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TOXIC ETHICS: ENVIRONMENTAL GENOMICS AND THE HEALTH OF POPULATIONS

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ABSTRACT

Dealing primarily with implications rather than foundations, and focusing downstream at the expense of upstream prevention, mainstream bioethics is at a toxic watershed. Through an extended analysis of the Environmental Genome Project (EGP), we offer new tools from the philosophy of science and from critical epidemiology to help bioethics to move ahead. Our aim in this paper is not to resolve the moral and conceptual problems we reveal, but rather to outline ways to prevent such problems from arising in future research.

INTRODUCTION

Recall a familiar story: a man is walking along the shore one day and he hears a plea for help from someone drowning in the river; he races over to pull her to safety, only to hear another cry for aid. Again, he makes his way over to the drowning victim, pulling him to shore and resuscitating him, only to hear yet another cry for help. After helping this third person, he is drawn further downstream to another, and still another victim, ushering them all to safety only to find someone else in distress. Though he is able to save one person after another for the time being, soon he will be overwhelmed. And because he is so busy saving people from drowning, he doesn't have time to turn upstream to see who keeps pushing them in in the first place.[1]

[1] The story is borrowed from: A. Weston. Toward a Social Critique of Bioethics. *J Social Philos* 1991; 22: 109–118, at 109; Weston borrowed the story from: I.K. Zola. 1970. *Helping – Does it Matter? The Problems and Prospects of Mutual-Aid*

Irving Zola recounted this familiar parable to highlight modern medicine's myopia; Anthony Weston then invoked it in his criticism of the myopia of bioethics in its narrow focus on clinical medicine; we now invoke it yet again, in both biomedical and bioethical contexts, to call attention to the character of the stream in question. Bioethics is at a toxic watershed. The toxicity in question stems from two sources, one literal and the other figurative. First, the literal. Health and disease are multiply determined by the interaction of any number of a broad range of socio-economic, ecological, historical, genetic, developmental, physiological, and cultural factors. These determinants of health and disease at both individual and population levels have been well documented and subjected to considerable critical scrutiny, primarily during the past three decades.[2] And yet governments and funding agencies have not altogether embraced strategies for grappling with the broad determinants of disease (such as the provision of clean drinking water in 'developing' countries or the clean-up of toxic landfills globally), tending to prefer instead to focus on genetic predispositions to cancer and heart disease, and on biotechnological engineering of crops and vaccines (and, now, of crops with vaccines) to be exploited in the Third World.[3] The global population is not any healthier as a result; in fact, and in conjunction with current environmental policy in the United States and elsewhere,[4] many populations may even be less healthy. And this is to be expected: the global disease burden is enormous, whether measured in personal, financial, social, or other terms,

Groups. Address to the United Ostomy Association. We ought not to forget a common intuition about this parable: though our hero may not be able to save everyone, at least he is able to save some people. Looking too far upstream may be just as problematic as focusing too far downstream.

[2] Canada. 1974. *A New Perspective on the Health of Canadians*. Department of National Health and Welfare; M.L. Barer, R.G. Evans & T.R. Marmor, eds. 1994. *Why Are Some People Healthy and Others Not? The Determinants of Health of Populations*. New York. Aldine de Gruyter; R.G. Wilkinson. 1997. *Unhealthy Societies: The Afflictions of Inequality*. New York, NY. Routledge; M.G. Marmot & R.G. Wilkinson, eds. 1999. *Social Determinants of Health*. Oxford. Oxford University Press; T. Schettler, G. Solomon, M. Valenti & A. Huddle. 2000. *Generations at Risk: Reproductive Health and the Environment*. Cambridge, MA. MIT Press.

[3] See, for instance: A.S. Daar, H. Thorsteinsdóttir, D.K. Martin, A.C. Smith, S. Nast & P.A. Singer. Top Ten Biotechnologies for Improving Health in Developing Countries. *Nat Genet* 2002; 32: 229–232.

[4] See the report prepared for Representative Henry Waxman by the Democratic Staff of the United States House of Representatives' Government Reform Committee (the Waxman Report). Available at: http://www.house.gov/reform/min/politicsandscience/report.htm (accessed 15 February, 2004).

and a significant component of this burden is a result of a polluted biophysical environment.

Now, more figuratively. Consider John Evans' historical and sociological account of American bioethics in the context of genetic engineering, *Playing God?* In this book, Evans argues that a substantive bioethical rationality has been replaced by a formal rationality. By this he means that mainstream American bioethicists are preoccupied with the formal evaluation of the means for efficiently (and ethically) achieving agreed-upon or taken-for-granted objectives, rather than with the more substantive task of debating the value and virtue of both means and ends.[5] It certainly is too often the case that bioethics is a *post hoc* add-on: consultation with a bioethicist generally occurs toward the end of protocol design and development, ensuring the adequacy of consent forms, for instance; and some bioethicists see their job as identifying and minimising negative implications of bioscience research. Even though such an arrangement presupposes and even encourages conflict between scientists and bioethicists, there is no doubt that this is important work. But it certainly does not, nor should it, exhaust what we mean by bioethical assessment of biomedical science and practice. Consider that feminist bioethicists, among others, have a much broader understanding of bioethics: they have long disputed the ends of medicine in particular contexts, and have attempted to focus attention very early on in research planning and organisation.[6]

With the widespread recognition over the past three decades that health is multiply determined and that medicine is presently less efficacious in improving the public's health than a range of alternative (e.g., social or environmental) interventions, one would have expected a broadening of mainstream bioethical attention far beyond medicine, and accordingly a turn toward bioethical treatment of the complexity of health. But, with several notable exceptions, this expectation has not been borne out.[7] In

[5] J. Evans. 2001. *Playing God? Human Genetic Engineering and the Rationalization of Public Bioethical Debate*. Chicago. University of Chicago Press: Chapter 1.

[6] S. Sherwin & the Feminist Health Care Ethics Research Network, eds. 1998. *The Politics of Women's Health: Exploring Agency and Autonomy*. Philadelphia, PA. Temple University Press.

