

Report on Alzheimer's Disease in 2007

Concept Paper

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Preface

Alzheimer's disease (AD) has joined the ranks of other chronic medical conditions (e.g., arthritis, cancer and diabetes) that have become part of the common household vocabulary. A Gallup poll commissioned by the Alzheimer's Association, indicated that 1 in 10 Americans surveyed said that they had a family member with AD and 1 in 3 knew someone with AD¹. Over 100 years have passed since Dr. Alois Alzheimer presented the clinical and pathological characteristics of the first case of what would later be coined "Alzheimer's disease"². At this writing, no effective treatment exists to stall, halt or reverse the horrific pathological processes in the brain that manifest in the functional and cognitive incapacitation of AD victims. This paper presents a status report on AD in 2007, including a foreboding forecast of the astronomical fiscal and tragic humanitarian impact to come in the absence of an effective treatment discovery. Also included is a lay review of emerging scientific and medical technologies with the potential to advance the progress of therapeutic strategies to predict, detect, prevent, defer, and quell the onset of the catastrophic cascade of physiological events leading to the development AD.

Prevalence and drug development

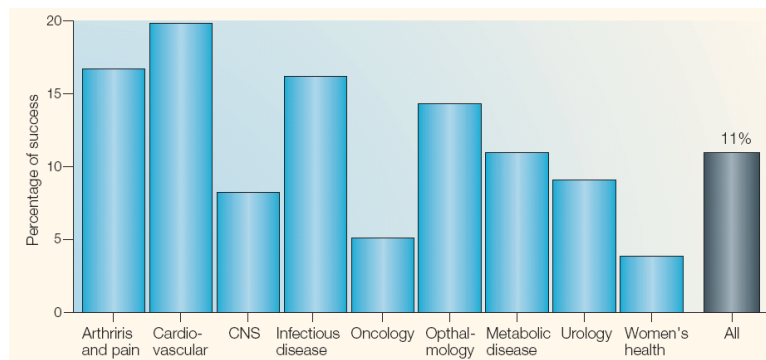
Alzheimer's Disease (AD) has become one of the most devastating medical disorders in aging people because it relentlessly, progressively and irreversibly destroys the brain. Early symptoms of AD include short-term memory loss and confusion, which deteriorate over time into personality changes and cognitive deficits such as thinking, decision making and language skills, eventually leading to complete memory loss, the inability to function and the development of a vegetative state. Symptoms typically appear after the age of 65, but it is important to emphasize that AD is not a normal part of the aging process. Every nation exhibiting increasing life expectancy also exhibits an increased incidence of AD. It is currently estimated that 5.1 million people in the United States (US) have AD; approximately 66,000 people succumb to AD while over 400,000 cases of AD are newly diagnosed annually³. The prevalence of AD essentially doubles for every 5 year age group over 65; nearly half of Americans over 85 have AD. What makes these statistics so alarming is that extrapolations by the US Census Bureau based on the impressive increase in life expectancy since the turn of the century, estimate that nearly 19 million Americans will be age 85 or older by the year 2050, the same year in which roughly 13.2 million Americans are predicted to be living with AD⁴.

These inauspicious trends in the prevalence of AD translate, if unimpeded, into an enormous socioeconomic burden. It is estimated that 50 – 80% people with AD receive care at home with the remainder of care provided in a variety of health care settings. Because the average life expectancy of AD patients following diagnosis is 8 years (with some living as long as 20!), extraordinary emotional, physical and financial stress is endured by friends^{4,5} and relatives, most of whom are women^{4,5}. The average cost for taking care of an AD patient at home is \$19,000/year, most of which is shouldered by the family⁵. Care of AD patients in nursing homes ranges from an average of \$42,000 - 70,000/year, with the lifetime cost for care of an AD patient averaging \$174,000⁵.

A recent analysis using "Alzheimer's disease" to query PubMed, a website service of the US National Library of Medicine that includes over 16 million citations from MEDLINE and other life science journals for biomedical articles, indicated that nearly 52,000 scientific articles related to AD have been published since 1949. Remarkably, about half of these have been published since the start of the new millennium, providing incontrovertible evidence of a virtual explosion in AD research. Not surprisingly, this observation begs the question: why is there no effective treatment for AD? One answer to this question can be found by tracking the drug development process. It is no secret that the clinical success rate for central nervous system (CNS) drugs, ~8%, is among the lowest of several therapeutic areas, given an overall average of 11%⁶ (**Exhibit 1**).

