

PERSPECTIVES

Transgenerational epigenetics and environmental justice

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Abstract

Human transmission to offspring and future generations of acquired epigenetic modifications has not been definitively established, although there are several environmental exposures with suggestive evidence. This article uses three examples of hazardous substances with greater exposures in vulnerable populations: pesticides, lead, and diesel exhaust. It then considers whether, if there were scientific evidence of transgenerational epigenetic inheritance, there would be greater attention given to concerns about environmental justice in environmental laws, regulations, and policies at all levels of government. To provide a broader perspective on environmental justice the article discusses two of the most commonly cited approaches to environmental justice. John Rawls's theory of justice as fairness, a form of egalitarianism, is frequently invoked for the principle that differential treatment of individuals is justified only if actions are designed to benefit those with the greatest need. Another theory, the capabilities approach of Amartya Sen and Martha Nussbaum, focuses on whether essential capabilities of society, such as life and health, are made available to all individuals. In applying principles of environmental justice the article considers whether there is a heightened societal obligation to protect the most vulnerable individuals from hazardous exposures that could adversely affect their offspring through epigenetic mechanisms. It concludes that unless there were compelling evidence of transgenerational epigenetic harms, it is unlikely that there would be a significant impetus to adopt new policies to prevent epigenetic harms by invoking principles of environmental justice.

Key words: transgenerational epigenetics; epigenetics; environmental justice; hazardous exposures; distributive justice

Introduction

Foundational research on transgenerational epigenetics is exploring a wide range of exposures, modes of action, and effects in various species. Thus far, no exposures have been widely accepted to cause transgenerational epigenetic effects in

humans. Nonetheless, because single generational (F0 in females and males) and multigenerational (F1 and F2 in females; F1 in males) epigenetic effects already have been observed in humans and the same exposures are known to cause transgenerational (F3 in females; F2 in males) epigenetic effects in other species, in the future, it is possible that some

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exposures will be determined to cause transgenerational effects in humans. This article begins by describing the scientific basis of transgenerational epigenetic inheritance and then discusses three important exposures with known epigenetic effects in animals and suspected in humans that may have transgenerational effects: pesticides, lead, and diesel exhaust.

Several key ethical and societal issues raised by epigenetics have been noted in the literature, including environmental justice, privacy and confidentiality, equitable access to health care, intergenerational equity, and eugenics [1]. This article focuses on the environmental justice issues raised by transgenerational epigenetics. After explaining the principles of distributive justice and environmental justice, it applies these principles to transgenerational environmental epigenetics. The article concludes that even though distributive justice requires heightened protection for vulnerable individuals exposed to transgenerational risks, additional scientific evidence would be required to promote the adoption of more protective environmental policies.

Transgenerational Effects

Transgenerational epigenetic effects are those that manifest in the first unexposed generation. Thus, a gestating female would be the F0 generation, a developing embryo or fetus would be the F1 generation, and offspring born after in utero germline exposure would be the F2 generation. The first unexposed generation following exposure in the maternal line would be the F3 generation [2]. In males, the exposed individual would be the F0 generation and the offspring born after germline exposure would be the F1 generation. The first unexposed generation following exposure in the paternal line would be the F2 generation [2].

Multiple methods of transgenerational epigenetic inheritance have been proposed, including DNA methylation, histone and chromatin changes, RNA differences, and prions [3]. The most discussed and studied method of epigenetic inheritance is DNA methylation, the process by which methyl molecules bind to DNA and hinder access to that DNA for transcription. There are two points in development in which DNA undergoes demethylation, once immediately following fertilization and once "during primordial germ cell development in the fetal gonads" [4]. Certain changes may escape this demethylation process, however, allowing for inheritance of those epigenetic changes.

Epigenetic inheritance of histone and chromatin remodeling is thought to use similar mechanisms, mainly that restructuring or acetylation of histones changes access to DNA for transcription [5]. Epigenetic inheritance via non-coding RNAs is postulated to happen through a more removed mechanism, either directly at epigenetic levels by affecting epigenetic modifications of the genome or controlling the expression of epigenetic modulators and thus indirectly inducing epigenetic changes [4].

Background Data

Studies in roundworms have demonstrated transgenerational inheritance for more than 20 generations, and other studies have demonstrated transgenerational epigenetic inheritance in plants, fruit flies, and rodents [5]. Numerous compounds have been associated with inherited epigenetic changes. For example, BPA and phthalates have been linked with obesity, ovarian disease, and testis disease, among others, in animals; such phenotypic abnormalities were associated with altered methylation

patterns [6]. Similarly, nicotine exposure of pregnant F0 rats led to physiological and molecular evidence of epigenetic inheritance of asthma in the F3 generation [7], and jet fuel exposure in F0 rats led to increased incidence of ovarian disease and obesity as well as different DNA methylation patterns in the exposed lineage [8]. DDT exposure may contribute to transgenerational epigenetic inheritance of obesity and related diseases, including diseases of the testes, polycystic ovarian syndrome, and kidney disease [9].