[7] N. Daniels, B. Kennedy & I. Kawachi. 2000. *Is Inequality Bad for Our Health*. Boston, MA. Beacon Press; D. Brock. Broadening the Bioethics Agenda. *Kennedy Inst Ethics J* 2000; 10: 21–38; D. Wikler. Bioethics and Social Responsibility. *Bioethics* 1996; 11: 186–192; D. Callahan. 1999. *False Hopes: Overcoming the Obstacles to a Sustainable, Affordable Medicine*. New Brunswick, NJ. Rutgers University Press; D.E. Beauchamp & B. Steinbock, eds. 1999. *New Ethics for the Public's Health*. New York. Oxford University Press; Sherwin & the Feminist Health Care Ethics

his 1996 presidential address to the International Association of Bioethics, Daniel Wikler traced a rough history of bioethics through three not entirely discrete phases. Phase I involved the generation of professional codes of conduct; Phase II focused largely on physician-patient relationships and advocated on behalf of patients; Phase III dealt mainly with aspects of the healthcare system beyond individual clinical encounters. Both of these latter phases remain with us, occupying centre stage in bioethics. But just off in the wings, almost ready for an entrance, is a fourth phase of bioethics. For Wikler, this fourth phase would focus bioethical attention beyond healthcare and toward public and population health concerns. Phase IV is not yet upon us.[8]

The impending fourth phase of bioethics, according to Wikler, will differ from what has come before in at least five ways.[9] First, high-tech medicine will cease to be the primary focus of ethical concern, and determinants of health will attain pride of place. Secondly, and related to the first change in focus, ethical attention will be paid to health generally and not simply to healthcare; moreover, attention will be paid to population health, and not just the health of individuals. Thirdly, ethicists will come to pay closer attention to the plight of individuals and societies in the 'developing' world, to environmental considerations, and to the international dimension of health inequalities. Fourthly, and related to the third focal change, ethical consideration of the needs of the worst off will prioritise the needs of those in 'developing' countries; and, finally, health ethicists will develop a new 'tool box' beyond the common principles and theories of bioethics to date. New tools, Wikler says, may include a human rights perspective,[10] but also the adoption of concepts and strategies from other disciplines, such as public health, health economics, and ecology. To this, we add the insights of philosophy of science as applied to biomedicine and epidemiology, which, we contend, will help to usher in a bioethics finally adequate to grapple with the complexity of health at the population level, and help mainstream bioethics reclaim a substantive rationality.

Research Network, *op. cit.* note 6; A. Jameton & J. Pierce. Environment and Health: 8. Sustainable Health Care and Emerging Ethical Responsibilities. *CMAJ* 2001; 164: 365–369.

[8] Wikler, *op. cit.* note 7.

[9] Callahan, *op. cit.* note 7.

[10] J. Mann. Human Rights and the New Public Health. *Health and Human Rights* 1995; 1: 229–233.

Mainstream bioethics should, as Weston, Wikler, Dan Brock, and a host of feminist bioethicists[11] have enjoined, broaden its agenda. In this article, through a sustained analysis of the National Institute of Environmental Health Sciences' Environmental Genome Project (EGP), we elucidate several dimensions of a broadened bioethics agenda and an expanded bioethical tool box. We begin with a discussion of the official rationale for the EGP, and then briefly summarise the stock bioethical issues as identified by EGP staff members. After introducing our new tools, we then critically reassess both the justification for and the ethical aspects of the EGP. In so doing, we explore the necessity for bioethicists to assess the conceptual foundations of research programmes (and not just their implications), and also the value of taking bioethics seriously in protocol design (which has the added virtue of potentially minimising conflicts between scientists and ethicists) and in the organisation of research. Such is our attempt to neutralise toxic streams in bioethics.

ENVIRONMENTAL GENOMICS

How can genetics and genomics positively impact the health of populations?[12] The usual answer is: by facilitating the prevention of phenotypic manifestations of diseases with a genetic component. The argument, as we reconstruct its logic, runs as follows: since humans are mutually 'determined' by (at least) the genes and other developmental resources and liabilities we inherit, by the web of social, socio-economic, physical, and political environments in which we find ourselves throughout the lifecycle, by a remarkably plastic neurology, and by our activities and experiences, we might be able to agree that all diseases have some genetic component (which is not to say that all diseases have some genetic basis). Further, if we attend sufficiently to cell-gene-tissue-environment interactions, in developmental context, then we might be able to begin to understand particular pathways of pathophysiology or neuropathology (though we need not have a complete understanding of development in order to have a sense

[11] Weston, *op. cit.* note 1; Wikler, *op. cit.* note 7; Brock, *op. cit.* note 7; Sherwin & the Feminist Health Care Ethics Research Network, *op. cit.* note 6; S. Sherwin. 1992. *No Longer Patient.* Philadelphia, PA. Temple University Press.

[12] By 'genetics and genomics' we mean to capture a wide range of techniques, from classical Mendelian and molecular genetics through newer tools such as genome-wide scans, DNA microarrays, and other techniques employing whole genome sequence data.

of where to intervene in a pathway). Intervening in pathways amounts to preventing phenotypic manifestation; preventing phenotypic manifestation in individuals is the mission of public health, and should also contribute in some way to increasing the health of populations (at least according to some measure of 'population health'[13]).

Prevention in this context could be interpreted in multiple ways: we could prevent particular illnesses by, for instance, preventing the birth of those likeliest to become ill. This sort of primary prevention, dubbed 'genotypic prevention' by Eric Juengst,[14] is generally neither politically nor ethically acceptable. Those enthusiastic about genomics and genetics in the context of public health are quick to distance themselves from the eugenic implications of genotypic prevention. More acceptable ethically are instances of what Juengst has called 'phenotypic prevention', which is 'the prevention of disease and death among people with specific genotypes.'[15] Phenotypic prevention strategies might include: identifying and interrupting causal pathways from genes to illnesses (though we should not underplay the complexity of these pathways – they are rarely linear, for instance); early identification of problematic genes and early interventions to prevent their usual sequelae (as in the case of phenylketonuria, or PKU); and intervening to mediate the complications and most severe outcomes associated with particular diseases that have a genetic component.[16]

Environmental genomics research comprises efforts to disentangle the genetic and environmental contribution(s) to complex diseases, in which multiple factors interact over the life course to produce disease phenotypes, with the aim of generating preventive measures aimed first at (sub)populations and eventually at individuals. Gene-environment interactions are widely believed to be involved in all complex diseases (sometimes a complex disease is simply defined as a disease resulting from gene-environment

[13] M.V. Hayes & J.R. Dunn. 1998. *Population Health in Canada: A Systematic Review. CPRN Study No. H01.* Ottawa. Canadian Policy Research Networks.