Exhibit 1. Clinical Success rates of drugs targeting various therapeutic areas

Data represent the ten biggest drug companies between 1991 – 2000. Source: *L. Kola and J. Landis, Nature Reviews Drug Discovery 3:711-715 (2004)*

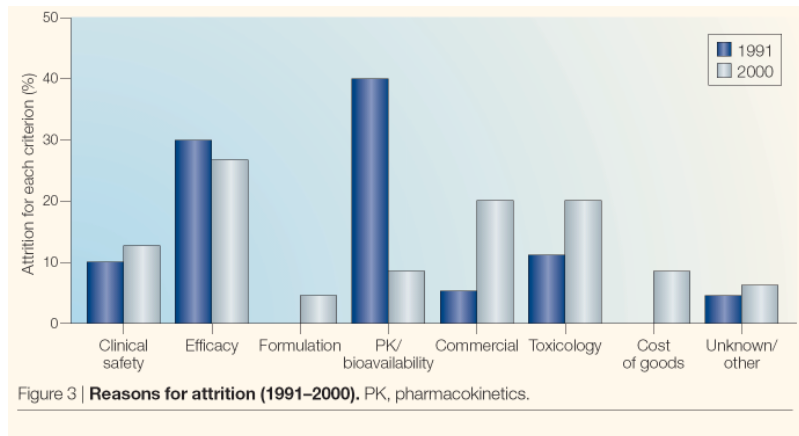


Digging a little deeper, the data reveal that approximately (~) 60% of drugs targeting the CNS successfully complete phase I clinical trials, ~ 40% successfully complete phase II clinical trials, ~ 50% successfully complete phase III clinical trials and ~ 70% of these will become registered. At these rates, an optimist would conclude that of the 14 therapies currently in phase III clinical trials for AD⁷, 5 will become registered, equaling the existing number of FDA-approved drugs for AD.

The leading cause of low clinical success rates is a lack of efficacy, which means the drug does not produce the desired effect (**Exhibit 2**).

Exhibit 2. Reasons for drug attrition between 1991 - 2000

Efficacy is currently the leading cause of drug attrition. Substantial progress was made in improving bioavailability (the percentage of drug that is detected in the systemic circulation after its administration) and pharmacokinetics (quantification of actual drug concentration) between 1991 and 2000. Source: I. Kola and J. Landis, *Nature Reviews Drug Discovery* 3:711-715 (2004)

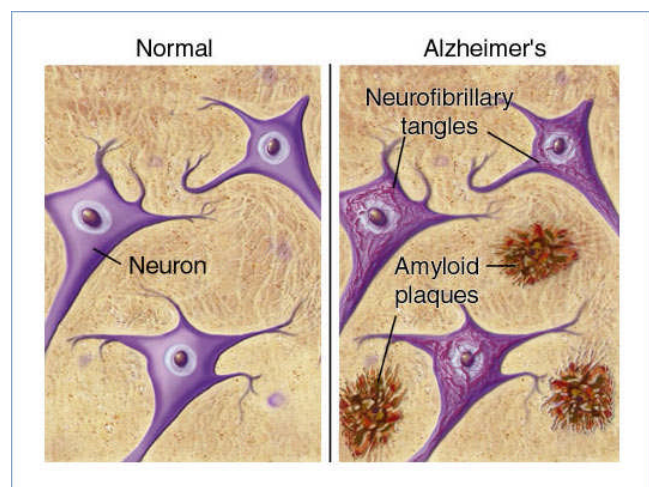


This observation is especially pertinent for drugs targeting the CNS because this therapeutic area suffers from the lack of adequate animal models, thus hindering the ability to confirm that candidate drugs administered under empirically determined dosing regimens actually halt or reverse the pathological processes implicated in the disease itself. For AD in particular, two hallmark pathological characteristics have been identified in the brain: amyloid plaques (APs, also referred to as senile plaques) and neurofibrillary tangles (NFT) (**Exhibit 3**).

