ABSTRACT: In this paper, we suggest some of the dimensions of the problematic concept of Alzheimer Disease (AD) as a natural disease discerned by increasingly sophisticated medical scientific progress. Taking a page from Max Weber concerning unique events, we show some of the conceptual building blocks and social processes that have coalesced into the perception of certain phenomena as abnormalities that are seen as implicated in the development of a degenerative disease distinct from the process of normal, but variable, brain aging. We note some of the decisions and social forces pushing for particular conceptualizations, interpretations, and reifications of brain alterations. In so doing, we do not argue that there is no “there” there. Rather, we suggest that the mystery of the “there” (i.e., AD, mild cognitive impairment) may not be much different (if at all) from, and probably is, the mystery of the “everywhere” (i.e., aging).

KEYWORDS: aging, Alzheimer’s disease, cholinergic hypothesis, culture, dementia, genetics, mild cognitive impairment, pathology, race

THIS PAPER CONSIDERS SOME ASPECTS OF HISTORY and what are termed advances in dementia study as a basis for questioning the empirical status of both Alzheimer's disease (AD) and its prodromal derivative, mild cognitive impairment (MCI). Our methods are historical, cross-cultural, and ethnographic; we draw from historical and prospective research as well as studies of scientific developments related to AD and MCI in the literature. Our studies include participant-observational work on international scientists at venues worldwide. Each method contributes to the overall goal, that of a cultural understanding the medical construction, rather than discovery, of AD as disease and an evaluation of the cultural and ethical significance of recent developments in AD research and its latest extension, MCI. This work adds to other work that involves cultural perspectives on AD (Whitehouse, Gaines, Lindstrom, and Graham 2005).

Herein we view the development of AD as an unfinished, on-going product-in-the-making borne of a series of decisive historical moments. Each of the moments that we discuss contributed to the construction of a disease called Alzheimer’s, the character of which was (and is) construed as a degenerative biological, clinical entity. However, greater precision about the nature of the disease is and has been lacking. The lacuna in knowledge leads to vagueness that, while serving creativ-
ity as elsewhere in science (Taylor 1987), also leads to the proliferation of (sometimes) new and sometimes retrograde ideas about etiology and pathophysiology. We show that the taking up of one idea or another by authoritative figures tipped the balance in favor of one view over another, none of which has proven to be definitive. We suggest that if, at virtually any of the decisive, key historical moments, another decision or another interpretation had been drawn, then today we would not—indeed, could not—find ourselves discussing a disease called AD.

Our processual view (seeing disease development as an ongoing, never finished, social process (Turner 1969)) of sociocultural construction (Gaines 1991, 1992a, 1992b) reveals increasing ambiguity and mystery, rather than clarity about the nature of AD. The enigma must be all the more profound for conditions like MCI, which are asserted to be precursors of a mystery. Increasing ambiguity has marked the path in the development of a sense of difference, difference that is here psychiatric, there psychological, here neurologic, and there, behavioral. It is a sense or senses of difference that have become reified into a disease phenomenon assertedly distinct from normal (although problematic at times) aging.

The irony is that despite—or, rather, because of—recent advances in genetics and neuroimaging, the classification of the dementias has become increasingly less certain and more mysterious. The boundaries that separate conditions are now less distinct, e.g., such as between AD and Parkinson’s disease, AD and vascular dementia (VaD), or the distinction between or among these and frontotemporal dementia(s) (e.g., Rabins 2004). Additionally, the distinctions between normal aging and disease are now less clear than they appeared to be during the last century (Kirkwood 2003; Whitehouse 2003b; Whitehouse, Maurer, Ballenger 2000a, xi).

In our interpretive, deconstructive interrogation of the notion of AD as discovered (i.e., a found, natural disease entity) and MCI as precursor to that disease we employ a notion from Max Weber. Weber argued that the understanding of events that have occurred only once requires a mental operation or test; one asks what would have happen if this or that event did not occur (Aron 1970, 239). Here we look at the development of a disease as an historical, conceptual entity and, ultimately, suggest that its reality is equivocal. We suggest that AD appears more as a discursive formation than a discovered pathologic entity. We also suggest that MCI, which constitutes the extension of the concept of AD, implicitly marks the increasing sense of uncertainty about AD and, in fact, serves to unmake the construction of AD itself.

The present work adds to the meager literature on the history of AD for, as we have noted, “it is ironic that the professional and popular discourse surrounding Alzheimer Disease (AD), whose most dreaded feature is the obliteration of memory, proceeds with little awareness of its past” (Whitehouse et al. 2000a, xi). The present article is intended as a contribution to the study of AD in particular and, more broadly, as a contribution to the transdisciplinary, culturally focused field of the cultural studies of science (Gaines 1998) and to the field of biomedical ethics.

