Part 3: The Human in the Body
Demoting the Genetic Body

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Abstract: A summary of research findings about the "genetic body" revealed through genetic testing is followed by a discussion of the emerging science of epigenetics in which genes are understood as just one actor among many in the onset of disease. Current knowledge about the genetics of Alzheimer's disease is set out and ethnographic data presented based on interviews with individuals who have been genetically tested for this disease. It is argued that genes will never be a powerful divinatory tool for the future in connection with common complex diseases such as Alzheimer's.

Keywords: genetic testing, epigenetics, susceptibility genes, Alzheimer's disease, risk, embodiment

Résumé : Un résumé des conclusions de recherches portant sur le « corps génétique » que révèle le dépistage génétique est suivi d'une discussion sur la science émergente de l'épigénétique, cette dernière considérant les gènes comme un élément parmi d'autres dans le déclenchement des maladies. L'article présente ensuite l'état actuel des connaissances sur les caractéristiques génétiques de la maladie d'Alzheimer et des données ethnographiques recueillies lors d'entrevues réalisées auprès d'individus ayant été testés génétiquement pour la détection de cette maladie. L'article soutient que les gènes ne seront jamais un puissant outil divinatoire dans le futur quant à la prévention de maladies aussi courantes et complexes que celle d'Alzheimer.

Mots-clés : dépistage génétique, épigénétique, prédisposition génétique, maladie d'Alzheimer, risque, incarnation

It is well known that Franz Boas (1940) adopted a concept of culture that was pluralistic, relativistic and devoid of biological determinism. Even so, his research, much of it explicitly designed to overthrow racialist arguments and erroneous assumptions about the relationship of biology to behaviour, was grounded in biological measurement that clearly demonstrated the inter-dependence among culture, social change and biological difference. When writing about Boas' approach, George Stocking argued it could well serve as a guide, not only for the history of anthropology, but also for its future direction (1982:18). I am inclined to agree, although, of course, things are not so straightforward as they appeared to be in Boas's time, and his belief that anatomical difference among humans could be explained on the basis of race is obviously a major stumbling block (but we must not stand guilty of presentism).

For much of the 20th century, anthropologists worked hard to refute the concept of race and the task continues. If anything, race is having a misplaced revival as a result of findings from molecular biology (Duster 2006; Montoya 2007) This subject has been so divisive over the years that the majority of cultural anthropologists have set the material body to one side on the assumption that it can, in effect, be treated as a universal. However, as Callon (1986), Goodman et al. (2003), Haraway (1991), Lock (1993, 2002) and others have pointed out, to "black box" the material body entirely, and with it any chance of considering the social ramifications of the co-production of nature–culture presents a problem. This is particularly so if we wish to gain some insight about the way in which biomedical technologies have the potential to fundamentally transform individual experiences of embodiment, identity-making, human relationships and allocation of responsibility for health and illness, thus enabling the remaking of what is assumed to be "natural" (Strathern 1992).

In this article I will focus on just one of these technologies, that of molecular genetics, and in particular on

genetic testing, a technology that will become increasingly used as whole genome scans at relatively low cost are made available. It is likely that, in the not too distant future, individuals will routinely be informed about details of their personal genome profile as part of basic clinical care (Brice 2004), while hundreds of DNA tests for identifying genes associated with specific disorders are already available (Yoon et al. 2001).

A growing body of social science literature has begun to both conceptualize and demonstrate the impact that this molecularized information is having on individuals and families who have been given information about their "genetic body." A few of the findings from this research pertinent to the main argument of this paper will be presented first, followed by a brief discussion of a paradigm shift currently taking place in molecular genetics, central to which is an argument about the "de-throning" of the gene. The recognition by scientists of the significance of this new "epigenetic" approach (to be explained below) calls into question the reliability of risk estimates for complex diseases based on genes alone. In the final part of the paper, current knowledge about the genetics of late onset Alzheimer's disease is set out. This is followed by findings from ethnographic research in which individuals believed to be at risk for Alzheimer's disease, after receiving individualized test results for the gene in question, discuss their responses to this newly internalized knowledge about embodied risk.

These research findings strongly indicate that a profound sense of identity transformation has not taken place as a result of this particular genetic testing; on the contrary, individual narratives about future confrontation with aging and possible dementia remain much as they were before testing. This finding is in large part due to inherent, irresolvable uncertainties associated with genetic information about complex disease, the social implications of which for further routinization of individualized genetic profiling will be spelled out in the conclusions.

The Genetic Body

Novas and Rose, seeking to theorize broadly the transformation that is taking place as a result of emerging knowledge in molecular genetics posit, following Foucault, that as a result of recent advances in the life sciences, including human genetics and genetic medicine, a "mutation in personhood" has come about (2000:485). This transformation is not merely, they suggest, a modification of lay, professional and scientific ideas about human identity and subjectivity, but is also a shift in "presuppositions about human beings that are embedded in and underpin particular practices" (Novas and Rose 2000:486). One result is the emergent figure of the "genetically at risk" individual. "Individuals [of this type] and their families...have taken unto themselves the responsibility for the government of their risky genes, in relation not merely to a secular norm of individual health, but an obligation to one's kin, to those one loves, and to the future" (Novas and Rose 2000:507). Novas and Rose are careful to qualify their claims: "Ideas about biological, biomedical and genetic identity will certainly infuse, interact, combine and contest with other identity claims; we doubt that they will supplant them" (2000:491).

Similarly, Rabinow has suggested that new congeries of people will emerge as a result of knowledge founded in molecular genetics, activities he labels "biosociality." But Rabinow (1996:103) too is careful to point out that older forms of cultural classification of bio-identity will not disappear. A sizeable body of literature has now shown that these qualifications are valid, and that when genetic information is incorporated by individuals into accounts about illness causation such knowledge supplements previously held notions about kinship, heredity and health. For example, writing about Huntington's disease, a single gene disorder with onset in adulthood (sometimes very late in life) for which there is no known treatment, Cox and McKellin argue that "theories of Mendelian inheritance frame risk in static, objective terms" abstracted from the messiness of human contingency and biography (1999: 140). In everyday life, genetically tested individuals and their families jointly engage in a complex "social calculus of risk" that is fluid, contingent and inter-subjective.