Exhibit 3. Hallmark pathologies of AD

Illustrative representation of brain lesions hallmark of AD. Deposits of an insoluble protein fragment (beta-amyloid, A β) along with other proteins and brain cells result in the formation of what are commonly called amyloid plaques (APs). Neurofibrillary tangles (NFTs) refers to abnormal clusters of twisted proteins (mainly tau) found inside neurons. Source:

www.ahaf.org/alzdis/about/AmyloidPlaques.htm



Ideally, the efficacy of a candidate drug to treat AD would be validated in an animal model as part of the pre-clinical drug development process, demonstrating its ability to reverse or impede the progressive formation of APs and NFTs prior to entering human clinical trials. The predominant animal models used for drug discovery are rodent models; however, there is no naturally occurring or spontaneous development of APs or NFTs in rodents that parallels the onset of AD in humans⁶. In the absence of an appropriate animal model or an alternative reliable target validation model, candidate drugs enter human trials sooner but with less data to predict a positive outcome with respect to efficacy. Fortunately, with the development of genetically engineered mouse models of AD appearing in the mid-1990s, came the ability to induce the formation of APs and NFTs in rodents. Until very recently however, these transgenic mice were criticized because they expressed either APs or NFTs, but not both. Coupled with the inability to monitor APs and NFTs in human subjects (except at autopsy), such challenges in the pre-clinical stages of the drug development process stifled progress in generating effective treatments for AD. Nevertheless, significant observations were made in human autopsy samples revealing dysregulation of neurotransmitters (biological chemicals that send a message from one nerve cell to another), notably acetylcholine and glutamate, leading to the development of the 5 drugs currently approved by the FDA for the treatment of AD. These drugs were designed to manipulate neurotransmitter systems and hence, target symptoms. To date, only modest symptomatic improvements in cognitive abnormalities have been reported in AD patients taking these drugs without indication that any of the drugs have the ability to halt the progression of the pathological processes underlying AD.

Fiscal impact of AD at a national level

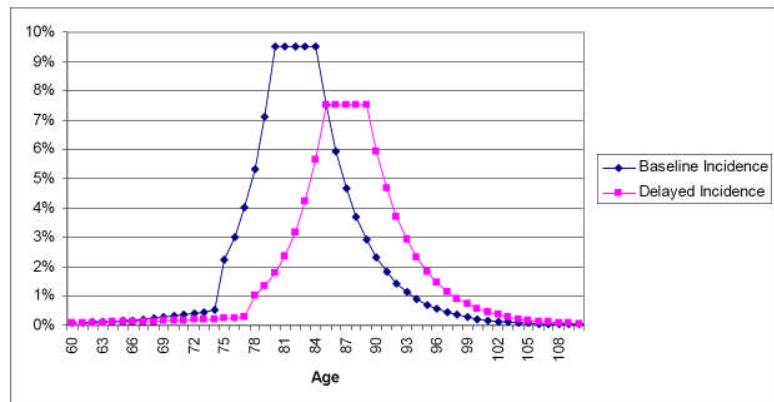
The lack of effective prevention or treatment regimens currently available to tame the onslaught of AD diagnoses expected to occur in the coming years has generated substantial interest in forecasting and protecting the future stability of the national health care economy. Based on the predicted prevalence of AD in 2050, parallel calculations based on fiscal trends have been made to predict the financial impact of AD in the US. In 2004, the Lewin Group, commissioned by the Alzheimer's Association, projected the longitudinal impact of successful breakthroughs in the treatment of AD on Medicare and Medicaid spending. Currently, the annual cost to the federal government for the care of patient with AD exceeds \$100 billion. Research by the Lewin Group, assuming that no effective AD treatment emerges in the near future, indicated that by the year 2050 federal spending for Medicare beneficiaries suffering from AD will surpass the \$1 trillion mark. State and federal Medicare funding to support AD care at this time will reach \$118 billion⁸.