[14] E. Juengst. Prevention and the Goals of Genetic Medicine. *Hum Gene Ther* 1995; 6: 1595–1607.

[15] Juengst, *op. cit.* note 14; see also M.J. Khoury, W. Burke & E. Thomson, eds. 2001. Genetics and Public Health in the 21st Century: Using Genetic Information to Improve Health and Prevent Disease. Oxford. Oxford University Press.

[16] M.J. Khoury & the Genetics Working Group. From Genes to Public Health: The Applications of Genetic Technology in Disease Prevention. *Am J Public Health* 1996; 86: 1717–1722.

interactions), such that unpacking such interactions is generally seen as the first order of business in the post-genomic era.

The Environmental Genome Project, initiated in 1997 by the National Institute of Environmental Health Sciences in the United States, is a case in point. The EGP is a second-generation genome project in that it builds on the now available 'reference' human genomes published in 2001.[17] Through a variety of projects, the EGP seeks to meet three objectives: to identify common variants in candidate genes conferring differential susceptibility to environmental toxins; to conduct population-based studies of gene-environment interactions in environmentally induced diseases; and to integrate findings into prevention strategies in public health. Previous research has tended to focus on alleles associated with relatively high penetrance, such as those involved in Tay-Sachs. (Penetrance is the conditional probability of an individual exhibiting a particular phenotype, given a particular genotype, relative to a particular environment and population.[18]) The EGP is innovative in that it intends to study common polymorphisms in alleles associated with low penetrance. This research will have broad applicability, as the specific focus is on common genetic variants (polymorphisms) that exist at a relatively high frequency in the general population; moreover, because the specific alleles are associated with low penetrance, their phenotypic effects are not at all straightforward.

But susceptibility genes are not ideal predictors of phenotypic outcome; unlike single-gene disorders in which the relevant allelic variant is practically sufficient for the production of the phenotype, susceptibility genes for complex diseases predict only an increased risk for a disease, and only under particular circumstances. Nevertheless, the bulk of human diseases are aetiologically complex, and susceptibility genes are deemed by EGP proponents to be an obvious starting point given the wealth of data generated through genome sequencing efforts. EGP scientists have likened

[17] J. Kaiser. Environmental Institute Lays Plans for Gene Hunt. *Science* 1997; 278: 569–570; F.P. Guengerich. The Environmental Genome Project: Functional Analysis of Polymorphisms. *Environ Health Perspect* 1998; 106: 365–368; R.R. Sharp & J.C. Barrett. The Environmental Genome Project and Bioethics. *Kennedy Inst Ethics J* 1999; 9: 175–188; K. Olden & S. Wilson. Environmental Health and Genomics: Visions and Implications. *Nat Rev Genet* 2000; 1: 149–153; K. Olden, J. Guthrie & S. Newton. A Bold New Direction for Environmental Health Research. *Am J Public Health* 2001; 91: 1964–1967; R.R. Sharp. The Evolution of Predictive Genetic Testing: Deciphering Gene-Environment Interactions. *Jurimetrics* 2001; 41: 145–163.

[18] S. Sarkar. 1998. *Genetics and Reductionism.* New York. Cambridge University Press.

the relationship between genes and the environment to 'a loaded gun and its trigger':

> A loaded gun by itself causes no harm; it is only when the trigger is pulled that the potential for harm is released. Genetic susceptibility creates an analogous situation, where the loaded gun is one or a combination of susceptibility genes (alleles) and the trigger is an environmental exposure.[19]

Whether this is a productive way to understand gene-environment relationships, especially in the context of public and population health, will preoccupy us in later sections.

ELSI AND THE EGP

Like the Human Genome Project before it, the Environmental Genome Project sponsors an ELSI programme, funding the exploration of possible social, ethical, and legal implications of environmental genomics research.[20] As noted above, ethicists are accustomed to addressing 'simple' genetic diseases;[21] considerably less attention has been paid to the ethical issues arising in (often population-based) research into complex disease.[22] Aside from the differential power of predictions on the basis of susceptibility genes, there are other important differences between 'simple' and complex diseases. For instance, single-gene disorders are exceedingly rare, whereas complex diseases are common in the population. Moreover, although behavioural and environmental changes can sometimes mitigate the effects of single-gene diseases (as in PKU, in which a diet poor in phenylalanine prevents developmental delay), as noted above it is widely believed that

[19] Olden & Wilson, *op. cit.* note 17.

[20] Sharp & Barrett, *op. cit.* note 17.

[21] Even single-gene disorders (such as PKU) are remarkably complex developmentally; for an especially enlightening discussion, see: C.R. Scriver & P.J. Waters. Monogenic Traits are Not Simple: Lessons from Phenylketonuria. *Trends Genet* 1999; 15: 267–272.

[22] Exceptions include: A. Lippman. Led (Astray) by Genetic Maps: The Cartography of the Human Genome and Health Care. *Soc Sci Med* 1992; 35: 1469–1476; Juengst, *op. cit.* note 14; L.S. Parker. Ethical Concerns in the Research and Treatment of Complex Disease. *Trends Genet* 1995; 11: 520–523; J.S. Robert. Moral Truthfulness in Genetic Counseling. *Business and Professional Ethics J* 1998; 17: 73–93; R. Wachbroit. The Question Not Asked: The Challenge of Pleiotropic Genetic Tests. *Kennedy Inst Ethics J* 1998; 8: 131–144; Sharp & Barrett, *op. cit.* note 17; Sharp, *op. cit.* note 17; D.C. Christiani, R.R. Sharp, G.W. Collman & W.A. Suk. Applying Genomic Technologies in Environmental Health Research: Challenges and Opportunities. *J Occup Environ Med* 2001; 43: 526–533.

preventive measures can allay the development of many if not most complex diseases.

