Nature, Nurture, and the Disunity of Knowledge

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ABSTRACT: The Human Genome Project and the tools of modern molecular biology bring enormous promise for the understanding of human biology. Juxtaposed, however, is a conceptual stagnation reflected in the continued nature/nurture debate. More sophisticated models reflecting the inevitable interdependence of gene and environment are essential if we are to realize the potential offered by today's technological advances.

KEYWORDS: Nature vs. nurture; Gene–environment interactions; Human behavioral gentics; Glucocorticoids; Socioeconomic factors and health

Following a public lecture, a journalist approached the renowned psychologist Donald Hebb and asked for his opinion on which factor contributed more to the development of personality, nature or nurture. Hebb responded that to pose this question was akin to asking what contributed more to the area of a rectangle, the length or the width. Like all good urban myths, there are multiple versions of this story. The context changes somewhat, but Hebb's quote remains intact in its piercing brilliance. Forty some years later, we pace about in the same state of confusion, asking the same foolish question, armed with the impressive tools of a new millennium, but without the wisdom of Hebb.

NATURE VERSUS NURTURE 40 YEARS LATER

Biomedical research is now positioned for an era of remarkable breakthroughs. The completion of the Human Genome Project, together with the availability of protein and gene array technology, provides the potential for incredible advances in our understanding of the biological basis of development and the processes that lead to disease. Coupled with this astounding technical success, however, is a failure to develop conceptual models that traverse the chasm that lies between gene and function. The technology of 2001 is employed in the service of questions that have been conceptually unchanged since the 19th century. Our technical brilliance is constructed on a conceptual scaffolding that, in many areas of biology, is little changed from the 1920s. We risk leaving little more to the next generation than elaborate facades.

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The most troubling example remains that of the question of genetic versus environmental determinism—the nature/nurture debate—and the theoretical divide that exists between researchers which fuels such fruitless controversy. As with a drunkard waking from sleep to swat a nonexistent fly whose humming derives from nothing but the chaos of inebriated ears, we construct fascinating statistical solutions to questions that are biologically nonsensical. We set out afoot, once again, to push the pendulum back and forth between nature and nurture in an exercise that only ensures that, eventually, we will find ourselves in exactly the same place at which we started. If we do not develop a more intelligent set of questions, all of this technical wizardry will produce but an empirical wasteland, like a World's Fair site some 40 years after the fact.

We have ample reason to celebrate the technical advances associated with the Human Genome Project. Yet, the same technology bears the risk of expanding the divide that lies between the biological and social sciences in the same way that access to computer technology expands the division between the developed and underdeveloped world: one group blindly infatuated with the explanations that might flow from gene technology, the other huddled in terror at the thought of a biological world of which they know nothing. Such divisions, by definition, only further confuse the study of development as scientists from different disciplines retreat ever further into the worlds they can still understand for explanations. More and more is explained on the basis of less and less.

Can you imagine, to expand on Hebb's metaphor, explaining to the public that the study of "rectangularity" comprises those who study "lengths" and others who are preoccupied with "widths?" The rectangle, someone might point out, is really an emergent property of length × width and cannot possibly be understood only in terms of one or the other. Hence, for all our knowledge concerning "lengths" and "widths," we would know little about actual rectangles. Ultimately, one would hope, individuals would emerge demanding an integrative approach that recognizes only the study of rectangles, dismissing the notion that anything meaningful can come from the study of "lengths" or "widths" alone. Such an advance would require no new tools, but rather a change in the way we think about rectangles.

So, too, is it with "nature" and "nurture," for life does not emerge as a function of either. It is equally wrong-headed to assume that, oh yes, phenotype derives from both nature and nurture. This would be only to repeat the misunderstanding in kinder, gentler terms, as if biological and social scientists had shaken hands and then gone off into their own corners of the universe to study "lengths" or "widths." Indeed, both conclusions are derived from additive models of determinism where gene + environment = phenotype. Such models make no biological sense whatsoever (see below). It is not nature *or* nurture. Nor is it nature *and* nurture. To paraphrase Richard Lewontin,[1] life emerges only from the *interaction* between the two: There are no genetic factors that can be studied independently of the environment, and there are no environmental factors that function independently of the genome. Phenotype emerges only from the interaction of gene and environment. The search for main effects is a fool's errand. In the context of modern molecular biology, it is a quest that is without credibility.

