Our genes, ourselves?

by Ari Berkowitz

"Now we know, in large measure, our fate is in our genes" (Watson quoted in Jaroff 1989, p. 67). So said James Watson, Nobel laureate, codiscoverer of the structure of DNA, and first leader of the Human Genome Project.

Is he right? We in the United States seem to be of two minds. Most of us have an intuition that, although our genes provide advantages and constraints, we retain great control over our lives. But we are developing a second, competing intuition that, like it or not, our genes determine our abilities, our preferences, and our emotions. Perhaps this second intuition is what induced Rutgers University president Francis Lawrence, a man who has spent years trying to increase opportunities for minorities, to say that blacks do not have "the genetic, hereditary background" (Lawrence quoted in Olen 1995) to do as well as whites on college admissions tests, a statement that caused an uproar across the country (Olen 1995). We would like to think we are much more than the sum of our genes, but according to news reports, scientists appear to have demonstrated that our genes determine some of our most complex behavioral and cognitive characteristics.

Science is not an unblemished source of objectivity. Science is an activity of scientists. Scientists both influence contemporary culture and are influenced by the culture. Research questions are chosen and framed partly in response to current medical, social, and political concerns. The process of obtaining research funding requires scientists to write proposals to compete for grants, and it encourages them to present flashy results on issues of immediate public interest. The development of powerful new methods for studying DNA in the past three decades has led to a proliferation of explanations of all sorts of human characteristics in terms of genes.

The focus on genes as the primary mode of biological explanation has been especially clear in the marketing of the Human Genome Project. In support of this project, some respected biologists have expressed views that are surprisingly similar to those once held by the leaders of the US eugenics movement (approximately 1890–1945), which resulted in racially based immigration quotas and laws for forced sterilization of the so-called feeble-minded.

Charles B. Davenport, the biologist who led the US eugenics movement as founder and director of the Eugenics Record Office at Cold Spring Harbor, New York, wrote in 1928:

> [T]he widespread existence of crime enforces the lessons of eugenics. We are breeding too many people with feeble inhibitions and without proper *social* instincts; persons who have a tendency toward periodic outbreaks of temper and to assaults; persons who are liable to periodic bad behavior, including the kind that is associated with the epileptic state; persons who are introverts, selfish and non-social. Satisfactory progress will be made only when we understand how those with congenital criminalistic make-up are bred and try to prevent such breeding. If we permit them to be born, then we must apply such special treatment as will prevent their behavior from disorganizing society. (Davenport 1928, p. 313)

Daniel E. Koshland Jr., a contemporary molecular biologist and at that time editor-in-chief of the journal *Science*, wrote in *Science* in 1990:

> Last week a crazed gunman terrorized hostages in a bar in Berkeley, killing one and wounding many others.... Schizophrenia (the disease from which the Berkeley gunman is thought to have suffered) and other major mental illnesses can have a multigenic origin. A sequenced human genome will be a very important tool for understanding this precise category of diseases.... The combination of new tools may not only let us help in reducing crime, but also aid some of our most disadvantaged citizens, the mentally ill. Although increased funding of mental health centers, stricter gun control, increased supervision of the mentally unbalanced, or higher standards for probation officers may be desirable, they are Band-Aid remedies. In the long run, the solution will be found in the knowledge required to produce accurate diagnoses and cures. The research to provide that knowledge will be far cheaper, and the results much fairer, than Draconian law enforcement. (Koshland 1990, p. 189)

Robert L. Sinsheimer, biologist and former chancellor at the University of California, Santa Cruz, and an architect of the Human Genome Project, wrote in 1969:

> The new genetics would permit in principle the conversion of all of the unfit to the highest genetic level.... I know there are those who find this concept and this prospect repugnant.... They are not among the losers in that chromosomal lottery that so firmly channels our human destinies... [such as] the 50,000,000 "normal" Americans with an IQ of less than 90.... Equality of opportunity is a noble aim given the currently inescapable genetic di-

> versity of man. But what does equality of opportunity mean to the child born with an IQ of 50? (Sinsheimer 1969, p. 13)

In 1991, in support of the Human Genome Project, Sinsheimer affirmed, "[i]n the deepest sense we are who we are because of our genes" (Sinsheimer 1991, p. 2885).