People who come from families with Huntington's disease vacillate about testing, sometimes for many years. This vacillation is partly a result of the uncertainties involved about age of onset of the disease which cannot be predicted with accuracy, and partly because there is no treatment for this condition. In this latter respect, Huntington's disease is the same as by far the majority of the so-called single gene, Mendelian disorders. Moreover, recently acquired knowledge complicates estimations of future risk—it is now known that an unequivocal link does not exist between the presence of a Huntington gene and the expression of the actual disease, as was formerly believed to be the case (Langbehn et al. 2004). There are a small number of cases where a clear prediction cannot be made, making "educated choices" about the value of testing problematic. As genomic knowledge accumulates it has become apparent that this situation also applies to certain other single gene disorders, so that the biopolitics of genetic risk are increasingly riddled with estimations that gloss over embedded uncertainty.

At the time when Rabinow (1996) first introduced the concept of biosociality, the idea of groups literally coming together on the basis of a specified chromosomal abnormality as Rabinow suggested (with a touch of irony one assumes) seemed farfetched to many. In retrospect his insight has proved to be prescient. An article in the *New York Times* in late December 2007 discusses the experiences of some families with extremely rare genetic mutations who, as a result of a new diagnostic technology—DNA microarray analysis—learn about the DNA mutation that has affected one or more of their children and, with access to email and the internet, have made contact with similarly affected families (Harmon 2007). Both disorders discussed in this article are usually diagnosed as autism or mental retardation, but by making use of microarray analyses, newly identified chromosomal disorders that are apparently fully determined by aberrations in specific segments of DNA can readily be spotted at a current cost of US$3,000. So far only six children have been diagnosed with the disorder known as 16p11.2, a condition that is not inherited. The other condition discussed in the *New York Times*, 7q11.23, has been found in 11 children worldwide. Without doubt, other cases will emerge as microarray analysis becomes more widely used. The making up of these "new" diseases is a powerful example of how certain syndromes and behavioural disorders are increasingly likely to be reclassified as genetic disorders once the molecularized body is rendered more visible. However, the question of what conjunction of variables brought about the chromosomal aberrations in the first place remains, of course, unaddressed.

The search by the parents of two children diagnosed with these new disorders forms the import of the article in the *New York Times*. In both instances the parents experienced considerable comfort and hope for the future as a result of talking with families where children had been given the same diagnosis as their own child. One parent complained before receiving the results of the microarray analysis that the diagnosis of autism they had previously been given did not mean anything because, quite simply, it was "too non-specific." He and his wife rejoiced at the genetic diagnosis because it relieved them of guilt and offered a glimmer of hope for treatment in the future, particularly after they had contacted parents in a similar situation; they were then able to take great solace from realizing that they were not alone (Harmon 2007).

Recently, Raspberry and Skinner (2007) have asked whether increasing use of genetic information and technologies will bring about a paradigm shift in the "knowable body" and in everyday conceptions of health. They question whether biomedicine is moving toward a single notion of "body as text"—an informatics notion of the body—or, alternatively, whether genetic information will simply "deepen" our understanding of the conventional biomedical body (Raspberry and Skinner 2007). Their findings from a study carried out with 106 ethnically diverse families in the southeastern United States in which children had been diagnosed with a genetic disorder showed that, in most instances, genetic information was simply incorporated to provide "another piece of the puzzle" in determining what was wrong with the child. Further, similar to the findings reported in the *New York Times*, they found that a genetic diagnosis frequently gives legitimacy to a disorder as "truly" biological, allowing families to escape from catch-all "soft" diagnostic categories such as autism and ADHD (Attention Deficit and Hyperactivity Disorder). And affected families dare to hope for a "cure" in the not too distant future by means of molecular engineering. Even so, a "hybrid notion of causality" persists in the minds of the families: despite the recognition that chromosomal deletions have caused very real bodily changes, questions about the range of phenotypic expression and its severity are inevitably uppermost. The genetic body made knowable through technology requires continual reassessment on the basis of its actual expression. Knowledge about genetic reality rarely transcends or precludes the ever present uncertainty, hope, wishful thinking and sometimes despair that constitutes everyday life when a genetic disorder has been identified.

In summary thus far: with remarkable rapidity, as genomic technologies advance, segments of DNA are being marked out as "natural" signifiers for who among us should be counted as genetically at risk, but DNA segments are rarely, and possibly never, straightforward *determinants* of disease, as was formerly assumed to be the case. When considering the responses of individuals and their families to proposed genetic testing, or alternatively to actual test results, the age of onset of the disease in question, its specific pathological effects, and the fluidity of basic science knowledge about the condition (subject to continual modification as the result of new technologies), affects the kinds of accounts that people create about personalized genetic information.

Moreover, it is well recognized today that genetic testing is not merely an individual matter, but inevitably has broader social consequences, not the least of which are the undeniable implications for kin, as well as possible stigma, and work and insurance related repercussions (Draper 1991; Nelkin and Tancredi 1989). It should also be noted that research in connection with several diseases

shows that only 10 to 20% of people come forward for testing when it is offered to them (Quaid and Morris 1993) and that, when tested, individuals often simply ignore or repress the results (Hill 1994; Rapp 1999). It appears that many people are choosing not to exert "genetic prudence" and that a burning desire to know about the genetic body is by no means always the case.

Before turning to a consideration of the genetics of late onset Alzheimer's disease—an example of a common complex disorder, a condition in which it is universally agreed that numerous genes and environmental variables are involved in causation, course and eventual outcome—I will introduce a little of the current thinking associated with the science of epigenetics. This emerging paradigm in the world of molecular genomics highlights the problematic nature of genetic testing for complex disease, raising a degree of uncertainty that far exceeds that noted above in connection with testing for single gene disorders.