The Tangible Difference(s):
Plaques and Tangles

Alois Alzheimer’s 1906 observations of amyloid plaques and neurofibrillary tangles (NFT) led him to classify these as empirical evidence of a presenile dementia (dementia praecox). As a category of affliction, dementia itself was well described and classified (often in behavioral terms) by the dean of German psychiatry, Emil Kraepelin (1919/1971), among many others. Kraepelin delineated a large number of distinct dementias based largely on “psychic” and clinical symptoms.

He did not classify AD as a separate form of dementia in his 1919 text, Textbook in Psychiatry, and it appears only in Chapter VIII on “Morbid Anatomy,” Kraepelin bestowed the eponym in his 1910 text, Psychiatrie. He stated there (from the 1919 edition)

that the morbid anatomy of dementia praecox does not show macroscopically any striking changes of the cranial contents; only occasional thickening and oedema of the pia are reported, the latter evidently a result of agonal processes. On the other hand, it has been shown
that in the cortex we have to deal with severe and widespread disease of the nerve-tissue. In some cases which succumbed in a condition of acute delirium and which were classed as catatonia, Alzheimer has described deep-spread changes in the cortical cells, especially in the deep layers. The nuclei are very much swollen, the nuclear membrane greatly wrinkled, the body of the cell considerably shrunk with a tendency to disintegration. (Kraepelin 1919/1971, 213)

Alzheimer himself, as Kraepelin noted, focused more on what researchers would later call neurofibrillary tangles than on the beta amyloid plaques. (Aβ or Abeta today is a term usually reserved for the major constituent protein of the core of the plaque. Amyloid or neuritic, rather than senile, plaque is the usual term for the microscopically visible pathologic feature itself.)

At the time, clinicians viewed these changes as causative of a clinical entity distinct from that normally encountered in older people, that is, senility. However, there was scant material evidence from which to draw such a distinction (Maurer, Volk, and Gerbaldo 2000). Psychiatrists and neurologists of the time did not distinguish senility very much, if at all, from normal aging (Holstein 2000). And it was Kraepelin who suggested that Alzheimer’s findings constituted sufficient “difference” to warrant a disease label. This label was bestowed by Kraepelin, in part, because of personal ties to Alzheimer himself and their mutual affiliation with a psychiatric school (Royal Psychiatric Clinic in Munich) that could be favored by the “discovery” and labeling of a new disease entity.

The term dementia praecox itself is an historical designation for what is now called schizophrenia. The original term, however, was the group of schizophrenias. This conception, of a multiplicity of forms of a disorder, or actually, schizophrenia as a category of illness, is increasingly deemphasized, if not entirely absent from, contemporary psychiatry (Gaines 1992b).

However, in Alzheimer’s time, clinicians and researchers focused little on what they thought was a rare condition. Indeed, with one case, the possibility of an atypical, idiosyncratic condition (not disease) was more probable than it was that a new disease had been found. A second case labeled AD, that of Johannes F., confirmed the existence to Alzheimer and others of the existence of the new disease. However, as we show below, that case was not without its problems.

As historians of science have shown (Ballenger 2000, forthcoming; Holstein 1997, 2000), the modest concern for AD in the first half of the twentieth century did not mean that no research focused on it, as some would suggest (e.g., Tabaton 1994). On the contrary, and contrary to popular scientific histories, there was a significant medical literature produced on clinical and pathologic aspects of age-associated dementias. This literature had emerged by the mid-1930s with roots in the late 1800s (Kraepelin 1919/1971; Maurer et al. 2000).

The Stain’s the Thing

An aspect of the early construction of AD was the tissue staining process. Staining, then and now, provided visual images of the focal lesions or tissue(s) whether normal or pathologic. The staining process is a centrally important one that, literally, brings the lesion into the medical gaze. As part of a process that made a thing visible, it thereby made it (appear) real. The staining process asserted a commonality of the pathologic lesions. The first observation, still used in pathologic diagnosis today, was that NFT and Aβ plaques were both argentophilic and congophilic—they both accepted the same stains (silver and Congo red, respectively). However, this commonality did not necessitate the conclusion that there was histopathologic or etiologic commonality. That is, although there was the commonality of taking up the stain because of the beta-pleated structure, such acceptance did not prove that NFT and Aβ were by definition related or had a common origin. Their unity remains an arguable point (Holstein 1997); but, historically, acceptance of the stains was interpreted as evidence of a common nature and or etiology. It could have been otherwise.

By the 1960s, the idea of a distinct disease of AD yet needed much firmer evidence than had existed previously for it to be accepted on a wider basis in the medical community. Roth and colleagues provided, in part, the firmer foundation for the assertion of an identifiable disease as distinct from an aspect of the aging process. They developed clinical scales and then attempted to
correlate results from their administration with the extent of plaques and tangles found in the brains of patients examined at autopsy (Blessed, Tomlinson, and Roth 1968; Roth 1955; Tomlinson, Blessed, and Roth 1968). Although there was statistical significance for this correlation, the research did not demonstrate anything approaching a one-to-one correlation. Indeed, in the interpretation of their results, the researchers side-stepped the paradox of dementia appearing in patients who evidenced neither significant levels of plaques nor tangles (Ballenger 2000).

