CHAPTER NINETEEN

Biomedical Research in Alzheimer Disease

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Until three and a half decades ago, there was little biomedical research in aging—not in aging in general, nor in Alzheimer disease (AD) in particular. This was largely because for many years societal efforts and resources were geared toward the young. Aging and medical conditions that affect older patients were viewed with fatalism by the lay and scientific communities. Advanced medical care coupled with increased longevity inevitably led to heightened awareness and research interest in age-related issues. As a consequence, dementing conditions clinically characterized by progressive deterioration of cognition, behavior, and activities of daily living became a major focus of medical and scientific investigations.

Several systemic and primary neurologic entities can cause dementia, but in the Western world AD is the most common etiology among middle-aged and elderly persons. AD affects between 5 percent and 10 percent of the population above sixty-five years of age (Ernest & Hay, 1994). Recent studies and the incidence and prevalence of AD increase with advancing age have indicated that at least 4 million Americans and 50 percent of nursing home patients in the United States suffer from the disorder (Hebert et al., 1995). The annual cost for AD has been estimated to be $110 billion, and since the fastest growing segment of our population is the elderly, the number of affected patients is expected to rise

steeply during the next several decades (Ernest & Hay, 1994; Hebert et al., 1995). If we take into account loss of income from caregivers, who frequently suffer from depression and other medical conditions, the total cost of caring for AD patients could easily escalate.

The early symptoms of AD are often difficult to appreciate because they are nonspecific, intermittent, and insidious; its clinical course usually evolving over a period of six to ten years. It affects all ethnic groups, but its incidence and age of onset may be modified by certain risk factors such as the frequency of the APOE-ε4 gene (Terry & Katzman, 1983). Although its etiology remains elusive, advancing age, genetic background, head trauma, and gender are considered other risk factors (Desai & Grossberg, 1999). Future investigations designed to offer a better understanding of the disease, develop more reliable diagnostic techniques, and provide safer and more effective treatment will have to be pursued in order to meet the challenges of prevention, early detection, and definitive therapy.

In general, memory loss for recent events is the clinical hallmark of AD. However, careful neurobehavioral assessment frequently reveals concomitant impairment of language functions, comprehension, judgment, orientation, calculation, and attention span. Behavioral symptoms, including depression, anxiety, delusions, hallucinations, insomnia, wandering, and violent behavior, are not uncommon manifestations that could precede decline of intellectual functions (Jost & Grossberg, 1996). Difficulty carrying out daily activities at home or at work may herald or coexist with cognitive and behavioral manifestations. As the disease progresses, patients will require more supervision and caregiving, either at home or in chronic care facilities. There is insidious loss of general body functions, and death usually occurs several years later from pneumonia, sepsis, or trauma.

Current epidemiological and clinical data have generated unprecedented enthusiasm in investigating factors that influence normal aging and AD. This was a major departure from the old notion that dementia and AD were untreatable normal consequences of aging. For the past three decades, neuroscientists, physicians, and other health care providers have independently or collaboratively produced an exponential amount of new and interesting data that have considerably enhanced our understanding, diagnosis, and treatment of AD.

Advances in biomedical research may be divided into (1) diagnostic; (2) therapeutic; and (3) preventive categories. These are essential because successful

management of a disease requires accurate diagnosis as well as safe and effective treatment and preventive measures.

Diagnosis of AD was significantly advanced by the introduction of validated clinical instruments for assessing (a) cognition: the Mini-Mental State Examination (MMSE), the Alzheimer disease assessment scale (ADAS), and the clinical dementia rating scale (CDR); (b) behavior: the neuropsychiatric inventory (NPI); and (c) activities of daily living: the progressive deterioration scale (PDS) and the global deterioration scale (GDS). These measures allow clinicians to verify presence, severity, and stage of disease and provide appropriate and timely recommendations to families and caregivers. Similar measures were recently utilized to identify seemingly "normal" individuals with mild cognitive impairment (MCI), many of whom represent the early stages of AD (Petersen et al., 1999).

Other diagnostic tools consist of neuro-imaging techniques such as computerized tomography (CT), magnetic resonance imaging (MRI), single photon emission computerized tomography (SPECT), and positron emission tomography (PET) scans. CT and MRI offer structural and anatomical views of the brain and cranium. Although there are no specific lesions associated with Alzheimer disease, CT and MRI are useful in excluding other conditions (e.g., strokes, tumors, and infections) that can mimic AD symptomatology. Functional MRI enables the simultaneous investigation of brain function and structure, whereas SPECT offers valuable information on cerebral blood flow changes that may differentiate strokes from AD. PET is presently a research tool that measures metabolism in certain parts of the brain. In some clinically diagnosed AD patients and asymptomatic cases with APOE-4 gene, PET has shown hypometabolism in posterior parietal and temporal regions (Ojemann et al., 1997). Results of longitudinal studies will determine whether PET could be a reliable method for diagnosing AD.