These empirical differences between monogenic and multifactorial diseases manifest in significantly intensified and sometimes novel ethical concerns as we move from individuals to populations in genomics research. To date, the bioethical literature on the EGP has been produced 'in-house', through the NIEHS' intramural research programme; the staff bioethicist was Richard R. Sharp (now at Baylor College School of Medicine) who worked in conjunction with senior NIEHS staff scientists to identify issues of particular initial ELSI research interest. Table 1 contains examples of EGP ELSIs drawn from this literature.

Although the stock EGP ELSIs sketched in Table 1 bear a strong resemblance to those raised in conjunction with the Human Genome Project, both in terms of content and in focusing on potential implications for individuals or groups of individuals, they are not simply 'more of the same' (as is plainly evident in the consideration of genetic privacy and confidentiality). But the issues identified in Table 1, picked out as salient by EGP staff, may not be the most pressing bioethical considerations about environmental genomics research, especially as they fail to engage with the conceptual foundations of such research. This is perhaps to be expected, in that these efforts were undertaken *within* the NIEHS, where critical distance is at a minimum and where the scientific value of the EGP is simply assumed; accordingly, their word should not be the last word on the ethical dimensions of environmental genomics. Let us then introduce some tools to help look more 'upstream' into environmental genomics research – and, more generally, environmental health research as such – and to attend more carefully to the place of bioethics in relation to public and population health.

NEW TOOLS FROM THE PHILOSOPHY OF SCIENCE

To facilitate research within a broadened agenda for bioethics, we suggest that part of ethical inquiry be the critical analysis of the foundational conceptual assumptions of research. Tools for exploring these foundational conceptual assumptions are more at home in philosophy of science than in bioethics, but here we argue that they should emigrate to the tool box of the bioethicist.

Conceptual assumptions are basic philosophical commitments that underlie any empirical investigation; they are the beliefs that shape the questions that are asked, how they are asked, and,

Table 1. Stock Ethical, Legal, and Social Issues related to the Environmental Genome Project, as Identified by NIEHS Intramural Staff and Collaborators[23]

Informed consent	Indeterminate research questions: when DNA samples are initially collected, investigators will be unable to say exactly which genes will be studied, nor will they be able to provide information about the particular diseases that may be associated with the genes examined; the nature of the initial consent to be given by participants is thus ambiguous.
Privacy and confidentiality	Discrimination on the basis of genotype may be less of an issue in the case of genetic variants that are common within the population; the usual focus on the special character of genetic data will be out of place in this research.
Disclosure of results	• The probabilistic nature of the data poses a challenge for the communication of results in ways that avoid the spectre of genetic determinism – and the anxiety such determinism may engender. • Given that the research involves common genetic variants within populations, and given that the research participants will be only a sample of these populations, any findings will have relevance to a large proportion of non-participants; whether (and how) these findings should be disclosed to non-participants is unclear.
Application of findings	Given the lack of straightforward pathways from allele variant to phenotypic outcome, the appropriate translation of this knowledge into therapeutic and preventive measures, in the clinic and/or in public health programmes, may prove to be difficult.
Shifting burdens	Well beyond the usual domain of personal responsibility for health, information generated through environmental genomics may shift the locus of moral responsibility for health outcomes *away from* those individuals, corporations, or other entities producing (and maintaining) environmental hazards *and instead toward* the individual as agent 'choosing' her/his environmental exposures (including workplaces and neighbourhoods).

[23] Sharp & Barrett, *op. cit.* note 17, pp. 175–188; R.R. Sharp & J.C. Barrett. The Environmental Genome Project: Ethical, Legal, Social Implications. *Envrion Health Perspect* 2000; 108: 279–281.

accordingly, how they are answered (as well as what we do with the answers.) Conceptual assumptions are not descriptions of an objective external reality, but are the ontological and epistemological posts to which methodology is tethered. Although rarely explored, the conceptual assumptions to which a research programme adheres affect protocol design, and good protocol design is an ethical issue.

Within public health epidemiology, several critics have drawn attention to some basic assumptions of epidemiological research.[24] Some have argued that epidemiology's conceptual models are deeply problematic (e.g. models of women's health may contribute to gender inequality).[25] More broadly, epidemiology as a discipline has been criticised for its lack of theoretical foundation, affecting the accuracy and implications of theories of disease causality.[26] As a result, there is now a body of critical epidemiology literature (some of which draws on feminist philosophy) illustrating how conceptual assumptions help shape the course of public and population health research (and, subsequently, interventions).[27]

For instance, Nancy Krieger, in her work on the metaphor of the web of causation in epidemiology, identifies *biomedical individualism* (a species of methodological individualism[28] as conjoined with the biomedical model of disease) as a set of assumptions to which most epidemiological investigations conform.[29] The basic tenets of biomedical individualism can be summarised in two

[24] A.V. Diez-Roux. On Genes, Individuals, Society, and Epidemiology. *Am J Epidemiol* 1998; 148: 1027–1032; N. Krieger. Epidemiology and the Web of Causation: Has Anyone Seen the Spider? *Soc Sci Med* 1994; 39: 887–903; D. Savitz. The Alternative to Epidemiologic Theory: Whatever Works. *Epidemiology* 1997; 8: 210–212.

[25] M.C. Inhorn & K.L. Whittle. Feminism Meets the 'New' Epidemiologies: Toward an Appraisal of Antifeminist Biases in Epidemiological Research on Women's Health. *Soc Sci Med* 2001; 53: 553–567.