In this regard, it is important to note that Dr. Alzheimer’s second case of diagnosed AD, that of Johann E., exhibited an absence of NFTs on autopsy. His clinical symptoms were consistent with the new diagnosis, but the autopsy results were not. However, the label and the relationship of plaques and tangles to disease held. This is early evidence of a lack of a firm correlation between or among plaques and NFTs and clinical symptoms. Others had described plaques, but the NFTs were Alzheimer’s original observation and his distinctive clinical emphasis (Whitehouse et al. 2000a). This lack of a firm correlation presaged the problem in pathophysiology that (re)appeared with Roth and colleagues and continues today.

Because Roth and colleagues, and other researchers, found some correlation, they felt empowered to overlook the many exceptions in the quest for what was then being taken on faith as a causal relationship between lesions and behavior (Ballenger forthcoming). Yet, as Ballenger shows, these findings were insufficient to launch an AD movement. Science and society needed more elements to create a critical mass that we may call a social movement focused around and reaffirming AD.

Kidd (in the United Kingdom) and Terry (in the United States) supplied the additional impetus toward the construction of a disease entity through their work in electron microscopy. Their research yielded distinct results or, more accurately, interpretations. It is important to note that Kidd and Terry interpreted the self-same material phenomena differently. That is, the data did not “speak” to researchers with one voice as is often claimed to occur in the natural, as well as the social, sciences (Hacking 1983; Porter 1995). Research thus yielded distinct interpretations of what was seen (twisted neurotubules for Terry [1963], but paired helical filaments for Kidd [Ballenger 2000]). Both characterizations were largely descriptive and implicated intracellular cytoskeleton pathologies. However, models of tubules and of filaments are different and could lead to the construction of different models of pathogenesis. An example of the importance of description and resultant model is Rosalind Franklin’s centrally important description of DNA as a double helix (a model and term borrowed by Watson and Crick).

**SEEING THE SMALL**

The ultrastructural work of electron microscopy opened a new avenue on the pathway to the construction of AD. Its importance lies in the fact that this work established AD as a suitable “project for modern biomedical sciences” (Ballenger forthcoming; Katzman and Bick 2000). That is, what was being called AD showed itself to be amenable to the latest technology and thereby it became a candidate for increased medical scientific interest. This same process of developing relevance as a result of technological advances was repeated with the later developing enterprises of neurochemistry and genetics. The development of each field heralded what was then thought to be new understanding(s) and clarity concerning AD. That is, progress was being made in understanding the disease of Alzheimer—for instance, its risk factors (age, Down’s syndrome, genetic predispositions) are increasingly better known (Reisberg et al. 1997)—despite its (if it is an “it”) etiology remaining unknown.

Although medical researchers were doing new work (e.g., Terry was distinguishing the neuronal loss in aging as opposed to AD), that work was not being used in the service of creating a new, more widely disseminated disease category. As historical researchers have shown, this required both political and social forces that transformed the rare condition into a common one, and asserted that it was distinct from the aging process. Thus, to be of importance to the medical scientific community, two conditions had to be met: (1) researchers had to separate AD from the normal aging process; and
AD had to be of some moment, some social import (Ballenger 2000, forthcoming; Holstein 1997, 2000). AD, as a disease, could conceivably be dealt with by medical science; aging itself could not, at least not then. (Today we have “anti-aging medicine” complete since 1998 with its own journals and research foci, such as that of limiting cell damage [Kirkwood 2003].) In addition, a motive was needed to make AD a celebrated cause or, at least, a focal concern both of a significant number of researchers and of significant, supportive funding sources (Ballenger 2000, forthcoming; Holstein 1997, 2000; Fox 2000).

The potential remediation of a disorder afflicting “only” the elderly was apparently insufficient motivation for medical scientific investment and progress (Binstock and Post 1991). However, two related phenomena spurred an interest in constructing a disease that was of wide concern. These subsequently led to AD’s “rediscovery” (Katzman and Bick 2000).

The first development spurring the (re)construction of AD was the aging of the population (and, of course a widespread recognition thereof) (Binstock and Post 1991; Iqbal and Winblad 2003). Second, a substantial consumer movement developed in the 1960s that pushed biomedicine in new directions (Fox 2000; Fox 1990). These new directions included, in the view of some, the development of modern bio(medical) ethics (Fox 1990). With respect to biomedical ethics, on the one hand, doctors saw the incursion into their domain(s) of nonphysicians who began to observe medical practice, a move that can be regarded as instrumental in the development of medical ethics (Gaines and Juengst, forthcoming). On the other hand, consumers began to question medical paternalism (Ehrenreich and English 1978; Hayry 1991), medical efficacy (Illich 1975; McKeown 1979), and medical practice (Fox 2000, Fox 1990, Gaines and Juengst forthcoming).