Does the available scientific evidence actually tell us that our genes determine our behavioral, emotional, and cognitive characteristics? Do single genes specify particular behavioral traits? To answer these questions, most nonspecialists depend upon the cursory reports of new research findings that appear regularly in the lay press. These reports are often oversimplified and may be shaped by the desire of both journalists and scientists to create an exciting story. Sober-minded assessments with broader perspectives seldom attract as much interest, either in the lay press or in scientific journals. As a result, our perceptions of the scientific evidence may be skewed by a few dramatic findings, some of which may be wrong.

Nowhere has this scenario been more clear than in the representation of the roles of genes in determining uniquely human characteristics, involving our thoughts, emotions, and behaviors. Within the past decade, there have been highly visible reports localizing genes for schizophrenia (Sherrington et al. 1988), manic depression (Baron et al. 1987, Egeland et al. 1987), alcoholism (Blum et al. 1990), and homosexuality (Hamer et al. 1993). Recently, there was even a report of a "gene site for bed-wetting" (Goleman 1995). Other groups of scientists have been unable to reproduce the findings for schizophrenia (Kennedy et al. 1988), manic depression (Detera-Wadleigh et al. 1987, Hodgkinson et al. 1987), and alcoholism (Gelernter et al. 1991, 1993). Authors of two studies claiming to have found a gene for manic depression (in two different places) have both published retractions of their conclusions (Baron et al. 1993, Kelsoe et al. 1989)—unusual and embarrassing events among scientists. These reversals have led to much methodological soul-searching within the pages of scientific journals and books but have been described cursorily in newspapers and less, if at all, on television. Research linking genes to complex human mental and behavioral characteristics has been tremendously successful in molding public opinion, in the absence of much lasting scientific evidence.

There is only one antidote for the effects of skewed research reporting: Nonspecialists must learn more about experiments and interpretations used in this branch of science. Examining the types of methods and experiments that are used to support simple genetic explanations of human behavior allows one to see how ambiguities and biases can lead to misinterpretations.

The relationship between a gene and a human behavior is rarely, if ever, a one-to-one correspondence, even though disruption of a single gene occasionally has a dramatic effect on behavior. Nor can one quantify the contribution of genes as a whole to any particular behavior or cognitive ability. Instead, each gene is a single player in a wonderfully intricate drama involving nonadditive interactions of genes, proteins, hormones, food, and life experiences and leading to effects on a variety of cognitive and behavioral functions. Our thoughts, emotions, and behaviors certainly have biological mechanisms but that does not mean we can separate and quantify the genetic contributions to these processes.

Linkage studies

It has long been observed that certain human behavioral characteristics tend to run in families, but these characteristics might be caused by either genes or environments, or by some combinations of the two. For much of this century, some investigators have attempted to demonstrate and quantify genetic contributions to human cognition and behavior, most notably IQ, by examining identical twins and applying questionable interpretations to them (see Kamin 1974, Lewontin et al. 1984, for examples). More recently, some researchers have taken advantage of new techniques for manipulation of DNA to attempt to locate individual genes that either determine or convey a propensity to behavioral characteristics. Such studies are much easier to conduct with nonhuman animals, in laboratory settings where environmental effects and mating pairs can be controlled, than with human beings. But it is eventually necessary to examine human DNA if one wishes to find genes that cause, for example, human psychiatric conditions.

Experiments linking a gene to a complex human characteristic can be informative, but they also can produce misconceptions if they are not interpreted with care. Such experiments generally rely on a statistical argument that a segment of DNA and a complex characteristic tend to co-occur in individuals more often than one would expect at random. In particular, the statistical argument relies on the natural process of crossing over, in which the matching chromosomes of each parent pair up and sometimes exchange pieces of DNA. Thus, two genes that had begun on the same chromosome can end up on different chromosomes. The probability that two stretches of DNA will end up in the same gamete (and thus the same person), despite crossing over, is related to their proximity on the chromosome: The closer together they are, the more likely they are to remain on the same chromosome.