Nature and nurture do not exist in a manner that can ever be considered independently quantifiable. There is, instead, simply a continuing process of development that emerges from the constant dialogue between gene and environment. At no level

can the function of a gene be separated from the cellular environment in which it functions; it is biologically absurd to assume otherwise. Every trait is a function of gene/environment interaction and, lest you think I am simply some environmental wolf in sheep's clothing, it is equally absurd to believe that the environmental factors can be studied independently of the genome and the constraints it places on the neural systems that serve as the inevitable bridge between environment and effect.

I am certainly not the first to make this argument, nor am I the most articulate. So I will content myself with a few examples, refer readers to more learned sources (e.g., Wahlsten and Gottlieb[2] and Lewontin[3]), and attempt to end on a note that provides some idea of what is to be scientifically gained by abandoning, once and for all, the nature/nurture debate.

GENE EXPRESSION

Scientific journals, regrettably, continue to provide examples of research that attempts to quantify the relative contribution of genetic versus environmental factors to the development of a specific trait, often intelligence. These studies use statistical models to partition variance across individuals into main effects of gene or environment. Inherent in the use of such models is the assumption that these factors, gene and environment, can operate independently (otherwise there could be no main effects) and the statistical models, as I understand them, would be rendered invalid.

The models are indeed statistically well-validated, and while debate continues on the importance of meeting specific assumptions, the main problem here is not mathematical, it is biological. Simply put, it is biologically impossible for gene and environment to operate independently of one another. Everything we have learned about molecular biology has shown that gene activity is regulated by the intracellular environment (FIG. 1). The intracellular environment is a function of the genetic makeup of the cell and the extracellular environment (e.g., hormones released by endocrine organs, cytokines from the immune system, neurotransmitters from neurons, nutrients derived from food). Signals from the extracellular environment, including hormones and neurotransmitters, can all serve to regulate gene expression. The extracellular environment is, of course, also influenced by the environment of the individual. Neurotransmitter and hormonal activity is profoundly influenced, for example, by social interactions, which lead to effects on gene activity, or expression. At no point in life is the operation of the genome independent of the context in which it functions.

It is, of course, not the mere presence or absence of a gene that is of functional importance, but rather the expression of the gene—its level of activity. The study of gene expression reveals remarkable complexity. A number of years ago, to cite but one instance, Keith Yamamoto's lab[4] provided a stunning example of the complexity of gene expression while studying the effects of glucocorticoids, a class of steroid hormones. Glucocorticoids are released in ample amounts during periods of stress and serve to mediate many of the adaptive responses occurring during periods of adversity, such as changes in blood glucose and heart rate, as well as altered neuronal function.[5] In large measure, glucocorticoid effects on cell function are mediated by changes in gene expression. Glucocorticoids bind to intracellular receptors, which serve as transcription factors, increasing or decreasing the activity of the gene. The

ligand-activated glucocorticoid receptor binds to regulatory sequences of the gene that modify the rate of gene transcription. One such regulated gene is proliferin. Yamamoto and colleagues found that glucocorticoids could either positively or negatively regulate proliferin, depending on the context. If intracellular levels of another transcription factor, cJun, were elevated, then the glucocorticoid receptor bound to a regulatory region of the proliferin gene and increased transcription. In the absence of cJun, activation of the glucocorticoid receptor was without effect on proliferin expression. But the story becomes increasingly complex. If intracellular levels of cJun as well as another, related transcription factor, cFos, were elevated, then the glucocorticoid receptor did indeed regulate transcription, but negatively. Thus, without cJun there was no glucocorticoid effect, with cJun there was an increase in gene transcription, and with high levels of both cJun and cFos there was a glucocorticoid receptor-induced decrease in gene transcription. The cellular context did not merely determine the magnitude of the glucocorticoid receptor effect on gene transcription, it determined whether that effect was positive or negative—all in relation to a single DNA target. The cellular context, and specifically levels of transcription factors such as cFos and cJun, are heavily influenced by ongoing activity; stress, social encounters—all serve to influence the cellular levels of these factors and can therefore have very potent influences on the nature of gene activity. From such systems will we derive main effects? I think not.

