examined in the previous sections, an understanding of the phenomenon of retrogenesis can provide insight into a person's true developmental age. Armed with a DA for each individual with Alzheimer's disease, a rehabilitation professional can engage the person in developmentally appropriate tasks that foster a sense of accomplishment and self-worth while maintaining dignity. As the disease progresses, just like an infant, the person with AD needs continued love, praise, acceptance, and opportunities for socialization. Even in the most severe stages of the disease, individuals maintain the capacity to remember, think, learn, and influence their environment within the context of their developmental age. Thus the amount and type of care required for a person with AD de-

pends on his or her DA (Reisberg, *et al.*, 1999b) and the kinds of activities enjoyed by a person with AD at a particular DA are mirrored by the types of activities enjoyed by children at the same DA.

One caveat to note is the lack of physical retrogenesis. It is possible that the physical capacities (e.g., lacing, buttoning, slipping on clothing) of a person with AD at a particular developmental age may exceed those of DA-comparable children. In addition, the grasp reflex can be much stronger in the individual with AD as a consequence of their size and strength compared to an infant. It is also important to recognize that those with AD have a longer attention span and better concentration than infants or children at the corresponding DA (Reisberg, 2002).

Findings from Intergenerational Program Interventions

Although some mutual benefits for participants of intergenerational programs (IGPs) have been identified, adults with dementia are not often targeted to work with children and adolescents. Young preschool-aged children may even pose special problems in this type of program. Indeed, early research by Seefeldt (1987) reported a negative impact on preschoolers after their visit to a nursing home; Short-DeGraff and Diamond (1996) concluded that the cognitive disabilities of older adults with dementia seem to prevent effective IGPs targeting these two groups.

Griff and colleagues (1996) sought to determine successful and unsuccessful IGP activities for preschool and elderly pairs who were either frail, living in the community or had Alzheimer's disease. Unfortunately, the majority of the activities were unsuccessful for the preschool-AD dyads. The researchers chose to cancel their second cycle programming, but there were a number of lessons to be learned. The unsuccessful activities required abilities that were beyond the developmental age of the individual with AD, i.e. blowing bubbles. These tasks resulted in frustration and distress. The children became confused and upset by the behaviors of the older adults with AD. Moreover, because of the mismatch between older adult and preschooler developmental ages, the adults with AD did not have to follow the same rules as the children and this double standard caused additional problems. On the other hand, the successful activities were developmentally appropriate and included tasks that relied on long-term memory (which is preserved until very late in the progression of AD), movement, and music.

However, positive effects of IGPs for older adults with dementia and preschoolers have also been reported. Newman and Ward (1992-1993) found that older adults with characteristics of dementia in a day care service increased their positive behaviors while children were present in an intergenerational music program. More recent studies have begun to use assessment tools to classify participants, especially older adults with AD, based on their cognitive and functional abilities. Jarrott and Bruno (2003) used scores on the Mini-Mental State Examination, a scale designed to assess cognitive function in dementia, to group individuals as severe, moderately, or mildly impaired. They found that cognitive impairment was *not* prohibitive of participation in IGPs, provided that the activities were carefully planned. Those adults who participated were more likely to experience positive affect and engage in behaviors that supported personhood (i.e., eating, crafts, or sensory stimulation). The researchers note that high activity consistency and high frequency opportunities for participation may be especially important to individuals with dementia.

A few groups of researchers have recently begun to employ a variety of Montessori-based activities for individuals with dementia. They have found that, for the individuals with Alzheimer's disease, such activities increased constructive (active engagement) and decreased in problem behaviors like agitation, aggressiveness, and withdrawal (Judge, Camp, & Orsulic-Jeras, 2000), as well as elicited greater pleasure and lower levels of fear and anxiety (Orsulic-Jeras, Judge, & Camp, 2000). Camp and colleagues (1997) use Montessori techniques within the context of an IGP for older adults with dementia and preschool-aged children. All participants were asked to perform Montessori tasks as baseline measures of cognitive, motor, and sensory functioning. They were then scored on their ability to complete each activity correctly with minimal cuing. All participants became familiar with Montessori-based activities and procedures *before* any intergenerational contact took place.