When scientists begin searching for a gene that may be related to a complex human characteristic, they usually know nothing about the likely location of the gene, the protein that it specifies, or the function of that protein. Instead of directly examining whether a particular gene causes a particular characteristic, they use easily traceable pieces of DNA, called genetic markers, to narrow down the possible location of such a gene. If a marker is consistently found in individuals who have a particular characteristic, and not found in other individuals, then it is inferred that there is a gene near the marker that is linked to the characteristic. The gene need not include the marker; if they are sufficiently close together, they will tend to remain together despite crossing over. Thus, linkage between a marker and

a trait does not indicate that a relevant gene has been identified, but it may indicate that a relevant locale has been found. In some cases, investigators begin with an educated guess: Rather than using random genetic markers, they look for linkage to particular genes that have already been identified, called candidate genes, which they believe might function in the behavior under study. Experiments on nonhuman animals sometimes suggest candidate genes, but animal results by no means guarantee that a similar gene in human beings will be linked to the behavior of interest.

This type of research has been successful in locating genes that cause a disease in an all-or-none manner. Huntington's disease, for example, is a complex behavioral disorder that is caused by a single gene. Proponents of genetic determination can point to this example and suggest that many other complex behavioral disorders are probably determined by single genes. But the inheritance pattern for Huntington's disease is different from inheritance patterns for conditions like manic depression, schizophrenia, and alcoholism.

For more than a century, Huntington's disease has been known to be caused by a single gene on the basis of its strikingly reliable pattern of inheritance: Half the offspring (on average) of each victim of Huntington's disease develop the disease. This pattern means that the disease is caused by a single gene that only needs to be present in one copy; it was just a matter of finding the gene.

In contrast, family patterns for manic depression, schizophrenia, and alcoholism are irregular and unpredictable. These patterns are not consistent with there being a single gene that determines whether or not one develops the condition (Risch 1994). Instead, if indeed there are genes that can have important effects on these conditions, there are likely to be several genes, each of which has only a small effect on its own, that may interact in a nonaddictive manner with one another and with environmental factors to generate each condition. An assumption of single-gene causation can lead to an unwarranted conclusion that linkage has been demonstrated, in addition to overinterpretation of genuine linkage.

A closer examination of one example illustrates some of the difficulties of genetic linkage studies of complex human characteristics. In 1987, Janice A. Egeland and her colleagues reported in the journal *Nature* (325: 783–787) that they had localized on human chromosome 11 "a dominant gene conferring a strong predisposition to manic depressive disease," and they had demonstrated "by a linkage strategy that a simple genetic mechanism can account for the transmission" of manic depression in the family they studied. *Nature* highlighted this report, saying, "[t]he use of DNA markers has shown that manic-depressive illness can be caused by a single gene" (Robertson 1987, p. 755). In the same issue, *Nature* published two related studies (Detera-Wadleigh et al. 1987, Hodgkinson et al. 1987): Each reported that they had found no linkage in other families between the same genetic markers used by Egeland and manic depression. These negative findings received little attention.

There were at least three possible reasons for the discrepancies in linkage results. First, either Egeland's study or both of the other studies could have been in error; in the former case, the apparent linkage might have occurred purely by chance. Second, manic depression might have been caused largely by a single gene in the family Egeland studied but in the other families it might have been caused by nongenetic factors and/or the interaction of several genes, each having a small effect. Third, manic depression might have been caused largely by a single gene in each of the families studied, but by a gene in a different location in the families with no linkage to the chromosome 11 markers, a situation known as heterogeneity. Surprisingly, only the third possibility was considered. Hodgkinson and colleagues (1987) concluded "that there is genetic heterogeneity of linkage in manic depression," despite the fact that Hodgkinson's study had found no evidence at all for a gene linked to manic depression. *Nature* said, "[t]his means there are at least two different genes predisposing to affective disorder" (Robertson 1987, p. 755).

There was apparently great eagerness to support a hypothesis of simple genetic causation for manic depression. Meanwhile, another group of researchers published, also in *Nature*, a report of linkage between manic depression and a region of DNA on a different chromosome (Baron et al. 1987). These researchers concluded that their results "provide confirmation that a major psychiatric disorder can be caused by a single genetic defect" (Baron et al. 1987).

In 1989, Egeland's group published a reevaluation of their own findings (Kelsoe et al. 1989), also in *Nature*, based on a change in diagnosis for two family members, as well as new data from additional family members. The updated analysis demolished the statistical argument; the scientists now excluded their proposed linkage. In discussing this reversal, they introduced the possibilities that the original linkage was "due merely to chance," that a single gene might not have a major effect on manic depression, and "that non-genetic factors may contribute" (Kelsoe et al. 1989). They suggested that the reevaluation had highlighted "problems that can be anticipated in genetic linkage studies of common and complex neuropsychiatric disorders" (Kelsoe et al. 1989).

