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Eclipse of the Gene and the Return of Divination[1]

by Margaret Lock

Research in the field of epigenetics challenges the assumption on which the molecular genetics of the past 50 years has been based, namely, genetic determinism. This paper reviews the social science literature that considers the social effects of the application of molecular genetics and genetic testing in connection with Mendelian conditions. It is argued that anthropologists must now go farther and respond to the challenge posed by current moves toward the implementation of genetic profiling and testing for susceptibility genes. Following a discussion of ontological problems associated with molecular genetics raised by philosophers and biologists who subscribe to epigenetics, current knowledge about molecular and population genetics of late-onset Alzheimer's disease and cross-cultural findings about the epidemiology of this disease are introduced. These findings illustrate the provisional nature of these bodies of knowledge and the complexity associated with susceptibility genes, which makes estimations of probabilities of individual risk unrealistic. A controlled clinical trial is discussed in which first-degree relatives of Alzheimer's disease patients are genotyped for risk for late-onset Alzheimer's disease. In conclusion, the social implications of testing for susceptibility genes are discussed, with comments about the role that anthropologists might play in future research.

Margaret Lock is Marjorie Bronfman Professor of Social Studies in Medicine at McGill University (3647 Peel St., Montreal, Quebec, Canada H3A 1X1 [margaret.lock@mcgill.ca]). Born in 1936, she was educated at the University of California, Berkeley (Ph.D., 1976). Her research interests include medical anthropology, the anthropology of biomedical technologies, and the anthropology of genomics. Her publications include *Encounters with Aging: Mythologies of Menopause in Japan and North America* (Berkeley: University of California Press, 1993), *Twice Dead: Organ Transplants and the Reinvention of Death* (Berkeley: University of California Press, 2002), and (edited with Sarah Franklin) *Remaking Life and Death: Towards an Anthropology of the Biosciences* (Santa Fe: School of American Research, 2003).
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When mapping the human genome, the scientists involved set aside approximately 98% of the DNA they had isolated, labeling it as "junk" because it did not conform to their idea of how the blueprint for life worked. In the short time since the announcement in early 2001 that the Human Genome Project was more or less complete, 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. A 2003 article in *Scientific American* notes that "new evidence. . . contradicts conventional notions that genes. . . are the sole mainspring of heredity and the complete blueprint for all life. Much as dark matter influences the fate of galaxies, dark parts of the genome exert control over the development and the distinctive traits of all organisms, from bacteria to humans" (Gibbs 2003:48). The article continues: "Some scientists now suspect that much of what makes one person, and one species, different from the next are variations in the gems hidden within our 'junk' DNA." This junk produces largely RNA[2] that does not code for protein production but, even so, is deeply implicated in gene expression and regulation and so must now be sifted through (Eddy 2001; Mattick 2003, 2004). The result is that we have entered an era, almost overnight, in which the "dark" parts of the genome are starting to fluoresce.

The activities of noncoding RNA are believed to comprise the most comprehensive regulatory system in complex organisms, a system that functions to create the "architecture" of organisms without which chaos would reign (Mattick 2003). To this end, noncoding RNA has been shown to have a profound effect on the timing of processes that occur during development, including stem cell maintenance, cell proliferation, apoptosis (programmed cell death), and the occurrence of cancer and other complex ailments (Petronius 2001). Consequently, the research interests of molecular biology are no longer confined largely to mapping structure but have expanded to unraveling the mechanisms of cell and organ function through time. Central to this endeavor is to understand gene regulation—above all how and under what circumstances genes are switched on and off.[3] In the rapidly developing science known as epigenetics, organized complexity is recognized and activities of the cell, rather than simply those of genes, are the primary target of investigation, although the effects of evolutionary, historical, and environmental variables on cellular activity, developmental processes, health, and disease are freely acknowledged.

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2. During the latter part of the twentieth century, molecular genetics was primarily concerned with the interrelationship between the macromolecules of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) and how these molecules synthesize polypeptides, the basic components of all proteins. Only in the past few years has attention been turned to the numerous critical activities of RNA that are not directly involved with protein production.

3. The importance of gene regulation was first noted by Jacob and Monod (1961), but the mapping of DNA structure was given priority.

This emerging knowledge has exploded the central dogma on which molecular genetics was founded. The 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. The result is that gene fetishism, never embraced wholeheartedly by all the scientists involved (see Berg 1991 and Davis 1990, to name just two), is now clearly on the wane among many (perhaps the majority of) experts, and this decline is hastened by the undeniable fact that genomic "deliverables" are as yet few and far between. Only one new drug the development of which was based on information obtained from genomics was marketed in 2003 (Dutton 2003; see also Angell 2004).

In this paper I want first to consider very briefly the rise and fall of the genotype/phenotype dogma—a position that increasingly appears as an aberration in the history of genetics (Fox Keller 2000, Rheinberger 2000*a*). This will be followed by a brief overview of social science commentary on perceived individual, familial, and social effects of the application of the molecularized genetics associated with the dogma. The epigenetic approach that rejects the dogma will then be discussed. It will be argued that, despite a shift of attention on the part of numerous researchers away from genes to cells and organisms, many basic scientists, even though they are emphatically opposed to genetic determinism, nevertheless embrace a form of neoreductionism in which virtually everything external to the material body remains black-boxed.

In the second half of the paper, a movement toward the routinization of genetic testing for susceptibility genes associated with complex diseases will be examined, using late-onset Alzheimer's disease as an illustrative example. This section will highlight an apparent contradiction in connection with this testing. On the one hand, given the current state of scientific knowledge, predictions about being at increased risk for complex, adult-onset neurological disease based on the presence of a specific susceptibility gene[4] in one's genotype are no more accurate than fortune-telling. Such calculations are what Ulrich Beck describes as "risks that cannot be known" (quoted in Yates 2003:96). In other words, for individuals to be told that they have one or more genes that *may* put them at an increased risk for a disease such as Alzheimer's under circumstances that are very poorly understood can hardly be counted as prescient knowledge upon which people should act. On the other hand, if scientific knowledge about human molecular genomics, proteomics, and epigenetics is to make headway, particularly in connection with preventive medicine and pharmacogenetics, then researchers must procure DNA samples from thousands of volunteer subjects. This is already taking place in clinics around the world when patients agree, with "informed consent," to donate blood that is then anonymized for use in basic-science research. Any right to be given test results is relinquished in such a situation, and individuals are told that their blood samples will not produce knowledge that will have any direct effect on their own clinical care. However, the long-term goal of such research is inevitably to create findings that will eventually be of relevance for the clinic. Although most researchers believe that we have not yet reached a point where such profiling should be carried out routinely, it is likely that in the not-too-distant future patients will be made aware of their genomic profiles as part of basic clinical care (Brice 2004). Furthermore, some researchers argue that, among patients with, for example, Alzheimer's disease, responses to medication will increasingly be shown to be dependent upon genotype, adding further incentive to genotype patients, their families, and eventually the public at large.

How might this tension be resolved as genomic profiling becomes increasingly routinized? Should such genetic testing be limited to the world of research, in which case individuals would not be made aware of their genotype until such time as they actually became sick, when, possibly, such knowledge might be of relevance for their care? Or should patients routinely be tested and receive information about susceptibility genes as part of basic medical care prior to the onset of sickness, in the same way as we are already informed about cholesterol levels, blood pressure, and the results of prostate-specific-antigens (PSA) tests?[5] Even though information about susceptibility genes is inevitably subject to misunderstanding (some would insist that this is "disinformation"), it is often argued that people have a "right to know" about their genomes and that if they are made aware that their genetic profiles place them at risk they may be better motivated to practice prevention. However, accumulating evidence in molecular genetics suggests that we may never be able to calculate risk estimates in connection with susceptibility genes that are meaningful predictors of future probabilities (Moss 2003).

Recognition of discontinuities and ruptures across knowledge domains is crucial in coming to grips with this predicament. Genes may no longer be conceptualized as deterministic by the majority of researchers, but sweeping claims continue to be made—by evolutionary psychologists and evolutionary psychiatrists, for example—about causal relationships between genes and behavior. We would do well to understand the extent to which basic scientists, clinicians, patients, families, advocacy groups, and the public are captivated by genetic

4. Many genes are polymorphic and have a number of variations that are widespread in the human population. Those allelic variations that have been associated with an increased risk of developing named disorders are known as "susceptibility genes." Such gene variants are neither necessary nor sufficient to cause specific diseases. However, compared with the population at large, an individual who carries one and especially two copies of such alleles is believed to have an increased risk of contracting the relevant disease. Even so, people with two copies of a susceptibility gene may not get the disease, indicating that other, as yet unidentified factors are involved. The gene that causes Huntington's disease, an adult-onset neurological disease, is not a susceptibility gene but an autosomal dominant, Mendelian-type gene in which accurate predictions can be made about disease susceptibility based on genetic testing.

5. The PSA test is used to detect early signs of prostate cancer.

determinism and how these same groups of people are likely to respond to an emerging discourse in which the gene no longer reigns supreme and the limitations of current genomic knowledge cannot be denied. At the same time, as a result of new technologies, genomic profiling is becoming increasingly easy to carry out, pressure is mounting to disclose genetic information to screened individuals, and testing is being promoted through direct-to-consumer advertising.

In conclusion I will reflect on why, even though genetic determinism appears to be on the wane, a reductionistic orientation confined to elucidating chains of molecular reactions believed to be intimately associated with neuropsychiatric disorders is given precedence among the majority of researchers working on dementia. The result is that the involvement of "mind," social behavior, and environment in disease onset and progression are essentially erased from professional discussion, except at times in connection with patient care, and in their place a somatized discourse is given precedence, in effect ensuring that findings from the social sciences continue to be marginalized in the worlds of genomics and epigenetics.

The Eclipse of the Genotype/Phenotype Dogma

A critical review of the history of genetics shows that struggles over what will count as authoritative knowledge have been the norm for over 100 years (Sapp 1983). The form that these disputes take was set in place with the introduction at the beginning of the twentieth century of the genotype/phenotype distinction, which caused friction among the separate fields of heredity, embryology, and developmental biology, each of which brought a particular orientation to research on the transmission of heritable material from one generation to another. The eminent Danish scientist Wilhelm Johannsen, eager to put theories about the biology of inheritance on a sound scientific footing, argued forcefully for the recognition of a split between structure (the genotype) and its expression (the phenotype). Johannsen insisted that earlier ideas about inheritance, described by him disparagingly as the "transmission conception of heredity," were not only outmoded but also wrong. In making this claim, he set himself up as the founding father of the science of genetics and distinguished himself from his predecessors, among them Gregor Mendel, Francis Galton, and August Weismann, all of whom assumed that personal qualities and behaviors could be transmitted from generation to generation (Gudding 1996:526).

Johannsen deliberately likened the new genetics to the "hard" science of chemistry. This hope was later reiterated by H. E. Armstrong, writing in the 1930s: "Some day, perhaps, biography will be written almost in terms of structural chemistry, and the doctrine of descent stated in terms of the permutations and combinations affected between genes" (quoted in Gudding 1996:528). Armstrong regarded any other order of explanation as superfluous. Thus was the stage set for a hard-line genetic determinism that matured, as is well known, when Watson and Crick argued 20 years later for a unidirectional flow of information from DNA to RNA to protein to phenotype—the central dogma of modern molecular genetics. But the technology that enabled molecularization and brought about that dogma has, in the end, been its undoing, because Pandora's box has proved to hold much more than anyone had anticipated. First, genome mapping showed that human DNA is closer to that of other living organisms than had been anticipated—we share more than 98% of our genes with chimpanzees and about 35% with daffodils. Second, it came as a surprise that humans have between 20,000 and 40,000 genes and not 100,000 as most earlier estimates had predicted. Now that the functions of noncoding RNA are beginning to be elucidated, it is clear that the original estimate of 100,000 was closer to the mark—that the junk must be restored to its rightful place as part of the transcriptional system.