Each adult was then paired with a child who was not yet at the adult's ability for specific activities. Older adults with dementia were assigned to be the mentors. They practiced presenting the activity with staff before teaching the lesson to the child. There were no instances of disengagement and no aggressive, disruptive, confused, or anxious behavior while with the children. The structure of the activities was important to the success of this program. The older adult with dementia did not have to remember the task that was taking place. The materials on the table served as external memory aids to see what steps had been completed. This form of external compensation for memory and executive functioning deficits allowed the older adults to use their abilities that remained in tact, such as social skills and long-term memories, to guide their interaction with the preschoolers.

Conclusions and Future Directions

This research offers numerous recommendations for the development and evaluation of future intergenerational programs. For example, the results from Camp and colleagues (1997) could be due to the implementation of Montessori techniques (as found in previous studies). Researchers must determine the unique impact of a preschooler mentoring program on the behavior and cognition of older adults with Alzheimer's disease, especially in the long term. Secondarily,

the consequences for the preschoolers should also be measured. According to their scores on the FAST, youth with developmental ages ranging from age one to six should be paired with older adults of higher developmental ages. Activities should be developmentally appropriate and incorporate movement, music, crafts, and games. For example, for a DA of one to two, the pair or group could play kick ball or balloon volleyball and engage in activities that tap into all of the senses. At DA two to four, the pair could engage in sorting tasks, simple counting activities, and sing songs with accompanying motions. At older DAs, the pairs can complete crafts together and read books to each other. Besides changing the method of evaluating functional and cognitive capacity, additional outcomes should be measured in both the older adults and the preschool children. Self-report and third-party evaluation of behavior and cognition change (or maintenance) both during and outside of the IGP must be recorded. The young children and older adults should be familiar with the activities before any intergenerational contact and the same groups should meet frequently (i.e., at least two times a week) in order to foster the development of close personal relationships.

These recommendations are based on the evidence for the retrogenesis phenomenon supported in this paper and can only be effective if the participants are appropriately paired based on their developmental age. With careful planning and implementation of evidence-based treatment practices such as this one, positive consequences can be expected for behavior and cognition, including a reduction in the speed of decline. Knowledge of such outcomes would add to the present literature on the effects of IGPs and em-

phasize the clinical importance of retrogenesis and determining corresponding developmental ages.

The American Health Care Association reports that 67%-77% of the 1.5 million Americans residing in nursing homes in the United States are suffering from dementia (Warchol, 2004). As people live longer and the proportion of older people continues to grow, only an effective pharmacological treatment will stop the disease process. However, until a cure is found, it must be remembered that individuals with Alzheimer's disease are people too, even in the severe stages of the disease. There are many things that suffers from AD are still able to do, and the implementation of programs based on current research can serve to remind them and their caregivers of that regardless of the stage of the disease, suffers retain their own personhood. Evidence-based rehabilitation activities such as those described in this paper are expected to enhance the quality of life of these individuals with dementia and have a beneficial impact on functioning. Although the retorgenesis theory may not be strictly true in all cases, it is a framework that may be helpful to developmental psychologists, neuropsychologists, occupational therapists, physical therapists, speech therapists and social workers and other rehabilitation professionals to examine the qualitative nature of the changes taking place in patients with AD. As an interdisciplinary team, these professionals are the ones who will be asked to design meaningful activities that are structured to accommodate the cognitive deficits seen in those with dementia while taking advantage of the abilities that remain preserved in order to foster a sense of pride and personal well-being, and possibly prevent further cognitive and functional decline (Arango, Fernandez & Ardila, 2003).

Referencias

Arango, J.C. & Fernández, S. (2003). La enfermedad de Alzheimer. In J.C. Arango, S. Fernández y A. Ardila (Eds.), *Las demencias: Aspectos clínicos, neuropsicológicos y tratamiento* (pp.191-208). México, D.F.: Manual Moderno.