[26] N. Krieger & S. Zierler. What Explains the Public's Health: A Call for Epidemiological Theory. *Epidemiology* 1996; 7: 107–109; N. Pearce. Traditional Epidemiology, Modern Epidemiology, and Public Health. *Am J Public Health* 1996; 86: 678–683; Diez-Roux, *op. cit.* note 24; Krieger, *op. cit.* note 24.

[27] See, for instance: S. Tesh. 1994. *Hidden Arguments: Political Ideology and Disease Prevention Policy.* New Brunswick, NJ. Rutgers University Press; J.B. McKinlay & L.D. Marceau. To Boldly Go . . . *Am J Public Health* 2000; 90: 25–33; Inhorn & Whittle, *op. cit.* note 25; Krieger & Zierler, *op. cit.* note 26; R. Crawford. You are Dangerous to Your Health: The Ideology and Politics of Victim Blaming. *Int J of Health Serv* 1977; 7: 663–680.

[28] See, e.g.: R. Bhargava. 1992. *Individualism in Social Science: Forms and Limits of a Methodology.* Oxford. Oxford University Press.

[29] Krieger, *op. cit.* note 24, p. 892.

claims: (1) that populations are merely aggregations of individuals; and (2) that the characteristics of individuals are merely the sum of their internal properties. Biomedical individualism implies that the health of populations is best understood by studying the health of individuals, and that individual health is determined by personal characteristics (genes and behaviours, mainly).

To illustrate the bioethical propriety of interrogating conceptual assumptions, we examine in detail the assumptions of biomedical individualism within the EGP, inasmuch as the EGP seeks to understand the incidence of disease arising from exposure to environmental agents in populations by studying the genetic polymorphisms purportedly conveying elevated disease susceptibility in individuals.

1. Populations as aggregations of individuals

While it is acknowledged that not all higher-order variables can be reduced or broken down into their component parts, biomedical individualism states that, in principle, it is possible, and in practice it is preferable, to disaggregate complex wholes. As a variant of reductionism, according to this method individuals are taken to be ontologically prior to populations. The presumption is that it is through the analysis of the individual (and her/his endogenous properties) that we can come to understand the whole. In this view, populations are no more and no less than the aggregation of individuals; the assumption is that nothing is thereby lost – we can understand the whole by examining the parts.[30]

This assumption commits what is in philosophical terms the fallacy of composition. Stated simply, it is a fallacy to believe that the characteristics of the composite are necessarily derivable from its component parts. Populations have structures and comprise relationships involving but not reducible to or deducible from individuals. Conversely, on the basis of population-level data, we

[30] There is a quite sophisticated literature on reductionism and aggregativity in the philosophy of science; unfortunately, this level of sophistication is lacking in standard accounts of biomedical individualism. For a more satisfactory account than we hint at here, see: W.C. Wimsatt. 1986. Forms of Aggregativity. In *Human Nature and Natural Knowledge*. A. Donagan, N. Perovich & M. Wedin, eds. Dordrecht. D. Reidel: 259–293; and W.C. Wimsatt. Aggregativity: Reductive Heuristics for Finding Emergence. *Philos of Science* 1997; 64: supplement. Proceedings of the 1996 Biennial Meetings of the Philosophy of Science Association. Part II: S372–S384.

cannot infer anything about particular individuals. So while individuals are not just parts of populations, neither are populations simply groups of individuals. Ana Diez-Roux notes that 'much of today's epidemiology conceptualizes populations merely as aggregates of individuals (useful from a statistical point of view), rather than as groups of interacting individuals with social relationships and social organizations and with group-level properties that may partly influence risk of disease.'[31]

Geoffrey Rose has famously discussed how this logical error is made by epidemiologists when they conflate the causes of cases with the causes of incidence – the number of new cases in a population at risk over a given period. Rose illustrated how the determinants of disease in individuals are not necessarily those that determine the incidence of disease in populations, and as a result, the investigation of each requires a different research question.[32]

The EGP seeks to understand the incidence of disease in populations by investigating the genetic risk factors for disease in individuals. Thus, the EGP assumes that the study of incidence is reducible to the study of individuals' risk, consistent with the first tenet of biomedical individualism. This fails to heed Rose's warning about the need to distinguish between the causes of cases and the causes of incidence in population-level studies. Consequently, the EGP takes as its starting point the question of why, after exposure to environmental agents, one individual develops disease whereas another individual does not. But this is not the only research question worth asking, especially when one takes a public and population health perspective.

In fact, if the aim is to understand – and eventually lower – the incidence of environmentally induced disease in populations, this is an inappropriate question. To study individual variance in disease outcome, as interesting as it may be, is to study causes of *cases*. But to explain the health of populations, we need to understand the causes of *incidence*, whose aetiology may not necessarily be located within the individual. By identifying the explanatory variables as residing within the individual, biomedical individualism excludes crucial explanatory variables. Epidemiologists' gaze is fixed primarily downstream on the individual case instead of upstream on the causes of incidence in populations.

[31] Diez-Roux, *op. cit.* note 24, p. 128.

[32] G. Rose. Sick Individuals and Sick Populations. *Int J Epidemiol* 2001; 30: 427–432. (Originally published in *Int J Epidemiol* 1985; 14: 32–38.)

2. Individuals as determined by their endogenous properties

In addition to the belief that populations and their characteristics are merely the sum of the characteristics of individuals, biomedical individualism holds that individuals should in turn be viewed as no more than the sum of their internal properties. Put another way, individuals differ because of their endogenous attributes. But such a conceptual framework has difficulty in accounting for how irreducible aspects of the environment affect the health of humans. The political organisation of a society is an important aspect of the social environment within which people act and interact; the persistence of inequality within any society is a property of a population that is not reducible to individual traits. Consider that life expectancy is positively correlated with one's socio-economic status: as one moves up within a socio-economic hierarchy, life expectancy increases – even if one experiences no actual material deprivation at any level in the hierarchy. Though it is obviously true that poor people tend to be less healthy than rich people, it has been shown that there is a gradient even within the middle class, where everyone is quite well-off. The differences in life expectancy are not negligible: in a study of the British civil service – the Whitehall study – the difference between the lowest grade and the highest grade was 4.4 years, or more than the effect of coronary disease on mortality.[33] So where one happens to stand, relative to others, within the socio-economic hierarchy will help to determine one's health status. But it is also the case that the greater the social inequality within a society, the worse the health impact of relative standing in the hierarchy will be. In societies in which there is very little income inequality (such as Sweden), infant health and morbidity even within the poorest classes are lower than within the wealthiest classes in societies with large socio-economic inequalities (such as Great Britain).[34]