In addition to these unanticipated findings denting the dogma, for more than a decade a good number of clinical geneticists have argued against what they regard essentially as hype, namely, that molecular genetics will revolutionize the way in which disease and illness are understood (see, for example, Hood 2000). Neil Holtzman is one such clinician. Early on he insisted that, with the exception of single-gene disorders inherited according to Mendelian rules, mapping and sequencing of the human genome would have relatively little impact on the understanding, treatment, or prevention of disease. Holtzman (1989) and others like him pointed out that for all the major common disorders, even though genes are undeniably implicated, they *determine* neither the time of onset of the disease nor its course. It was clear to these critics that the dogma simply was not holding up.

In key disciplines that are largely independent of clinical genetics, including molecular and cell biology, developmental biology, and population genetics, critical arguments have also been made with growing intensity about claims that have commonly emanated from the world of molecular genetics. These researchers base their criticisms on emerging knowledge in their own fields that corroborate arguments made by the evolutionary biologist Richard Lewontin and others for well over two decades (1982; Feldman and Lewontin 1975). The cell biologist Richard Strohman argues, for example, that unfolding knowledge in cell biology and related areas "has progressively revealed important deficiencies in the genetic paradigm of biology" (1993:112). With increasing energy, the attention of many researchers is focused on a new space situated *between* the genotype and phenotype, a site where "endophenotypes" (Sing, Haviland, and Reilly 1996; also known as "intermediary phenotypes") make their appearance and arguments about causality based on linearity and determinism make no sense. Recognition of the contributions of individual development, aging, and the environment to activity at the molecular level has dethroned the preordained genetic body

and set in its place a much more fluid, elusive entity (see Oyama 2001). Organisms are clearly more than the sum of their parts (Scriver and Waters 1999:271), and it is now undeniable that genes *determine* very little, if anything, and are merely actors in an extraordinarily complex scenario (Moss 2003).

Geneticization and Genetic Citizenship

Following the discovery in the 1950s of the double helix, numerous technologies were developed to advance the molecularization of genetics and its application in medical practice. Among those in routine clinical use, genetic testing and screening have been shown to have complex social repercussions. Two decades ago Edward Yoxen (1982) suggested that our newfound abilities to detect "pre-symptomatically ill" individuals would ensure that virtually all of us would soon be subject to increased medical surveillance. A decade later Lippman created the concept of "geneticization" to gloss such surveillance, by which she meant a process "in which differences between individuals are reduced to their DNA codes" (1998:1470). Lippman was concerned above all with an indirect reinforcement of racism, social inequalities, and discrimination of various kinds resulting from a rekindled conflation of social realities and an essentialized biology grounded in small differences in DNA sequences among individuals. She argued that we might well be witnessing an incipient neo-eugenics, a consequence of the voluntary termination of pregnancies on the basis of results obtained from fetal genetic testing. Other writers have made similar comments, noting that what in the early twentieth century was enforced by the state through involuntary sterilization programs is now being carried out under the rubric of individual choice (see, for example, Kitcher 1997).

Given that the complexity of molecular biology is undeniable, the assumed contribution of environmental and other factors is frequently noted in scientific discourse as contributory to disease causation; nevertheless, genetic explanations are usually prioritized and divert attention away from nongenetic ones (Hedgecoe 2001, Spallone 1998). Adam Hedgecoe (2001:877) argues that the use of genetic knowledge and technologies is just the latest in a long line of attempts to advance our understanding of the body at the molecular level.[6] Further, he has pointed out that geneticization, along with medicalization more generally (Lock and Kaufert 1993, Lock 2005), can have positive attributes (Hedgecoe 2001). For example, it is abundantly clear that once symptoms are medically recognized as constituting disease, particularly when psychiatric and behavioral disorders are diagnosed, social stigma and the assignment of responsibility for their occurrence to individuals and families are reduced (McGuffin, Riley, and Plamin 2001). What is more, many families apparently get comfort from being told that disabling conditions are the result of faulty genetics and therefore, by implication, have nothing to do with moral shortcomings (Turney and Turner 2002).

Focusing on lethal single-gene disorders, Rapp, Heath, and Taussig (2001; Heath, Rapp, and Taussig 2004) have posited the concept of "genetic citizenship" as one response to the intractable situation in which families confronted by these diseases find themselves. They have documented how networks of families increasingly coalesce around shared knowledge about the conditions that afflict their children. Such groups provide mutual social support and lobby the United States Congress for increased research funding (similar activities happen in many other countries). These activists are painfully aware that, because of their relative rarity, drug companies will seldom invest in research into these kinds of diseases; there is no profit to be had in studying the so-called orphan diseases, over 1,500 of which are distributed across a mere 2% of the population. Lobbying for public funding, much of which is directed initially at locating the relevant mutations on the human genome, is deemed essential. Such lobbying constitutes genetic citizenship in action and involves not only the mobilization of affected people but new ways of envisioning the future, one in which gene therapy may *possibly* become a realistic option. Similarly, Rabinow's (1996:91) concept of biosociality points the way to possibilities for new forms of identity making on the basis of shared knowledge about genes.

The sociologists Anne Kerr and Sarah Cunningham-Burley (2000) have written extensively about how tests and screening programs associated with molecular genetics in theory offer new choices but at the same time construct new forms of risk and generate both professional and public ambivalence. They are strongly critical of the systematic exclusion of the public from discussions about the clinical implementation of this new knowledge, and much of their work focuses on the "mobilization of lay expertise" (Kerr, Cunningham-Burley, and Amos 1998). Like Lippman, they are concerned about geneticization and the associated individualization of disease causation that comes with it.

Novas and Rose (2001) have asked important questions about what it means to be designated as "genetically at risk." On the basis of perusal of Huntington's-disease web-site exchanges, they argue that genetic testing generates not a sense of fatalism, as many have predicted, but "genetic responsibility," a bonding that is grounded in a molecular optic and that transforms relationships between expert and patient and among affected individuals, families, and communities. However, it has also been shown that among families in which Huntington's disease is prevalent, only 10–15% of implicated individ-

6. A shift toward a molecular approach in biology began in the 1930s (Kay 1993). This shift was associated with a search for what constitutes "life" and was made possible by the development of several new technologies. For two decades molecular biology focused on protein structure and function. After 1953, when the significance of the discovery of DNA was recognized, emphasis switched dramatically to genes, culminating in the Human Genome Project. In recent years proteomics has again become a major focus in molecular biology, and now epigenetics has been adopted as a new approach to elucidating complex biological pathways.

uals choose to undergo genetic testing (Craufurd et al. 1989, Wexler 1992), raising the question of whether people who participate actively in chat groups are representative of affected families in general.

Bob Simpson (2000) brings Benedict Anderson's concept of "imagined communities" into play in his arguments about the new genetics. He points out that although the task of experts is to "read" genetic information, inevitably this information functions as more than a professional commentary about abnormality and future disease because it has political significance for what can count as a "real" community and provides justifications for inclusion in or exclusion from such a community. Renewed nationalism associated with the collection of countrywide or regional genetic databases, notably in Iceland, Quebec, Estonia, and elsewhere, is now well documented (see, for example, Bibeau 2004), although, paradoxically, it is also evident that these databases are unlikely to produce the extensive scientific information that was hoped for when vast financial investments were made to set them up.[7]

Gabriel Gudding (1996) argues that the technologies that enabled rapid DNA analysis permitted a massive redeployment of agency and morality to the gene. He reminds us that DNA evidence is increasingly used as the irrefutable mark of individual identity, whether in the courtroom as forensic evidence or in determining whether a female athlete is really what she claims to be. Our biographies are written, at least in part, in terms of structural chemistry, as many of the early geneticists had envisioned. Genotype may 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 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.

In summary, there is no doubt that screening programs in connection with, for example, thalassaemia and Tay-Sachs disease have brought enormous relief to some families (Angastiniotis, Kyriakidou, and Hadjiminas 1986, Kuliev 1986, Mitchell et al. 1996), and the Cuban government reports success with a screening program for sickle-cell disease (Granda et al. 1991). The ability to test individuals for specific genes that cause deadly single-gene Mendelian disorders such as Huntington's disease has also brought comfort to certain individuals and families, but, as noted above, relatively few people designated at risk for genetic disease or for carrying a fetus believed to be at risk for a genetic disease have made use of testing (Quaid and Morris 1993, Beeson and Doksum 2001) and others, when tested, have ignored the results (Hill 1994, Rapp 1999).

It is undeniable that molecularized genetics has brought about a fundamental transformation in the way the body is conceptualized and that this change has implications not only for what constitutes a normal body and the labeling and management of disease but also for insights into self and identity and, equally, for new forms of social cohesion and exclusion. But the same technologies of molecularization that enabled systematic manipulation of DNA have been the undoing of the genotype/phenotype dogma and have brought about a consolidation of the discipline of epigenetics that has simultaneously contextualized the gene in a cellular environment and highlighted recognition of the gene as a concept—as a heuristic device for research purposes (Beurton, Falk, and Rheinberger 2000, Fox Keller 2000). It is eminently conceivable that a paradigm shift of enormous significance is now under way in basic biology, a shift that could potentially transcend outmoded nature/nurture debates and simplistic discussions of gene-environment interactions. Whether this shift will become mired in another form of material reductionism is open to question, and thus far the omens are not promising.

Social science commentary on the new genetics is exceedingly rich and has set a standard for future research, but it is time to broaden our sights. First, molecular biology and the associated clinical practices are riddled with competing discourses that must be contextualized and analyzed in their own terms prior to making a move toward deconstruction. Second, rapid technological developments ensure that knowledge and practices associated with genomics are ceaselessly being transformed, heightening the ruptures among some disciplines but at the same time bringing together networks of researchers who formerly would not have engaged actively with each other. Third, the focus of attention today, primarily for political and economic reasons, is on complex conditions that account for 98% of the disease burden in the "developed" world. In China, India, Indonesia, and elsewhere, the absolute numbers of people affected are many times greater than in the developed world, although in these countries infectious disease continues to be the bigger burden. Globally, the emphasis of governments and allied research scientists is increasingly on preventing complex diseases and on understanding what sets off the train of events at the molecular level that eventually precipitates an irreversible, lethal pathology.

Documenting lifelong interactions among DNA, coding and noncoding RNA, proteins, enzymes, cells, and the environment is central to this endeavor, but as yet few research programs are in place that can rise to the challenge. One arena where this is beginning to take shape is the memory clinics found in some of the principal hospitals of large North American and European[8] cities. Much of the basic-science research carried out in conjunction with these clinics is concerned not with "gene hunting" per se—such research is conducted in genetics departments and genomic centers—but with de-

7. The Icelandic database deCode Iceland has, however, provided some important insights into the genetics of schizophrenia, asthma, and other diseases (Roberta Palmour and Gustavo Tureki, personal communication).

8. The city of Montréal, for example, with a population of 3 million, has five memory clinics.

tecting biomarkers[9] thought to be precursors of disease long before any symptoms are recognized subjectively or uncovered in clinical encounters. Analyses of the blood of virtually all the clients and patients at memory clinics who agree to be research subjects is central to this endeavor. Neither patients nor clinicians are given the results of such tests, nor do patients expect to learn anything about their own DNA (although there is some "leakage" of information at times), and many are not informed that DNA testing is part of the package.