Beyond the Dogma of Genetic Determinism

Genes have recently suffered the indignity of being demoted by many, perhaps the majority of experts in the world of genomics, from real, substantial entities to the status of a concept. Although genes continue to be very powerful heuristically, research has made it clear that scientists do not know where genes begin or end (Stotz et al. 2006); nor are they stable and they do not, on their own, *determine* either individual phenotypes or even the biological make up of future generations. Quite simply, genes are not *us* and the gene can no longer pass as the fundamental animating force of human life; it has been dethroned, Fox Keller informs us, from its place as "part physicist's atom and part Plato's soul" (2000:277).

It is paradoxical that this current definitional disarray of the gene was brought to a head as a result of the Human Genome Project. As is now well known, when mapping the human genome, scientists involved labelled 98% of the DNA they had isolated as "junk" because it did not conform to their idea of how the blueprint for life was assumed to work. In recent years, things have changed dramatically and junk DNA, thrust summarily to one side in order to focus on the task of mapping only those genes that code directly for proteins, can no longer be ignored. This junk is composed largely of RNA that, although it does not code for protein production, is nevertheless deeply implicated in gene expression and regulation and so must now be sifted through systematically (Eddy 2001; Mattick 2003, 2004). The activities of noncoding RNA are believed to comprise the most comprehensive regulatory system in complex organisms; they function to create the "architecture" of organisms, without which chaos would reign (Mattick 2003). This noncoding RNA has also been shown to profoundly affect the timing of processes that take place during development, including stem cell maintenance, cell proliferation, apoptosis (programmed cell death), the onset of cancer and other complex ailments (Petronis 2001). Consequently, the research interests of many molecular biologists are no longer confined largely to mapping structure, but have expanded to the elucidation of the mechanisms of cell and organ function throughout the lifespan of individuals and through evolutionary time. Central to this endeavour is to understand gene regulation—above all how, and under what circumstances, genes are switched "on" and "off"—in other words, what brings about their expression.

Using this new approach, the effects of evolutionary, historical, environmental and cultural variables on developmental processes, health and disease are acknowledged. Determinist arguments are, in theory, no longer appropriate, and both micro- and macro-environmental effects on cell activity and its immediate surroundings are key to this type of research. This emerging epigenetic knowledge (as it has come to be known) has exploded the central dogma on which molecular genetics was founded. Metaphors associated with the mapping of the human genome—the Book of Life, the Code of Codes, the Holy Grail and so on—are entirely outmoded. With the cell at centre stage, genetic pleiotropy,[1] gene-gene, gene-protein and gene-environment interactions cannot be ignored and biological pathways are no longer thought of as necessarily linear or unidirectional. A space has been opened up between genotype and phenotype, a space of endophenotypes—unstable, shifting interim states—that was partially recognized one hundred years ago but then conveniently set to one side until relatively recently (Gottesman 1994).

One can argue that Mendelian genetics—particularly the hard-nosed, reductionistic, deterministic version created by James Watson and Francis Crick—"fit" very neatly into the sweep of modernity. Genes make us what we are in this vision. The hope of some, especially with the mapping of the human genome, was that we would be able to engage in fundamental genetic engineering and manufacture genomes designed to eradicate disease, poverty, ignorance and criminality (as the past editor of *Science*, Daniel Koshland, so infamously said (1989)), while at the same time enhancing our desire for aesthetically pleasing, perfect offspring.

The molecularized universe has turned out to be so very much more complicated and exciting than most people had imagined. It is a universe entirely in tune with postmodernity. It is a landscape littered with a pastiche of

shape-shifters (smart genes, transcription factors, jumping genes and so on), an environment of the unexpected in which boundaries formerly thought to be stable are dissolved. It is evident that some genes encode for more than one protein, while many others do not encode for proteins at all—entirely upsetting the central dogma of genetics that prevailed until the beginning of this century, namely that any one gene sets off a unidirectional flow of information from DNA to RNA to protein to phenotype. Increasingly it has become clear that multiple factors, including events both internal and external to the body, enhance or inhibit gene expression with the result that it is now agreed by many molecular biologists that research into phenotypic expression must make use of a "wide-angled lens," one that takes into consideration a systems biology, multifaceted approach that includes social variables.

This means that our efforts to divine individual futures by means of genetic testing for anything but the rare Mendelian disorders are precarious indeed and the majority of clinicians and basic scientists, with some notable exceptions, are well aware of this.

Epigenetics—Contextualizing the Molecular Body

The philosopher Lenny Moss has pointed out an enigma evident in the natural sciences that periodically comes into stark relief whenever conceptual ground begins to "shake or shift" (2002:219). The problem is how to account for the "apparently 'purposive' nature of the living organism in the purely mechanistic terms of our post-17th century understanding of nature" (Moss 2002:219-220). Even more vexing, argues Moss, is the question of "how to locate ourselves—the purposive, flesh-and-blood investigators—within the conceptual framework of our biological inquiry" (2002:220). Moss identifies a continuum along which strategies for coping with this enigma can, in theory, range. At one end lies full-blown pre-formationist theory in which The Creator determines all. René Descartes fell closer to the other end of the spectrum—one of pure epigenesis—where "ostensibly purposive life-forms were spontaneously generated from inert matter" (Moss 2002: 220) although many of Descartes' followers never did make the break with preformationism.