Studies of dynamic neural functions, such as learning and memory, involve precisely the same type of events, and even greater complexity.[6] In simpler cell culture systems, from which the Diamond *et al*.[4] findings emerged, perhaps 3,000 to 5,000 genes might be operating. In the brain, the figure could hit 20,000 or more. The potential for protein–gene and gene–gene interactions is seemingly limitless. Drug effects will inevitably alter not only expression of a target gene, but also the context in which that gene and many others function. This is the reality of cell biology.

> Nor can the response of the individual to an environmental signal be considered independent of the relevant target system and the genetic composition of that system. Environment regulates the actions of genes, and genes via changes in the nervous system influence the sensitivity of an organism to changes in the environment. The two causes are not separable developmentally. Statistical procedures that appear to separate variance according to genetic and environmental causes do not provide a valid representation of physiological reality. (Wahlsten and Gottlieb,[2] p. 178)

So why, in the face of such profound contradictions, do we pursue the definitive resolution to the nature/nurture debate? Why do disciplines that attempt to measure the relative contribution of genetic versus environmental factors, such as quantitative human behavioral genetics, exist? The answer, I think, lies in the immense gap that exists between social and biological scientists and in the dangerous assumptions each is forced to make in order to achieve any level of explanation without leaving the comfort of their own discipline.

HUMAN BEHAVIORAL GENETICS

The study of human genetics has many dimensions, including crucially important efforts to link specific genes, and variants of these genes, to human traits. It is clear that any attempt to understand the relevant gene–environment interactions begins with an identification of the relevant gene(s). Likewise the study of inheritance, the

transmission of traits within families, has proven useful for understanding the risk factors that predict pathologic conditions. Although twin studies, particularly those comparing monozygotic and dizygotic twins, have constraints (see Wahlsten and Gottlieb[2]), the results, if interpreted with appropriate caution, can provide information about the associations between developmental events and outcomes. Moreover, differences in the inheritability of apparently related factors provide valuable information on the processes by which pathology emerges and can clearly point researchers in the direction of significant sources of influence on health. It is, for example, of considerable interest that traits associated with chronic disease often show a higher rate of inheritance than does the disease itself, which would seem to suggest that what is inherited is a source of vulnerability and not the disease per se. However, such studies do not define either genetic or environmental factors in a way that meaningfully identifies cause–effect relationships. Indeed, prominent researchers in the field have correctly identified the fact that gene–environment interactions undermine any such simplistic enumeration of genetic and environmental "loading" across populations. For example, Kendler[7] has, quite correctly, pointed out that genetic background can influence the individual's response to environmental events, rendering environmental stressors, for example, a more potent source of mischief for some than others. Likewise, individuals are not passive recipients of experience; we actively construct environments on the basis of temperament, self-esteem, and sociability, all of which can potentially be influenced by the genome. What this means, very simply, is that certain environmental influences may be crucial for some individuals and less so for others. Conversely, because environmental factors regulate gene expression, genetic factors may be a more significant source of influence in some individuals than in others. In sum, studies of inheritance ultimately beg the crucial question: What are the mechanisms of inheritance? The answer to that question will emerge only from studies that focus on gene–environment interactions.

However, a variation of this endeavor has emerged as the field of human behavioral genetics that actually attempts, according to its champions, to quantify nature and nurture—to ascribe numbers to the importance of genetic versus environmental factors. The field of human behavioral genetics appears to have two broad objectives[8]:

(a) To establish that genetic variations can influence the development of individual differences in cognition, emotion, and behavior.
(b) To quantify the relative contributions of genetic and environmental factors in the development of individual differences in cognition, emotion, and behavior.

It is interesting to note that the most fervent practitioners of quantitative human behavioral genetics come not from genetics nor even from biology at all. They are very commonly persons trained in psychology. It is unfortunate that psychology has exerted a much greater effort in training its students in statistics than in biology—with the predictable result. It is really nothing more than a convenient myth to believe that one can study the influence of genes without understanding anything of molecular genetics.