These social forces pushed for research on a condition that was increasingly burdensome to members of the general public. Thus, biomedical conceptualizations are often strategically related to the development and emergence of social concerns. With respect to AD, these social concerns were the political and social forces of voluntary associations focused on it (Fox 2000). Here we see a social impetus for the formulation of a disease entity, one that is conceptualized in ways that make it appear that the “it” so delineated is or will be treatable and, perhaps, even curable or preventable; that is to say, there is the development of a discourse of hope (Moreira forthcoming). We find parallels in other fields of biomedicine such as oncology (DelVecchio Good 1991; DelVecchio Good, Good, Schaffer, and Lind 1990).

For a discourse of hope to develop, the common, expectable condition of senile dementia needed to become the exceptional disease of AD. Additionally, the epidemiology of dementias had to be strategically used to claim that an epidemic of major proportions was in the making. The “ticking time-bomb” concept was the recognition of the aging of the population with its potential afflictions, care burdens, and skyrocketing medical and social costs (Binstock and Post 1991).

As a consequence of the social interest, the US government intensified its role as a supporter of biological research on dementia. This support added another, nonscientific motivation for scientific action related to the cultural construction of AD. That is, political interest translated into financial support for research into AD, thus serving to reify the concept. The reification occurs because making funding available for a specific disease affirms the reality of that disease. This is an important aspect of the social construction of disease because funding and motivation to do research or even pay attention to an entity may depend on its characterization and its geography of affliction. The characterization of a disorder clearly affects scientific action related to it, as we see below in the case of the cholinergic hypothesis.

**Reframing Alzheimer’s Disease: Remembering the Cholinergic Hypothesis**

Anticipating MCI, we can look at how dementia researchers construed the cholinergic hypothesis. The finding that a reduction of acetylcholine in specific parts of the brain was related to memory problems (Whitehouse et al. 1982) was taken by some as a key to the unraveling of AD. So much
so that memory loss became a synecdoche for AD itself (Ballenger forthcoming). In actuality, the cholinergic hypothesis related only to one feature, memory, out of the broad range of problems associated with the condition. Furthermore, in the main the hypothesis related to recall memory rather than any of the numerous other subtypes of memory.

The cholinergic hypothesis was more a political statement than a scientific claim (Whitehouse, Maurer, and Ballenger 2000b). It asserted that loss of cholinergic function (related to the neurotransmitter acetylcholine) is but one substrate for the cognitive impairment, particularly in recall memory, associated with AD. The (re)construction of AD as a disease largely of “memory” represented a narrowing of the subject. The effect of the narrowing was to give the appearance of more knowledge and more (potential) control over the condition than existed in reality. The ability of biomedicine to affect “memory” was palpable. This palpability in turn lends the appearance of progress and contributes to the discourse of hope related to AD.

The synecdoche also provided the illusion of medial scientific progress. In fact, drugs were eventually approved worldwide that were based on an understanding of cholinergic dysfunction. They remain the only type of drug approved for use in AD. However, the therapeutic effects of these agents are relatively modest or minimal at best (and for only some patients), despite the rhetorical flourishes employed by researchers and the pharmaceutical companies themselves in characterizing these agents (Karlawish 2002). And, even these very modest benefits may accrue to less than ten percent of sufferers, and even for them, effects are short-lived.

**Medical Advance/Retreat**

Research advances (as they are termed) in AD are occurring on different, even mutually exclusive, fronts. The newer, very diverse, paths include examination of the inflammatory processes, amyloid buildup and removal, the impact of hormones, continuing concern for neurologic issues, and, once again, vascular changes, cholesterol, and genetic processes (Iqbal and Winblad 2003). In addition, extracorporal hypotheses are gaining currency. These include the renewed interest in psychoanalytic interpretations and the role of exercise, environment, meditation, and “healthier” living, the latter as therapeutic and preventative strategies (Ballenger 2000; Healy 2004; Kirkwood 2003; O’Connor 2003; Rabins 2004).

Are these developments in AD actually advances or do they move us laterally or even backward rather than forward as the notion of medical progress would indicate? And, does not this increasing diversity of approaches actually imply that we are dealing with the aging process and not with a specific disease? It is now clear that there is expanding heterogeneity in explanations and understandings rather than a narrowing of the medical gaze on one or a few specific implicative processes, etiologies, or lesions.