If effective preventive strategies able to delay the onset of AD emerge in 2010, the Lewin Group assumed that the incidence of AD would be reduced by roughly 4 million people such that the median age of onset would be delayed 6 years (**Exhibit 4**) and a larger proportion of AD victims would be in the milder stages of disease. Based on those assumptions, the projected federal spending for Medicare beneficiaries suffering from AD in the year 2050 will be closer to \$600 billion and state and federal spending for nursing home care of AD patients will approximate \$48 billion, a savings of \$444 billion and \$70 billion, respectively.

Exhibit 4. Current Incidence and Delayed Onset Incidence of Alzheimer's Disease by Age.

Lewin Group Assumptions.

Source: Lewin Group Report to Alzheimer's Association, 2004.



Federal dollars spent on AD research has fallen over \$10 million dollars since 2003, to an anticipated \$645 million in 2007. This investment in research pales in comparison to the estimated \$100 billion federal investment to care for individuals suffering from AD, such that for every dollar spent on care, less than one cent (0.645) goes toward treatment and prevention. In this regard, The Lewin Group projected the return on investment of federal dollars based on an increased \$1 billion annual budget for AD research. Assuming that effective preventive strategies able to delay the onset of AD emerge in 2010, the return on investment for federal dollars was calculated to approximate 100 to 1. In short, the staggering projections reported by the Lewin Group has fueled a demand to increase NIH budget allocations to AD research.

Humanitarian Impact

Medical developments such as vaccines and antibiotics in the last century have dramatically lengthened the average human lifespan. Unfortunately, extending physical lives has been met with an increased incidence of age-related diseases such as AD. An epidemiological study of a cohort of 1201 people living in Southwestern Pennsylvania examined the "active life expectancy" associated with AD⁹. The 10-year epidemiological study compared the "total life expectancy and the average amount of life lived with different degrees of disability" between people with or without AD. The results of the study indicated that AD shortened the average lives of the patients, and increased the number of years that the patients lived with impairments in 7 basic daily life activities. In summary, AD patients are expected to live shorter lives, and sadly, a larger portion of lives are spent less active, and with more disabilities. The increase in disabilities generates financial, social, and psychological burdens to the patient's caregivers.

Following AD diagnosis, the average patient lives 8 years, but people can live as long as 20 years with AD. Unfortunately, the emotional effects of witnessing the deterioration of a loved one with AD is compounded by the physical, financial, and psychological burden of caring for the person; a job that is 24 hours a day. The Alzheimer's Association estimates that 75% of AD patients are cared for by family or friends. The emotional, physical, and social burden is difficult for the patient's loved ones. Often the care givers compromise their careers, resulting in lost family income and social contact, and increased stress. A controlled trial examining

the impact of counseling and support intervention for spousal-caregivers demonstrated that emotional support counseling resulted in an additional 329 days of care at home for the patient¹⁰. The counseling and support for the care-giving spouses demonstrates the dramatic need and real impact of psychosocial support for caregivers. Extending the amount of time the AD patient stays at home, relieves some of the financial burden on the family, but the psychological and social burden remain.

Epidemiology and social psychology try to quantify the effects of conditions like AD, however; statistics fail to convey the gravity of the emotional burden generated by AD. Only the testimony and feelings from people impacted directly from having loved ones affected by the disease give justice to its toll. The passing of former US President Ronald Reagan on June 5th, 2004 brought AD to the forefront of the public's attention. Approximately 10 years before his death, he declared, "I now begin the journey that will lead me into the sunset of my life. I know that for America there will always be a bright dawn ahead. Thank you, my friends. May God always bless you." The devastating effects of AD were all too evident in the former President's 10 year decline to death. On the June 12, 2004 episode of the CNN show "House call with Dr. Sanjay Gupta" AD was discussed just a week after the passing of Ronald Reagan. When asked about a conversation with Nancy Reagan weeks before the former President's death, Dr. Gary Small (Director of the UCLA Center on Aging) replied, "I definitely sensed an acceptance, that she had come to terms with the long, devastating, emotionally tiring experience of being with a loved one who is suffering from this illness, and this is typical of family members who have to deal with Alzheimer's disease, that they go through a long process where [they] literally mourn the loss of the person. The human being is no longer emotionally there. The physical person is there. And it isn't until they die that they do the final mourning process. It can be very confusing emotionally." Similarly, the speech by George Vradenburg at the Center for Health Transformation's "Preparing the country for the Alzheimer's epidemic: A view from science, business, government, and caregivers" meeting on November 14, 2006 set a similar tone. Speaking from the voice of caregivers, he described AD "not as a soft passing into the night. This disease is a cruel, vicious, ripping of life and soul and identity out of the human psyche. Comforting messages about the disease and its treatment-memories should last a lifetime; the long goodbye; maintain your brain-ignores the daily horrors faced by its victims and their caregivers."ⁱ