Yet, it would be unfair to lay bare the apparent weaknesses of such quantitative behavioral genetics without attempting to understand its origins. A primary objective of the research that strives to quantify the relative contribution of genes and en-

vironment is simply to demonstrate that variations in the genome can influence the expression of individual differences in behavior, cognition, and personality in humans.[8] Perhaps one of the most frustrating features of the current nature/nurture debate lies in the simple fact that this should be completely obvious. Try to imagine a scenario in which variations in the genome bear no relevance whatsoever for the development of the brain and personality, as if cells in the brain could grow and differentiate under a totally different set of rules from those in the rest of the body. Were this to be true, evolutionary theory would crumble and modern neuroscience along with it. Of course variations in the genome are relevant for neural development, and the interactionist perspective should be no more tolerant of resistance to this idea than to those suggesting that environmental variations, other than in the extreme, have little influence over the course of normal development.

The problem, of course, is that we need not wander too far across our respective campuses to find precisely this level of resistance to the study of genes and individual differences in personality, usually cloaked in the guise of opposition to theories of genetic determinism. And of course, historically at least, such opposition has been well-founded.[9] Differences in genetic composition have been postulated as a basis for exclusion of individuals based on race and gender. But none of this makes any sense whatsoever in the context of modern genetics and, fortunately, the time should have long passed when such eugenics was confused with real science. A true appreciation of development will never emerge without a focus on the genome and its regulation by the environment, and it is precisely this field of biology that most forcefully demonstrates that mere presence of a genetic variant, in all but the more extreme cases, is not sufficient to explain variation at the level of phenotype. In many cases, I suspect that this is all that many researchers in human behavioral genetics wish to point out—that genetic variation is relevant to the study of individual differences. Ideological resistance to this idea does little to further the quality of discussion on human development.

Interestingly, the very structure of the genome highlights the importance of gene–environment interactions. Cellular function emerges as the constant interaction between gene and environment, one determining the influence of the other. Cellular activity occurs within a context. The genome is constructed accordingly. Estimates are that over 95% of the DNA sequences do not directly participate in the coding of proteins. Rather, these noncoding sequences often determine the activity of those regions of the genome that do actively code for proteins. These regions are known as enhancers or suppressors, or more simply perhaps as promoter regions of the genome. These regions respond to signals derived from the cell's environment. This simple fact would imply that variation is most likely to occur in the promoter region and to be associated with environmental signals that direct gene expression. Moreover, many of the relevant polymorphisms (variants in gene sequences) exist not in the coding region of the gene, but in the promoter region. The very existence of a polymorphism in the promoter regions implies that the relevant level of analysis is that of gene–environment interactions, and not simple main effects.

Indeed, studies of environmental regulation of gene expression and cellular function would seem to provide a natural bridge between the social and biological sciences. It may well be that the degree to which we are able to use the advances in genetics to advance the understanding of human development will depend on our

ability to create a unified science of human biology that appropriately integrates social and biological sciences and embraces the idea that explanation can very meaningfully derive from multiple levels of analysis. My impression is that we are not yet there.

GENE–ENVIRONMENT INTERACTIONS

Perhaps the greatest tragedy in the continuation of the nature versus nurture debate is not so much its mere futility, but that it distracts from the spectacular rewards to be derived from the study of gene–environment interactions, because such studies hold the promise ultimately of understanding how environmentally derived variation in genome and gene activity is related to function. The sheer complexity of the phenomena under study demands no less.