The study of transgenerational effects in humans is extremely challenging. First, it is ethically impossible to use multigenerational experimental designs in humans and therefore transgenerational research in humans is based exclusively on epidemiology. Second, the life cycle of humans is much longer than other species commonly studied, such as fish and rodents. Third, in evaluating long-term exposures of humans, it is difficult to control for possible confounding factors.

Despite these challenges, the lifelong or multigenerational effects of extreme nutritional deficits have been postulated by foundational epigenetic epidemiology studies, including the Overkalix cohort in Northern Sweden [10] and the Dutch Famine cohort study [11]. Paternal [12–14] and maternal [15–17] smoking also have been investigated as a source of transgenerational harms. Other exposures linked with possible heritable epigenetic changes in humans include paternal betel nut chewing [16], arsenic and lead exposure [12], radiation exposure [18], exposure to BPA and phthalates [19, 20], and certain reproductive treatments [21, 22].

When coupled with the animal data of transgenerational epigenetic inheritance, the knowledge of epigenetic effects on humans of certain compounds and experiences suggests the possibility of transgenerational inheritance of epigenetic changes in humans. In the sections that follow, we discuss in more detail the possible transgenerational epigenetic effects caused by exposure to pesticides, lead, and diesel exhaust fumes. These three examples were selected because they: (1) represent major and well-established environmental public health problems; (2) involve a known environmental justice element due to disparate exposures to a vulnerable population; (3) have at least suggestive evidence of a transgenerational epigenetic effects; and (4) represent diverse exposure and responsibility profiles. Pesticides are commercial products that are deliberately sprayed primarily in or near agricultural communities, lead is a toxic metal whose current exposures primarily affect children and result from historical environmental contamination, and diesel exhaust is an ambient population exposure resulting from an important sector of society (transportation).

Pesticides

The term pesticide is being used generally to encompass chemicals used to minimize harm from insects, weeds, fungi, or other living things that may cause injury to plants or homes. Hence, pesticides can be used in homes, on farms, in playgrounds, in schools and other buildings, or anywhere where insects or other pests may reside. Within the past 10 years, data show that over 1 billion pounds of pesticides are used yearly in the United States and approximately 5.6 billion pounds are used worldwide [23].

Vinclozolin, a pesticide used on many fruits and vegetables in the recent past, has been found to be an endocrine disruptor and has been linked to epigenetic changes in animals [24]. In California, vinclozolin use has been declining – from 54719 pounds in 1998 to 512 pounds in 2008 [25]. Nevertheless, many

pesticides no longer in use are found in the environment years later because of innate resistance to degradation. In addition, vinclozolin has been studied in great depth; it is logical to conclude that other pesticides may have similar biological effects and vinclozolin can therefore serve as a useful case study.

There are significant data linking vinclozolin to transgenerational epigenetic inheritance of numerous abnormalities in several different organs. Most of these data come from studies of rats or mice. In several studies, pregnant rats or mice were exposed to vinclozolin and either F3 or F4 generation animals were studied for effects. These later generation animals were found to have higher rates of abnormalities of the testes, prostate, and kidneys [24]. Other studies similarly found F4 generations had developed prostate disease, kidney disease, immune system abnormalities, breast tumor development, hypercholesterolemia, and in F1–F4 generation rats, premature aging [26]. Another study found abnormalities through the F4 generation in sperm motility, count, and apoptosis [5].

Some of the studies compared the epigenetic makeup between the offspring of vinclozolin-exposed and control animals. One study found alterations of DNA methylation in the F3 generation sperm [24], and another found RNA in F3 vinclozolin-exposed rats was different when compared to F3 control rats [27]. Another study found an overlap between DNA methylation regions and relevant epigenetic control regions [28]. In fact, somatic transcriptomes from several different organs in F3 generation vinclozolin-lineage rats were altered in line with expected inheritance of the germline epigenome [29]. In other words, transgenerational epigenetic inheritance in animals of vinclozolin-induced changes is supported by both phenotypic and molecular data.

Numerous health consequences in humans have been associated with long-term pesticide exposure. (Acute toxicity is also associated with numerous health consequences, but this article focuses more on long-term exposure and transgenerational inheritance.) Prenatal and infant exposure to pesticides has been linked to higher rates of impaired cognitive development [30], reduced birth weights [31], and higher rates of cancer [32]. In addition, adult exposure to pesticides is associated with prostate cancer and lung cancer [33]. Neuro-degenerative diseases, such as Parkinson's disease and Alzheimer's disease, also seem to be associated with pesticide exposure, as are asthma, autoimmune diseases, reproductive issues, and type 2 diabetes [33]. These health consequences of pesticide exposure may be mediated by epigenetic mechanisms. For instance, studies have found an association between persistent organic pollutants, including some pesticides, and changes in DNA methylation [34, 35]. Another study determined that exposure to three different pesticides (fonofos, parathion, and terbufos) led to DNA methylation changes, and many of those changes were near genes associated with cancer [36]. Given the evidence of transgenerational inheritance of vinclozolin-mediated epigenetic changes in animals, it is plausible that similar transgenerational impacts may be seen in humans. Though pesticide exposure is nearly ubiquitous, certain human populations are at risk of greater exposure or greater health risks from exposure.