Those who have witnessed the decline of AD patient's firsthand can attest to the harsh realities of the disease. Treatments that merely prolong physical life, but fail to delay the progression of the disease ultimately prolong the burden for the caregiver. Only the development of effective treatments will provide humanitarian relief.

The Promise of Emerging Technologies

This past year marked the 100th anniversary of the 1906 Nobel Prize awarded to Cajal and Golgi for their work on the structure of the nervous system. Over the course of the last century, the field of neuroscience has evolved rapidly. In the past 25 years alone, the scientific community has witnessed a tremendous surge in breakthrough discoveries in neuroscience and related disciplines. Advances in genome sequencing technologies and bioinformatics have provided scientists with the tools needed to identify the genes involved

ⁱ Event transcript available at: www.healthtransformation.net.

in many diseases, including Alzheimer's disease. Understanding which genes are playing an important role in Alzheimer's disease pathology not only improves the design of potential drug targets for treatment of AD, but also allows scientists to create better animal models that recapitulate the mutations and pathologies occurring in patient populations. This is especially important for diseases such as AD, in which the number of patients with the inherited (or familial) form of the disease is just a small fraction compared to the rest of the patients suffering from these diseases. Early-onset familial AD (FAD) accounts for only 5-10% of total AD patients, and can be caused by specific mutations (or polymorphisms) in several genes, including amyloid precursor protein (APP), presenilin 1 and 2 (PS1 and PS2), as well as the AD susceptibility gene, apolipoprotein E. Although patients with late-onset AD typically do not have these mutations, the pathological features of the disease are ostensibly identical.

The majority of current FDA-approved AD drugs were designed to increase the levels of the neurotransmitter acetylcholine (ACh) by inhibiting acetylcholinesterase (AChE), the enzyme that breaks down ACh. While these drugs provide modest symptomatic improvement, they do not address the underlying mechanism(s) of pathogenesis. The race to identify new drug targets for AD has already begun, and there are promising candidates on the horizon. For example, the elucidation of processes mediating the formation of APs has facilitated the identification new targets of AD.

It is now known that the amyloid-beta ($A\beta$) peptide that forms the major constituent of AP is produced by the sequential processing, or cleavage, of the amyloid precursor protein (APP) (**Exhibit 5**). The enzymes responsible for cleaving APP are called secretases, and there are particular forms of the secretases important for AD (β - and γ -secretase). Many of the new drug candidates are specifically aimed at inhibiting these two enzymes.

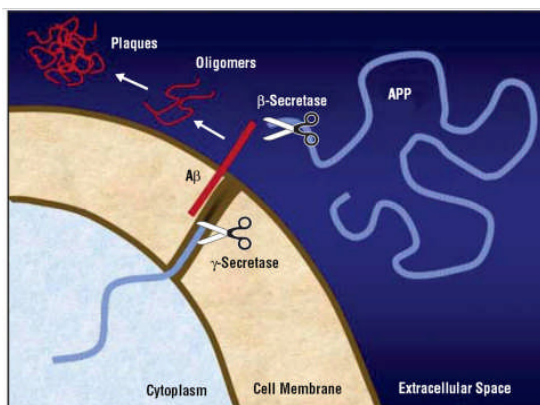


Exhibit 5. A schematic diagram of amyloid precursor protein (APP) processing.

APP is sequentially cleaved by β -secretase and then γ -secretase, leading to the formation of the toxic beta amyloid peptide ($A\beta_{42}$).

Source: D. Selkoe, *Archive Neurology* 62:192:195.