Another important component of the diagnostic workup for AD includes tests that utilize serum, cerebrospinal fluid, and brain tissue. These are critical in order to exclude systemic and other neurological disorders that can mimic the symptoms of AD. In spite of a comprehensive workup, AD is solely established by neuropathologic examination of postmortem brain tissue. Diagnosis is confirmed by the presence of large numbers of neuritic plaques (NPs) and neurofibrillary tangles (NFTs). Synaptic changes and neuronal loss are important observations but are not required for neuropathologic diagnosis (Wright, Geula, & Mesulam, 1993).

AD treatment was purely symptomatic until cholinergic and other neurotransmitter deficits were discovered in the brains of affected patients. Among the various neurochemical abnormalities, the level of cholinergic deficiency correlated best with severity of dementia in AD (Coyle, Price, & DeLong, 1983; Perry et al., 1998; Schegg et al., 1992). Cholinergic neurons in the nucleus basalis of Meynert are lost, in addition to there being diminished activity of choline-acetyltransferase (ChAT), the synthesizing enzyme for acetylcholine (ACh), and reduced levels of neocortical ACh, a neurotransmitter vital for maintaining memory related processes (Geula, 1998; Younkin et al., 1986). Clinical trials utilizing acetylcholinesterase inhibitors have produced modest response and delayed symptom progression in AD patients with mild to moderate dementia (Anand, Messina, & Hartman, 2000; Nordberg & Svensson, 1998; Polinsky, 1998; S. L. Rogers & Friedhoff, 1998; Schneider, Anand, & Farlow, 1998). Neuroprotective agents such as vitamin E, estrogen (for postmenopausal and surgically sterilized women), and nonsteroidal anti-inflammatory drugs are prescribed to reduce neuronal degeneration (Desai & Grossberg, 1999; Gibbs & Aggarwal, 1998; J. Rogers, 1995). Furthermore, the public is inundated with herbs, food supplements, and other forms of medicinals that are advertised as "safe and effective" treatment for memory loss, depression, anxiety, and other forms of cognitive and behavioral deficits without the benefit of controlled clinical investigations. We have to verify the purity, beneficial effects, and complications of herbs before they can be endorsed for *therapeutic* purposes. To date, there is no cure for AD, and none of the pharmacological agents approved for its treatment can reverse or stop the progression of the disease.

Molecular biology and genetics have produced some of the most exciting knowledge on aging and AD. Studies on Down syndrome and familial AD cases have yielded invaluable information that will influence our therapeutic approach. Initial experiments were largely driven by the concept that beta amyloid, the protein core observed in NPs, is central to the etiopathogenesis of AD. For the past several years investigations have focused on beta amyloid's biochemical, ultrastructural, molecular, functional, and toxic properties. Similarly, NFTs are now known to be mainly made up of hyperphosphorylated protein called tau. Future research in these areas could provide clues as to the evolution of AD and lead to formulation of novel pharmacologic compounds that might avert disease development and/or progression. Successful development of such drugs could offer preventive as well as definitive therapies. Genetic studies have confirmed

mutations of chromosomes 1, 14, and 21 in early onset familial AD and identified certain secretases, the enzymes that are thought to cleave the beta amyloid protein from its parent molecule, the amyloid precursor protein (Cruts & Broeckhoven, 1998). Drugs that can block the action of such secretases may prevent the NP formation. Moreover, a transgenic mouse model for AD has been developed, and APOE-4 gene is now considered to be a risk factor because its presence significantly raises disease susceptibility (Saunders, 2001).

Most recently, biomedical scientists found a class of stem cells, called pluripotent due to their potential to develop into different cell types in the body (Svendsen & Smith, 1999). These cells are found in embryos and fetal tissue. In the few years since this discovery, evidence has emerged that these stem cells are, indeed, capable of becoming almost all of the specialized cells of the body and may have the potential to generate replacement cells for a broad array of tissues and organs. Thus, this class of human stem cell holds the promise of being able to repair or replace cells or tissues that are damaged or destroyed by many devastating and currently untreatable diseases that are usually associated with serious disabilities and fatal outcome. New data have emerged that stem cells from adults can be found in bone marrow, cornea, retina, and the brain. Adult and embryonic stem cells have different properties. The latter are currently preferred for experimental purposes.

The potential role of stem-cell research in clinical practice has generated significant controversy after investigators have shown that differentiated cells obtained from both adult and embryonic stem cells can repair or replace damaged cells and tissues. Researchers are pursuing two fundamental strategies to explore this discovery. One is, by starting with undifferentiated neural cells, to grow differentiated cells in a laboratory dish that are suitable for implantation into a patient. The other repair strategy relies on finding growth hormones and other "trophic factors" that can stimulate a patient's own stem cells and endogenous repair mechanisms to allow the body to cope with damage from disease or injury. Efforts to develop stem-cell based therapies for Parkinson's disease provide a good example of research aimed at rebuilding the central nervous system. Historically, one of the first attempts at using cell transplantation in humans was tried in Parkinson's disease cases (Allen et al., 1989). Although dramatic improvement in Parkinson's patients was initially reported after transplanting dopamine-producing cells from the patients' own adrenal glands to the affected area of their brains, subsequent studies showed limited, short-lived, and

inconsistent improvement of patients' symptoms. Similarly, previous human transplantation studies on Parkinson's disease using fetal brain tissue removed from an elective abortus demonstrated encouraging but inconsistent benefit to patients. Although not all patients improved, some patients who received fetal tissue transplants had a clear reduction in the severity of their symptoms. Furthermore, autopsies done on these few patients revealed a robust survival and differentiation of the grafted neurons. Most investigators remain optimistic that cell-transplantation will be effective in treating Parkinson's disease. At present, there has been no therapeutic trial utilizing stem-cell transplantation for AD.