Fetuses can be exposed to pesticides that cross the placental barrier, and infants can be exposed via breast milk [37]. Children, especially toddlers, have multiple routes of exposure to pesticides, including via food consumption, playtime on the ground, and frequent placement of objects in their mouths [38]. Because fetuses, infants, and young children may have similar or even higher levels of exposure to pesticides than adults, their smaller body size, developing organs, and lower levels of

detoxifying enzymes suggest that the impact of a similar dose of pesticides may result in more significant health effects than in adults [38].

Those mixing pesticides and those who work in greenhouses have significant exposure to pesticides [39]. Even farmworkers who do not spray pesticides have higher levels of pesticide markers in their bodies, including detectable levels of pesticides no longer in use [40]. In fact, the NIH has funded a study through 2018 of Latino immigrant farmworkers with direct and frequent exposure to pesticides to determine the effect of that exposure on the epigenetic makeup of sperm [41].

Those living in agricultural areas have higher rates of exposure to pesticides; family members may be particularly susceptible because pesticide residue may be brought into the home on clothing worn to work [42]. Dietary patterns are shaped by culture, race, and socioeconomic status; such differences have been documented with fish consumption with regards to mercury exposure [43]. Similarly, pesticides may accumulate in some animal products disproportionately consumed by certain populations [44].

Lead

Lead exposure is an environmental problem that has long been associated with environmental justice concerns, and which may also exhibit epigenetic activity. Lead is a well-known neurological toxin, especially in the developing brains of children, and thus can cause developmental problems in exposed juveniles. Lead exposures are associated with neurological impacts in children, including reductions in IQ test scores, lower performance on standardized testing, and decreased graduation rates [45]. These cognitive effects occur at even low levels of lead exposure [46]. Lead also causes elevated blood pressure, increased attention-deficit behavior, memory loss, and behavioral problems [47].

Traditional exposures to lead have historically been disproportionately concentrated in low income and minority communities [48]. For example, the largest exposure pathway for lead is through children's contact with lead paint [49], mainly found now in older homes, including inner city housing units occupied overwhelmingly by low-income and minority residents. Another primary exposure pathway was from emissions of vehicles operating on leaded gasoline. Again, inner city and other lower income housing was often located close to roads that produced high lead exposures, and even though leaded gasoline was phased out in 1995, soils in such areas still contain elevated lead levels to which children in poor neighborhoods are exposed.

Hazardous waste sites may produce lead exposures to nearby residents, especially in lower-income countries [50]. The recent events in Flint, Michigan, demonstrate the vulnerability of low-income and minority families to lead toxicity [51]. A decision by the local government to switch to a cheaper water source resulted in high lead exposures to households in Flint that had lead water pipes, which were most common in poor and minority homes [52]. In addition to the disparate physical impacts on low income and minority homes [53], the Flint crisis was also worsened by procedural environmental justice concerns, because the interests and voices of those disadvantaged populations were not given the same consideration and weight that a more affluent population likely would have received [52].

The disparate developmental impact of lead exposures tends to be self-perpetuating across generations. Children exposed to significant lead during their early years and

adolescence tend to have diminished IQs, high blood pressure, and more behavioral and conduct problems when they grow up to become adults [47]. For example, recent studies suggest an association between childhood lead exposures and subsequent criminal arrests in adulthood [54]. These lasting effects of lead exposure might impede the economic success of exposed persons, leading them to live and raise their own children in the same impoverished neighborhoods, with the residual effects of the parental lead exposures reinforcing the detrimental impacts of new exposures by the next generation of children. Of course, this "doubling down" effect raises methodological challenges, because it is hard to distinguish the effects of direct lead exposures to children from the transgenerational detrimental social effects (e.g. higher crime, poor education performance) resulting from environmental exposures of their parents and grandparents.

The combined effects of disproportionate lead exposures and multi-generational impacts put children in disadvantaged communities at risk of a cycle of disadvantage and impairment. This environmental justice problem is potentially intensified by evidence suggesting that lead has epigenetic effects as well. Recent data from animal and human studies suggest that long-term adverse neurologic effects in aging adults exposed to lead as children may be mediated through epigenetic mechanisms [55, 56]. At least one study has suggested a multigenerational impact in humans, in which a mother's blood lead levels affect methylation patterns in the grandchildren [57]. Although the evidence is only suggestive to date that these lead-induced epigenetic effects are transgenerational, these effects interact in a cumulative or possibly even synergistic way with the ongoing lead exposures to stack the deck even more unfairly against disadvantaged children disproportionately exposed to lead.

Diesel Exhaust

Diesel exhaust includes a mixture of harmful toxicants, such as fine particulates, polycyclic aromatic hydrocarbons, and volatile organic compounds. A variety of studies have demonstrated that residents living near roads with significant traffic have a variety of health risks suspected to be attributed to diesel exhaust, but also potentially associated with noise and other air pollutants [58]. Up to 90 percent of particulate matter produced by traffic sources are attributed to diesel exhaust, and these particulates are primarily in the ultrafine size range (<100 nm) that can be deeply deposited in the respiratory passage and lungs [59]. Health effects that have been attributed to diesel exhaust include oxidative stress and airway hyper-responsiveness, which enhance allergenic and asthma responses [60]. In addition, diesel exhaust has been associated with cardiovascular and cancer risks [61].