Arango, J.C. & Rogers, H. (2002). Signos y síntomas psicológicos y comportamentales más comunes en la enfermedad de Alzheimer. *Revista Suma Psicológica, 9* (1), 35-53.

Arango, J.C. (2004). Alteraciones neuropsicológicas en la enfermedad de Alzheimer. In Grupo de Neuropsi, Universidad Surcolombiana (Eds.), *Memoria y demencias* (pp. 77-86). Neiva, Colombia: Grafit Plast.

Arango, J.C., Fernández Guinea, S. & Ardila, A. (Eds.)(2003). *Las Demencias: Aspectos Clínicos, Neuropsicológicos y Tratamiento.* México, D.F.: Manual Moderno.

Auer, S.R., Sclan, S.G., Yaffee, R.A., & Reisberg, B. (1994). The neglected half of Alzheimer disease: Cognitive and functional concomitants of severe dementia. *Journal of the American Geriatric Society, 42*(12), 1266-1272.

Braak,H. & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica, 82,* 239-259.

Camp, C.J., Judge, K.S., Bye, C.A., Fox, K.M. Bowden, J., Bell, M., *et al.* (1997). An intergenerational program for persons with dementia using Montessori methods. *The Gerontologist, 37*(5), 688-692.

Centers for Disease Control and Prevention (2005). Deaths and percentage of total deaths for the 10 leading causes of death, by race: United States, 2002. *National Vital Statistics Reports, 53* (17, March 7).

Cohen-Mansfield, J., Reisberg, B., Bonnema, J., Berg, L., Dastoor, D.P., Pfeffer, R.I., *et al.,* (1996). Staging methods for the assessment of dementia: Perspectives. *Journal of Clinical Psychiatry, 57*(5), 190-198.

De Ajuriaguerra, J. & Tissot, R. (1968). Some aspects of psychoneurologic disintegration in senile dementia. En C.H. Mueller, & L. Ciompi (Eds.). *Senile Dementia* (pp. 69-79). Switzerland: Huber.

Franssen, E.H., Souren, L.E.M., Torossian, C.L., & Reisberg, B. (1997). Utility of developmental reflexes in the differential diagnosis and prognosis of incontinence in Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology, 10,* 22-28.

Griff, M., Lambert, D., Dellman-Jenkins, M. & Fruit, D. (1996). Intergenerational activity analysis with three groups of older adults: Frail, community living, and Alzheimer's. *Educational Gerontology, 22,* 601-612.

Hebert, L.E., Beckett, L.A., Scherr, P.A., & Evans, D.A. (2001). Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050. *Alzheimer's Disease and Associated Disorders, 15*(4),169-173.

Hebert, L.E., Scherr, P.A., Bienias, J.L., Bennett, D.A., & Evans, D.A. (2003) Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Archives of Neurology, 60*(8), 1119-1122.

Jarrott, S.E. & Bruno, K. (2003). Intergenerational activities involving persons with dementia: An observational assessment. *American Journal of Alzheimer's Disease and Other Dementias, 18*(1), 31-37.

Judge, K.S., Camp, C.J. & Orsulic-Jeras, S. (2000). Using Montessori-based activities for clients with dementia in adult day care: Effects on engagement. *American Journal of Alzheimer's Disease, 15*(1), 42-46.

Larson, E.B., Shadlen, M.F., Wang, L., McCormick, W.C., Bowen, J, Teri, L., *et al.,* (2004). Survival after Initial Diagnosis of Alzheimer Disease. *Annals of Geriatric Psychiatry, 140*, 501-509.

Launer, L.J. & Hofman, A. (2000). Frequency and impact of neurologic diseases in the elderly of Europe: a collaborative study of population-based cohorts. *Neurology, 54*(suppl. 5), S1-S3.