In addition to the many conceptions of the pathology of AD, there is a proliferation of pharmaceutical agents now in development. Their number is about fifty. The mechanism of actions of these drugs varies and includes anti-inflammatory, hormone blocking or enhancing, cell death preventing, amyloid or tangle clearing, and cholesterol reducing. The great range of variation in novel pharmaceuticals is again suggestive of a lack of specificity in the identification of a cause for AD. That is, although there is a range of advances, they do not lead us, nor have they led us, in a single direction toward a clarification of the nature of AD or to a consolidated view of AD as a unitary disorder.

Earlier theories from the 1930s to the 1970s posited psychosocial factors as implicated in the genesis of the dementias. That is, for psychological and psychoanalytical researchers, biological factors were unconvincing. Older theories should simply be replaced, if we are speaking of advances in a linear model of medical/scientific progress as was thought to exist before Thomas Kuhn’s classic (1962/1970). New theories, it is presumed, build upon and go beyond earlier theories. In today’s terms, this would mean analytic theories should be replaced by vascular theories (Healy 2004) that, in turn, would be trumped by genetic theories and now, proteomics (or proteomics)
may claim the top spot in the medical theoretical hierarchy. Prote(n)omics (as we will call it here) is an important new paradigm that signals the end of the dominance of the genetic paradigm and "the Age of the Gene."

The Human Genome Project's enumeration of the genome essentially ended this age (Gould 2001). The enumeration demonstrated that there are far fewer genes in the genome than researchers had assumed, thus making impossible all the pet theories of genetic etiologies. The subsequent shift to proteins, however, is not necessarily an advance. This shift is another application of the tendency toward atomism in biomedicine. This tendency assumes that a lower level of biological reality can explain all that is above it and derives therefrom.

Also, in the biomedical sciences, one assumes that moving to "lower, more basic biological levels" allows one to eliminate culture and other "biases" that inhibit or distort science's allegedly objective gaze. It allows one to "really see what is going on," to use the common visual metaphors of the medical field. Thus, biology is the singular, ultimate, cross-culturally valid reality for biomedicine (Gaines 1992a; Gaines and Davis-Floyd 2004; Lock and Gordon 1988; Mishler 1981).

In psychiatry, a similar move toward the biological explanation was intended to indicate a more scientific and, therefore, mainstream medical, psychiatry. It represented a shift from talk as intervention to biological etiologies and somatic interventions. The biological paradigm was the basis for the formulations of the Third Edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-III) and its subsequent revisions (concerning which see Gaines 1992b). However, to weaken the case of biology as ultimate reality, let us consider closely the universal human biology that biomedicine believes it "discovers" rather than invents through its knowledge and practice.

**ALL BIOLOGY IS LOCAL**

Recent medical anthropological research suggests that the word biology should be a plural—biologies—for we do not find on the world stage a single unitary, universal biology that serves as the bedrock of theory and practice in the world's popular or professional medical systems (e.g., Gaines 1992a, 1992b, 2004; Kuriyama 1999; Leslie and Young 1992; Lock 1980; Unschuld 1985). Biologies are, in fact, constructed differently in different countries (and at different times). Notions of human biology appear as local discursive formations. As such, they constitute what Gaines calls local biologies (1992a, 1998, 2004, 2005, submitted).

The biologies that form the bases for understandings of human health and illness vary among the world's professional medicines. The biologies of Japanese traditional professional medicine (Kampo), traditional Chinese medicine, Ayurvedic (classical Indian medicine), and Unani (Arabic professional medicine) are all quite dissimilar. Each possesses detailed but distinctive biological constructions, some of which are considerably older than those we find in the West. Indeed, some of these traditions influenced the West's constructions of human biology or share with the West a common foundation (e.g., vitalism in the West was influenced by the Chinese notion of Chi; Unani derives in part from Classical Greek medicine; Leslie and Young 1992).

Often, we may distinguish the professional medicines by their central metaphors around which, at the most abstract level, disease classification, diagnosis, and treatment are organized. Traditional Chinese medicine uses a botanical metaphor (Kuriyama 1999; Unschuld 1985); Ayurvedic uses an ecological one (Zimmerman 1988), and the US uses a mechanical model (Lock and Gordon 1988). Japanese Kampo has a range of distinctive notions about individual bodies and their specific, and idiosyncratic, afflictions (Lock 1980, 1993). In Japan, Western biomedical ideas are often co-opted in the service of the cultural folk and professional medical belief system (Ohnuki-Tierney 1984). Each of the professional medicines uniquely conceives of human biology; their distinctive conceptions make sensible and reasonable a range of therapies and afflictions that are local rather than universal.

Why do biologies differ? One might assume that the variations arise because non-Western medicines are cultural, or more traditional. Unlike
them, modern biomedicine, it is asserted, has a uniform notion of biology because it is more scientific, acultural, and evolved (a term that is often, and incorrectly, assumed to signify improvement, which it does not; evolution simply means different from a earlier state or form; Hahn and Gaines 1985; Lock and Gordon 1988). Such a view would be erroneous for two (other) reasons.