Diesel exhaust presents another potential association between toxic exposures, epigenetic effects, and environmental justice. Residential areas bordering the most heavily traveled roads, especially those with heavy duty trucks that emit the highest levels of diesel exhaust, tend to be in low-income and racial minority communities [62]. For example, the trucking routes coming in and out of major ports, such as Los Angeles, are highly concentrated with disadvantaged populations that receive disproportionately high exposures to diesel exhaust [63].

A growing body of data suggests that diesel exhaust may also have epigenetic effects by altering DNA methylation patterns [59, 64]. Most of the studies have been done in animal models, but there are some human studies showing similar

effects [59, 64]. These methylation alterations have been associated with asthma and other adverse effects in humans [65, 66], although the dose, mechanism, and interactions involved with such responses need further study [59]. While most of the studies to date have focused on the exposed generation, one animal study has found persistent sperm hypo-methylation in mice, suggesting the possibility of an intergenerational effect [67]. Another published abstract reported F2 and F3 generations of mice had increased susceptibility to asthma from diesel exhaust exposure of the F0 generation, which was mediated through an epigenetic mechanism [68].

Environmental Justice

The preceding section of this article provides an overview of the scientific literature on transgenerational epigenetic effects in humans and other species, as well as examples of the epigenetic consequences of some specific environmental exposures. These findings indicate a significant environmental justice problem that could be exacerbated by epigenetic mechanisms. Many harmful environmental exposures occur with greater frequency or concentrations in locations where vulnerable individuals are exposed. Furthermore, it is well-known that disadvantaged populations with poor nutrition, substandard or nonexistent healthcare, stress from factors such as housing instability and fear of violence, and high-risk lifestyle factors increase susceptibility to environmental exposures [69]. Epigenetic effects may result from the synergistic action of environmental and social stressors to further enhance the risk to future generations in such impoverished communities, and may help explain why these populations suffer from increased health risks [70]. One final dimension of the issue that should be noted is that unlike genetic mutations, epigenetic marks are often quite unstable [2], and their effects may be reversible with dietary supplements or other interventions [71].

This section explores the philosophical foundations that support the concept of environmental justice in the context of epigenetic risks. According to the Environmental Protection Agency (EPA), "environmental justice is the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies" [72]. The "fair treatment" of individuals means that the burdens of environmental policies should not be borne disproportionately by individuals based on the four listed criteria. "Meaningful involvement" refers to the opportunity of individuals to participate in and contribute to the regulatory process and to have their concerns addressed by decision makers.

The environmental justice movement began in the 1970s and 1980s with civic activism, protests, and litigation [73]. The federal government's commitment to environmental justice dates back at least to 1993, when the EPA established the National Environmental Justice Advisory Council to provide independent advice and recommendations to the Administrator of the EPA [74]. In 1994, President Clinton signed an Executive Order directing all appropriate federal agencies to strive for environmental justice [75]. Significantly, the civil rights and regulatory aspects of this formulation of environmental justice are related to economics, human rights, social equality, and public health [76]. At its core, environmental justice is a movement to aid the vulnerable and disempowered facing environmental exposures that represent serious,

disproportionate, and unfair threats to their health and well being [77].

The EPA definition is valuable to consider, but it is a political definition to guide regulatory and civil rights action rather than a foundational definition on which to construct a more detailed moral framework. To understand the broader issues of environmental justice it is necessary to consider the moral theories from which the environmental justice concept emerged.

Justice is concerned with fairness in both means and ends, a point illustrated by legal conceptions of justice. As to "means," justice requires that the process for drawing distinctions among individuals, allocating societal goods, or imposing legal penalties or conditions is fair and equitable. In Anglo-American law, the principle of "due process" can be traced to the Magna Carta of 1215, which, among other things, limited the power of the king to act unless authorized by law [78]. In the United States, the term due process was used by colonial legislatures even before the United States Constitution was drafted in 1787, although today "procedural due process" generally refers to constitutionally-mandated procedures of both the criminal and civil law that must be met before the government may deprive an individual of life, liberty, or property [79]. The right to notice, the right to be present in court, the right to counsel, the right to call witnesses, the right to an impartial decision maker, and similar protections are within the ambit of the contemporary legal concept of procedural due process [79].

Fair means or procedures are necessary but insufficient conditions of justice because justice is also concerned with ends. The gap between facially neutral means and disparate ends or outcomes has animated a contentious and ongoing political debate about what compensatory or restorative measures are appropriate to reduce the disparity in conditions of individuals or groups, especially when the disparity can be traced to past unequal societal treatment based on race, ethnicity, income, or similar characteristics [80]. In the environmental context, current procedural fairness often fails to cure historically based and persisting unequal distribution of societal benefits and burdens, such as the results of inequitable exposure to toxicants, discriminatory zoning, or segregated housing [81]. Thus, the question is raised as to what, if anything, ought to be done to improve the health of everyone, including those with significant and disproportionate environmental exposures.