In 1993, Baron et al. also published what amounts to a retraction of their linkage claims, based on a similar reevaluation. Despite these retractions, a recent human genetics textbook (Lewis 1994), without citing evidence, informs students that manic depression "can be inherited as a sex-linked recessive trait or as an autosomal recessive trait." In 1994, there were two more reports of genetic links to manic depression, each pointing to yet another chromosome (Berrettini et al. 1994, Straub et al. 1994). Similar events have already undermined the reported genetic linkages to schizophrenia (Cloninger 1994, Kennedy et al. 1988) and alcoholism (Gelernter et al. 1991, 1993).

Why did the genetic linkage studies of manic depression go astray? Alper and Natowicz (1993) have argued that a "preconceived belief that the primary cause of these illnesses is in fact genetic" can lead to "erroneous conclusions." Ambiguity and bias can potentially creep into at least two important phases of genetic linkage studies of complex human characteristics: the diagnosis or categorization of the characteristic and the statistical evaluation of linkage.

Given the variety and complexity of human behavior, it may be difficult, or even impossible, to assign each person unambiguously to a category such as *normal* or *manic-depressive*. Is there exactly one condition that goes by the name *manic depression*? Can the diagnosis be shaped partly by the currently available methods and categories for diagnosis or by the objectives of the study?

Analogous questions need to be asked regarding diagnoses or assignments for many other complex human characteristics, including schizophrenia, alcoholism, homosexuality, and intelligence. For example, following the 1990 report of a gene linked to alcoholism, authored by Kenneth Blum, Ernest P. Noble, and their colleagues, several other scientists expressed skepticism (Peele 1990) and later reported that they were unable to replicate this finding (Gelernter et al. 1991, 1993). Noble initially countered that the gene they studied was not linked to alcoholism per se, but to "pleasure-seeking behaviors" (Peele 1990). Later, Blum and Noble (1994) amended this description to "addictive-compulsive behaviors." Their claim thus became a moving target.

The appropriate statistical methods for concluding that there is genuine linkage to a complex human characteristic are a matter of considerable debate within the field. In order to calculate the probability of linkage to a complex human trait, researchers have usually proposed a model for genetic transmission of the trait—a model that includes values of several parameters that cannot be measured independently. These parameters include the frequency of occurrence of each form of the gene of interest and the probability that a person carrying the gene will in fact exhibit the trait (this probability is often less than 100%, even when a single gene is linked to the trait). Researchers estimated or assumed values for these parameters in the families they studied. The calculated probability of linkage, as well as its interpretation, depends importantly on the validity of these assumptions.

Many human behavioral geneticists now believe that each of these more complex behavioral disorders is caused by a combination of several disrupted or altered genes (Gershon and Cloninger 1994). Each of these genes may have only a small effect, they may interact in nonadditive ways, and different abnormal forms may occur in different families. So each of these disorders might be due to genes alone, but the complexity of the genetic mechanisms might preclude a definitive finding with current techniques.

This suggestion is theoretically possible and may in itself lead to useful experiments in which additional relevant genes are identified. However, it also may be what scientists call an unfalsifiable hypothesis. That is, there may be no way of disproving it even if it is false; a proponent of genetic causation could always argue that there has been no reliable demonstration of the effect of a particular disease gene because there are additional unknown disease genes or gene interactions that cloud the picture.

In essence, this view retains the mind-set that applies for a single-gene disorder, even while recognizing that several genes may be involved. But if interactions between a gene and other genes or environmental factors are acknowledged to influence a condition, it becomes difficult to describe or quantify the effect of one gene, or all genes, on the condition.

In the absence of definitive evidence, the language of human behavioral genetics may create a bias in favor of simple genetic explanations. For example, by defining any mental condition or characteristic as a *trait*, one suggests that the characteristic is somehow like Mendel's traits of wrinkled or smooth peas and thus may show a regular pattern of inheritance. Similarly, *disease* suggests a biological process that is relatively independent of psychological influences. Attaching a name like *schizophrenia* or *intelligence* to a set of behaviors or functions suggests that the named category corresponds to a physiologically well-defined entity or state, which it may not. Even if a gene has a real effect on a cognitive or behavioral characteristic, such categorization may create a distorted view of what the gene's effect really is (Cloninger 1994).