First, Western biomedicines are not unitary; they too exhibit distinctive foundational biologies. For example, French biomedicine, distinct from German (Maretzki and Seidler 1985) or US biomedicine (Hahn and Gaines 1985; Lock and Gordon 1988), is centrally concerned with maintaining a unique body aesthetic and terrain, with pollutions/toxins often not recognized by US medicine, and with noxious social contexts. Afflictions must be treated in terms of the maintenance of corporal uniqueness, especially as concerns surgeries, and the terrain (Gaines 1992a; Payer 1989). German medicine, on the other hand, is focally concerned with the wearing down of the body and organ insufficiency, especially that of the heart, and with “racial” identity and affinity (Barkan 1992; Gaines 1992a; Maretzki and Seidler 1985; Payer 1989).

In the United States, the body is both racialized and conceived of as a machine. This conception makes possible a variety of interventions such as transplants and prostheses, that are unacceptable in other cultures, for example, Japan. There, the body in life and death should maintain its integrity. As a result of these views, there is great social and legal opposition to transplantation (Lock 2001). These distinct beliefs constitute local biologies. These biologies are the logical and material foundations of conceptions of diseases, therapies, and medications even for the same conditions across cultures. The differing foundations result in distinctive therapeutic interventions and or levels of efficacy of pharmacologic agents.

**Ideal Corporality: The Past in the Present**

As noted, the body in US medicine is racialized. This racialization is a prime example of local biology. The “racial” conception holds that “races” exist and are biologically distinct. This “racial” biology is absent from the biomedicines of other cultures and, given recent work in genomics, logically should experience a precipitous decline in the United States. However, this local biology of “race” is incorporated into nearly all comparative medical work in the United States and, in fact, its use appears to be growing, not retreating. Although distinct groups are now sometimes labeled ethnic groups, the clear referent is an implicit racial group, for example, the ubiquitous comparison of “blacks and whites” (Barkan 1992; Duster 1990; Gaines 1992a, 1998). Such comparisons were favored in the “racial” evolutionary theories of the nineteenth century (Gould 1996). The cultural notions of race and racial differences and corresponding distinctive therapies contradictorily and simultaneously assert universality and uniqueness (Gaines 2004).

In some circles, assertions of racial differences are considered evidence of medical progress. However, an historical view shows them to be (re)invoking and (re)creating two century-old, disproved cultural notions of “race” and “racial” differences (Barkan 1992; Duster 1990; Gaines 1992a, 2004, 2005; Gould 1996). Thus, one finds geneticists (re)asserting the reality of “race” (e.g., LeRoi 2005). In Duster’s terms (1990), there is a return of “eugenics through the backdoor”; genetic science bent on misinterpretation.

This effort at (re)racing social reality includes the development and recent approval of a cardiovascular medicine (BiDil, a combination vasodilator) for use specifically by “self-identified” African Americans. Somehow, self-identification is isomorphic with a putatively distinct biology. However, members of this social category, in fact, have more or less (or even no) West African ancestry. But as well, they have Western European and Native American ancestry in proportions that vary with each individual (Gaines 2004, 2005). That is to say, there is no genomic or biological unity of individuals in this US social category. Any commonality appearing as a result of African ancestry would also appear necessarily in all human populations, not just one. We find this “racial” ideology in AD research as biomedicine seeks biological explanations for differences in rates of affliction and/or disease progression (Gaines 2004).
Cultural differences also affect the development of so-called “personalized” medicine: the idea that knowledge of an individual’s genes will allow more individually tailored drug treatment. The ambiguities about “race” demonstrate the limitations of using statistics on social categories and population statistics to understand individual lives (Barber and Whitehouse 2002).

A second reason one should not assume that “modern” US medicine is more advanced is that its early ideas have not been replaced by newer, more scientific ideas (the linear theory of scientific advancement). That is, as Kuhn (1962/1970) showed, scientific paradigms shift from one to another without a linear progressive development. New ideas often do not build on the old ones that they replace; they are simply different models altogether.

Thus, we see a renaissance today of older theories about AD, such as the psychodynamic, precisely because of the growing vagueness of etiologic hypotheses. In addition, instead of a narrowing of genetic links to AD, we see a growing expansion thereof, now involving some thirteen chromosomes (Iqbal and Winblad 2003). This expansion appears in the context of the new prote(n)omic paradigm. However, although it is clear that more implicated genes are being identified, such work is more problematic than ever because the evidence for the validity of all thirteen implicated chromosomes is incomparable.