An excellent example was raised by Wahlsten and Gottlieb[2] in their description of the studies of Cooper and Zubek[10] working with the so-called "maze-dull" and "maze-bright" strains of rats selectively bred at McGill University in the 1950s. Sadly, these strains no longer exist. But in the 1950s researchers had selectively bred animals based on their performance in the Hebb-Williams maze. Over generations, the performance of the strains diverged, reflecting a genetic basis for the difference in this learning and memory task. In the Cooper and Zubek study, the researchers reared the weanling offspring of bright and dull parents in enriched, impoverished, or control conditions. In adulthood the animals were then tested on the maze, and the results revealed a stunningly simple example of gene–environment interdependence (FIG. 1). Indeed, the strain difference was revealed, but only in animals reared under control conditions. The "brights" were so profoundly affected by the conditions of impoverishment that their performance declined to the level of the "dulls." In contrast, following rearing under conditions of enrichment, the performance of the "dulls" ascended to levels that were indistinguishable from those of the "brights." The most impressive feature of these results is that the effect of the rearing environment was determined by the genome, a finding that has been repeated using mouse strains. Likewise, the effect of genetic variation was apparent only in animals reared under standard lab conditions. I can only begin to imagine the potential impact of the research that defines how and why the expression of genes involved in the differences in the learning and memory performance of the "brights" and "dulls" might be differentially affected by different post-weaning rearing environments. Likewise, this study and many others with selected strains of rats have demonstrated that the impact of environmental events can be determined by genetic factors.

Comparable examples of the degree to which strain differences depend on environment abound (e.g., Crabbe *et al.*[11]). A brilliant example emerged recently from the Piazza laboratory (Cabib *et al.*[12]). These investigators found that highly reliable mouse strain differences in sensitivity to the psychostimulant amphetamine could be completely abolished if the animals experienced a brief period of food restriction at some point before drug testing. Many might view such findings as a miserably unwelcome complication. But imagine, as I am sure the Piazza group does, the opportunity for studies of gene–environment interactions. Identify the gene(s) involved in mediating the differences in sensitivity to amphetamine and then study the regula-

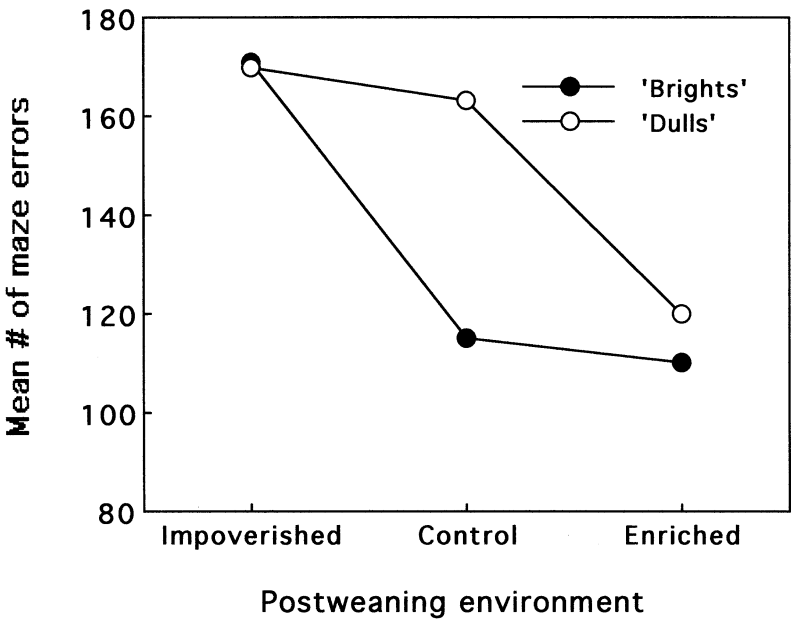

FIGURE 1. Gene–environment interdependence among maze-bright and -dull rats.

tion of gene expression by feeding. On the basis of such studies, we might then begin to develop the conceptual scaffolding upon which technical advances, like the genome projects, could truly advance our understanding of development.

The interaction between genetic factors and the postnatal environment is also revealed in the study of mouse strains. For example, the BALBc mouse strain is highly fearful, and maze-dull in the extreme. By comparison with the more phlegmatic C57 mouse, these animals show increased endocrine and behavioral responses to stress, and they are hyperactive and show profound learning and memory deficits that are associated with, among other things, impaired hippocampal development. Is this evidence for the importance of genetic factors in determining differences in personality? Clearly. But the BALBc mouse also shows differences in maternal behavior compared with the C57 mouse. C57 mothers lick and groom their offspring about three to four times as frequently as do BALBc mothers. In rodents, maternal licking/grooming enhances hippocampal synaptogenesis[13] and decreases emotional reactivity.[14] Thus, BALBc animals cross-fostered at birth to C57 mothers emerge as animals that are very much like C57 adults. Moreover, in presenting a finding that holds hope for BALBc parents everywhere, Anisman and colleagues[15,16] reported that neonatal handling of BALBc pups, which increases maternal licking/grooming, has the same effect as cross-fostering to C57 stepparents. Does this mean that the differences in behavior between these animals are not really related to genetic factors? Not at all. The genetic differences between the BALBc and C57 strains do contribute, but in a manner that is mediated by the pre- and postnatal environments.