Should this type of testing be freed of the constraints imposed by research protocols and introduced into the clinic for routine use, as is the ultimate objective, individuals will have to be informed in advance that their blood will be DNA-typed and provided with the estimated population risk conferred by, for example, the susceptibility genes associated with Alzheimer's disease. Estimates of individual risk will have to be discussed again with both patients and families once the genotype is actually known. But how such risk is calculated is inevitably suspect, in large part because so little is understood about the epigenetics of complex disease. Furthermore, in the case of late-onset Alzheimer's disease, knowledge about genetics has had no effect thus far on prevention, diagnosis, prognosis, or treatment of the condition. In other words, this probabilistic information—this divination of the future—has no clinical or personal utility but nevertheless inevitably has the allure of "future promise." The moment that a biomarker of apparent significance in the detection of the earliest signs of Alzheimer's disease is agreed upon by the majority of researchers or it is demonstrated that a particular medication has a significantly greater effect on patients with a specific genetic profile, the dam will burst, and expectations on the part of both clinicians and patients that genetic information will be routinely disclosed are likely to soar. At the same time, the complexity is such that breakthroughs of this kind may never come about.

Epigenetics: Beyond Genetic Determinism

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" (2001:219). 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" (pp.219–20). 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." He identifies a continuum along which strategies for coping with this enigma can, in theory, range. At one end lies full-blown preformationist theory, in which the Creator determines all. René Descartes fell closer to the other end of the spectrum—one of pure epigenesis, in which "ostensibly purposive life-forms were spontaneously generated from inert matter" (Moss 2001:220)—although many of his followers never did make the break with preformationism.

Moss concludes that neither of these extremes has been of direct relevance for biological investigation over the past 100 years; investigators have come to some sort of an agreement that both genes and levels of interaction greater than the gene are involved. However, as the philosopher Paul Griffiths (2001:1) 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." 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 (2001:222) 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.

This is where epigenetics—a science devoted in part to contextualizing the genome—comes in. 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, Van Speybroeck, and De Waele 2002) and that the discipline is not new but was born in the 1940s (Jablonka and Lamb 1995:82). At times the term has been used by sociobiologists in a way that most epigeneticists would consider entirely contrary to their intent to contextualize genes and the genome (see, for example, Lumsden and Wilson 1981). Most current research into epigenetics focuses primarily on the expression and regulation of genes. In other words, the question becomes under what conditions a gene is "switched on" or "switched off." Related questions at the phenotypic level are 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 apparent.

A broader, more critical form of epigenetics known as "developmental systems theory," supported by a mix of philosophers and biologists, is currently gaining ground. Advocates of this approach argue that epigenetic phenomena should be recognized as independent from genetic variation. The starting point is an ontological reversal of genetic determinism and gives priority to dynamic interactions among many variables with numerous possible outcomes. The biologist Scott Gilbert (2002:213) argues that this approach implies that "our 'self' becomes a permeable self. We are each a complex

9. The term "biomarker" is usually applied to genes, intermediate endophenotypes, and clinical phenotypes when they are understood as precursors or markers of a specific disease under investigation.

community, indeed, a collection of ecosystems." At the biological level a fundamental question arises 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). Moss (2002:227) calls attention to emerging evidence that points toward "the evolutionary intensification of the capacity of organisms to flexibly and sensitively self-produce themselves." Closely related to this insight is a second, namely, that over the course of evolutionary time, noncoding RNA constitutes a large percentage of that which is routinely transcribed by complex organisms to be drawn upon in what is characterized as "niche construction" (Odling-Smee, Laland, and Feldman 1996).

Paul Griffiths (2001:4) summarizes the developmental-systems approach in the following way: It 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." Contingency is the name of this game. Thus far, most basic research in this broader approach to epigenetics has been carried out in connection with developmental and evolutionary biology, and virtually all of it makes use of ecological and animal models; it appears that the majority of clinical geneticists have as yet paid little heed to epigenetics. One well-known geneticist, when I asked him about his position with respect to this discipline, replied tartly, "That's developmental biology, not genetics." And inquiries on my part have made it clear that almost without exception clinicians have not read the literature on noncoding DNA or epigenetics, even that which appears in semipopular form in *Scientific American*.

For the remainder of this essay I will focus on the most common form of Alzheimer's disease, the late-onset form. Basic-science research in connection with this form of the disease is thoroughly molecularized, and, further, the majority of clinicians conceptualize the disease very differently from a few years ago and now assume that genetics is deeply implicated in complex ways (Lock 2005). Virtually nothing has changed, however, in clinical practice, because this type of dementia remains thoroughly resistant to prevention and treatment. Despite this impasse, there is recognition that testing for the one susceptibility gene that experts agree is definitively associated with an increased risk for late-onset Alzheimer's disease, together with other candidate genes thought to be possibly associated with the disease, is essential for cutting-edge basic-science research in connection with dementia. In this type of research, a gene-centered form of epigenetics focusing on the relationship of these targeted genes to their products, that is, to biomarkers thought to be precursors of the disease, has come to dominate (rather than a full-blown developmental-systems approach). As will become clear below, there is a significant likelihood of questionable familial and social repercussions from these research activities.

Wandering Minds and Somatized Bodies

Lawrence Cohen (1998; see also Fox 1989) points out that it was families burdened by care of their elderly relatives who started to push late in the 1960s for medical recognition of what was understood at that time as "normal" dementia associated with aging. Over the past three decades individuals have increasingly sought medical assistance when elderly family members exhibited memory loss or showed signs of confusion, with the result that late-onset Alzheimer's disease is now by far the most commonly diagnosed form of dementia. Alzheimer's disease has been a medically recognized concept for nearly 100 years, but until the latter part of the twentieth century the diagnosis was applied only to the rare forms of this type of dementia that strike in middle age. To this day the disease remains an elusive entity, subject to competing professional interpretations. In Ian Hacking's idiom, the "dynamics of classification" are at work. Alzheimer's disease has undeniable bodily effects, both mental and physical, that eventually result in death. Nevertheless, dispute continues as to whether Alzheimer's is a distinct disease, because it remains unclear whether this condition has a characteristic pathology affecting a relatively large minority of older people or, alternatively, is a "natural" effect of aging to which we are all liable if we do not first die of something else. Furthermore, from the perspective of epigenetics, some of us may be less susceptible than others to the senile processes associated with late-onset Alzheimer's disease because of intra- and extrabodily environments—that is, the micro and macro environments in which our gestation, early childhood, and daily lives have been enacted.

The atrophy of brain cells accompanied by dense plaque formations and neurofibrillary tangles—changes that can be demonstrated only at autopsy—is the consistent, irrefutable pathological evidence associated with Alzheimer's disease. Recently it has been shown that although the majority of individuals whose brains reveal plaques and tangles at autopsy exhibited behavioral changes associated with Alzheimer's disease while alive, this is not always the case (Swartz, Black, and St. George-Hyslop 1999). Some people with the late-onset form can apparently "adapt" to these neurological changes or at least are relatively unaffected by them compared with others. Such individuals are described as having better "cognitive reserve" (Schmiedeskamp 2004). Conversely, a few individuals whose brains after death show a relatively small number of anatomical changes exhibited marked behavioral changes while alive.

These paradoxes immediately raise the question of the ontological status of Alzheimer's disease. What is it, and where exactly does it reside? Do behavioral changes diagnosed on the basis of psychological testing or the anatomical pathology demonstrated at autopsy constitute

the actual disease? Or, alternatively, is it manifested as changes that commence much earlier, in midlife or even sooner—tiny incremental transformations that when detected are candidates for labeling as molecular biomarkers for the disease? Or is it more appropriate to think in terms of a co-production among development, aging, anatomy, and behavior but explicitly recognize that some significant anomalies cannot as yet be explained? Adding to the complexity, it is now evident that dementias often come in mixed forms, so that cerebrovascular dementia is frequently present together with Alzheimer's disease, or the disease may be mixed with fronto-temporal dementia that causes hallucinations. Virtually no one today would argue that dementia is a social construction, as was argued by some not long ago; nor are plaques and tangles fantasy. Alzheimer's disease, however, is perhaps a convenient fiction or, at the very least, a shifting, unstable target that experts agree, on the basis of a series of repeated neuropsychological tests, must be noted on diagnostic charts as "probable Alzheimer's disease" until an autopsy, should one be done, confirms the diagnosis. Meantime, at least one clinician/researcher has argued that a focus on "quality of life" must be better integrated into the findings from the biological sciences in order to move forward our understanding of the disease (Whitehouse 2002*a*).

As a result of genetic research Alzheimer-type dementia is now conventionally divided into early- and late-onset forms. Early-onset, "familial" Alzheimer's (the form documented by Alois Alzheimer in 1906) is an autosomal-dominant, rare disease associated with about 170 families worldwide. In the past 15 years, genetic markers for this form of the disease have been found on chromosomes 1, 14, and 21, one variation of which is inevitably present in vulnerable families. These genes are described by most specialists as genetic "determinants," although twin studies have shown that the age of onset of the disease can vary by as much as 20 years. This suggests that although the genes have very high "penetrance" (phenotypic expression of the disease in individuals who have one of these genes is virtually 100%), a simple case of cause and effect is not at work, and other factors, internal and/or external, must be implicated (Tilley, Morgan, and Kalsheker 1998). Onset of familial Alzheimer's disease is almost without exception between the ages of 35 and 60, with one form starting a little later in life and occasionally not making an appearance until age 70. In most cases of early-onset Alzheimer's disease, the condition progresses rapidly to florid dementia and death.

Much more common is the late-onset form, which until recently was thought of as "sporadic," that is, the end result of pathological changes associated with aging but in effect random and not associated with an individual's genetic profile. However, as the result of a significant breakthrough in molecular genetics in the past decade, it has come to be widely accepted that a large number of people and, by extension, many families are at increased risk for the disease because they have inherited a susceptibility gene known as APOEϵ4, an allelic variation of apolipoprotein E, a gene found on chromosome 19 that is indispensable for lipid metabolism.

APOE exists in three forms, APOEϵ2, APOEϵ3, and APOEϵ4, each of which produces a slightly different protein. The significance of these small differences is currently being elucidated. It is estimated that approximately 60% of so-called Caucasian (white) populations have the APOEϵ3 variant, and it is argued that this variant places individuals at an "average" risk for late-onset Alzheimer's disease (some estimates put this at one in two for individuals of 85 and older). It has also been shown in over 100 studies, again almost exclusively with white populations, that the risk for the disease is 3 times greater among individuals with one APOEϵ4 allele than in individuals with either the APOEϵ3 or the much rarer APOEϵ2 allele. For individuals with two APOEϵ4 alleles, the risk increases somewhere between 8 and 30 times. In the presence of the APOEϵ4 alleles, the age of onset of the disease decreases by as much as seven to nine years. However, about half the subjects homozygous for APOEϵ4 never develop the disease, and approximately half the individuals studied who do develop it do not have APOEϵ4 alleles. The APOEϵ4 allele is neither necessary nor sufficient to produce the disease. Other genes and/or environmental factors *must* be implicated, and an intense search is currently under way to locate such genes.

Because of the heterogeneity of the etiology of late-onset Alzheimer's disease and of its behavioral effects, a shift in research emphasis has come about over the past few years. Although gene hunting continues to engage many research networks, as noted above, the search for postulated biomarkers has also become a very attractive goal. In the space between genotype and phenotype lies secreted, it is assumed, the keys to prevention of the disease, its early diagnosis, and the development of effective medication, and this is where most basic-science research activity is now directed. It is agreed by the majority of researchers today that there are at least three complex molecular pathways that can lead to the onset of the disease.