The genetic understanding of AD can be divided into knowledge about autosomal-dominant forms and so-called genetic susceptibility loci. The mutations on chromosomes 1, 14, and 21 are inherited in an autosomal-dominant fashion, meaning that the risk of inheriting a gene from an affected parent is fifty percent. Many different mutations have been identified that carry this kind of high risk. Onset is often in the forties and fifties, and the penetrance, that is, the likelihood of showing the phenotype if the genotype is present and the individual lives long enough, is high. Despite the genetic inheritance patterns being relatively clear cut, few families have engaged in genetic counseling with these kinds of mutations. As well, there are very few families with this sort of pattern; as few as two percent of AD patients belong to this category (Post et al. 1997).

The genetic susceptibility locus associated with chromosome 19 shows the cholesterol carrier protein, apolipoprotein (Apo) E. In this case, inheriting the isoform, ApoE 4, especially in the homozygous state, that is, a gene from each parent being E4, increases one’s susceptibility for AD. However, one can be homozygous for E4 and not get AD, and one can get AD without an E4/4. Although this observation has been made in a variety of populations, translating this information into clinical practice is difficult. Providing a precise risk for an individual in a counseling session is impossible given the limitations of the empirical data sets and the theoretical models. Moreover, the consequences of carrying an E4 in terms of life-altering decisions are unclear (Post et al. 1997). Perhaps one should buy long-term care insurance. However, the raising of the issue of insurance leads to the controversial ethical issue of whether insurance companies should have access to genetic testing results.

In our preliminary findings from a multicenter, randomized controlled study funded by the National Institutes of Health, it seems clear that the participants are more strongly influenced by the test result, that is, whether they are E4 or E4/4, than they are by the overall risk assessment, which is also presented to them. These findings suggest that the integration of genetic information into clinical practice is more difficult than the proponents of so-called personalized medicine would suggest.

**Paradigm Shift**

In 2002, the once fertile field of genetic interpretations in AD ran into a wall; at the 6th International Congress on Alzheimer’s and Related Disorders, key figures in the field flatly stated to the authors that they did not believe that new or significant genetic findings were in the offering or would be presented at the conference. Slightly earlier, there was, in Stephen J. Gould’s estimation (Gould 2001), the literal collapse of the genetic paradigm on the heels of the publication of the human genome.

This was a signal moment, as Gould noted. We now find ourselves in the early stage of the new paradigm of prote(n)omics. However, we can ex-
pect that genetic research will carry on, as Kuhn would suggest, for it was the normal research paradigm and so will run its course before being drowned out by the new paradigm. We point out here, however, that we are unsure as to whether or not prote(n)omics represents real progress. It represents a closer focus on a pregenetic model and may be a repackaging of older biological models for political and economic gain. The term itself may be no more than a label employed to take advantage of the newly minted power of the -omics root (from genomics) and so to incorporate the halo effect of that term's cultural capital.

The paradigm shift throws into relief the local biology of contemporary biomedicine and its atomistic march; the level of relevance gets smaller and earlier biological locals of focal concern shifts from structures, to genes, to proteins. However, these shifts derive ultimately from the German parent medicine of some US specialties (internal and psychiatry), which assumes all significant differences are biological. Although “race” is important in these medicines, it is not in most others of the world. Many medicines—as in India, Japan, the Middle East, and China—see the external world, not increasingly minute biological levels, as most implicated in health and illness.

CHANGING THE SUBJECT: FROM ALZHEIMER’S DISEASE TO MILD COGNITIVE IMPAIRMENT AND BEYOND

Recent research suggestive of this point includes shifts in research foci that amount to a scientific changing of the subject. This is the research “progress” alleged to be demonstrated by the focus on MCI. The impending decline of genetic explanations and the proliferation of pharmacologic agents in testing (perhaps more for symptomatic treatment than treatment of any disease [Healy 2004]) bode ill for the continued (re)construction of AD as “disease.” One now sees an increasing vagueness in etiologic hypotheses, rather than a narrowing, and a retreat from beliefs that an “answer” is imminent. The proliferation of drugs, the loss of confidence in simple genetic explanations and the move to prote(n)omics all suggest AD is becoming less an identifiable disease than a recognizable cultural complex based upon interpretations of normal, if problematic, biological and neurologic variations in aging.

Thus, the nature of the connection of MCI to AD is quite unclear. As such, the term is fundamentally problematic (Whitehouse 2004). MCI was invented to identify people at risk for AD to enroll them in trials designed to prevent dementia. Unfortunately, the term is not consistently used even by the academics who invented the concept. Moreover, MCI represents just another of many labels that have been applied to the pre-Alzheimer part of a continuum of cognitive aging, starting with benign senile forgetfulness and including another popular term, aging-associated memory impairment (Whitehouse 2004).