Principles of distributive justice are used to analyse whether the allocation of societal benefits and burdens are fair, equitable, and appropriate [82]. Although there is widespread recognition of the value of distributive justice analysis in the abstract, there are many different theories of distributive justice. According to Tom Beauchamp and James Childress there are four traditional and two newer theories of justice. The traditional theories are utilitarianism, libertarianism, egalitarianism, and communitarianism. The newer theories are the capabilities and well-being approaches [82, p.253]. If Amartya Sen is correct, that "every summary is ultimately an act of barbarism" [83], then the summaries that follow are surely barbaric. Nevertheless, with this note of caution, it may be valuable to follow these brief summaries with a more detailed discussion of the two theories commonly cited in the literature on environmental justice, egalitarian and capabilities.

John Rawls' theory of justice as fairness is a form of social contract egalitarianism. (Table 1) Rawls built on the premise of an ideal "original position" for the basic structure of society, which consists of the principles that free and rational persons would select if they chose under a "veil of ignorance," without knowledge of their social position or personal attributes. Based

on this key assumption, Rawls advanced two principles of justice. First, each person has an equal right to basic liberties compatible with liberties for all. Second, social and economic inequalities are acceptable only if two conditions are met: there must be fair equality of opportunity in life options and any differential treatment is acceptable only if it benefits the least advantaged members of society [84]. Rawls' second principle thus consists of two underlying elements, the "fair equality of opportunity principle" and the "difference principle." These apply, however, only if the first principle is satisfied.

The difference principle is especially relevant to environmental justice. According to Rawls, the difference principle is related to the principle of redress. Society must give more attention to those "with fewer native assets and to those born into less favorable social positions" to redress the bias of contingencies and move in the direction of equality [85]. Rawls did not further describe what innate limitations or acquired deprivations qualify one for favorable treatment or what that would entail. Rawls also did not specifically address the issue of health, although some followers of Rawls, including Norman Daniels, have done so [86]. Therefore, it is not clear what redress associated with environmental injustice follows from this formulation. Nevertheless, Rawls is often invoked for the broader principle that any public and private actions involving differential treatment, including health, should be designed to benefit those with the greatest need.

Rawls did not believe in absolute equality, only of the need to redress differences borne of social disadvantage. Viewed in this light, epigenetics plays a unique role because it is situated at the confluence of natural endowments and socially produced differences. Thus, it poses the question of whether multigenerational or transgenerational epigenetic inheritance, where an individual's natural endowment is caused by parental or even more remote ancestral exposures, is subject to Rawls' difference principle. On a more fundamental level, epigenetic discoveries require adherents of Rawlsian notions of equality of opportunity to choose between broader and more restrictive versions of egalitarian ethics [87].

Sen was a colleague and great admirer of Rawls, but his capabilities approach to distributive justice differs from Rawls' justice as fairness approach. The capabilities approach assesses individuals' quality of life according to the capabilities individuals have to do the things they value. In Sen's construct, a capability is the freedom and ability to achieve valuable "functionings," which may be broad or specific and vary with the individual. Although Sen has not provided a list of capabilities, another well-known advocate of the capabilities approach, Martha Nussbaum, has created a non-exclusive list of ten "central human capabilities": (1) life (the ability to live a normal lifespan in a manner worth living); (2) bodily health (good health, nutrition and shelter); (3) bodily integrity (ability to move freely secure against violence); (4) senses, imagination and thought (ability to obtain an education and have freedom of expression); (5) emotions (ability to have emotional attachments to people and things without fear); (6) practical reasoning (ability to critically reflect on planning one's life); (7) affiliation (ability to live meaningfully in company with others); (8) other species (ability to live with concern for animals, plants, and nature); (9) play (ability to enjoy recreational activities); and (10) control over one's environment (ability to actively participate in choices about one's life and property) [88].

The capabilities approach has been adopted as a measure of political and economic development. Among its supporters, the capabilities approach is valuable because it can be used to evaluate existing policies or conditions as well as proposals for

Table 1: theories of justice

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| <i>Utilitarian</i> –To each person according to rules and actions that maximize social utility. |
| <i>Libertarian</i> –To each person a maximum of liberty and property resulting from the exercise of liberty rights and participation in fair free-market exchanges. |
| <i>Communitarian</i> –To each person according to principles of fair distribution derived from conceptions of the good developed in moral communities. |
| <i>Egalitarian</i> –To each person an equal measure of liberty and access to the goods in life that every rational person values. |
| <i>Capabilities</i> –To each person the means necessary for the exercise of capabilities essential for a flourishing life. |
| <i>Well-being</i> –To each person the means for the realization of core dimensions of well-being. |

Source: Beauchamp TL, Childress JF. Principles of Biomedical Ethics, 7th ed. New York: Oxford University Press 2013, pp. 252–3.

change [89]. In effect, the capabilities approach helps to create a blueprint for setting goals, benchmarks, and metrics to address deficiencies or unfair inequalities in living conditions, including environmental conditions. A key element in applying the capabilities approach is public deliberation, which relates to the procedural fairness element of distributive justice. The capabilities approach also takes account of the heterogeneity of modern societies by considering the distinctive social conditions that affect individual capabilities.