Under normal circumstances, of course, BALBc mice are reared by BALBc mothers. The genetic and environmental factors conspire to produce an excessively fearful and intellectually "challenged" animal. Can one then meaningfully apply mathematical formulas to calculate the relative contribution of one versus the other? Well you could, but it would be of greater mathematical than biological usefulness. To even imagine such a process is to court misunderstanding. I can use statistical models to predict the differences in behavior between C57s and BALBc animals quite accurately simply from a knowledge of the differences in the genome of the animals. In a linear regression model, which estimates the strength of association between factors, information on the genomic differences between BALBc and C57 animals is sufficient to distinguish one strain from the other; virtually all BALBc mice behave differently from C57s on tests of fearfulness or learning/memory. Knowledge of differences in the postnatal environment, such as variations in maternal behavior, adds absolutely nothing to the ability of the equation to predict differences in behavior. A linear regression analysis of variation in, say, timidity would yield no insight whatsoever into the potential importance of environmental factors—partitioning of the variance would slide entirely onto the so-called genetic factors. Hence, we might be tempted to conclude that the differences in fearfulness emerge largely, if not exclusively, from genetic factors. Because the addition of the environmental variables has not increased the predictive value of the equation, these variables must not be important in determining the endpoint. Precisely this type of data has given rise to such remarkably specious debates as "whether parents really matter." Something is terribly wrong when this question forms the basis of debate in the year 2000.

The conclusion from such a linear regression analysis is not merely wrong, it is irrelevant. Dramatic alterations in the phenotype of the BALBc mouse occur if it is reared in the care of a C57 mother. Moreover, such effects can be transmitted across generations through a nongenomic mechanism of inheritance.[14–16] In rats, the offspring of low-licking/grooming mothers are, like the BALBc mouse, emotionally reactive and intellectually unfavored. If the offspring of low-licking/grooming mothers are cross-fostered to high-licking/grooming mothers, there is a reversal in patterns of neural synapse formation and behavior.[13,14] Hence, environmental events occurring at a later stage of development, as we saw with maze-bright and -dull rats, can alter a developmental trajectory. This, in fact, is the adaptive value for plasticity in the first place. The reason why in many of these linear regression studies environmental factors do not add predictive value is that they serve to enhance the genetic differences; they are redundant mechanisms. Children of depressed parents commonly not only inherit genes that confer an increased risk for depression, but also they inherit the depressed parent. Attempting to tease one apart from the other is, it seems to me, substantially less interesting than identifying the relevant genes and parenting styles (as well as the myriad of other relevant factors) and then understanding how one alters the expression of the other so as to create the conditions from which depression emerges. The latter approach would also seem to hold the hope for treatment, and possibly intervention.

The redundant, nonlinear nature of development that lays waste to the significance of linear regression studies of nature and nurture is, by the way, a key feature of development in the brain. The brain has multiple routes to the same endpoint.

What is the value of this process? Simply that it can provide for diversion. If the developmental trajectories established through gene–environment interactions in early life are not adaptive for the animal, they move in the direction of the current environmental signal through a modification of the expression of the relevant genes. This is why there is so much room for the influence of postnatal factors and why they can override earlier influences—it is the basis for reversibility. In most cases, this is not likely to occur, but the potential for the reversal of developmental patterns suggests a level of nonlinearity that should be a crucial focus for developmental studies. It also suggests, importantly, that population-based studies will often underestimate the potential importance of particular developmental events, since only certain segments of the entire population will be affected: Environmental enrichment is a boon to BALBc mice or the offspring of low-licking/grooming rat mothers. It has little effect on the C57 mouse or the offspring of high-licking/grooming rat mothers. Similarly, studies of early infant intervention reveal dramatic effects in children from undereducated homes, whereas children of well-educated parents are generally less affected.[17]