Thus, biomedical individualism commits a sort of double reductionism. Reductionism is generally seen as being accompanied by an implied causal order so that the chain of causation runs from the parts to the whole.[35] While perhaps entirely appropriate to understand the aetiology of cancer in an individual at a

[33] See, e.g.: G. Davey Smith, M.J. Shipley & G. Rose. Magnitude and Cause of Socioeconomic Differentials in Mortality: Further Evidence from the Whitehall Study. *J Epidemiol Community Health* 1990; 44: 265–270; Wilkinson, *op. cit.* note 2; Marmot & Wilkinson, *op. cit.* note 2.

[34] See also Daniels et al., *op. cit.* note 7; Brock, *op. cit.* note 7.

[35] S. Rose, R.C. Lewontin & L.J. Kamin. 1984. *Not in Our Genes: Biology, Ideology, and Human Nature*. London. Penguin Books: 5–6.

molecular level, the application of the biomedical model to explain disease outcomes from environmental exposure in populations is, from our perspective, misguided. This is not to say that reductionism is always inappropriate. But reductive strategies should be pursued only to the point at which they continue to yield insight. When more is masked than revealed by a reductionistic approach, a new methodology is required. Moreover, even though there is nothing wrong as such with an examination of the endogenous properties of individuals, it is important to recognise that this strategy, and its validity, are also tied to the nature of the research question and of the answers sought.

The outcome of environmental exposure is influenced by many factors. So why focus on genetic ones? While the genome clearly plays a role in the development of disease in individuals after exposure to environmental agents, and while genetic (among other) variants explain some of the differences in susceptibility between individuals, why does the EGP take these truisms as the starting point for understanding incidence?[36] For as we discussed earlier, genetic and environmental factors, *inter alia*, may indeed be implicated in the development of disease – but the environment is not a property of individuals.

That the genome is identified as 'explanatory bedrock' can be understood as a requirement of biomedical individualism. In their discussion of methodological individualism (of which biomedical individualism is an instance), Roland Chrisjohn and Sherri Young illustrate how the identification and selection of independent and dependent variables in any explanatory scheme is a matter of preference.[37] That is, to support one's choice to include one variable or exclude another, one cannot offer empirical data as decisive evidence. In this case, the evidence can be used as part of a persuasive or logical argument, but a decision cannot be dismissed or supported on purely factual grounds. From the perspective of methodological individualism, the preference for variables located within individuals is obvious. Moreover, as a requirement of the basic conceptual assumptions of

[36] Lisa Gannett argues that the emphasis on genetics in disease aetiology is based not on objective empirical grounds but is the result of pragmatic considerations, such as who is asking the research questions, and the nature of the technological means available to answer them. See: L. Gannett. What's in a Cause? The Pragmatic Dimensions of Genetic Explanations. *Biol Philos* 1999; 14: 349–374. See also: J.S. Robert. 2004. *Embryology, Epigenesis, and Evolution: Taking Development Seriously*. New York. Cambridge University Press.

[37] R. Chrisjohn & S. Young. 1992. *The Circle Game: Shadows and Substance in the Indian Residential School Experience in Canada*. Penticton, BC. Theytus Books: 92–93.

methodological individualism, those variables that cannot be measured or observed as a feature of the individual and their constitutive properties are excluded. That the EGP selects the genome as the variable of interest is not a logical (nor is it a scientific) requirement, but rather a function of the commitment to biomedical individualism.

We are not hereby suggesting that we believe that *social* factors explain variance between individuals; we make no such claim. Poor inferences about relationships between variables can be committed in any direction; drawing conclusions about individuals based on group-level data, or about groups on the basis of individual data, can lead to false conclusions.[38] Rather, we are using the EGP as a case study to explore the impact of biomedical individualism on the focus and direction of research. With the EGP, the other primary etiological factors (toxins and their persistence) are not under investigation because of the adoption of a methodological and conceptual framework that necessitates their being bracketed. What the case of the EGP illustrates is that epidemiologists (and, as we will momentarily show, ethicists) can benefit from critical analysis of fundamental concepts in the development of research programmes and the organisation of research agendas more broadly.

RE-EVALUATING THE EGP

Clarifying conceptual foundations and conceptual assumptions of scientific research is generally a job for the philosopher of science. But insofar as this work facilitates discovery and in-depth analysis of ethical issues that would otherwise go unnoticed, it is indispensable for the bioethicist, too. As indicated above, the Environmental Genome Project includes an ELSI component; this may seem both prescient and pre-emptive. But the issues identified by ELSI (and, in particular, those highlighted by EGP staff, as cited above) are by no means exhaustive. In fact, in adhering to a focus on the consequences of research, while taking the research programme itself for granted as scientifically and ethically acceptable, attention is detracted from larger concerns about environmental, public, and population health. Here we agree with Weston that a narrow focus on the instantiation of individual ethical dilemmas forces other larger, and perhaps

[38] A.V. Diez-Roux. Bringing Context Back into Epidemiology: Variables and Fallacies in Multi-Level Analysis. *Am J Public Health* 1998; 88: 216–222; S. Schwartz. The Fallacy of the Ecological Fallacy: The Potential Misuse of a Concept and the Consequences. *Am J Public Health* 1994; 84: 819–824.

more important, ethical considerations to be ignored. There is a methodological corollary: in the case of the EGP, current scientific investigations have kept larger environmental questions off stage – and this has important implications for health. As Weston urges, 'bioethics too has a responsibility to raise the questions that actually matter to health'[39] – we take this as our starting point for a more revealing evaluation of fundamental conceptual and moral issues in environmental genomics research.