As mentioned, the capabilities approach has been used to support economic development, but economic development also may result in conditions that give rise to concerns about environmental justice. For example, the three exposures discussed in this article as likely to cause epigenetic effects in humans – pesticides (vinclozolin), heavy metals (lead), and diesel exhaust – all may be seen as byproducts of economic development. They also involve exposures of vulnerable populations, such as migrant farmworkers and low-income residents of polluted neighborhoods. It is not clear how traditional theories of distributive justice would regard these tradeoffs on either the societal or individual level.

The Rawlsian and capabilities approaches are not the only ways of analysing the issue of distributive justice, but they figure prominently in the literature of environmental justice. Therefore, they are logical foci for analysing the potential role of transgenerational epigenetics in new conceptions of environmental justice.

Besides the literature on theories of justice, there is a separate literature specifically devoted to environmental justice that, among other things, addresses the issue of tradeoffs. According to Robert Bullard: "Poor people and poor communities are given a false choice of 'no jobs and no development' versus 'risky low-paying jobs and pollution'" [90]. The same issue, often presented in even starker terms, is faced by individuals and government officials in the developing world [77].

Whereas traditional theories of justice often speak in terms of avoiding harm, environmental justice, an analytical approach often linked to science, tends to speak in terms of risk. Here, participatory justice and recognition of community vulnerabilities are important in determining risk acceptability. Recent conceptions of environmental justice are expanding to include more diverse environmental and social conditions [91].

Applications

Transgenerational epigenetic effects raise profound ethical issues potentially affecting both existing and future generations. The applied ethics discussion that follows is based on three key points made in earlier sections of this article: (1) human exposures to conditions that cause or might cause transgenerational epigenetic effects are not distributed evenly

throughout the environment or population; (2) levels of human exposures are associated with, among other things, substandard living conditions, toxic pollutants, and hazardous occupational exposures; and (3) the most highly exposed individuals also are more likely to have preexisting health problems, poor nutrition, and inadequate health care.

The following three questions present an opportunity to apply ethical principles of environmental justice to transgenerational epigenetics: (1) Is there a heightened societal obligation to protect the most vulnerable individuals from hazardous environmental exposures and, if so, what is the nature of the obligation? (2) Is the societal obligation further heightened if there are known or suspected transgenerational epigenetic effects? (3) How, if at all, do notions of personal responsibility affect societal obligations?

Is There a Heightened Societal Obligation to Protect the Most Vulnerable Individuals from Hazardous Environmental Exposures?

The answer to this first question depends on answers to these related questions: (1) Does society have an obligation to protect vulnerable individuals? (2) Assuming the answer is yes, who should be deemed vulnerable? (3) How should vulnerable individuals be protected?

Because of their inability to survive on their own, humans always have regarded babies and children as needing and deserving special care [92], a view that now also generally applies to old people [93] and those with disabilities [94]. Beyond the young, old, and disabled, who else qualifies as "vulnerable" and does being vulnerable mean that an individual is among the "least advantaged members of society" that Rawls would say should be the beneficiaries of the "difference principle"? In the context of environmental justice, although some individuals with higher incomes are exposed to environmental toxicants [95], individuals considered vulnerable are those who have a low income, have been subject to discrimination, have limited political power, have ongoing health problems, or have lacked continuous and quality health care. To restate the question in terms of the capabilities approach, should vulnerability be defined as the lack of essential "capabilities" [96]? If vulnerable individuals are beneficiaries of additional societal consideration, it is important to develop logical and defensible criteria for determining who qualifies for these benefits.

Assuming there is a duty to protect vulnerable individuals and that individuals and groups disproportionately exposed to substances and conditions causing epigenetic-based harms are vulnerable, the next question is what specific duties are owed to these individuals. Is there a duty to prevent any or further exposure and, if so, how? Would it require lowering exposures; moving vulnerable individuals to healthier locations; or

supplying them with medical supplies, air filters, bottled water, or personal protective equipment? In some occupational and environmental settings, there may be a considerable difference in burden and effectiveness of measures that control exposure at the source versus measures that attempt to mitigate exposures downstream.

When vulnerable individuals are exposed to hazardous environmental conditions the issue of equitable access to health care is inevitably raised. It is easy to make a moral argument that these individuals are entitled to health care. It is more difficult to argue that in a society that currently does not provide health care access to all, or even all vulnerable individuals, that a subgroup defined by the nature of their harmful exposures ought to be given preference. For example, it is hard to argue that an adult with a respiratory problem caused by exposure to pollutants is more deserving of health care than a child with asthma who was not exposed to pollutants. Thus, distributive justice issues may require additional careful analysis when it adds the health care setting to exposures, modes of biological response, and variation in effects or future risk [97].