Moss (2002) concludes that neither of these extremes has been of direct relevance for biological investigation over the past 100 years; investigators have instead come to an agreement that *both* genes and levels of interaction greater than the gene are involved. However, as philosopher Paul Griffiths notes, "it is a truism that all traits are produced by the interaction of genetic and environmental factors [but] the almost universal acceptance of this view has done little to reduce the prevalence of genetic determinism—the tendency to ignore contextual effects on gene expression and the role of non-genetic factors in development" (2001:1). Both evolutionary and developmental processes are reduced to a purely mechanical reproduction of genes and any deviation from this is understood as mutational, as not normal. Moss argues that the idea that living matter can organize itself into a "self-sustaining, self-organizing, boundary-maintaining entity" has been difficult to establish in the face of the apparent attractiveness of genetic determinism. Demands that the door be opened to fundamentally different conceptions of the organism, in which the genome is situated in a living organism, have been rebuffed (Moss 2002:222).

This is where epigenetics comes in as a science devoted in part to contextualizing the genome. Space does not permit a detailed summary of current theories of epigenetics; suffice it to say that the very word *epigenetics* has more than one meaning (Van de Vijver et al. 2002), and that the discipline is not that new, but was born in the 1940s (Jablonka and Lamb 2005:82). Most current research into epigenetics focuses primarily on the expression and regulation of genes. Related questions at the phenotypic level ask why monozygotic twins do not always manifest the same diseases and, why, when they do, the age of onset can differ by up to two decades (Schmiedeskamp 2004). This narrowly conceptualized epigenetic approach immediately makes the limitations of genetic determinism patently evident.

A broader, more critical form of epigenetics, known as "developmental systems theory" (DST), supported by a mix of philosophers and biologists is currently gaining ground. Using this approach, it is argued that epigenetic phenomena should be recognized as having independence from genetic variation. The starting point is an ontological reversal of genetic determinism and gives priority to dynamic interactions among very many variables with numerous possible outcomes. The biologist Scott Gilbert argues that the DST approach implies that "our 'self' becomes a permeable self. We are each a complex community, indeed, a collection of ecosystems" (Gilbert 2002: 213). At the biological level a fundamental question arises as to whether a gene, defined as a DNA sequence, can indeed count as *the* unit of heredity, especially as recent research strongly suggests that epigenetic phenomena can be transmitted from one generation to another (Champagne and Meaney 2001). Griffiths summarizes the DST approach as one that encourages researchers "to investigate how a trait actually develops, what resources its reliable development depends upon, whether there are many

developmental routes to this outcome, or only one, over what range of parameters is this developmental outcome stable, and how the 'environment' changes as a function of initial development differences that produce this trait" (2001:4).

At a more general level, the question currently being frequently asked is: "if the program for life is not in our genes, then where is it?" Biologist Richard Strohman notes that many developmental biologists have been arguing quietly for a long time that "there *is* no program in the sense of an inherited, pre-existing script waiting to be read." Rather, he argues "there are regulatory networks of proteins that sense or measure changes in the cellular environment and interpret those signals so that the cell makes an appropriate response" (2001:25) and Evelyn Fox Keller argues for the notion of a "distributed" program (2000:146). This regulatory system, a dynamic-epigenetic network, has a life of its own, so to speak, with rules that are not specified by DNA. Systematic research into epigenetics is just beginning to take off (Jablonka and Lamb 2005; Neumann-Held and Rehmann-Sutter 2006) and, although genetics play an indispensable role in this research, ultimately the objective is directed towards explaining what it is about life, health and illness that genetics alone cannot explain.

The "significance" of DNA has been radically altered as a result of all these recent findings and contingency is the name of this game. The question becomes one of whether or not DNA has any "agency" or "activity" at all, concepts that Neumann-Held and Rehmann-Sutter argue are, in any case, thoroughly anthropomorphic (2006:2; see also Moss 2003). From the societal perspective, what, then, does it mean to assume, as biological determinists apparently do, that mapping the human genome actually configures human identity; that biology fully informs who we are? Can we indeed "know" ourselves on the basis of our genetic make-up?

Gudding (1996) argues that technologies that enable rapid DNA analysis permit a massive redeployment of agency and morality to the gene. He reminds us how DNA evidence is increasingly used as the irrefutable mark of individual identity, whether in the courtroom as forensic evidence, or in determining if a female athlete is really what she claims to be. Our biographies are today written, at least in part, in terms of structural chemistry, as many of the early geneticists had envisioned. Genotype does not determine phenotype, but traces of DNA can determine, with considerable certainty, whether someone was present or not when a particular event took place and DNA analyses are now routinely used to verify the remains of people who have been "disappeared," during the Argentine Dirty War and in Kosovo for example. Similarly, by conflating sex, gender and genes we assume that we can be "truthfully" informed on the basis of DNA testing, about who among us are men and who are women. But this is only one very limited aspect of embodied identity, a decontextualized glimpse of a chemical identity, leaving the dynamics of individual growth and change, self-reflection, the effects of early nurturance and social and environmental interactions of all kinds entirely out of the picture.

Fox Keller sums up where she believes we now stand:

> Genes have had a glorious run in the twentieth century, and they have inspired incomparable and astonishing advances in our understanding of living systems. Indeed, they have carried us to the edge of a new era in biology, one that holds out the promise of even more astonishing advances. But these very advances will necessitate the introduction of other concepts, other terms, and other ways of thinking about biological organization, thereby loosening the grip that genes have had on the imagination of the life sciences these many decades. [2000:147]

Fox Keller, while she is clear that the concept of the gene is "good enough" for many experimental purposes, concludes that it is time to think about adopting new concepts to bring about more appropriate insights into the workings of living systems. Gelbart (1998) insists that the term *gene* may have become a hindrance to the understanding of many biologists, and Fox Keller adds that this problem is no doubt even more marked among "lay readers" (2000:148). However, the research findings set out below suggest that, at least in connection with some diseases, people from affected families are by no means wedded to the idea of the gene as a powerful deterministic force.