The problems of applying MCI in clinical practice are even greater. Depending on the clinician involved, MCI can mean either that one has early AD or that one does not have AD, or that one might or will develop AD or, as in some studies, it means that one has a temporary condition (because some cognitive impairments have been shown to improve). Moreover, every progressive degenerative dementia, including Parkinson’s disease and frontal lobe dementia, as well as VaD, logically must go through a stage when clinical symptoms are present but not of sufficient severity to warrant a diagnosis of dementia. The critical issue in differentiating MCI from dementia relates to the relative preservation of activities of daily living (ADLs). However, relative is very vague. Decline or maintenance of ADLs depends on the occupation, hobbies, and cultural expectations of the individual in question as well as the assessment process used by the clinician(s).

Some clinicians emphasize the use of neuropsychological tests and require objective demonstration of performance one to one-and-a-half standard deviations less than normal elderly on various cognitive tasks. Here the issue is how much objective impairment must exist and on which specific tests impairment is reliably demonstrated.

MCI is not only problematic itself, but in fact, points to some of the ambiguities in the label AD at the end of the continuum of cognitive aging. We suggest that attempts to place people into
discrete categories are highly problematic when we are dealing with the wide and diverse continuous process of cognitive aging. Seeking a new paradigm (or reinventing an old one) may not be a sufficiently fundamental change unless the new thinking incorporates the continuum of brain aging in its formulations and better understands science and biology as cultural phenomena.

Despite the original findings by Alois Alzheimer at the beginning of the last century, AD became a focal medical concern only in the last third of the twentieth century. Spurred by popular demand for research into a condition that causes enormous suffering for individuals and their caregivers, by government interest and funding, by the biologization of psychiatric theory, and the aging of the population and its ominous (and ageist) implications for the epidemiology of AD, biomedicine constructed AD as the primary culprit. Pharmaceutical interests now also have arisen as important in the construction of disorders, sometimes before biomedicine identifies them (e.g., social anxiety disorder; female sexual dysfunction). MCI’s formulation thus, in part, appears motivated by pharmaceutical company interests as well as by a changing of the research subject away from AD, where progress at etiologic clarification is increasingly problematic.

On the psychocultural and social levels, the social concern and mobilization against AD as a tragic and devastating disease derives from its cultural construction as a threat to the self’s most valued attributes in the context of Northern European Protestant culture, that is, cognitive functioning/memory (Gaines 1992b; Post 1995). This construction also now implicates increasingly narrow medical notions of normality and, hence, a widening range of behaviors that may require care (thereby increasing burdens; Gaines 1992b; Whitehouse 2003a) and pharmaceutical interventions (increasing profits; Graham 2000).

“Discoveries” about the cause(s) of AD continue to proliferate and to cloud understanding of the nature of AD as a unified disease. Indeed, researchers now flatly assert that AD is a heterogeneous disease (Iqbal and Winblad 2003; Morris 1994). We noted that Alois Alzheimer’s second case of AD in the early literature did not evidence the implicative NTFs upon autopsy. Despite their absence, which attracted Alzheimer’s attention in the case of Auguste D, Alzheimer still considered Johann F to be the second case of the disorder Kraepelin named after him.

A proliferation of drugs with different loci of action also reflects the growing lack of clarity about AD as a unitary disease. The role of profit in disease construction and the problems of “early diagnosis” for conditions that are uncertain (e.g., MCI) and cannot be efficaciously treated raise a variety of ethical issues. These issues include the acceptance of a pharmaceutical push for the designation of a precursor of a disease, the reality of which is, itself, increasingly unclear and mysterious. Second, the designation of individuals with MCI or its variants can and does cause negative psychosocial effects on those to whom it is applied (Whitehouse, Frisoni, and Post 2004). The label AD can be interpreted to mean that life is over—the past will disappear and the future does not exist. Yet it is too harsh to assert that there are only disadvantages to such labeling. Providing a diagnosis can result in access to medical approaches and social resources. It can provide a sense of control. However, there are broader negative issues.

There are also issues of creating MCI in the context of a hypercognitive culture (Gaines 1992b; Good 1994; Post 1995). That is, those from traditions other than the dominant one within or outside of the United States are at risk for being labeled as impaired when what is observed is that they are not as hypercognitively oriented as is the ideal (as distinct from a real) cultural standard (Gaines 1992b). Various cultures exhibit more or less interest and elaboration of particular cognitive and affective processes; here color terms are important, there, cattle color patterns, and elsewhere, the minute descriptive details of a mythical world are central (Shore 1994; Shweder 1991).

Cultures do not uniformly encode or cognitively assess their environments or experiences after the fashion of the Protestant dominant tradition in the United States. In the cognitive emphasis, we see the issue of cultural bias once again invading diagnosis as well as disease conceptualization (Gaines 1992b, 1998, 2004; Good 1994; Lock
and Gordon 1988; Post 1995). And we recall that senility was once considered an age-appropriate condition.

**Note**


**References**


——. Submitted. *Figures of speech: Local biology, race and culture in millennial medical anthropology*.