Other potential targets are the proteins and metal ions thought to be involved in the process that leads to $A\beta$ aggregation. Recent therapeutic targets also involve both active and passive immunization strategies¹¹. The major difference between these newer classes of 'anti-amyloid' strategies and the currently available AD drugs, is that these treatments are directly aimed at modifying the underlying disease process, rather than just the symptoms. As a result, reliable methods used to test and validate the efficacy of these therapies in clinical

trials will need to be different. In this regard, innovative techniques for neuroimaging and biomarker identification have moved to the forefront in AD diagnosis and treatment.

Advances in brain imaging technology provide scientists unprecedented insight into brain structure and function (**Exhibit 6**). The development of magnetic resonance imaging (MRI) significantly increased image resolution and the ability to visualize pathological disturbances in the brain. Functional MRI (fMRI) took this technology to the next level by permitting rapid imaging and assessment of blood flow corresponding to brain activity, and is therefore a measure of brain function. Similar to fMRI, positron emission tomography (PET) is another imaging method frequently used to visualize changes in blood flow as well as brain glucose utilization. These techniques provide an important clinical diagnostic aid for AD, as patients with AD display reduced brain metabolism of both glucose and oxygen. Most exciting is the development of novel PET scan probes/tracers that permit real-time visualization and density determination of APs in brains of AD patients. A similar tracer for NFTs does not yet exist, and although a small molecule has been identified that binds both APs and NFTs¹², further research is needed to develop such compounds that would allow doctors to image these and other abnormal proteins associated with AD and other neurodegenerative diseases. This capability would revolutionize the diagnosis of AD, as well as our ability to monitor disease progression. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a major collaborative research effort specifically investigating whether brain imaging can be used to reliably predict onset and monitor progression.

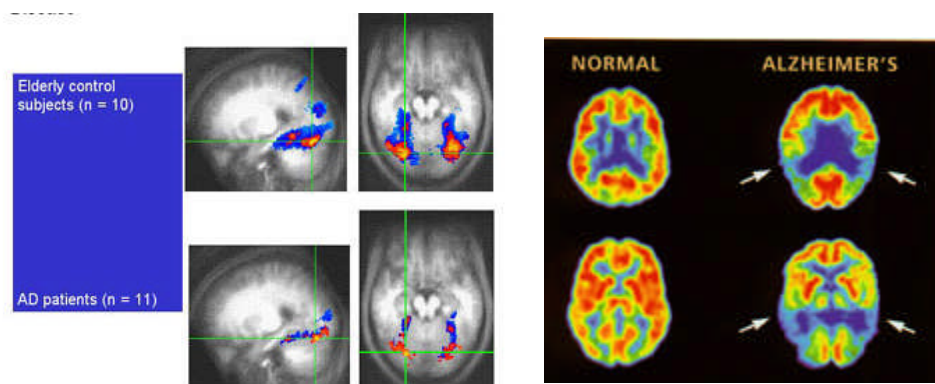


Exhibit 5. Examples of brain images.

fMRI (left panel) and PET scan (right panel) images from healthy adults and AD patients. Functional MRI images taken during memory encoding of outdoor scenes in healthy and AD patients. Arrows in PET scan point to areas with decreased metabolism in AD patients compared to healthy adults.

Source:

MRI scan: *Rombouts SA et al. American Journal of Neurology, 2000;21(10)1869-75.*

PET scan: <http://hometown.aol.com/utstudentmem/Page2.html>

Biomarkers are biological entities whose detection indicates a particular disease state. There is a huge emphasis in the identification of reliable AD-specific biomarkers that can be consistently and non-invasively followed in order to better diagnose and treat AD. In this regard, biomarkers may be useful as indirect measures of disease severity in order to monitor drug response and to optimize treatment regimens. Current biomarker candidates include cerebral spinal fluid (CSF; also cerebrospinal fluid) levels of A β 42, tau, and

phosphorylated tau – the three main components of APs and NFTs. Additional biomarkers of AD include lipids such as cholesterol and sulfatides, and isoprostanes, an indicator of oxidative stress¹³. These biomarkers may also help to distinguish between AD and other non-AD dementias. For AD, biomarkers play a role both in neuroimaging and in drug development. Identification of relevant biomarkers can be further improved with advancing technologies in genomics, proteomics, metabolomics, computational and systems biology, mathematical modeling, as well as high throughput screening methodologies.