Sometimes, researchers find that a characteristic (or phenotype) can be caused entirely by nongenetic factors; these nongenetic cases are termed *phenocopies* (i.e., copies of the phenotype), as if they are facsimiles of the condition rather than the real thing. For example, fruit flies develop with four wings instead of two if they have a mutation in the *bithorax* gene or if they are exposed to heat or chemical stress at a critical phase of embryonic development (Capdevila and Garcia-Bellido 1978). The environmentally induced effects are termed *phenocopies of bithorax*, but one might just as well term the bithorax mutation a *genocopy*, following Rose (1995).

The less scientists know about the chain of events linking a gene to a behavior, the greater the likelihood that a correlation is established that does not indicate causation. Even if a correlation between a stretch of DNA and a well-defined, complex human characteristic can be firmly established, what does this correlation tell us? We would like to know what causative role a gene plays in the chain of events leading to a behavioral outcome. This chain of events should include: which gene is involved, which protein it codes for, what the function(s) of this protein is, and how this protein could produce changes in the nervous system that could underlie the mental characteristic. This task is obviously a daunting one, but it is a necessary one. Research addressing such questions, mainly using nonhuman animals, constitutes a major part of current biological research. But such

causal schemes can be elucidated only gradually, while new linkages between genes and human behaviors can appear at any time.

To see how misleading linkage studies might be in the absence of a plausible causal scheme, consider genes about which we already know something. If I have one of the genes that contributes to pale skin, and I sit in the sun for several hours without sunscreen, I will probably get a bad sunburn. If I do it enough, I may increase my risk of getting skin cancer. If we knew only that there was linkage between that segment of DNA and occurrences of sunburn or skin cancer, we might conclude that it was a gene for sunburn or even a gene for skin cancer. Consider another gene, one that contributes to extraordinary growth. Suppose that researchers found linkage between this segment of DNA and the tendency to play NBA basketball. Would we say that this is a gene for basketball playing?

Twin studies

When human genetic linkage studies are unable to provide definitive evidence for a gene's role in causing a complex condition, proponents of genetic causation often fall back on twin studies to demonstrate that genes are crucially involved in the condition. For example, following retraction of Egeland's reported genetic linkage to manic depression in 1989, *Nature* stated, "this leaves us with no persuasive evidence linking any psychiatric disease to a single [genetic] locus" (Robertson 1989, p. 222). Nonetheless, *Nature* argued on the basis of twin studies that readers "should have no reason to doubt the existence of genetic predisposition to psychiatric disease, nor the ability of molecular geneticists eventually to identify the genes responsible" (Robertson 1989). In 1993, following the retraction of the report by Baron and his colleagues of genetic linkage to manic depression, there was no substantiated evidence remaining for genetic linkage to either manic depression or schizophrenia. Nonetheless, David L. Pauls, one of Egeland's coauthors, asserted that "there is overwhelming evidence that genetic factors play an important role in the manifestation of all major neuropsychiatric conditions" (Pauls 1993, p. 5).

Twin studies are also used as evidence that genes play a large role in determining normal mental characteristics, such as those labeled *personality type* or *general intelligence*. Such categories of normal cognitive function are not generally expected to derive from a single gene, even if some complex disorders are due to alteration of a single gene. As an analogy, one can break a transistor radio by removing one component, but no one would seriously argue that the missing component alone normally causes the radio to play a particular radio station. No one has yet claimed to have located a gene for intelligence. But twin studies are used to estimate the net effect of all genes on a characteristic.

Twin studies are often based on the premise that one can estimate the heritability for complex human traits. *Heritability* here is a technical term, indicating the proportion of variation (or variance) in a measurable trait (or phenotype) that is statistically associated with genetic variation.

There are several major problems with the use of this measure in human studies (Hartl and Clark 1989, Kempthorne 1978, Lewontin 1974). The first is that heritability can only be estimated accurately if one can compare the effects of different sets of genes (or genotypes) in organisms that face controlled environments throughout development. This condition requires that individuals mate randomly with respect to their environments, to eliminate gene-environment covariance, a situation that cannot be achieved in studies of human beings. Only then could one estimate how much variance is associated with the genotype. But one would also need to estimate the variance associated with the environment and the variance associated with gene-environment interactions, because the effects of genes and environments are not generally additive. Again, this condition is not possible in human studies. In the absence of such controlled experiments, researchers have attempted to estimate the variation associated with different genotypes by comparing individuals who are categorized by the researchers as having faced similar environments.