Potential adverse events may accompany stem-cell use in medicine. If embryonic stem cells are injected into a mouse with a compromised immune system, a benign tumor called a "teratoma" can develop. For this reason, scientists do not anticipate that undifferentiated embryonic stem cells will be used for therapeutic applications. These cells will need to be differentiated or otherwise modified before they can be used clinically. Current challenges are to direct the differentiation of embryonic stem cells into specialized cell populations and to control their development or proliferation once placed in the patient. With the exception of the clinical application of hematopoietic (blood making) stem cells, adult stem cells are not ready to be utilized for therapy. In order to use adult stem cells safely in tissues other than the tissue from which they were isolated, researchers will need purified populations of adult stem cells. In addition, modifications to the cells, to the immune system, or both will be a major requirement for their potential application in instances of tissue rejection after stem-cell transplantation.

The development of stem-cell technology (SCT) has offered hope to many patients and families who suffer from incurable diseases such as cancer, brain and spinal cord trauma, AD, Parkinson's disease, heart failure, and several genetic and degenerative disorders that cause irreversible organ damage. It also raises important ethical, legal, and economic concerns that have polarized segments of our society. Therefore, it is imperative that we approach such a subject with sufficient background knowledge, utmost objectivity, and minimal emotionalism.

It is clear that SCT could become a viable form of treatment for particular diseases, and stem cells may be derived from embryonic, fetal, and adult tissues. In general, materials from elective abortions are preferred and utilized for research

studies. As technology evolves, it is conceivable that adult tissues could provide the needed number of cells for clinical application. If SCT becomes a treatment option, the need for aborted fetuses and embryonic tissues would increase exponentially. This could lead to a disproportionate rise in the number of abortions, as well as private ventures designed to generate revenues from products of abortion. Second, significant scientific concerns like tumor-growth complications, long-term survival of cells, effects of environment on cell integrity and lifespan, and other factors that influence successful stem-cell treatment must be addressed before we can recommend SCT for therapeutic purposes. Moreover, we have to determine the overall cost for the type, extent, and duration of benefits we intend to achieve and the potential adverse events that may accompany SCT. More importantly, introduction of SCT as a therapeutic tool must take into account our legal system, economic resources, and ethical, moral, and spiritual values.

A preventive approach for AD is in its infancy due to our limited insight into the pathogenesis of AD. However, we now know that certain risk factors could increase the chance for developing the disease. These include advancing age, APOE-4 gene, female gender, and head trauma (Desai & Grossberg, 1999; Terry & Katzman, 1983). Investigations of neurobiologic phenomena involved in normal aging and AD have to be pursued to obtain relevant information on cell death, degeneration, and regeneration. Paradoxically, increased knowledge on cell death, due to necrosis and apoptosis, and regeneration is crucial in order to prevent cell degeneration and promote quality of life in later years. It is important to emphasize that unlike chromosome mutations that almost always lead to Alzheimer disease, APOE-4 gene is a susceptibility gene that simply augments the risk for the disorder. Estrogen is believed to have neuroprotective properties in postmenopausal women, and nonsteroidal anti-inflammatory drugs (NSAIDs) have been advocated to reduce neuronal damage due to inflammation. Vitamin E, a known antioxidant, is prescribed to lessen the deleterious effects of free radicals in the brain parenchyma (Desai & Grossberg, 1999; Gibbs & Aggarwal, 1998; J. Rogers, 1995). Head trauma can predispose patients to AD (Reyes et al., 1989), months or years after the injury. It is hoped that in the future we could reduce our exposure to or counteract the ill effects of risk factors and/or neutralize the influence of genetic abnormalities. These possibilities have given rise to heightened enthusiasm and expectation that AD could potentially be arrested, if not be prevented.

The availability of new diagnostic tests and therapies for AD has considerably influenced our medical approach and management of AD and other previously untreatable neurodegenerative disorders. It has given patients and families hope for safer and more effective treatment options. These same developments, however, have generated interesting and challenging medical and philosophical issues. Who should undergo and pay for more sophisticated and comprehensive neurobehavioral assessment? When do we start and terminate treatment? Who should have genetic testing and access to the results of genetic testing? Lastly, as we develop more sophisticated scientific techniques such as SCT, we also need to establish strict guidelines for their use in medical practice. Otherwise, we can potentially destroy the humanity we are attempting to save.

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