The Genetics of Alzheimer's Disease

Alois Alzheimer originally observed a case of what is now known as "early onset" Alzheimer's disease (AD). This form of dementia occurs in only approximately 170 extended families worldwide, has long been thought of as a "genetic disease" and is associated with three specific genetic mutations each of which has been mapped (St. George-Hyslop 2000). It is not strictly true to claim that the gene determines even this autosomal dominant form of the disease because the age of onset for identical twins can vary by as much as a decade (Tilley et al. 1998). Early onset AD usually (but not inevitably) manifests itself somewhere between the ages of 35 and 60, progresses relatively quickly to death, and accounts for 2 to 5% of all diagnosed cases of the disease.

In 1993, the first publication appeared that made an explicit association between a variation of the gene known as APOE and increased risk for the common, late onset form of AD (Corder et al. 1993). This finding forced some revisions of the received wisdom of the time—namely that Alzheimer's disease in older people is "sporadic" and does not "run in families." The APOE gene, present in all mammals, is located in humans on chromosome 19 and is essential for lipid metabolism. This gene comes in three universally distributed forms APOEε2, APOEε3, and APOEε4, and evidence from over 100 laboratories indicates that it is the APOEε4 allele that puts individuals at increased risk for AD. From 14 to 16% of Caucasian populations (the most extensively studied population) carry at least one ε4 allele, however, it is unanimously agreed that the presence of the allele is neither necessary nor sufficient to cause the disease for reasons that are as yet very poorly understood. In other words, the ε4 allele is an example of a "susceptibility gene," one that contributes to disease causation only under certain circumstances (Bertram and Tanzi 2004).

It is estimated that at least 50% of ε4 carriers never get AD. Research in connection with the allele shows that when it *is* implicated in AD, exactly the same final biological pathway is involved as that set in motion by the autosomal dominant genes associated with the early onset form of the disease; but the biological changes in which APOEε4 in its homozygous form is implicated become manifest later in life, usually between the ages of 65 and 75 (Selkoe 2002). For individuals who are heterozygous and have only one ε4 allele, the age of onset is usually later. Given that somewhere between 30 and 60% of patients diagnosed with late onset AD do not have the ε4 allele (Myers et al. 1996), there must be at least one other and probably several more pathways to AD. Scientists involved assume that such pathways are constituted by mutually interactive genes and non-coding DNA in conjunction with environmental factors, internal or external to the body. These alternative pathways become evident late in life, usually after age 70 or later, but they too result in the same final common pathway as that for early onset and ε4-linked AD, with the characteristic pathological signs (evident in most but not all cases of AD) that can only be seen at autopsy—plaques, tangles, and cell loss in the brain. Because, in addition to APOEε4, it is assumed that several more genes must be implicated in late onset AD, intensive gene hunting continues unabated.

The current situation has recently been summarized by neurogeneticists, Bertram and Tanzi, as follows: "First, and most importantly, the heritability of AD is high...this had been demonstrated in various studies...over the past decades." But, these experts go on to note, "most of the research currently being done has faulty methodology, lacks replication, and is inattentive to haplotype structure" (Bertram and Tanzi 2004:R135). Using the citation index *PubMed*, Bertram and Tanzi show that in 2003 alone a total of 1037 studies were carried out on the genetics of AD, of which 55 analyzed genes were reported to have a positive association with increased risk for the disease, while 68 tested negative. On repeat testing, most of the positive associations could not be shown again. Candidate genes have been examined on every single chromosome and mitochondrial DNA has also been investigated. These authors conclude with a caveat: "while the genetic association *per se* [of APOEε4 with AD] has been extremely well established...there is no consensus as to *how* this association translates pathophysiologically," nor how it functions in conjunction with the other numerous candidate genes (Bertram and Tanzi 2004:R137).

Until recently, because the disease is limited to older people and because researchers thought that it was sporadic in origin, pedigree studies with large extended families have not been carried out in connection with late onset AD. Now that the results of such research are beginning to accrue, the inconclusive nature of knowledge about APOE is glaringly evident. The more such articles appear, a clear impression is created that too much weight has been given by most researchers to the assumed contribution of the ε4 allele to AD, although there is virtually unanimous agreement that this allele is regularly implicated in both familial and sporadic forms of AD and also in heart disease. Alan Templeton, a biological anthropologist, is particularly critical of the conclusions drawn by most researchers in connection with APOE function. He points out that genomes are "commonly organized into clusters of functionally related genes" and that APOE is part of one such cluster. Templeton argues that when this type of gene is associated by linkage with a specific phenotype, great caution is called for because the gene may simply be a marker for another gene or genes located nearby on the same, clustered segment of DNA (Templeton 1998:376).

Even given the obvious complexity, Mayeux, a genetic epidemiologist commenting on the genetics of AD in a *New Yorker* article, made it clear that he does not believe researchers will be held back too much longer from genuinely insightful knowledge: "a decade from now your doctor will look up your gene profile and decide whether you have a high risk for Alzheimer's, and then give you a prophylactic treatment of some sort." But, he adds, "right now, you don't know what the hell to do!" (Halpern 2005:93).

Despite this optimism, population research in connection with the genetics of both early and late onset AD suggests that no straightforward solution is in sight; this epidemiologically based approach has amply demonstrated that genes are shape-shifters without peer, the products of evolutionary and recent human history, dietary and climatic patterns, possibly of toxic environments and, at times, of serendipitous mutations. Most epidemiological research into the genetics of AD has been carried out since the early 1990s, when the significance of the ε4 allele was first identified but, as noted above, these studies have been confined largely to so-called Caucasian populations (Growden 1998; Korovaitseva et al. 2001; Roses 1998; Saunders 2000; Silverman et al. 2003). Even though the methodology has been criticized, this research makes it clear that the relationship between APOEε4 and AD incidence is probably significantly weaker than is commonly assumed. For example, one community-based study found that 85% of elderly homozygous ε4 individuals whose average age was 81 showed no sign of dementia when given standard tests for cognitive functioning (Hyman et al. 1996).