The first is kick-started by the switching on in midlife of the autosomal dominant genes associated with early-onset Alzheimer's disease. A second, much more common pathway involves activity of the protein produced by the APOEϵ4 susceptibility gene, almost certainly brought about in conjunction with other key biomarkers that are the products of yet other internal and external environmental stimuli. These complex changes lead to a "final common pathway," the same as that produced by the autosomal dominant genes. Given that in at least 50% of late-onset Alzheimer's disease cases the patient does not have the APOEϵ4 allele, there must be *at least* one other pathway. Such a pathway is constituted, it is assumed, by mutually interactive genes and noncoding DNA in conjunction with internal and/or external environmental factors. This third alternative results in the same final common pathway as the other two pathways. As noted above, the behavioral changes associated with these processes may become manifest at different ages,

and deterioration may progress at different rates. In some cases, even though neuropathological changes are found at autopsy, few or no behavioral effects were evident during life, but even so, the common pathway—the molecular endophenotype—is essentially the same (Selkoe 2002).

In the case of early-onset Alzheimer's disease, presence of the genetic mutation constitutes a ticking time bomb that cannot be averted; it is the chain reaction—the pathway—initiated by the mutation that is of prime interest to researchers and that actually informs questions asked about the other, more common forms of the disease. In the case of individuals with APOEϵ4, one question that inevitably arises is who among those who carry this allele are at greatest risk. Further, who among the extended families in which the allele is present are at greatest risk and why? Alternatively, what characterizes those families in which the disease is common but the APOEϵ4 allele is not present? Numerous "candidate" genes are being investigated, but it is almost certain that the effects of any one of these genes will be small. It will be knowledge about their interaction and the specific cellular and environmental contexts in which they function that may eventually provide some clearer answers.

Millions of dollars are currently being spent on trying to map the molecular pathways in the hope of elucidating which of the changes constitute the first signs of incipient dementia. Once entry to the final common pathway has taken place, a point of no return is reached, and no drug on the market can combat this condition, except perhaps fleetingly for a few months (the familial and social environment almost certainly has more effect at present than do drugs [Brierley et al. 2003, Burns et al. 2002]). It is agreed that even if an effective drug is found it will, at best, slow down the process; once the disease has really taken hold, a "cure" is out of the question. If prevention is to be effective, then the key or keys to its success will be the detection of biomarkers that may appear, some researchers claim, as early as 30 years before the pathology of the final common pathway becomes evident. With this in mind, most research currently focuses on cell biology and related extracellular activities in people in their 40s and 50s in an attempt to track the precursors of toxic build-up harmful to brain function.

Neuropsychological tests are routinely carried out in memory clinics with the intent of demonstrating behavioral signs of prodromal dementia, the behavioral endophenotype for late-onset Alzheimer's disease. In 1994, a condition known as mild cognitive impairment was enshrined in the Diagnostic and Statistical Manual of the American Association of Psychiatry (DSM4). This condition is diagnosed by administering the Mini Mental State Examination (MMSE, the usual assessment tool for Alzheimer's disease and other forms of dementia), together with other tests of cognitive performance. Described as "a transitional state between the cognition of normal aging and mild dementia," this condition is freely acknowledged by experts to be heterogeneous or even a noncondition (Whitehouse 2002*b*). Several large clinical trials are currently taking place with the aim of discovering biomarkers associated with the memory difficulties that characterize mild cognitive impairment. The hope is, on the basis of these findings, to create subtypes of patients—those with mild cognitive impairment who convert to Alzheimer's disease and those whose cognitive decline is regarded as "normal" and does not progress to outright pathology or even reverts to its former "healthy" condition.

Neuro-imaging, including PET scans and other very new imaging technologies, is crucial to this research, the results of which have thus far highlighted two indicators that are currently thought to be biomarkers for premorbid signs of Alzheimer's disease. Needless to say, clinical activities of this type and the associated research endeavors involve extensive medicalization of thousands of healthy people who are monitored frequently for signs of memory decline—signs that may or may not be significant predictors of future disease (Working Group 2000).

The Contribution of Population Genetics

That age and the effects of severe head trauma (dementia was formerly known as pugilist's disease) put one at increased risk for late-onset Alzheimer's disease is beyond dispute. Down syndrome is also an incontrovertible risk factor because the same part of chromosome 21 as is affected in this congenital disease is involved in one form of early-onset Alzheimer's disease. Increasingly family history, from the time *in utero* on, and gender are assumed to be indisputable risk factors, as is the APOEϵ4 allele. It remains unclear how exactly these variables play out in concert with each other and with yet other variables. For example, low levels of education have been consistently correlated in the published literature with greater risk for late-onset Alzheimer's disease, and poor performance on psychological tests for cognitive functioning is the evidence on which such assertions are based (Anstey and Christensen 2000). Among 12 studies, 6 with sample size of well over 1,000 and the others ranging from 300 to over 500, all showed increased risk for cognitive decline with age among individuals with less formal education. Only 2 studies using smaller samples proved otherwise.

Frequently cited in demonstrating the importance of education is the so-called nuns' study. The filed written statements of 575 young novices about why they wanted to enter a nunnery were analyzed for use of complex thinking. These statements were matched years later with responses to the MMSE of the same nuns in old age. It was found that the women with less education, who had exhibited a relatively poor ability for complex thinking when they were young, showed a more rapid cognitive decline in old age. However, this difference was not increasingly magnified with age. The conclusion drawn from this research by the majority of experts is that a high level of formal education creates numerous synapses in the brain, giving individuals a greater

"cognitive reserve" to fall back on as they age (Snowdon 2001).

A recent newspaper article following a similar line of argument suggests that adults with hobbies who exercise their brains by reading, doing jigsaws, playing chess, and so on, are less likely to become demented than are individuals who spend long hours in front of television (*Globe and Mail*, March 6, 2000). This study adds to the widely held sentiment among Alzheimer's disease specialists that the brain, like other organs of the body, thrives on regular exercise. A "use it or lose it" slogan is regularly touted as explanatory in accounting for what is assumed to be a firm association between levels of education, styles of cognition, and incidence of the disease. Even the recent well-publicized death of Iris Murdoch has not seriously dented the assurance with which this kind of argument is made.

The form that this research takes leaves a lot to be desired and is mired in unexamined assumptions, but thus far it is the only contribution to research on late-onset Alzheimer's disease, other than a few diet-related studies, that considers social factors that may in the long run contribute to dementia incidence. There is also some interesting research that considers the possible effects of prion-like proteins on memory loss (Si, Lindquist, and Kandel 2004), but a consolidated developmental-systems approach to the disease is not in evidence.

By contrast, population research in connection with the genetics of both early- and late-onset Alzheimer's disease is abundant and has amply demonstrated that genes are shape-shifters without peer, the products of evolutionary and recent human history, possibly of toxic environments, and, at times, of serendipitous mutations. Most of this research has been carried out since the early 1990s, when the significance of the APOEϵ4 allele was first identified (Corder et al. 1993), and a great deal of it has been confined to white populations (Growden 1998, Korovaitseva et al. 2001, Roses 1998, Saunders 2002, Silverman et al. 2003). Inconsistencies within this literature have the potential for causing confusion. For example, estimates of the number of individuals with Alzheimer's disease who carry the ϵ4 allele range from 30 to 90% (Liddell, Lovestone, and Owen 2001, Ritchie and DuPuy (1999), and many studies do not specify whether these numbers refer to those who are hetero- or homozygous.[10]

In addition to retrospective studies of individuals who already have the disease, several prospective attempts have been made to estimate the number of people with APOEϵ4 alleles who will eventually develop it. There is considerable variation among these estimates: depending on the study consulted, the number of individuals who are heterozygous for the APOEϵ4 allele and who are expected to develop the disease ranges from 7.6 to 47%. For homozygous individuals the range is enormous: 21.4 to 91% (Holmes 2002, Farlow 1997). In contrast, there is better agreement about the increased relative risk of developing Alzheimer's disease among individuals with the APOEϵ4 allele, although the confidence intervals remain very large. The literature suggests, as noted above, that a person with one ϵ4 allele has 3 times the chance and a person with two ϵ4 alleles has between 8 and 30 times the chance of developing the disease as a person with no ϵ4 alleles (Holmes 2002, Swartz, Black, and St.George-Hyslop 1999). However, the baseline on which these probabilities are estimated is rarely provided, and without this information relative risk estimates are highly misleading. To further confuse matters, it has been claimed that APOEϵ4 can become a protective factor for people in clinical populations over 90 years of age. One of the principal causes of confusion about Alzheimer's disease and genetic risk is inherent in the research design. Holmes (2002) and Ritchie and Dupuy (1999) suggest that, because most research is based on clinical samples, the results are not representative of the population at large. When general population samples are employed, the relationship between APOEϵ4 and disease incidence appears to be significantly weaker than is commonly suggested.

Clearly, making inferences about the specific risk of individuals on the basis of data such as the above is fraught with potential difficulties. Adding further confusion, APOEϵ4 has been shown to work in unexpected ways in certain populations. For instance, among Pygmies and other groups of people whose subsistence economy was until relatively recently predominantly one of hunting and gathering, possession of an APOEϵ4 genotype apparently protects against Alzheimer's disease, and this finding holds when age is controlled (Corbo and Scacchi 1999). Low rates of the disease have been reported for parts of Nigeria, and the presence of an APOEϵ4 allele does not appear to place individuals at increased risk when it does occur. At the same time, APOEϵ4 is significantly associated with dementia among African Americans, albeit less so than in populations of whites (Farrer 2000). Although researchers acknowledge limitations to the research methodologies used to date, the data appear sufficiently robust to conclude that other risk-reducing factors (in Africa) and risk-enhancing factors (in North America) must be implicated, among them other genes, their protein products, diet, and environment.

Another study found that the greater the "genetic degree" of Cherokee ancestry (as documented in tribal records) the greater the protection against developing Alzheimer's disease (Rosenberg et al. 1996). This study was carried out with 26 Alzheimer's disease patients aged 65 and over and a control group of 26 also selected from the Cherokee community. It was established that the control group had a "higher degree of Cherokee ancestry." This "protective factor" was independent of the APOE allele and was shown to diminish with age. The study, frequently cited, is similar to one involving 192 Cree aged 65 and over in which only 1 case of dementia was found. Among the obvious difficulties with this type of research

10. The term "heterozygous" refers to the case in which a person carries only one APOEϵ4 allele (along with an APOEϵ2 or 3, for example). Someone who is homozygous for APOEϵ4 has two of these alleles.

are the sample size, the conflation of tribal identity with something variously labeled as "race" or "ethnicity" presumed to correlate with specific biological characteristics, and the use of "standardized dementia evaluations" to determine the presence of Alzheimer's disease. Standardized tests such as the MMSE are psychological "instruments" designed to "measure" cognitive capabilities and were originally developed for use among middle-class urban populations; they are not very reliable under any circumstances but prove to be considerably less so and often blatantly misleading when language differences, education, familiarity with psychological testing, and so on, are not taken into account (Lock 1993).

Several other frequently reported studies are summed up in an article pointing out that most of the work done on APOE has been carried out with white populations. Concern is expressed because the number of elderly among African Americans in the United States is growing faster than that of whites and the number of Hispanics aged 65 and over is estimated to increase by 555% in the next 40 years, as compared with 95% among "non-Hispanic whites." Given this situation, a plea is made for carrying out research on dementia as soon as possible using samples drawn from African American and Hispanic communities (Farrer 2000).