There are roughly 225 AD drugs currently in the development pipeline, and more than half of those candidates are only in the preclinical development stage. Seventy of the drug candidates are split between Phase I and Phase II clinical trials, and only 14 are in Phase III trials⁷. As discussed above, the high failure rate associated with AD drugs is typical for CNS therapeutics. One contribution to the high failure rate is the lack of rapid, inexpensive, and reproducible assays that can weed out the compounds during the preclinical phase that are most likely to fail later down pipeline. Following target identification, potential drug compounds go through a preclinical screening process and are evaluated on 5 criteria: adsorption, distribution, metabolism, excretion and toxicity (ADME-Tox). These pharmacokinetic (PK) characteristics influence drug levels and ultimately the performance of the compound as a drug. Second to efficacy, toxicity is another significant cause of drug attrition.

ADME-Tox properties are routinely measured using a variety of techniques including cell-based (*in vitro*) assays and animal models (*in vivo* assays). While the animal models are the gold standard, they are time consuming and extremely costly. The recent development of automated, high-throughput assays has greatly enhanced *in vitro* approaches to ADME-Tox screening. To significantly increase the efficiency and success rate of preclinical screening, scientists are developing new computer-assisted (*in silico*) or virtual techniques to analyze and model the physiochemical properties of a compound in order to predict how it would behave in a complex system like the human body. The most significant challenge in computer-aided drug discovery is developing computational ADME-Tox modeling tools that can accurately predict the toxicity of a potential new drug.

Elucidation of the mechanisms underlying AD, coupled with advances in the fields of genetics, bioinformatics, and molecular biology has led to substantially improved animal models for AD. A major limitation of the early mouse models of AD was that the mice only developed some of the hallmark pathologies of the disease, such as APs, neurodegeneration and cell loss, but not NFTs. As with transgenic models of other diseases, it is rare that one mouse model develops the full spectrum of AD neuropathology. To address this problem for AD, researchers recently created a triple transgenic mouse model containing mutations in PS1, APP, and tau that progressively developed both plaques and tangles, and demonstrated cognitive defects¹⁴. This particular transgenic mouse promises to be a valuable animal model for evaluating potential AD therapeutics.

A large number of scientific, financial, and regulatory factors contribute to the complexities of drug development. The process is long, expensive, and uncertain. Increases in research and development expenditure do not guarantee returns on investment. In order to address the diminished returns on investment, many studies have been conducted; the general consensus is that there is a need for innovation in the drug development process^{15,16,17}. Recent scientific and technical advances and achievements have the potential to profoundly impact the pace of drug development. The regulatory components of the world's

governments must keep pace with the scientific and technical aspects of drug development to realize the potential. The U.S. entrusts the Food and Drug Administration (FDA) to ensure the safety and efficacy of drugs and biological products. One of the FDA's vital missions is to regulate and monitor all clinical trials activity. When clinical trials are developed, specific FDA-approved criteria are used to define success or failure. Previously, the clinical monitoring of AD involved techniques such as measuring the Neuropsychiatric Inventory at multiple time points. Unfortunately, this type of measurement can result in data that is statistically, but not clinically significant. The identification of new biomarkers for AD and advances in imaging technology discussed above offer quantifiable "hard" metrics that have the potential to improve the clinical trials process by identifying promising therapies sooner. At the same, clinical trials in which the therapy fails to meet metric expectations can be terminated earlier in the process.

Concluding Remarks

A cruel irony exists in the observation that the substantial progress in medical science and technology that contributed to the increase in human life expectancy, which rose dramatically from 47 to 77 years of age over the 20th century¹⁸, concomitantly increased the number of victims that ultimately suffer the agonizing death of AD. Moreover, achieving the goal of ameliorating AD is dependent yet on further advances in medical science and technology. Without rapid advances, the US will soon confront devastating fiscal and humanitarian burdens that are escalating in real-time to astronomical proportions. In this regard, the field of AD research, now fertile with an armament of new scientific and technological advances, is ripe for strategic investment. The number of new targets and therapies in the pipeline coupled with new diagnostic and monitoring technologies has generated unprecedented optimism for the discovery of an effective treatment for each American every 72 seconds that develops AD³.

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