Adding to the uncertainties, APOEε4 has been shown to work in unexpected ways in specific populations. Among Pygmies and other groups of people whose subsistence economy was, until recently, predominantly that of hunting and gathering, possession of an ε4 genotype *apparently* protects against AD. This finding holds when controlled for age (Corbo and Scacchi 1999). Low rates of AD have been reported for parts of Nigeria and the presence of an ε4 allele does not appear to place individuals at increased risk (Farrer et al. 1997). On the other hand, APOEε4 is significantly associated with dementia among African Americans, although less so than in Caucasian populations (Farrer 2000). Once again, the methodology of this research has been criticized, but the data appear sufficiently robust to conclude that risk reducing factors (in Africa) and risk enhancing factors (in North America) must be implicated, among them other genes, their protein products, diet, environment and, quite possibly, still other variables. An over-emphasis on ε4 and more generally the genetics of AD in the research literature obscures the fact that many other risk factors are associated with AD, ranging from toxic environments, head trauma, education levels, chronic stress, prions and so on.

It is evident that basic science and epidemiological findings about late onset Alzheimer's disease are subject to continual revision and are far from conclusive. Moreover, and adding greatly to the uncertainty, although usually not openly acknowledged, the diagnosis of AD is disputed by some researchers, particularly because, even though it is the most commonly diagnosed of the dementias, it is nevertheless a "waste basket" category applied after other diagnoses have been ruled out (Whitehouse 2008). It is no surprise then, that current guidelines about genetic testing for APOE status do not support its routinization in clinical care, particularly because there is no known treatment for the disease. However, it is possible that this situation may change in the not too distant future. Recently, the *Pharmacogenetics Journal* presented preliminary findings concerning a new drug, Rosiglitazone (Risner et al. 2006). This drug alters glucose metabolism in the brain and, it is reported, has a positive effect on cognitive functioning but only on those patients with mild to moderate AD who are APOEε3. This finding, by the team of Allan Roses who was the first to report that APOEε4 puts individuals at increased risk for AD and who is now the CEO of the pharmaceutical company GlaxoSmithKline, suggests that *should* this drug move successfully through clinical trials, AD genotyping will likely become routinized in clinical settings. Other researchers are working on similar drugs believed to function differentially according to genotype.

What does this current state of knowledge about late onset AD genetics imply for biosociality and subjectivity? Clearly, learning that you carry an ε4 allele should not precipitate such a dramatic effect as learning that you have one of the deadly genes associated with early onset Alzheimer's disease or the toxic form of the gene associated with Huntington's disease. Learning about ones APOE status does not provide information about a highly probable future; it only raises a possible scenario involving the kind of uncertainty that anyone living in a family where AD is present has inevitably confronted as part of their daily life.

Embodying Knowledge about the APOE Gene

Several private companies offer testing for APOE, and an "Early Alert Alzheimer's Home Screening Test" kit is marketed directly to consumers (Kier and Molinari 2003). In addition, an NIH-approved (National Institutes of Health) randomized controlled trial under the name REVEAL (Risk Evaluation and Education for Alzheimer's disease) is in progress. I am going to turn, in the concluding section of this paper, to findings from interviews with individuals involved as subjects in the REVEAL study.

Families where one or more members have been diagnosed with AD were enrolled as subjects for this research. The educational level of these individuals is high—a mean of 17 years at three research sites, and of 15 years at one other. As a group, participants were given a lengthy power point education session about the genetics of AD; if they

then decided to continue to participate in the project, blood was drawn and a few weeks later everyone was informed in private which of the APOE alleles they carry. At the same time, they were shown a graph that depicted increased risk estimates for individuals with their particular APOE type. This "disclosure session" was followed by 12 months of follow-up monitoring during which the research subjects responded to three rounds of structured interviews. The intent was to find out what impact knowledge about their respective APOE genotype had on anxiety levels, sense of wellbeing, and other variables, all "measured" using standardized scales.

I was asked to contribute a qualitative component to the REVEAL study and, after much thought, having obtained an understanding that the findings might well not support the original objectives of the project, I agreed.[2] Open-ended interviews were carried out with a sub-sample of 79 REVEAL subjects at four sites in the United States 12 months or more after REVEAL participants initially received their genotype (Lock et al. 2007).[3]

Participants in the study identified it as an important source of information about Alzheimer's disease and the information they were given emphasized the role of genetics in risk for AD, although it was made absolutely clear during the education session that in none of its forms does the APOE gene determine Alzheimer's disease. Perhaps not surprisingly then, having completed the REVEAL study, people continued to rely on predictions about the future rooted in family histories and personal experience; data about genetics and risk based on personalized probabilistic risk estimates most often supplemented rather than competed with or displaced existing thoughts people already held about AD causation and their own particular risk.

Furthermore, it is difficult to imagine how genetic information given out as part of REVEAL might radically transform the way individuals perceive their own risk when only 27% of the interviewed sample was able to recall their genetic results correctly, and an almost equal number (23%) remembered either incorrectly or nothing at all. The remaining participants retained the "gist" of the information they were given. This was so despite the fact that many volunteered to participate in REVEAL specifically because they wanted the genetic test done, although the main reason for participation was to assist in scientific research. When asked about their genetic results, responses like that of Vicki were not uncommon: "I was just thinking on my way in here today, oh I bet they're going to ask me about which genes I have. And I can't remember!...I should have reviewed." Paul also emphasized the difficulty he had recalling his results:

> Even though she [the genetic counsellor] has explained this to me several times, I still couldn't tell you which one of the markers, of the four, they were watching–you know, she just handed me some information and said, "Here are your markers."...we had gotten all this information at the opening meeting. And we all dutifully took home our notes of this. And come back three months later or whatever, and they'd throw out these things again and I said, "Oh, cripe." And I still don't know whether I have a 10% or a 20% or a 50% chance.