Among the best of the epidemiological studies examining dementia are those currently being put into practice by what is known as the 10/66 Dementia Research Group. This is an international consortium of researchers centered on the Institute of Psychiatry in the United Kingdom who argue forcefully that research is urgently needed into dementia and its management in developing countries, where more than two-thirds of the world's elderly live. A revealing statement by this group suggests that studies such as those from Nigeria with low reporting of Alzheimer's disease may well simply reflect lack of recognition of dementia as anything other than "normal" aging, possibly resulting in early deaths for many demented people because their plight is not brought to public attention. Research carried out in India is used to back up this claim (Dementia Research Group 2000). Although care is now being taken to use improved methodology in much research of this kind and population-based samples rather than clinical samples are identified, a sensitivity to the indispensable contribution that can be made by good ethnography (such as that of Cohen 1998, Herskovits 1995, Ikels 2001, Leibing 2002), including recognition of the heuristic construction of population boundaries, the creation of interview protocols based on local knowledge, elicitation of local narrative and subjective accounts, and an interpretation of findings in local contexts, is not yet evident.

Clearly, the specific role of APOEϵ4 and its associated proteins in the onset of Alzheimer's disease is far from well understood. Similarly, the contribution of epigenetics remains obscure, as does that of history, culture, local politics, and the environment. Space does not permit elaboration, but the APOEϵ4 allele is implicated not only in placing individuals at increased risk for Alzheimer's disease but also in the development of serious illness associated with lipid metabolism and heart disease. It exhibits what is known as "antagonistic pleiotropy" in that it has positive properties early in life that become detrimental in postreproductive life, particularly in unfavorable environments or when the diet is high in sugar and/or fats (Gerber and Crews 1999).

In summary, virtually all of the research to date, whether it be basic-scientific, clinical, epidemiological, population genetic, biological anthropological, or ethnographic, is carried out in relative isolation from other approaches, making for considerable ruptures across these different domains. It is above all elucidation of the involved molecular pathways that currently attracts the greatest interest and, in most people's minds, holds out the best hope for prevention and effective intervention. Such an approach shows an appreciation of epigenetics (although this is rarely voiced explicitly by the researchers involved) in that it is not genetic determinism that drives the research questions. Even so, most researchers remain resolutely reductionistic and focused on cellular activities, although others juggle several variables, among them the APOEϵ4 allele, age, gender, and education, in the hope of demonstrating which of them has the most explanatory power.

Testing for APOE

Given the equivocal findings set out above, one would expect that risk assessments for late-onset Alzheimer's disease based on genetic testing of individuals would be deemed of little or no use by the majority of involved clinicians and researchers, and to date this has been the case, although it is acknowledged that this may change (Farlow 1997, Liddell, Lovestone, and Owen 2001, St. George-Hyslop 2000, Tilley, Morgan, and Kalsheker 1998). Currently the official guidelines of professional and health-policy-making institutions and organizations involved with Alzheimer's disease and by the Alzheimer's disease societies of the United States, Canada, and the United Kingdom state that genetic testing for APOE status should not be routinely performed (see also McConnell et al. 1998). This recommendation is easily justified because there is no known prevention or treatment for Alzheimer's disease that is more than minimally effective. Knowing the APOE status of a patient has no effect on clinical care, although occasionally the test is carried out to add support to a diagnosis.

Even so, several private companies offer testing (the U.S.-based Athena Diagnostics holds the patent for it), and an "Early Alert Alzheimer's Home Screening Test" kit is marketed directly to consumers in their homes (Kier and Molinari 2003). Furthermore, the National Institutes of Health have funded a randomized controlled trial that goes under the name of REVEAL (Risk Evaluation and Education for Alzheimer's Disease).[11] Subjects

11. The REVEAL project was supported by NIH 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).

for this trial were recruited either through systematic ascertainment from American Alzheimer's disease research registries kept at Boston University, Case Western Reserve, and Cornell University or through self-referral at each site (Cupples et al. 2004). The 162 participants came from families in which late-onset Alzheimer's disease had been diagnosed in at least one first-degree relative, and upon recruitment they were randomized into intervention and control groups. Participants first attended a semiscripted education session in which the genetic counselor provided information about Alzheimer's disease, with emphasis on theories about causation, including genetic susceptibility. Following the education session, they were asked to return to the research site at a later date for a blood draw for the determination of APOE genotype. People in the intervention group were informed a few weeks later about their APOE status. Individuals assigned to be controls were not given this information. The reactions of the participants who were informed of their APOE status were systematically monitored by means of three structured follow-up interviews conducted by genetic counselors over the course of 12 months and then compared with the reactions of individuals in the control group, whose blood had been stored but not tested (Green et al. 2002).

In the "risk disclosure" portion of the study, all subjects were shown a "risk curve" developed by drawing on gender- and age-specific incidence curves for first-degree relatives of persons with Alzheimer's disease that had already been calculated on the basis of a meta-analysis of studies involving very large samples of Caucasian subjects (Green et al. 1997). The curves were further subdivided by incorporating the APOE-genotype-specific odds-ratio estimates for gender and age reported in a second pooled analysis of 50 studies worldwide (Farrer et al. 1997). This produced a total of 12 curves based on the six possible combinations of APOE alleles for both males and females. Risk curves for the control group were based on gender, age, and family history alone. Genetic counselors showed each participant the appropriate risk curve and explained the participant's estimated increased risk for Alzheimer's disease into old age. The graph for participants who were assigned to the control group had two curves, one the curve for the "normal" population and a second, slightly steeper one representing increased risk by age for individuals who were first-degree relatives of Alzheimer's disease patients. Participants who had undergone genotyping were shown three curves, the third one representing increased risk on the basis of genotype. The risk for individuals who were APOEϵ2/3 or ϵ3/3 was increased only a small amount on the basis of their affected relative alone. For individuals who were APOEϵ3/4 and especially ϵ4/4, risk was clearly increased but to a maximum for the 4/4's of 52% by age 85. Creating these risk curves entailed exceedingly complex mathematical formulations (Cupples et al. 2004). Variables such as ethnicity and education were not factored in, nor were they discussed informally with participants (who had, on average, 17 years of formal education). Virtually everyone enrolled in the trial was white, but REVEAL 2, due to start shortly, will include at one of its sites individuals recruited through Howard University who will be African American (the risk estimates to be used with these volunteers are currently being created).

One justification for this research is that testing for susceptibility genes is likely to become increasingly common, especially in the private sector, and therefore knowledge about how people deal with risk information when it is impossible to make predictions with a high degree of confidence is urgently needed. A second justification is that to withhold information about their bodies from people is patronizing. A third is that in many families in which someone has died of Alzheimer's disease some members of the next generation may well believe that they have a virtually 100% chance of contracting the disease. If individuals can be taught that, even if they are homozygous for APOEϵ4, their lifetime risk for getting Alzheimer's disease never approaches anything more than approximately 50%, then anxiety levels may well be lowered. The fourth explicit justification for the research is to create a pool of APOEϵ4 individuals whose bloods can be used at any time to "enrich clinical trials." The majority of people who participated in the NIH study stated that they did so to assist with research in addition to learning about their own APOE status. Only 27% could accurately recall their own genotype when asked about it a year later, although many reported that they had the "good" gene or the "bad" gene (but at times they were wrong about this, too).

A controlled trial such as this one is perhaps a sign of creeping geneticization, but because the counselors stressed a multicausal explanation for late-onset Alzheimer's disease and everyone knows that the condition is one of old age, it is open to question whether these volunteer subjects experienced anything remotely approaching a profound personal or identity change based on the test results. Indeed, they apparently experienced raised anxiety levels for no more than a week or two about what the future held in store for them. They were already well aware of what it was like to live with someone with Alzheimer's disease, and most believed that the disease "ran in their family" (Lock et al. n.d.). Given the relatively low lifetime probability rates people were given, this testing in effect told participants nothing negative that they had not already internalized as part of their possible future. On the contrary, a good number expressed relief because they had come into the study with the belief that they were at 100% risk for the disease. Most participants were under 60 years of age, and it is possible that when they become older those who learned that they have an APOEϵ4 allele will experience increased anxiety. However, if the genetic counselors did their work well, then *everyone* in the study should have been equally concerned; given that one or more of their parents had Alzheimer's disease, they were all to some extent at increased risk compared with the general population, regardless of their genotype. Offsetting this, no recommendations for preventive care apply to the participants that do not apply to all of us as we age. Follow-

up interviews showed that every single participant came away with the knowledge that APOEϵ4 does not *cause* late-onset Alzheimer's disease. In this respect the trial was a success (although it is possible that the participants already had this knowledge). Research unrelated to this particular trial shows that, even for people who have direct experience of late-onset Alzheimer's disease in their families, the majority believe that *both* environment and genetics contribute to disease causation, and people usually note that one can perhaps do something about the environment but nothing about genetics. Moreover, concern about one's own genetic status takes a back seat to the pragmatics of living with and caring for an elderly relative afflicted with the "living death" (Lock, Lloyd, and Prest n.d.).

As the trial was nearing its completion I was asked to add a qualitative component to the project. In my opinion, qualitative methods should have been incorporated from the outset, but, nevertheless, I agreed to participate at this late date.[12] Sixty of the REVEAL participants were given semistructured open-ended interviews a little more than a year after they had entered the trial. When asked to reflect on what they had learned from it, they often made statements such as the following:

1. I think it provides useful information; just don't ask me how I would use it. I honestly don't know.
2. Well, I know where I'm at, where I stand. I can let my kids know where we stand. You know, I mean, maybe get it, maybe not.
3. When I was tested I had two genes that weren't bad. We said that means my father didn't have two. If he had two, I would have had one of them. So he developed it maybe based on one [APOEϵ4] gene, maybe based on none. We don't know because he wasn't tested.
4. I understand basic genetics and, you know, Mendelssohn, and those plants and stuff. I know now that APOEϵ4 is bad and I have one, but I don't know why it's bad or what it does.

It must be reiterated that most people entered the trial with the hope of assisting in Alzheimer's disease research. The detailed findings (Lock et al. n.d.) suggest strongly that this particular group of individuals took the information they were given about their risk status and incorporated it into their already-well-established ideas about who in their families were likely to get Alzheimer's disease in the future. Over half of the informants drew on a highly prevalent concept of "blended inheritance," the idea that one receives a mixture or blending of entities from both parents passed on from generation to generation in clusters, with phenotypic resemblances among certain family members—physical features, personality types, and so on—indicating that these individuals also share a susceptibility to disorders that "run in their family" (Richards 1996). A number of participants were emphatic that the genotype test result must be wrong because it did not correspond with what they already believed about their future. It seems likely that if they had been given increased risk estimates of 90% or more for a disease that struck at around age 60, then their reactions would have been different, but when one is told that by age 85 one has just over a 50% increased risk of getting Alzheimer's disease as compared with a "normal" population, it makes sense to translate such an estimate into the reality of everyday life, family histories, sibling rivalries, and so on. In any case, most people assume (wrongly, in my opinion) that 20 years hence we will have reasonably effective medication for late-onset Alzheimer's disease.

Conclusions

The mapping of susceptibility genes, molecular genomics and proteomics, and epigenetics are proceeding apace, albeit on largely separate trajectories. As a result, new and ever-more elusive bodies without organs are lighting up computer screens, challenging the usual assumption of a materially individuated body that corresponds closely to an internalized awareness of a singular self. None of these scientific findings have as yet had any effect on the incidence of Alzheimer's disease, and professional claims that this situation will be rectified in the new few years have largely receded into the background. Attention has shifted to younger and younger populations of healthy people in an effort to locate the very first indications of molecular changes that may eventually lead to a toxic build-up in the brain (Dekosky and Marek 2003). No systematic research has as yet been carried out in connection with the impact of enrolling many thousands of healthy people in clinical trials and other forms of research designed to monitor brain function—research that involves genotyping, imaging of brain activity, and repeated psychological testing—and then correlating these findings with postulated risk for disease. These activities may well represent the thin edge of the wedge in connection with routine disclosure of genetic information about susceptibility genes to the public at large. The controlled trial described here is perhaps an early sign of things to come. It is now an urgent matter for social scientists to ask what counts as well-established knowledge in the world of genetics, what in effect is knowledge-in-the-making, what is essentially nonsense or bad science, and what impact this plethora of confused information is likely to have on publics as they are increasingly asked to contribute to research and to submit to genetic testing.