Even in breeding studies of plants or nonhuman animals, where heritability can often be estimated accurately, the measure only indicates the proportion of variance associated with genotypic variation for the particular population of genotypes and the particular range of environments tested. Even if a trait has a high heritability within each of two groups of genotypes (e.g., African Americans and Caucasian Americans), the results say nothing about the source of any differences between these groups. If a trait has a high heritability in the environments tested, a major change in the environment (which might include improving education or health care) may dramatically alter not only the phenotypes but also the heritability. In short, heritability cannot be measured accurately in human studies and, even if it could be, it would not indicate the relative importance of genes and environments. The persuasive value of heritability measurements when used by proponents of genetic causation (especially when considering IQ) seems to be the result of confusion of the statistical term *heritability* with the ordinary use of the word *heritable*.

In human twin studies, heritability is estimated by comparing phenotypic variance in identical twins, who share 100% of their genes, and in fraternal twins or other siblings, who share 50% of their genes (on average). This estimate also assumes that the similarity in environment for identical twins is no greater than for fraternal twins. However, there are many reasons for thinking that identical twins share an unusually similar environment. For example, parents often dress them identically and involve them in the same activities; in addition, identical twins often have an extraordinarily close relationship with one another.

The heritability estimates produced by these studies have generally ranged between 40% and 70% for general intelligence or personality type (Bouchard et al. 1990, Plomin et al. 1994). Billings and his colleagues (1992) have pointed out

that these numbers are likely to be overestimates for the general population. Identical twins share all their genes, which may include unique combinations of genes that produce behavioral effects via nonadditive interactions. In such cases, even a small change in the combination of genes, such as is likely to occur for fraternal twins, can have a large effect on the characteristic. Thus, while identical twins have twice as many genes in common as do fraternal twins, identical twins can have much more than twice as many functional combinations of genes in common, which would inflate the estimate of heritability.

Because studies of twins raised together are ambiguous, much of the weight of genetic causation of complex human mental characteristics sits on the shoulders of the relatively few studies of identical twins raised apart; approximately 300 pairs of such twins have now been studied (Powledge 1993). These cases appear to provide well-controlled accidental experiments that demonstrate the role of genes alone. However, there are subtle reasons why this rationale may not apply. Twins in such studies often were raised by relatives or close family friends; in some cases, the twins came into contact with each other and became close friends, as has been documented by psychologist Leon J. Kamin (1974, Lewontin et al. 1984). These kinds of events confound the effect of identical genes with the effects of similar environments; moreover, information on potentially correlated environments is often not available for reexamination.

Another factor now recognized to be important is the different responses (and hence different environments) elicited by children who have different characteristics early on (including race, sex, size, attractiveness, and activity level). That is, children partly create their own environments, and children who are initially similar (due mainly to their genes) are likely to create similar environments, which in turn lead to additional similarities.

Thomas J. Bouchard Jr. and his colleagues, the authors of some of the most influential twin studies, have argued that identical twins "tend to elicit, select, seek out, or create very similar effective environments and, to that extent, the impact of these experiences is counted as a genetic influence" (Bouchard et al. 1990). Richard Dawkins, an ethologist and popular author claims that "[i]f a genetic sex difference makes itself felt through the medium of a sex-biased education system, it is still a genetic difference" (Dawkins 1982, p. 12). These comments underscore the fact that even the simple term *genetic* can be used in a manner that misleads the unwary reader into believing in a simple scheme of genetic causation.

A commonsense view of this situation is that interactions between genes and environment in human child-rearing may be too complex to disentangle by examining such cases. In fact, one might argue that any comparisons of identical twins are rigorously useful only for measuring nongenetic factors; any differences in individuals who have identical genes must be due to nongenetic factors.

In addition to the methodological drawbacks of twin studies, there is a fundamental difficulty with heritability estimates: They supply a number in place of an explanation. A satisfying explanation of the cause of a human mental characteristic would describe a chain of causal events (including activation of genes) rather than just arithmetic. If we knew everything we would want to know about a single gene whose protein interacts with the environment to produce additional effects, we might end up with a progression like, "A caused B, which combined with C to produce D, which was modified by E," and so on. How does one then quantify the role of A or C? It is a bit like asking what percentage contribution George Washington made to the establishment of the United States. Any sensible answer would not be a percentage; it would be a story.