While few remembered their APOE status or risk assessment, 50% retained at least the gist of the information—often expressing their results in general terms such as "having a lower risk than I imagined," "having the bad gene," or being "next to worst." For example, Tessa said: "I keep forgetting. I have problems with it, I know I'm either an e2 or e4, but keep forgetting which. The thing that I do remember is whichever one I am, that it's not a factor." This was equally the case for people like Jacqueline who were given higher risk estimates because they had at least one ε4 allele: "You know, I can't even remember. I would come in from one meeting to the next, and I couldn't remember what my risk was. And to this day, I'm not 100 percent sure, but I know that it's elevated."

On the other hand, for some individuals the genetic results were memorable, but this did not necessarily mean that their significance was understood, as Helen's reaction suggested:

> In fact, when I first came back to have the follow-up study after we found out the results they asked me that percent and whether it was 3/4, 2/2 or whatever. I don't even remember. The number didn't stick...to me it was simply like a 50/50 probability...okay, it's 3/4—so I put that down. It's more like a parrot thing than a, "yes, I know what this means."

One of the individuals tested had seven relatives affected with AD and, not surprisingly, despite learning from the REVEAL education session that ε4 alleles do not *cause* the disease, she found it difficult to come to terms with this information, particularly when she was informed that she was homozygous and had tested as an ε4/4.

Given that there is little that can be done either to prevent or treat AD, responses of the following kind were not uncommon: "I think [REVEAL] provides useful information...Just don't ask me how I would use it.... I honestly don't know." Another said: "Well, I know where I stand, and my children know where they stand—maybe get it, maybe not."

Explanations for Alzheimer Causation

Although some REVEAL subjects entered the study precisely because they believed that AD is intimately related to genetic makeup, upon completion of the project, virtually everyone considered genetics to be just one of several possible causes for late onset AD—and this is what they were taught in the education session. Only 4% regard genetics as the *only* factor involved. Other popular theories in addition to genetics included diet (35%), environment (29%), level of physical activity (19%), aluminum (19%), age (16%), depression (17%) and mental activity (17%). Less popular but consistently named explanations included stress, head injuries, smoking and alcohol. Muriel did not know what causes AD exactly, but she juggled several different ideas based on her own experience with her mother:

> I mean there's always the diet thing and I do somewhat watch that because I'm certainly aware of the diet connections...there is this other thing about keeping your mental activity up as you get older, you know, stimulate the brain; do crossword puzzles, learn new things and keep your brain working. My mother did that though. She watched her diet and she was very careful and doggone it, it didn't keep it from happening. And the genetic side, of course, is also not understood. There's not just one cause.

Rosie speculated about the role pollutants in the environment play in causing AD; she takes vitamins, exercises and avoids using aluminum cookware in the hope of preventing the disease. However, she links her mother's illness to the stress of having many children late in life, smoking and "slowing down" as she got older. For her, the role of genetics is complicated and ambiguous:

> I think (genetics) are a minute aspect of it. It's genetics and environment. People want to say a lot about genetics, and I have to say, we don't know enough. I think that genetics is the big buzzword...Now, with my mom, I think that it could have been a predisposition, but with the stress of having three little ones in her fifties and I guess going through the change of life or whatever, I don't know, all of that could have played a role. Maybe she got depressed and the depression could have led—I don't know. I can't say that I a hundred percent think that it's genetics, even though I did the APOE test. And I forgot what I had! But I refuse to buy into that paradigm. I refuse to believe that there is really an increase [in risk]. I think there are other things that they don't know about...and I think that stress and environment helps make a weakness into a disease.

Ideas of "susceptibility" or "predisposition" were very common among REVEAL participants. Julia's view of genetic risk, for example, stressed the interaction of genetic factors with other variables:

> I think at some point that genes act up. And I don't know what the trigger is, but it's going to send some message that's going to cause something else to happen. I think we can recognize the gene, but I don't know that they know what causes the gene to do the bad stuff...so I think there's something larger happening that allows these abhorrent genes or whatever, to run havoc in your body...I don't think they really know how to take a mixture of factors of genetics and gender and whatever, to say, okay, this is what really sparks this clogging of your brain.

Lila also speaks of "genetic potential" but believes she has some control over the manifestation of the disease. She draws from her experience with diabetes:

> I'd like to think that I have something to do with how it manifests itself. It's sort of like diabetes, which I have a very strong family history for. And knowing that there's certain things in terms of diet or exercise that research has shown may avoid triggering that genetic potential helps. You have the genetic potential, no question. Whether or not it shows up or not has a lot to do with what you do, your environment. I'd like to think the same way about Alzheimer's.

The concept of "blended inheritance," put forward some years ago by Richards, refers to a prevalent understanding he documented among the British public in which a mixing or blending of influences from each parent is common, rather than one entailing a Mendelian transmission of genes (1996:222). Such ideas stem from a long tradition of such reasoning evident as early as classical times (Turney 1995:12).

The REVEAL qualitative findings showed, like earlier work on single gene disorders such as that of Richards (1996), of Cox and McKellin (1999), and of Raspberry and Skinner (2007), that there is a tendency among many respondents to identify a family member who in some way resembles the afflicted person as the individual most likely to be at risk for developing the disorder, whether individual genotypes are known or not. For example, Katherine said, "I showed you the picture of me and my dad. We look like clones, practically, physically. And nobody's really said—I don't know whether or not that makes a difference, a person's physical appearance. But I have a suspicion that it does." Robert commented:

> Do I think I have a higher than normal chance? Yes. Heredity. And also I'm so much like my mother, who had Alzheimer's. There's a very high likelihood that one or more of her children will have a predisposition toward it. And I would say I'm front-runner because of so many other characteristics I have that are very much like my mother's.