Knowledge that has accumulated over the past few years in connection with Alzheimer's disease has ensured that virtually no scientist is complacent about the discovery of a panacea for this condition. Many are humbled in the face of the complexity that confronts them, although at the same time excited about the challenge

12. Janalyn Prest and Stephanie Lloyd, both affiliated with the Anthropology Department of McGill University, acted as research assistants and conducted and coded most of the qualitative interviews. Heather Lindstrom, in the Anthropology Department at Case Western Reserve, also conducted interviews.

posed by this remarkable puzzle. However, several have admitted to me to being unable to understand the significance of the findings of researchers in related subspecialties, let alone incorporate these findings into their own hypotheses and projects, and the response of most is to delve deeper into the workings of their favorite protein or enzyme. Many researchers argue that we must now fill in the enormous gap in our knowledge between the poles of neurodevelopment and neurodegeneration, and in order to bring this about the entire aging process is being reconceptualized as one long continuum rather than being fragmented into discrete segments as has until recently been the case (Silver et al. 2001). Deterministic talk has been replaced by discussion about the effects of clustered associations and interactions among numerous genes and their products, both intra- and extracellular, on normal and pathological aging. More specifically, understanding the conditions under which genes are switched on and off along the paths to dementia has become a major challenge. Numerous genes, proteins, and enzymes have been isolated that contribute to a build-up of plaques and of tangles in the brain, and genes and their products have been isolated that promote early cell death or, alternatively, contribute to the formation of new neuronal pathways, but the conditions under which these changes come about remain largely a mystery.

Research that focuses on environmental and social variables attracts far less attention than do the activities of basic scientists, but it is notable that the APOE gene is now routinely included as a variable in epidemiological projects, alongside age, gender, and education. However, there are as yet no signs of a developmental-systems approach to dementia, one that would attempt to fully contextualize the genome, pay attention to feedback loops and networks of interaction, privilege a synchrony of events over linear trajectories, and take seriously the idea that social and macro-environmental contexts can influence the regulation of genes (even to a limited extent in connection with Mendelian genes including those implicated in early-onset Alzheimer's disease).

What is missing almost entirely is research into the effects of human relationships over the life span on the aging brain. It is widely agreed that biomarkers can lead to toxicity and neuropathology; these biomarkers, that is, genes *and* their products, have become agentive but are not deterministic. Critical epigenetics has successfully overturned the dogma of genetic determinism but is, I would argue, vulnerable to abuse by those who persist in creating crude, deterministic links between biology and behavior. Anthropologists must join like-minded biologists to counter such crudities, recognizing that epigenetics can be an entry point for transcending the nature/nurture divide. If, as epigeneticists have shown, maternal behavior influences the switching on of genes in rat pups, then why should not anthropologists begin to think about the ways in which human social life may influence gene regulation and function—as protective of human health, for example? Without a doubt ethnography will provide some valuable insights in such an endeavor, but much of this research will in all probability have to be conducted in partnership with epigeneticists.

Comments

SARAH CUNNINGHAM-BURLEY
Public Health Sciences and Centre for Research on Families and Relationships, University of Edinburgh, Medical School, Teviot Place, Edinburgh EH8 9AG, Scotland, U.K. (sarah.c.burley@ed.ac.uk) 19 VII 05

Lock's impressive essay combines the best of critiques from medical anthropology and sociology and from the sociology of scientific knowledge in successfully exposing the myth of genetic determinism. Moreover, she analyses the remarkable tenacity of reductionism even as epigenetics and systems biology embrace complexity in their theories and methods. As expected from such a thorough ethnographer, Lock's essay provides sound and recent empirical evidence alongside a broad-brush review of relevant work from the social as well as the natural, clinical, and population sciences. Her work on late-onset Alzheimer's disease, of which we get a tantalizing glimpse towards the end of this essay, will provide a platform for reassessing the implications of medical science for families, individuals, and communities. It will also help us to understand and develop the role of social scientists, ethnographers in particular, in the frantic and overwhelming postgenomic scientific activity about human health, development, and disease.

It is in provoking reflection about this latter area—the role of social science—that I found this essay the most stimulating. I hope it will precipitate further debate not just within anthropology and sociology but also within the increasing range of disciplines and networks engaged in epigenetic and related research. As ever, sociologists and anthropologists find themselves in close collaboration with the very subject matter of their gaze, whether this is "the eclipse of the gene," the everyday production of scientific knowledge, the way in which families take in uncertain information about susceptibility to disease, or the impact of research participation on ever-increasing sectors of populations. Maintaining critique, contributing to interdisciplinary research, and influencing both the direction of research and its impact on individuals and populations all require a careful balancing of our disciplines' position in elucidating "the space between genotype and phenotype."

I agree with Lock's description of the "urgent matters" for social scientists—the need to examine the "black box" of science as well as the impact it is likely to have on publics. It is also important for social scientists to work together to build on their accumulating knowledge. There have been many years of research activity, and as funding continues to be earmarked for this field this is likely to continue. Working within and across the social

science disciplines is as important as working with our basic and clinical scientific colleagues.

The relationship between social science and the wider public sphere is hinted at but not developed in Lock's essay. Collaboration here is not so much with other disciplines but with a wide range of publics, whether constructed as citizens, activists, co-researchers, research subjects, patients, or consumers. Such engagement is not new to anthropology (see Lassiter 2005) or sociology; indeed, social scientists have been very active in the whole arena of the public understanding of science. My colleagues and I are trying to deal with the difficulties and ambivalences that public engagement and interdisciplinary work bring, and we are not very close to constructing a satisfactory place in either arena for our disciplines or ourselves, but at least we are working on the margins of perhaps considerable transformations in science and science/public relations.

People make sense of risk information in ways that are relevant to their own lives and are less engaged in genetic hype than might be predicted from the status hitherto ascribed to "the gene." However, given the wider processes of medicalization and geneticization and the regulation and governing of bodies, the opportunities to resist, collectively or individually, the research, clinical, and commercial imperatives that drive this field may be limited. Globally, intractable health problems continue to shorten the lives of millions, and we know already how some of these could be ameliorated.

To uncover the complexity of the cellular activity within the human body in the context of its ever-changing interpersonal and wider milieu would require lifelong surveillance of our bodies, intimate and personal lives, and environment. I am not sure that the fragile promise of a better life through improved understanding of disease and its prevention, treatment, or cure is a sufficient motive to contribute substantively to such a project. However, the risks associated with not being thus involved are perhaps even greater. We can improve such research through our theoretical and methodological insights, although, as Lock notes, this will require working in partnership with epigeneticists, among others, and therefore raising to the surface expectations and assumptions about motives, roles, responsibilities, and expertise.

SARAH FRANKLIN
BIOS, London School of Economics, Houghton St., London WC2 2AE, UK (s.franklin@lse.ac.uk) 28 VII 05

With characteristic perspicacity, Lock masterfully summarizes several of the most important recent developments in the field of genetic medicine and shows that they are not entirely what they seem. Regarding the shift from the gene to the cell as the main theatre of opportunity for contemporary *in vitro* innovation, she points to the now unavoidable question whether "the rise and fall of the genotype/phenotype dogma" is, as Evelyn Fox Keller suggested earlier (2000), a historical aberration. The consequences of this "return to the cell" spring readily to mind—among them whether the vocabulary of "tinkering," which belonged to the early modelling years of DNA in the 1950s but gave way to the more precise technologies of sequencing in the 1980s, is now a more accurate description of what is going on in stem-cell science, tissue engineering, or embryo surgery. Certainly constructivist analogies abound in these fields, where "scaffolding," "tight junctions," and "mechanical manipulation" are commonly used to describe the working environments of bespoke biology. An accompanying shift is from molecular precision to the "vaguely genetic" (which is more or less what "familial" has always meant in medical terms) and from "targeted effects" to "cascades" in which "terminal pathways" appear inevitable only at the penultimate moment. One of the big questions Lock is investigating here is whether this species of the biological is ordered, both conceptually and technologically, by different regimes of time and space and thus of causality, which is profoundly consequential in terms of how successful therapeutic interventions will be imagined or achieved. Systems biology and models of synchronic biological action such as those described by the cell biologist Lynne Margulis (1998) appear to be increasingly useful in the void of explanatory certainty created by the success of somatic cell nuclear transfer and its ilk.

Meanwhile, as Lock notes, vast amounts of human material are being collected, sorted, classified, screened, and probed in the creation of a kind of dispersed biobank in which a new type of shared human substance is coming into being (Parry 2004). This new virtual human feeder-layer, or *cellularium*, is both the object and the source of new (and old) biotechniques that are often based on modelling, copying, or mimicking of a "found" event or process with an artificial, surrogate, or "cloned" replication (Rheinberger 2006*b*). These two biologies, which we might call the inner and the outer human, constitute a defining biological polarity of contemporary social organization in everything from biosecurity, surveillance, and forensics to regenerative medicine, cosmetic surgery, and "genetic identity" (Stacey 2005). The twin goals of *mimicry* and *repair* are the two aspects of the new hope for a kind of bioturf, or vital soil, out of which almost anything can be reseeded and regrown.

This is the point that brings Lock to the question of "genetic profiling," and it is here that her analysis is, in a sense, redoubled—going both forward and back, within and without, tracing the paradoxes of the individual and the many. One vital consequence of this misplaced concreteness that Lock sharpens to a fine point of anthropological advice is that in the move from "susceptibility genes" to the vaguer but undoubtedly more accurate "biomarkers," an overinvestment in genetic symptomatology will be at the direct cost of diagnostic benefit, which must not only be "multifactorial" but include public participation in the creation of a corresponding diagnostic practice. If the complex developmental model of aging and neuro-degeneration that Lock and many of her informants point toward is to become fully functional, account must be taken not only of "lifestyle choices" and the "clustered associations" of events that unfold around

them but also of the relational qualities of human social life, which can be as "agentive" as DNA in the determination of one epigenetic event rather than another.

One way to take this point farther is to reconsider the issue of commercialization through a "relational" lens. While much has been made of the driving forces of commercial investment in stem cells and regenerative medicine, it is notable that both within the United States and overseas most of the investment in postgenomic cellular downloading technologies is from the public sector, including charities such as the Wellcome Trust and the Juvenile Diabetes Research Foundation. The sociality of biobanking, at issue in practices surrounding informed consent, donor screening, and traceability, *will also be strongly shaped by its commercial characteristics*. This too will be agentive in the future in shaping health inequalities for both rare and widespread diseases. As a consequence, part of the story of biocapital will be about how much public control will be wielded over the capacity to manipulate the delicate circuitry of life itself.

STEPHANIE MALIA FULLERTON
Department of Medical History and Ethics, University of Washington School of Medicine, Seattle, WA 98195, U.S.A. (smf15@psu.edu) 10 VII 05

Hype and hyperbole have characterized much of the 15-year period surrounding the emergence—and, now apparently successful, completion—of the international scientific undertaking known as the Human Genome Project (HGP). In its wake the "gene" has gained widespread currency and explanatory agency among lay and professional audiences alike, supplanting an array of alternative explanations for disease predisposition. Yet, if we are to take Lock's title at face value, it seems that the pervasive and unwarranted genetic determinism spawned by the project may have at last run its course, displaced by a growing recognition of the complex interplay of genetic and environmental influences on the development of complex biological phenotypes. The irony of a molecular genetic reductionist research agenda's effectively demonstrating its own empirical inadequacy is a major theme of Lock's insightful and thought-provoking article.