Matteson, M.A., Linton, A.D., & Barnes, S.J. (1996). Cognitive developmental approach to dementia. *Image Journal of Nursing Scholarship., 28*(3), 233-240.

McGeer, P.L., McGeer, E.G., Akiyama, H., Itagaki, S., harrop, R., & Peppard, R. (1990). Neuronal degeneration and memory loss in Alzheimer's disease and aging. *Experimental Brain Research, Suppl 21*, 411-426.

Newman, S. & Ward, C. (1992-1993). An observational study of intergenerational activities and bahvior change in demented elders at adult day care centers. *International Journal of Aging and Human Development, 36,* 3211-3333.

Orsulic-Jeras, S., Judge, K.S. & Camp, C.J. (2000). Montessori-based activities for long-term care residents with advanced dementia: Effects on engagement and affect. *The Gerontologist, 40*(1), 107-111.

Ouvrier, R.A., Goldsmith, R.F., Ouvrier, S., & Williams, I.C. (1993). The value of the Mini-Mental State Examination in childhood: a preliminary study. *Journal of Child Neurology, 8*(2), 145-148.

Peters, A., Rosene, D.L., Moss, M.B., Kemper, T.L., Abraham, C.R., Tigges, J., *et al.* (1996). Neurobiological bases of age-related cognitive decline in the Rhesus monkey. *Journal of Neuropathology and Experimental Neurology, 55*, 861-874.

Piaget, J. (1952). *The Origins of intelligence in children* (M. Cook, trans.). New York: International University Press.

Reisberg, B. (1988). Functional assessment staging (FAST). *Psychopharmacology Bulletin, 24*(4), 653-659.

Reisberg, B., Ferris, S.H., Anand, R., et al (1984). Functional staging of dementia of the Alzheimer's type. *Annals of the New York Acacdemy of Sciences, 435*, 481-483.

Reisberg, B., Franssen, E.H., Hasan, S.M., Monteiro, I., Boksay, I., Souren, L.E., *et al.*, (1999a). Retrogenesis: clinical, physiologic, and pathologic mechanisms in brain aging, Alzheimer's and other dementing processes. *European Archives of Psychiatry and Clinical Neuroscience, 249* (Suppl 3), 28-36.

Reisberg, B., Franssen, E.H., Souren, L.E., Auer, S.R., Akram, I., & Kenowsky, S. (2002). Evidence and mechanisms of retrogenesis in Alzheimer's and other dementias: management and treatment import. *American Journal of Alzheimer's Disease and Other Dementias, 17*(4), 202-212.

Reisberg, B., Franssen, E.H., Souren, L.E.M., Auer, S.R., & Kenowsky, S. (1998). Progression of Alzheimer's disease: Variability and consistency: Ontogenic models, their applicability and relevance. *Journal of Neural Transmission, 54* (Suppl 1), 9-20.

Reisberg, B., Kenowsky, S., Franssen, E.H. *et al.* (1999b). President's Report: Towards a science of Alzheimer's disease management: A model based upon current knowledge of retrogenesis. *International Psychogeriatrics, 11*, 7-23.

Sclan, S.G. & Reisberg, B. (1992). Functional assessment staging (FAST) in Alzheimer's disease: Reliability, validity, and ordinality. *International Psychogeriatrics, 4*, 55-69.

Seefeldt, C. (1987). The effects of preschoolers' visits to a nursing home. *Gerontologist, 27*, 228-232.

Short-DeGraff, M.A. & Diamond, K. (1996). Intergenerational program effects on social responses of elderly adult day care members. Educational *Gerontology, 22*, 467-482.

Watchol, K. (2004), An interdisciplinary dementia program model for long-term care. *Topics in Geriatric Rehabilitation, 20*(1), 59-71.

Weiner, M.F. (2003). Clinical diagnosis of cognitive dysfunction and dementing illness. In M.F. Weiner & A.M. Lipton (Eds.), *The Dementias: Diagnosis, treament, and research.* Washintgon, D.C.: American Psychiatric Publishing, Inc.