Despite the high education level of the REVEAL participants, given the uncertainty about the way in which the APOE gene contributes to AD causation and the emphasis in the REVEAL study on the undoubted contribution of other variables, it is not surprising that narratives about the allocation of future risk among participants' families were grounded in ideas about blended inheritance. Furthermore, contributing greatly to the uncertainty is the late onset of the disease and the fact that the increased risk estimates given to these research subjects exceed a "normal" population by only 10% by age 70 and 30% by age 85, for all but the four individuals heterozygous for the ε4 allele. These figures apparently did not constitute potent omens of the future for any of the participants and many assumed they might well die of something else. Unless knowledge about AD causation advances considerably, it seems that in families where AD has been diagnosed, even after genotyping, few of the next generation will think of themselves in any straightforward way as "genetically at risk."

Conclusions

The hubris associated with the Human Genome Project was always out of place. Most scientists involved knew from the outset that mapping the genome was a relatively straightforward step towards a second challenge of a much bigger order, namely, understanding how genes function in vivo. As the extent of the complexity of functional genomics became increasingly apparent, it was abundantly evident that there were going to be few, if any, easy answers to the problems confronting society in connection with complex diseases. DNA is one actor among very many others, internal and external to all organisms, that influences disease causation, and the boundaries of organisms are permeable (Fox Keller 2006). Aside from rare mutations, DNA alone should not be understood as a reliable signifier for individual futures (Lock 2005).

The REVEAL researchers argued, as part of their justification for carrying out the trial, that it is patronizing *not* to hand out information that can readily be made available to people. But what kind of knowledge is this genomic information, embedded as it is in abundant uncertainty? And, given the contingency associated with the action of APOE, and the way in which risk estimates are created on the basis of age, gender, family history and APOE genotype alone, can these estimates be considered to have much value? Should such genotyping, even though it is of use for basic science research, count as disinformation as far as individuals are concerned?

Given that the interview results make it abundantly clear that little or no change in connection with embodied identity takes place on the basis of knowledge about the APOE genotype and that family histories, family likeness, past experiences and care-giving duties trump genotypic information (see Lock 2008), it seems that the guidelines as they exist are appropriate. But, as genetic profiling becomes cheaper, it is very likely that APOE typing will become a routine part of medical care.

As noted above, the epigenetic model strongly suggests that, for complex diseases, DNA will never, on its own, be a powerful divinatory tool, even when gene functioning is better understood. However, we have all been schooled to take individual responsibility for health and illness, to practice risk avoidance and exert prudence. It was pointed out long ago that an individualized, depoliticized approach to disease causation permits government to rescind responsibility for toxic environments and reinforces societal inequities making the poor more vulnerable to ill health and shortened life expectancies. Globalization and the neoliberal economy exacerbate this situation and make it unconscionable.

Genetic testing and screening, not surprisingly, follows the same individualistic approach. After all, genes are by definition an individual matter, but equally they are a family matter and they respond to human pre-history, history, the immediate past and the present. As research in molecular biology surges forward, the interpenetration of nature with history and culture and the permeable boundaries of self and other, are made increasingly apparent. It is encouraging to find that many of the individuals who participated in the REVEAL study apparently have an intuitive, if somewhat inchoate, grasp of what is at issue.

The image of the "genetic code" is one of the most powerful metaphors of our time (Neumann-Held and Rehmann-Sutter 2006). But we can hope, perhaps with the assistance of new concepts and an increasingly successful dissemination of recent scientific insights, that the extreme fascination that genes have exerted on so many of us, scientists and the public alike, in which they are anthropomorphized as extraordinarily powerful agents will begin to abate. However, this change will be uneven because, in the case of the relatively rare single gene disorders, the genetic contribution clearly outweighs other variables. And the fear associated with certain genes, such

as the symbolically powerful BRCA genes linked to breast cancer, will not easily dissipate.

Even so, to persist in taking a reductionistic approach to disease causation and its management would be perverse and short-sighted in the extreme. Robust epidemiological findings of long standing, local and global, about the impact of poverty and inequities on development, health and illness, are increasingly substantiated by epigenetic insights and demand action. A redistribution of responsibility for human development, health and illness involving a move away from decontextualized bodies—assumed to be largely determined by genes and individual behaviour—is urgently needed. If he were alive today, I am certain that Franz Boas would wholeheartedly embrace such a move towards the re-situating of bodies in context—a move that would have been supported also by key founders of the field of genetics in the late 19th and early 20th centuries. But before this transformation can be fully accomplished, some new captivating metaphors will have to be created and adopted into everyday usage.

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Notes

1 Pleiotropy means the diverse effects of a single gene or gene pair on several organ systems and their function.

2 One justification for this research, it was argued, was that testing for susceptibility genes was likely to become increasingly common, especially in the private sector, and therefore knowledge about how people deal with risk information when it is not possible to make predictions with a high degree of confidence was urgently needed. A second justification was that to withhold information about their bodies from people is patronizing. A third justification was that in many families where someone has died of AD, some members of the next generation believed that they had a nearly 100% chance of contracting the disease. If individuals could be taught that even if they were homozygous for APOEε4, their lifetime risk for getting AD was never more than approximately 52% for men and 58% for women, then anxiety levels may well have been lowered. The fourth explicit justification for the research was to create a pool of APOEε4 individuals whose blood could be used at any time to enrich clinical trials.

3 The four sites were Boston University, Case Western University, Cornell University and Howard University. Janalyn Prest and Stephanie Lloyd, formerly affiliated with the Anthropology Department at McGill University, acted as research assistants and conducted and coded the qualitative interviews from Phase I of the REVEAL study. Heather Lindstrom, formerly in the Anthropology Department at Case Western Reserve, also conducted some interviews. Julia Freeman and Gillian Chilibeck, formerly affiliated with the Anthropology Department, McGill University, conducted the interviews at Howard University and transcribed and coded the data. Funding for this research was provided by the Social Science and Humanities Research Council of Canada (SSHRC), grant # 205806. The REVEAL project was supported by National Institutes of Health grants HG/AG02213 (The REVEAL Study), AG09029 (The MIRAGE Study), AG13846 (Boston University Alzheimer's Disease Center), and M01 RR00533 (Boston University General Clinical Research Center.

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