This account is no doubt a welcome relief to those who are unfamiliar with the rapidly shifting terrain of the so-called postgenomic period. Determinism is dead, developmental systems theory is on the ascent, and just as soon as clinicians have time to flip through their back copies of *Scientific American* they will recognize the analytical cachet of the epigenetic program and begin taking the role of nongenetic influences on phenotypic development and disease progression far more seriously. We may even be able to avert the troubling and, to many minds, near-inevitable introduction of routine genetic testing for presymptomatic susceptibility to common chronic conditions such as cardiovascular disease and Alzheimer's disease. Indeed, "it is eminently conceivable that a paradigm shift of enormous significance is now under way." Would it were really so! Instead, as Lock documents throughout her critique, deterministic thinking, while frequently disavowed, is still alive and well in the day-to-day of the biomedical research enterprise. The human genome sequence may be in hand (or more accurately, in the computer), but the HGP marches on, having morphed into two large-scale descendent projects coordinated by the U.S. National Institutes of Health. The first, project ENCODE (for ENCyclopedia Of DNA Elements), aims to characterize the functional properties of the genome sequence. The second, the International Haplotype Map, or HapMap, Project is focused on defining the variability of the human genome, with the express aim of facilitating the eventual localization of genes and genetic variants relevant to human disease. And efforts are currently under way to initiate the largest prospective cohort investigation of genes and disease ever undertaken in the United States, a complement to the UK Biobank and related research programs being pursued in other countries. All promise to commit tens of thousands of healthy individuals to decades of longitudinal biomedical surveillance in an effort to define those elusive risk estimates which will be needed to usher in the much-promised era of "individualized medicine."

That such institutionally spearheaded initiatives do not represent the majority of biomedical research is beside the point. These programs and their prominence in the national research portfolios of numerous countries exert an authority and influence far beyond the limited number of researchers directly involved in specific investigations. It is precisely because of the HGP, ENCODE, and HapMap that neurobiologists who study late-onset Alzheimer's disease regard APOE genetic testing as "essential for cutting-edge basic science research," even when the implicated risk genotypes do not adequately predict disease onset or progression, appear differentially associated with disease risk in different populations, and do not provide any clear indication of the role of the associated apolipoprotein in disease etiology. Researchers persist in this deterministic vein because while specific genes rarely definitively predict the occurrence of disease in a given individual, in the aggregate genetic associations may point to less apparent (and, as was the case with APOE, wholly unexpected) biochemical pathways involved in the eventual progression to the diseased state. The hope, which (as Lock notes) remains unrealized, is that the identification of novel etiological pathways will help target drug development or perhaps even provide a base from which environmental contributions to disease risk can be better evaluated and assessed.

What drives the ongoing appeal of determinism is the real puzzle of Lock's account, and it is not clear that the failure of clinicians to take up the insights and methods of developmental biologists can be regarded as the best explanation. As has been pointed out to me on several occasions, clinicians and other researchers with clinical experience appreciate better than most the multifactorial, contingent, and highly variable nature of disease manifestation. For such researchers, the continuing recourse to the neo-reductionism of biomarkers and genetic testing represents a form of conscious oversimpli-

fication adopted for a specific empirical end, not a failure to appreciate the full etiological complexity of the disease or trait of interest. Determinism will wither when the conceptual alternatives prove epistemically more potent. It is not clear, for biomedicine at least, that that day has yet arrived.

ALAN H. GOODMAN
School of Natural Science, Hampshire College, Amherst, MA 01002, U.S.A. (agoodman@hampshire.edu) 18 VII 05

One interpretation of U.S. history is that the Union won the wrong Civil War. Its victory reunited the country and ended slavery, but the racists maintained ideological supremacy; minds and behaviors were unchanged, and as a result other racist laws and institutions quickly replaced slavery. The war for racial equality was meekly fought and lost. Lock's excellent article provides scholarly evidence that something similar is stirring when it comes to contemporary biomedicine. We may understand more about how bodies work, but ideologies remain unchanged.

A steady attribute of Lock's scholarship is not only that she writes about intellectually interesting topics but that she articulates the stakes for healthy bodies and minds. Lock contrasts genetic determinism with a more interactive, contingent, and contextual view of biology. As she notes, most working laboratory biologists have had enough experience with complexity and contradictory results to know that genes do not simply establish complex phenotypes such as late-onset Alzheimer's disease. Yet, the message seems to have incompletely filtered down to physicians, patients, and seekers of patents. She advocates for complexity and contingency as well as for a fuller understanding the culturalness of illness and biology.

Lock shows that research and practices around the genetics of late-onset Alzheimer's disease tend to drown out competing explanatory systems. Study participants who have been tested for "risk" genes repeat both an ideology of future hope/hype and a sense that the data are useless. These vignettes provide a glimpse of the importance of ethnographic research on the medical-care industry. The genetic determinism that Lock articulates here is linked to racial and genetic determinism of other medical conditions through powerful institutions such as the Food and Drug Administration (FDA): witness its June 16, 2005, Cardiovascular and Renal Drugs Advisory Committee meeting to evaluate Nitromed's request for a patent for BiDil™ (isosorbide dinitrate/hydralazine HCI), a combination of two medications that purport to improve nitric oxide status for African Americans only. The committee used the day to evaluate apparently the only thing it felt competent reviewing: an epidemiological study that had enrolled only African Americans. Members hotly debated, for example, whether the proper level of statistical significance was $p = 0.01$, 0.02, or somewhere in the middle. Except for comments from Jonathan Kahn and members of Harvard's Human Genome Center, nobody mentioned that African Americans are genetically diverse. Because the study could not evaluate whether the results might have been due to lived experience or genetics, the advisory panel never addressed this key question. Toward the end of the day, the panel turned to the question of whether approval should be recommended for African Americans alone. Steven Nissen, a cardiologist from the Cleveland Clinic and the committee chair, broke the silence (http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4145T2.pdf):

> My view . . . is that drugs are not racist; people are racist. . . . We are moving forward in medicine toward the era of genomic-based medicine. There is no question that in 10 or 15 years it is going to happen. I know it has been predicted for a long time and hasn't happened yet but it is going to happen, trust me. . . . So, what we are doing is we are using self-identified race as a surrogate for genomic-based medicine. . . . I wish we had the gene chip.

Nobody seems to know how BiDil works or for whom. What is certain is that Nitromed won the ideological battle by enlisting the support of groups such as the American Association of Black Cardiologists and the Congressional Black Caucus and the heart-rending appeals of two black women who were in the BiDil trial. One of them, 48-year-old Debra Lee, her trip paid by Nitromed, said: "I take 23 pills a day but my joy comes from knowing that my medication is truly working its best to correct something that can't be fixed, my heart. . . . What do I contribute as the cause of this turnaround? It is my strong faith in God and a little pill called BiDil" (http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4145T2. pdf). The return to divination is readily apparent. The committee voted unanimously to approve BiDil for use in African Americans only, and the FDA has now agreed.

Who wins the ideological battle over the etiological framework for late-onset Alzheimer's disease? Will we base medicine and biology in the twenty-first century on determinism and a gene chip, as Nissen suggests, or on the integration of different types of knowledges, in line with my own views, Lock's, and developmental systems theory? I doubt that the gene chip can deliver individualized medicine as promised, but one should never underestimate the hegemonic power of big medicine to make it seem that a square peg really does fit into a round hole. And once the peg is jammed in, we have all the more work to get it out. Whatever the answers, work such as Lock's is necessary (though not sufficient) to show options to genetic divination.

KENNETH C. MAES AND GEORGE J. ARMELAGOS
Department of Anthropology, Emory University, Atlanta, GA 30322, U.S.A. (antga@learnlink.emory.edu). 15 VII 05

The attempt to characterize late-onset Alzheimer's disease has progressed slowly, with ambiguity among genetics findings (see Rodriguez-Santiago and Nunes 2005) and treatment-focused clinical results (see Jansson 2005)

that is a sure sign of a complex disease. Late-onset Alzheimer's disease gathers the pathogenic input of several genetic polymorphisms as well as environmental and behavioral factors over the course of a lifetime. Genetics has been at the forefront of research on the disease, and a full-fledged developmental-systems-theory approach is undeveloped. Aside from genetics, diet is currently heralded as a major and ideally modifiable behavioral factor (Jansson 2005), since dietary antioxidants combat reactive oxygen species, the dynamic mediators of the macromolecular damage and pathology associated with the disease. This is a good example of the invisible connections that exist between behavior in a social environment and biochemical pathways. Lock encourages the magnifying and illuminating of such connections not only because they are key to an understanding of the etiology of complex disease but also because this is the next logical step in the evolving disciplines of developmental and medical epigenetics. But in her concern to highlight this gap she has failed to cite the scarce research whose marginalization she laments. There are some possible avenues that demonstrate her ideal of collaborative research; discussion of them would be helpful and enlightening.

Oxidative stress occurs when reactive oxygen species exceed antioxidant defenses, leading to significant biomolecular damage (Zhu et al. 2003). Steen and colleagues (2005) point to the debate about the dynamic roles of oxidative stress in the etiology of late-onset Alzheimer's disease, including how mitochondria—the primary source of endogenous reactive oxygen species—are involved. This debate is a manifestation of the complexity of the etiology, the diversity of methodology, and the fact that researchers tend to focus on specific pathways among many (Perry et al. 2003). Indeed, oxidative stress is not the whole story (de la Monte and Wands 2005, Steen et al. 2005, Summers 2004), but it is the focus of intense research.

Lock overlooks the related role of somatic mitochondrial mutations in the brain. The somatic mutations in neuronal mtDNA are believed to lead to mitochondrial defects (Coskun, Beal, and Wallace 2004) and, through interactions with other pathways, to late-onset Alzheimer's disease. Such mutations play a role in only some patients' development of the disease. Such mutations are also difficult or impossible to identify *in vivo*. Still, this is another prime example of a place where genetic and behavioral realms meet. Somatic mutation rates in neuronal mtDNA can be hypothesized to respond to factors that "originate" in the behavioral realm. Again, the food we eat and perhaps factors of maternal environments (the environment of the bulk of human neurogenesis) lead to increased somatic mutation with functional outcomes, whether mutation strikes in protein-coding or noncoding DNA. Unfortunately, those who generate evidence of somatic mutations in mtDNA have not gone beyond genetics. For instance, Coskun, Beal, and Wallace (2004) hypothesize that "a variety of factors could modulate the mtDNA . . . somatic mutation rate and thus increase the probability of dementia" (p. 10731) but give no hint of what some epigenetic factors could be.

Responding to epidemiologic data, Jansson (2005) suggests that late-onset Alzheimer's disease is an "industrial-nation disease," a loose tag shared with other ailments associated with the set of demographic, dietary, and lifestyle risk factors located in industrial, urban contexts. Jansson argues that diets low in antioxidants and marine fatty acids and the social isolation of the elderly are risk factors with us today but not experienced by our preindustrial ancestors or contemporaries. Missing is a developed knowledge of just *how* these putative dietary and social-behavioral risk factors would influence the cellular and metabolic pathways that eventually lead to the onset of the disease.

Diabetes (another complex disease) and diet affect reactive oxygen species production and clearance, respectively, and they are key components of the "industrial-nation" set of epidemiologic, demographic, and lifestyle risk factors. The same research and recommendations as applied to these factors' effects on our health might eventually be applied to late-onset Alzheimer's disease. Dietary antioxidant deficiencies and Type 2 diabetes are expected in modern cultures with easy-access, energy-rich/antioxidant-poor food when and where antioxidant supplementation has been rare. Still, we need more research to test whether preventing diabetes and antioxidant deficiencies during pregnancy is also preventive for mtDNA mutagenesis during neurogenesis and, in turn, late-onset Alzheimer's disease. In step with Lock's message, research should explore the *interactions* among all possible risk factors for the disease.