Beyond stock concerns (Table 1) about informed consent, privacy and confidentiality, and stigmatisation – all of which are undoubtedly important – a critical assessment of the conceptual assumptions of environmental genomics research reveals a range of otherwise invisible ethical considerations. Some of these arise, like the stock issues, only as implications of putatively acceptable science. Consider that with the EGP, we witness research involving vulnerable populations (about which there is a quite large literature[40]) but with a novel twist: as this research aims to identify populations at increased risk for environmentally induced diseases, it is research that in some ways *makes* a population vulnerable, rather than research with a population whose vulnerability is pre-existing.[41] The character of this vulnerability, and just how wide its impact will be, is of distinct ethical concern; for it is not only those with genetic susceptibility to environmental toxins who are at risk.

'Not genetically susceptible' does not mean not susceptible – far from it. The environmental agents under investigation have, after all, been previously identified as *toxic*. Through its

[39] Weston, *op. cit.* note 1, p. 113.

[40] Actually, two literatures are relevant here: that on community consent, participation, and engagement (e.g.: E. Juengst. Groups as Gate-Keepers in Genetic Research: Conceptually Confusing, Morally Hazardous, and Practically Useless. *Kennedy Inst Ethics J* 1998; 8: 183–200; C. Weijer. Protecting Communities in Research: Philosophical and Pragmatic Challenges. *Camb Q Healthc Ethics* 1999; 8: 501–513; D.S. Davis. Groups, Communities, and Contested Identities in Genetic Research. *Hastings Cent Rep* 2000; 30: 38–45; E. Juengst. What Community Review Can and Cannot Do. *J Law Med Ethics* 2000; 28: 52–54; C. Weijer & E.J. Emanuel. Protecting Communities in Biomedical Research. *Science* 2000; 289: 1142–1144) and that on human genome diversity and variability research (e.g.: D.B. Resnik. The Human Genome Diversity Project: Ethical Problems and Solutions. *Politics and the Life Sciences* 1999; 18: 15–23; K.K. Kidd & J.R. Kidd. Experience and Preliminary Results in Human Genome Diversity Research. *Politics and the Life Sciences* 1999; 18: 314–316; M. Lock. The HGDP and the Politics of Bioethics. *Politics and the Life Sciences* 1999; 18: 323–325).

[41] E. Juengst. 25 October, 2002. *Science, Ethics, and Public Health.* Presentation in a Session on Environmental Genomics. Baltimore. American Society for Bioethics and Humanities. Baltimore.

commitment to biomedical individualism, the questions the EGP investigates (and answers) fail to address upstream considerations about the production and dissemination of toxic agents into the environment – rather, it takes their persistence as normal. More specifically, the EGP takes exposure for granted; by identifying the genetic make-up of individuals as the explanatory variables for developing disease, larger structural conditions are taken as a given. The EGP assumes that exposure to dangerous and toxic environmental agents is the norm – which it is, for now, under current economic and political conditions both locally and globally. But this state of affairs is not simply a given; the persistence of toxins is optional. The EGP, though, interprets it as a given – environmental genomics aims at investigating the effects of *toxins* on molecular processes; toxins are, by definition, harmful.[42] When ethical evaluation of the EGP is directed entirely downstream, at the stock issues highlighted by NIEHS intramural staff and of mainstream bioethical significance, a toxic environment is simply taken for granted.

A related consequence of the EGP's endorsement of genetic susceptibility as the explanatory bedrock is that it amounts to blaming the victim. Apparently we should believe that it is the result of the individuals' own constitution that they develop disease, not because of their exposure to toxins.[43] Clearly this relates to the shift in the burden of responsibility identified in Table 1 as a central bioethical implication of the EGP; but beyond the shift itself, we should notice which responsibilities are ignored by the EGP's approach to public health. William Ryan, who coined the phrase 'blaming the victim' as an outcome of individualism, gives the example of lead paint poisoning. While he states that it may in fact be a sensible public health campaign to warn parents about the risk of lead poisoning through their children's consumption of lead paint, he also maintains that 'to campaign against lead paint only in these terms is destructive and misleading . . . The presence of the lead is illegal. To use lead paint in a residence is illegal; to permit lead paint to be exposed

[42] We acknowledge that the determination of toxicity itself is complicated, convoluted, and contested terrain. See, e.g.: S.N. Tesh. 2000. *Uncertain Hazards: Environmental Activists and Scientific Proof.* Ithaca, NY. Cornell University Press: 24–39; see also S. Krimsky. 2001. *Hormonal Chaos: The Scientific and Social Origins of the Environmental Endocrine Hypothesis.* Baltimore. The Johns Hopkins University Press.

[43] For related comments about the Human Genome Project, see: Lippman, *op. cit.* note 22; see also L. Gannett. Tractable Genes, Entrenched Social Structures. *Biol Philos* 1997; 12: 403–419.

in a residence is illegal . . . to load a burden of guilt on the mother of a dead or dangerously ill child is an egregious distortion of reality.'[44] Thus, the investigation of an individual's contribution to their health status should not occur at the expense of acknowledging other factors.[45] In the case of the EGP, this means that an individual's risk to disease needs to be understood within the context of the production and diffusion of toxins, where the production and diffusion of toxins is an option, not a given.

Sylvia Tesh has argued that individualism, as the dominant conceptual framework, leads 'most Americans to conceive of disease causality in a way that steers prevention policies away from the most effective actions.'[46] As a biomedically individualistic investigation of disease aetiology, the EGP fails to lead to the development of broad population-based prevention strategies. Investigating the health of populations by studying molecular contributions to risk ensures that the level of intervention will be the individual. Consequently, and ironically, the EGP may lead to some healthier people, but unhealthier populations overall. For instance, if environmental genomics research is successful in identifying genetically vulnerable populations and in generating appropriate prevention strategies tailored to them, we may witness pressure to increase the tolerable level of toxins in the environment – a clear reversal of the trend in environmental health research and policy that may in fact make us all unhealthier in the long term.