In theory, a powerful case can be made that there is a heightened societal obligation to protect all vulnerable individuals from hazardous environmental exposures. In reality, mere vulnerability is unlikely to be considered sufficient to trigger Rawls' notion of an obligation for redress. Many of the people who are considered vulnerable because of environmental exposures are also vulnerable because of their unsafe neighborhoods, lack of access to health care, lower quality educational and other social services, or otherwise lack "central human capabilities" on Nussbaum's list. Rather than receiving extra consideration and benefit from society the most vulnerable individuals often get significantly fewer societal goods in a self-perpetuating cycle of deprivation. In light of this reality, are there types of exposures, such as those linked to transgenerational epigenetic harms, which might cause a change in societal obligations or conduct?

Is the Societal Obligation Heightened If There Are Known or Suspected Transgenerational Epigenetic Effects?

The unique aspect of transgenerational epigenetic inheritance is that an indeterminate number of future generations could be placed at risk from the exposures of their male or female forebears. Beyond scientific novelty and reflexive concerns about the health of future children it is important to undertake detailed risk assessments, implement sensible and nondiscriminatory policies, and pay attention to the larger societal issues of intergenerational equity [98].

Transgenerational epigenetic processes may be a new area of scientific inquiry, but prior policies addressing reproductive risk assessment are instructive on some of the broader ethical and policy issues. Several policies of public and private actors over the last several decades were designed to prevent harms to future generations. The policies were usually directed exclusively at pregnant women, which might be a function of incomplete scientific knowledge, paternalism, or discrimination. For example, product warnings in advertising and on packages have indicated the fetal risks of smoking cigarettes [99] and drinking alcohol [100] during pregnancy. Women have been cautioned to avoid certain pharmaceutical products and, in a few cases, most notably thalidomide, drugs prescribed to pregnant women have been removed from the market because they caused severe birth defects [101]. In a well known legal case, an employer refused to assign non-pregnant, but fertile, women to

jobs with exposure to lead because of the teratogenic risk to possible offspring. A unanimous Supreme Court held that the employer's action constituted sex discrimination and that the decision whether to work with lead exposure belonged to each woman and not the woman's employer [102]. The potential for transgenerational epigenetic risks has focused new attention and controversy on the role and responsibilities of pregnant women to minimize risks to their offspring [103].

The most fascinating issue in transgenerational epigenetic inheritance is intergenerational equity, defined as "the inherent relationship that each generation has to other generations, past and future, in using the common patrimony of natural and cultural resources of our planet" [104]. Each generation is considered a custodian of the planet for future generations, and each generation is charged with leaving the planet in no worse condition than when it was received. According to Rawls, any generation's expectations and responsibilities should be evaluated by using a "veil of ignorance" as to its actual place in the sequence of generations [85, pp.136-137].

Intergenerational equity has been applied to several difficult environmental issues, such as the disposal of nuclear waste, extinction of species of plants and animals, climate change, overpopulation, and destruction of natural resources [1]. It has been asserted that if humankind has a responsibility, among other things, to refrain from activities that endanger future generations of wildlife, then the responsibility also extends to environmental harms that damage the genomes and epigenomes of future generations of humans. In essence, current exposures would cause epigenetic harms, with the result that adverse health effects would be inherited by future generations through transgenerational epigenetics [105].

A slightly different way of looking at the issue is to apply traditional ethical principles to the actions of current generations that create the environmental conditions that, in addition to risks from current exposures, could lead to epigenetic harms in subsequent generations following future exposures. Using the example of irresponsible use of DDT, the environmental damage would violate the principle of nonmaleficence by engaging in harmful conduct and violate the principle of justice by having future generations bear the burden of the conduct of the current generation. Furthermore, future generations obviously cannot consent to the environmental harms caused by their predecessors [105]. Consequently, a practical problem of intergenerational equity is how to ensure that the interests of future generations are protected by the present generation. Indeed, the issue may be regarded as even broader, including protecting the "interests" of the environment now and in the future [106]. At a minimum, transgenerational epigenetic harms should be considered in the cost-benefit weighing of current regulatory options to control toxic exposures.

Another issue to consider is whether harms caused by epigenetic inheritance are sufficiently unique as a matter of ethics, policy, or law that they ought to be subject to different regulatory or legal standards than harms caused by other biological mechanisms. Harms to future generations also can result from traditional harms, such as air pollution, water pollution, or other environmental degradation that is likely to persist for many years. Genetic mutations also result in direct harm to future generations. Is it logical or politically expedient to focus on the biological basis of the harm? The same issue arose in the 1990s when the Human Genome Project led to numerous advances in identifying the genetic factors in environmentally-mediated disorders. The policy response in the United States was mostly to enact specific laws and regulations applicable

only to genetic harms or genetic discrimination, what came to be known as "genetic exceptionalism." With the adoption of genetic-specific approaches [107], one practical argument could be that it is also necessary to adopt "epigenetic exceptionalism" because otherwise, epigenetic harms might not be subject to existing (genetic-specific) laws [108].