According to Robert, Hall, and Olson (2001), there exists a sentiment that developmental-systems theory is nothing more than armchair philosophy—that it questions genetic reductionism and attempts to overturn neo-Darwinism rather than contributing to evolutionary and developmental thinking. But proponents of the theory have made a clear call for empirical unification of genomics, evolutionary developmental biology, physiology, and behavioral sciences. Lock has identified complex neurological diseases as not only grounding but also fruitful research projects for the theory. Perhaps a mutually beneficial relationship can develop between this approach and the questions that remain for late-onset Alzheimer's disease research.

RAYNA RAPP
Department of Anthropology, New York University, 25 Waverly Place, New York, NY 10003, U.S.A. (rr77@nyu.edu). 14 VII 05

We are all in Lock's debt for so ably summarizing a very messy sea change, indeed, a cosmological transformation now ongoing in the life sciences. Having effectively synthesized the growing social science commentary on genetics and medicine and married it to the layered complexity of contemporary biology, she then illustrates this vast scientific transformation by turning to the case of

Alzheimer's disease as a bridge between older and newer understandings of what genetic "causation" or "risk" might entail. This unstable ground is also foundational to shifting popular attempts to remake older enduring social relationships of kinship, responsibility, dependency, community, and citizenship under the rapid-fire conditions of the new—notably, the expanded commodification of Life Itself and pharmaceutical/ biotechnological remedies for its sufferings. This is, of course, where anthropologists conducting medical and science studies (or might we say "we epigenesists"?) enter the picture.

As a lesson for the discipline, Lock summarizes many transitions now in progress. The logic of single gene mutations that characterize Mendelian rare autosomal genetic disorders like Tay-Sachs and sickle-cell anemia, for example, has now been supplemented by the search for biomarkers of widespread complex diseases like the cancers, Alzheimer's, or cardiovascular disease. In these latter afflictions, "lifestyle" environments appear to co-produce susceptibility in ways not yet well understood. These scientific projects suggest a move from a molecularized understanding of nature to a molecularized understanding of culture or, at least, of the pathways through which environmental effects leave their molecularized signatures. Indeed, Lock usefully highlights the transition from genetics to epigenetics as a key arena of theory and practice in the life sciences: histories of toxic environments, dietary patterns, exercise, and the black box of psychosocial stress now appear to mark our bodies across multiple generations. It is here that we see the widening gap between genotype and phenotype which seems to index a movement from the modern(ist) rule-governed patterns of rare genetic disease to the epigenesis of common contingency: a Lamarckian revenge of sociocultural patterns now rears its head.

Yet Lock is suitably skeptical about how and even whether rare autosomal forms of hereditary disease (early-onset Alzheimer's or familial breast or colorectal cancer) will actually serve as bridges to understandings of common complex and contingent varieties: the rising diagnostic presence of late-onset Alzheimer's, the breast and prostate cancer "epidemics" produced, in part, by mammography and PSA tests, or the powerful statistics of lowered cholesterol levels for those lucky drug-planned populations now on costly statins. We anthropologists scamper behind these rapidly moving social currents, querying the scientific hybrid lineages, health provider and policy protocols, and desperate people in search of alleviation even as we note the strategies of globalization by which huge multinationals test, invest, and market their medicines in increasingly health-conscious communities. There is an expansive social world deeply unsettled by the promissory notes, fears, fantasies, and volatile economics of potent life-science materiality. It now includes Hadassah's determined advocacy of universal health coverage to include genetic services in the U.S.A., India's crap-shoot patenting legislation, enabling both national entry into the international community of WTO/TRIPS signatories and development-focused sliding-scale profit rates for its international market campaigns, and Brazil's innovative constitutional right to HIV/AIDS meds and its compact with postcolonial Portuguese-speaking nations now attempting to import or develop relevant drugs. As we continue to study relations among life-science volatility, comparative pharmaceutical and health provision policy, and the creative desperation of health activists, Lock's clear-sighted perspective on the present imperfect and near future of genetic cosmology will prove extremely useful. Her analysis signals that the stories we want to tell can only be constructed retrospectively. Yet commercialized life sciences thrive on optimistic predictive contingency. What better space to exercise the return of classical divination?

Reply

MARGARET LOCK
Montreal, Quebec, Canada. 5 VIII 05

I appreciate the many perceptive and constructive remarks made about "Eclipse of the Gene." As several commentators have discerned, the paper under discussion is part of a larger project that has a tripartite focus. One of my concerns is of course with the molecularized body of the biosciences—the product of ongoing technological manipulation and innovation and associated forms of representation. What counts as normal and abnormal and where exactly pathology is located must be reimagined as molecularized knowledge is increasingly assembled; the means of knowing these new bodies extend beyond clinical examinations, visualization technologies, and assessment of genetic susceptibilities to the currently elusive biomarkers. These emergent bodies are largely confined for the time being to what Latour has termed "the world of research"—a world that by definition incites controversy and uncertainty (1998). People practice what I term corporeal citizenship when they agree to become research subjects and in doing so willingly participate in the uncertainty surrounding research. Their cells, tissues, and brain scans are unlikely to further their own well-being but will, they hope, contribute to the greater good of society.

My second focus, not so evident in the present paper, is on what is increasingly being characterized as the transfer and uptake of knowledge across domains. When this phraseology is used in the medical world it is limited to the movement of knowledge from the basic sciences to the clinic. In common with other social scientists I take a broader view, one concerned primarily with the circulation of knowledge among basic scientists, the clinic, the media, advocacy groups, involved individuals and their families, and publics. Inherent in this part of the inquiry is the question of geneticization and to what extent if at all this is taking place. Are affected patients and families undergoing biologized identity transfor-

mation? Are new forms of kinship and social relations, based on genotypic or phenotypic alliances or some combination of the two, emerging? Is the idea of a controlled life and mastery of risk, so central to modernization and the production of Beck's risk society, being reinforced through the allure of DNA testing? Or, on the other hand, as information about genetic susceptibility with its inherent uncertainty is increasingly disseminated, is a belief in a technologically assisted future of bodily mastery disappearing below the horizon, to be replaced by a postgenomic angst of uncertainty? As the present article hints towards the end, knowledge about susceptibility genes, in the case of late-onset Alzheimer's disease at least, is at present so problematic and loaded with uncertainty that tested individuals often appear indifferent to their results. Ethnographic findings show that just over a third of the tested population in the REVEAL study either forget their results entirely or cannot recall them effectively, but they also show, as Goodman notes, that research subjects have a grasp of complexity (Lock et al n.d.).

The third focus is hinted at throughout the paper, largely in the form of complaints about what I perceive to be a rapidly consolidating neo-reductionism centered on elucidation of cell activity that has replaced genetic determinism. The language of genomics cannot be described as deterministic; virtually no expert, whether basic scientist or clinician, argues that organisms are mere expressions of their genes. Genes are not conceptualized as blueprints, and sequencing of genes is understood primarily as partial knowledge. It is indeed the case, as Fullerton notes, that most clinicians, in the abstract at least, are sensitive to the "multifactorial, contingent, and highly variable nature of disease manifestation." But equally, their task is to provide reassurance and cures of named conditions, usually under enormous time pressure, and this results in "oversimplification for a specific empirical end." Of more significance is that, when contingency and variation among human bodies are explicitly considered, the overworked, undifferentiated, stereotyped categories of race, gender, and socio/economic status are assumed to be sufficient to the purpose, to which genotype is currently being added. Arguments about gene/environment interactions are almost without exception limited to efforts to integrate the findings of population genetics with epidemiological research designed to uncover the "social determinants" of health. This is how risk is calculated, and it is in part why vast sums of money are being put into the setting up of large, longitudinal cohort studies involving storage of data in banks and designed to be monitored for years on end, often with commercial interests as the driving force. On a related note, Cunningham-Burley, Fullerton, and Franklin are rightly concerned about the life-long citizen surveillance that inevitably accompanies the emerging genomics and will surely be a feature of many epigenetic projects.

At a recent conference on Alzheimer's disease an epidemiologist participating in a plenary session argued that, even before birth, genes influence the building of "cognitive capacity." But her argument does not stop there: those of us who grow up in environments of deprivation who are genetically predisposed to have fewer synapses will be more vulnerable to dementia than those of us raised in enriched environments, who will largely compensate for the predisposition. Arguments such as these remain reductionistic and in effect decontextualized. Goodman reminds us that genetic diversity is repeatedly mismanaged or ignored and the results of years of social science research in which the concepts of race, gender, and economic status are deconstructed appear to have fallen on stony ground. Steve Epstein, in commenting on the NIH Revitalization Act of 1993, makes a related point. He notes that this policy, designed specifically to include women and members of racial and ethnic minorities as subjects in all clinical research funded by the agency, is a product of a "vexed history" of attending to or ignoring bodily difference (2004:119).

The developmental-systems approach to epigenesis is promising, in my opinion, because history—evolutionary, environmental, and life-cycle—is integral to its theoretical orientation with respect to biology. However, as I noted in the article, this promise is as yet far from fulfilled. I have taken note of the references provided by Maes and Armelagos; it is significant that they are obliged to state with respect to a paper that deals with somatic mitochondrial mutations possibly linked to dementia that the authors give no hint of the epigenetic factors that might influence these mutation rates. And in another paper, they note, the author gives no hint of "just *how* . . . putative dietary and socio-behavioral risk factors would influence . . . cellular and metabolic pathways." Social life is indeed agentive, but how exactly? Statistical regressions are not going to provide the answers. Clearly our work as social scientists is cut out for us, and we have a long way to go before we begin to elucidate a "molecularized understanding of culture," in Rapp's felicitous phrase. It is my belief that we will make little headway unless a strong program in which recognition of the coproduction of the material/environmental and the historical/cultural/social/political is the starting point. Something along the lines of Latour's (1993:144) call for a recognition of object-discourse-nature-society is in order, or Haraway's (1991:200) earlier argument that "bodies as objects of knowledge are material-semiotic-generative nodes," that their boundaries materialize in social interaction and through this interaction bodies and body parts are constituted as objects, sites for manipulation. My own research has focused on local biologies, the politics of medicalization, ruptures in medical discourse, hegemonic cultural assumptions about bodies, and discourses of subjectivity and embodiment (Lock 1993, 2001; see also Franklin and Lock 2003 for other relevant essays). Franklin and Rapp both challenge us to think big. The global reach of what now confronts us is undeniable, and the extent to which the future promise of genomics is tied up with the interests of biocapital is daunting. I believe that anthropological research, sociopolitical and ethnographic, into the pro-

liferation of genetically modified organisms is equally as urgent as are medically oriented projects.

One example of the interdisciplinary linkages recommended by Cunningham-Burley is that of Melissa Melby, a Ph.D. candidate in physical anthropology at Emory University, who is currently analyzing data derived from blood samples, diet, and quantitative and qualitative interviews conducted in Japan as part of a project designed to elaborate on my earlier menopause research (see Melby 2005 for preliminary results). Cunningham-Burley notes another important area for collaborative research that is particularly relevant when genomics is being scrutinized—the public understanding of science and the role of the media in diffusing information. Media hype in connection with genetic engineering and the enhancement of the material in all its forms has been particularly pronounced.

One thing is clear: the time is ripe for a rapprochement between biological and cultural anthropologists. Such a move will not appeal to everyone, that much is certain, but for those of us willing to engage the future could be bright.

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