Whether to construe allelic polymorphisms or toxic environments as the 'loaded gun' is entirely optional; in either case, exposure is supposed to be the 'trigger'; the EGP takes for granted that the 'gun' is firing automatically – leaving open the question of whether environmental genomics or rather a much more upstream approach is the best way to mitigate its effects. Accordingly, we must consider whether EGP scientists are wise to envision a future in which prevention activities are targeted

[44] Tesh, *op. cit.* note 27, p. 154 citing. W. Ryan. 1976. *Blaming the Victim.* New York. Vintage Books: 23–24. The story of lead illustrates this point further, with industry's resistance and government's reluctance to remove the neurotoxic metal from gasoline, a common mechanism of urban exposure; see D. Davis. 2002. *When Smoke Ran Like Water: Tales of Environmental Deception and the Battle Against Pollution.* New York. Basic Books.

[45] Levins and Lopez maintain that while it is not true *either* that 'we are responsible for our own health' or that 'health is socially determined', it is true *both* that 'we are responsible for our own health' and that 'health is socially determined'; see R. Levins & C. Lopez. Toward an Ecosocial View of Health. *Int J Health Serv* 1999; 29: 261–293, at 270, 281.

[46] Tesh, *op. cit.* note 27, p. 156.

toward susceptible individuals at slightly elevated risk or rather toward whole populations at risk of exposure. EGP scientists and the policy-makers eventually using their data should consider the possibility, noted by Ruth Ottman and also by Patricia Baird, that 'restriction of [preventive] intervention strategies to genetically susceptible persons will, under many plausible conditions . . . result in less disease prevention than would be possible with a strategy aimed at all exposed individuals.'[47] For instance, common toxins might be problematic independently of so-called susceptibility genes and of particular diseases investigated – so subpopulation *x* and Betty and Joe avoid the toxin because of susceptibility concerns, and the aim of prevention, we might think, has been met. But there are plenty of reasons to believe that it won't have been met, because that particular toxin is still out there, it may have numerous effects on so-called non-susceptible populations, possibly over the long term, possibly only during critical periods, and we might not know because of particular research and policy decisions. That would surely be a morally toxic result, especially since it is preventable.

CONCLUSIONS

While it may very well be the case that environmental genomics, and related research in toxicogenomics, will 'revolutionize the practice of public health as it relates to environmental health protection',[48] we are not convinced that this will be either a welcomed revolution or lead to healthy outcomes. Even so, while we suspect that it will not lead to results anticipated (namely, a positive impact on public or population health), the history and philosophy of science advises us that we can never be certain *a priori* what scientific investigation may yield. While the Human Genome Project did not lead to the dramatic consequences envisioned early on, it did however provide some very helpful insights into the limits of genome sequence data in understanding development and aetiology – limits that were, incidentally, anticipated from the outset. But, given the ethical concerns raised by our

[47] R. Ottman. 1995. Gene-Environment Interaction and Public Health. *Am J Hum Genet* 1995; 56: 821–823, at 822. See also: P.A. Baird. 1994. The Role of Genetics in Population Health. Why are Some People Healthy and Others Not? In *The Determinants of Health of Populations*. R.G. Evans, M.L. Barer & T.R. Marmor, eds. New York. Aldine de Gruyter: 133–159; and P.A. Baird. Identification of Genetic Susceptibility to Common Diseases: The Case for Regulation. *Perspect Biol Med* 2002; 45: 516–528.

[48] Olden, Guthrie & Newton, *op. cit.* note 17, p. 1966.

analysis, we do object to the promotion of environmental genomics as beneficial to the public's health. Despite the hype and hoopla of genomics research in general, it is eminently unclear how the objectives and methodology of the EGP can lead to prevention of disease in any but a superficial and limited way. We are thus calling for mainstream bioethics to take seriously the task of worrying the conceptual foundations and assumptions of public, population, and environmental health research, in addition to the usual tasks of assessing implications and minimising harmful outcomes of biomedical research more generally.

The EGP assumes that the exposure of individuals and populations to environmental agents is normal, perhaps even unavoidable. Accordingly, focusing on differential genetic susceptibility detracts attention and resources away from looking upstream. Thus the EGP may be construed as population-based research, but lead to interventions incompatible with the population and public health goal of disease prevention.

Mainstream bioethics has ignored this altogether. The focus on research implementation and implications (formal rationality) and the correlative failure – as Wittgenstein said – to 'put the question marks deep enough down',[49] has failed to call into question the assumptions inherent in the EGP. This may in part be the result of the ethical commentaries on the EGP having been produced in-house by the National Institute of Environmental Health Sciences. But bioethicists cannot be complacent about this lack of critical distance, and cannot assume that all of the ethical issues have been identified through this process. In particular, the assumption that the EGP is sound epidemiologic science has resulted in a failure to consider the potential implications of the EGP for human health.

If mainstream bioethics is to enter Wikler's Phase IV, and so be relevant to public and population health, it is necessary to attend to relevant conceptual issues in which the research is grounded and to attend early on to the organisation of the research agenda and the design of research protocols. Feminist bioethicists have learned this lesson well. Public and population health ethicists must learn it, too, and endeavour to determine whether proposed and ongoing research is indeed in the interest of population health. This includes making explicit the logic and hypothetical benefit of any particular scientific investigation.

The best way to do this is not, as we have, retrospectively, but rather prospectively, in conjunction with the scientists designing

[49] L. Wittgenstein. 1980. *Culture and Value*. Oxford. Basil Blackwell: 62.

the protocols and with the agencies defining the research agenda. Bioethicists equipped with critical conceptual tools from philosophy of science – and from ecology, human rights, health economics and more – must engage scientists, funders, and policy-makers at the earliest stages of the research process. Such a collaborative arrangement will not only prevent noxious disputes between scientists and ethicists at the research implementation stage, but will also help bioethics reclaim a sorely needed substantive rationality. In the particular case of population-based research on the determinants of environmentally induced disease, this approach will afford a much-improved opportunity to look upstream and possibly stem the toxic effluent.

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