This multidimensional profile of development suggests that when chronic illness hits, many factors are usually well represented at the table. And this is certainly true for mental health. For example, Cadoret and colleagues[18] studied children adopted at birth from families with or without a history of antisocial behavior. Thus, the children came into their adoptive families with or without a family history, and presumably a genetic loading, for aggressive, disruptive, criminal behavior. I fully realize the leap here in assuming that the "family history" reflects a genetic influence, but for the sake of the argument, I ask the reader's indulgence. The researchers also examined the behavioral outcomes as a function of whether there was a history of antisocial behavior in the home into which the children were adopted. The authors found that when the adoptees had little or no family history of antisocial behavior, the adopted family environment really was unimportant in determining whether or not the children ultimately developed antisocial behavior. If the children carried the predisposition for antisocial behavior derived from the biological family, however, then the influence of the environment was remarkably important. Children with a family history of antisocial behavior adopted into "good" homes were far less often to exhibit antisocial behavior (13%) than were children of a similar family background adopted into "bad" homes (45%). Children with no family history of aggressive behavior were unaffected by the foster home, at least with respect to aggression. In this case the impact of the environment was determined by what I am assuming, temerariously, is the genetic background of the child.

Again, such findings reveal the weakness of linear regression models imposed on large populations. If we asked whether early family conditions were significant predictors of aggressive behavior, the obvious answer would be one that clearly underestimates the potential importance of the family, since only in a selected population of children would such effects be readily apparent. For the vulnerable children, the difference is crucial. This is the reality of gene–environment interactions, and its mysteries will simply not submit to solutions derived from linear models of correlation. This is the inherent weakness of population-based studies: They are forced, by design, to ignore such interactions. By analogy, toxicologists have learned that host–toxin interaction effects can be crucial. Such studies can be important in identifying

potential sources of influence, but negative findings should be interpreted with extreme caution or ignored. Are peanuts bad for health? Of course not, unless you happen to have an allergy to peanuts, in which case they can be disastrous. Population-based studies, with all their merits for the initial phase of investigation into any topic, cannot reveal such subtle relationships. It is of little use to pretend that such studies can ever clearly define the pathways that lead to variation in phenotype: It is like waiting for the *Sports Illustrated* prediction of who will win the World Series—they'll make one, and you can believe it if you wish, but it often has little relationship to what will actually transpire in October (just ask fans of the Cleveland Indians).

IMPLICATIONS FOR HEALTH SCIENCE RESEARCH

Focusing on gene–environment interactions leads to the next generation of scientific questions: What does it mean, for example, to carry a gene, or set of genes, that confers a 45% chance of developing type II diabetes? How do such genes promote vulnerability? What are the conditions that increase or decrease the likelihood of diabetes among such vulnerable populations? What factors determine when the disease might emerge, or regulate its severity? Do socioeconomic factors, which have such a pervasive effect on metabolic disorders such as diabetes, ultimately act on comparable cellular targets? What are effective and realistic targets for intervention/prevention in high-risk populations? In all cases, the answer to these questions involves an understanding of the factors that regulate the relevant gene targets. The story begins with the identification of the relevant genes and then progresses with studies on the environmental regulation of these and other relevant genes. Studies of gene expression move to the forefront. Success will depend on sophistication at all levels of investigation. The reward will be the ability to assemble an integrated explanation of individual differences in vulnerability/resistance to disease that spans from the level of gene activity to socioeconomic factors. Logically, the conclusion of such research may reveal that the most effective treatment for the control of a disruptive gene might derive from psychosocial or nutritional interventions.

In essence the goal is that of clearly defining the pathways that lead to disease. In this sense, the question is no different than it would be if one is working with a set of epidemiologically defined "risk factors." In such instances the critical question is one of how such risk factors might be associated with the onset of disease, as well as identifying mediating conditions. Whether we are considering environmental risk factors or the presence of specific genes, the question becomes basically the same: What are the pathways? What are the processes by which social and economic factors are "biologically embedded" and thus influence health? An integrative, multidisciplinary research approach is required in all cases with the understanding that the endpoint of such efforts is not that of endless flow charts, but of a clear understanding of mechanisms.

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