Finally, there is the issue of eugenics. Whenever current generations engage in activities to influence the genetic or epigenetic makeup of future generations in any way, the issue of eugenics must be considered. Although the continued revulsion to twentieth century eugenic practices still dominates much current thought on the issue, it is important to recognize the undesirability of having a strict policy of not engaging in any activities that might have any effect on the genetic legacy transmitted to future generations. For example, whenever modern medicine intervenes to save a child with a genetic disorder the result is that the child's survival to reproductive age allows the mutation to be transmitted to offspring. On the other hand, failing to take action because of a desire to cleanse the gene pool of deleterious mutations is the embodiment of eugenics and inhumane treatment. It is doubtful that our successors on the planet would be well served by inheriting "good genes" from a generation of heartless and horribly misguided predecessors.

How, If at All, Do Notions of Personal Responsibility Affect Societal Obligations?

Notwithstanding the potential to identify future generations that are likely to have an increased and unfair environmental risk from today's exposures, possible confirmation of transgenerational inheritance of epigenetic risks in humans will not necessarily lead to environmental justice. As mentioned above, vulnerable people are not treated better today; if anything, they are treated worse. In addition, if there is insufficient public will to improve environmental conditions to benefit the health of people who are alive today, it is unlikely there is sufficient will to improve conditions to benefit the health of unknown people who might be born in the future. Thus, it should be recognized that, at the present time, environmental justice arguments based on vulnerability and intergenerational equity may be given little weight by policy makers or the public. Furthermore, other arguments might be raised to thwart environmental justice.

One such argument involves personal responsibility. For example, tobacco smoke is known to cause severe epigenetic effects [10]. If tobacco smoke were shown to cause transgenerational harms in humans, it is foreseeable that smoking by individuals would be used as evidence of their lack of personal responsibility. Therefore, the argument would be that there is no reason to remediate environmental conditions to prevent transgenerational epigenetic harms when individuals with environmental exposures have high rates of smoking, because tobacco smoke is an independent basis of transgenerational epigenetic risk. Inasmuch as the lifestyles and health habits of vulnerable individuals are likely to reflect a range of unhealthy behaviors, a lack of personal responsibility could be invoked routinely as a defense to environmental remediation. Similar thinking also might be used to shift the blame to women for harms caused to their children from prenatal exposures [103, 109], as well as disclaiming any societal responsibility to workers with occupational exposures that cause epigenetic harms.

In the extreme, the personal responsibility argument is a form of victim blaming [110]. Analogous arguments about personal responsibility have been made in connection with access

to health care [111] and eligibility criteria for various social welfare programs [112]. It is reasonable to expect that arguments based on personal responsibility would be made to oppose efforts to promote environmental justice in the context of transgenerational epigenetic risks even if such arguments may be problematic on both policy and ethical grounds [113].

Conclusion

The scientific evidence of transgenerational epigenetic inheritance in humans is less established than evidence of multigenerational inheritance in humans or transgenerational inheritance in non-human animals. Nevertheless, the argument could be raised that the possibility of transgenerational harms is a compelling reason to apply principles of environmental justice in the remediation of exposures causing epigenetic changes. Thus, the epigenetic-associated harm of adverse health effects in future generations serves to amplify the separate, but related, harm of differential exposures that are the target of environmental justice. Although some theories of distributive justice recognize additional societal obligations to vulnerable populations, theoretical responsibilities have not yet translated into substantial policy enactments with regard to numerous environmental hazards.

In light of the current state of environmental injustice, it is important to assess the likely effects on environmental policies of changes in scientific evidence, social conditions, and political circumstances. The analysis involves three main considerations. First, environmental exposure assessment should take into account not only the absolute risk and severity of harm, but also the relative risk, which may reflect differential exposures and remediation efforts. Second, it is important to determine whether epigenetic mechanisms may cause harms in exposed individuals as well as result in possible multigenerational and transgenerational effects in future generations. Third, an environmental justice analysis should assess the appropriateness and nature of measures to prevent or ameliorate the harms of exposure based on the extent of the harms, as well as the cost, economic consequences, and effectiveness of possible interventions.

At the present time, there is little to suggest that even with greater evidence of transgenerational epigenetic inheritance in humans there will be a significant impetus for environmental action based on concerns for environmental justice [97]. In the future, however, if there is significant evidence of transgenerational epigenetic inheritance in humans resulting from differential exposures and related risks, this situation is more likely to be given serious attention by policymakers. The application of principles of environmental justice can serve to frame the scientific and societal issues for current and future generations.

Identifying an epigenetic mechanism for environmental-molecular interaction, however, is not without its own risks. In a society transfixed by technology and frequently indifferent to the plight of the less fortunate, there is a risk that the societal response to transgenerational epigenetic harms will emphasize clinical rather than environmental interventions to treat those afflicted rather than address the underlying social and economic causes of hazardous exposures. "Thus epigenetics, possibly more than any other biological science, transforms external determinants of health into internal ones" [114]. In evaluating the societal implications of epigenetics, as with other areas of emerging science, biological processes should not obscure the role of human actions in the etiology of environmentally-related health effects.

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