Gene regulation

An indication of the kind of story that is likely to emerge for complex human mental characteristics can be gained by examining recent findings in the areas of gene regulation and the neurobiological mechanisms of behavior. It has become clear in recent years that the story of how a particular gene leads to production of a particular protein at the right time and place, and in the right amount, is often much richer than was previously believed.

Our current understanding is based on a large number of careful studies by molecular biologists working with nonhuman animals or with generations of cells grown outside the body. For many genes, there is a sophisticated network of regulatory mechanisms that fine-tunes the production of the protein. This regulatory network includes pieces of DNA adjacent to the gene and other pieces of DNA quite distant from the gene, both of which strongly influence the amount of protein produced. These regions of DNA can have their effects modified by interactions with multiple proteins produced by other genes and with substances acquired from the diet. Interactions with intermediary RNA molecules are also common. Each interaction can either increase or decrease the amount of protein produced; these interactions are not necessarily additive. The net effect of all these interactions is that the amount of protein produced from a particular gene in a particular cell can depend on its history of cell division, its location in the body, its hormonal environment, and the amount and existence of substances from the diet found in the bloodstream. The picture is one of an immensely complex regulatory system, something like the federal bureaucracy, but one that runs smoothly and efficiently in most circumstances.

Many gene regulatory systems probably include important environmental contributions at the molecular level. Such influences are still difficult to study in human beings, but some have been studied in detail in microorganisms. For example, when the bacteria *Escherichia coli.* is grown in the presence of two sugars, glucose and lactose, it uses all of the glucose first, then switches to lactose. To do so, it activates, via interactions among several types of

sugar and protein molecules, several genes for lactose metabolism only when lactose is present and glucose is absent.

If such complex interactions with food molecules occur in single-celled organisms, which are often thought of as being entirely programmed by their genes, interactions with the environment are likely to be extensive in human beings, leading to a variety of changes in metabolism and physiological functions. Most genetic and environmental effects on behavior are mediated by the nervous system. Environmental conditions have been shown to affect the growth of individual neurons (nerve cells) and the number and strength of connections amongst neurons, both during development and in adults (Greenough and Bailey 1988).

For example, adult rats develop more structural elaboration in neurons if they live in a complex environment, full of toys, than if they live in a blank cage (Greenough and Bailey 1988). More dramatic changes can occur in early development. For example, if a cat or monkey is reared with one eye closed during the first several weeks of life, the organization of inputs to a visual portion of the cerebral cortex is permanently altered, and neurons that would normally respond to an object seen by either eye now respond only via the eye that remained open (Purves and Lichtman 1985).

In embryonic stages, when the numbers, types, and locations of all cells are determined, genes specify players and rules for an extraordinarily complex game, which must be played out to create the body design. The conditions of the playing field can play a critical role. Imagine that the Los Angeles Raiders are playing football against the Chicago Bears; it could make a great difference whether the game is played on a warm, sunny day in Los Angeles or in a snowstorm in Chicago.

For example, a human fetus is normally exposed to sex hormones that have diverse effects on gene regulation, leading to changes in the brain and laying the groundwork for all external sex differences (Breedlove 1994). Most, but not all, of the hormones are produced by the fetus itself. However, if for some reason the fetus or the mother produces too little or too much of a specific hormone (e.g., testosterone or another androgen), or if the fetus lacks appropriate receptor molecules for the hormone, the results can be dramatically different. In cases of androgen-insensitivity syndrome, for example, a genetically male human being can become a completely normal female, except that her internal reproductive organs are inadequately formed; in these cases, the fetus has a defective gene for the androgen receptor protein. In other cases, the amount of circulating androgen can be too great and cause prenatal masculinization of genetic females, transforming the clitoris partly or completely into a penis; this condition can be caused either by a genetic defect (producing adrenal hyperplasia) or by treatment of pregnant women with the hormone progestin (a practice that occurred in the 1950s, before the effects were realized; Money and Erhardt 1972).

For most genes, it is difficult to predict what will happen if you delete or alter one gene. The effects are not likely to be limited to the amount of the protein coded for by that gene. Instead, there may be positive or negative effects on several other proteins, because each gene may interact with other DNA, RNA, proteins, hormones, and substances from the diet to mediate gene regulation. An analogy can be drawn between these interactions and the interactions amongst neurons that mediate behavior. The concept that each neuron can affect many other neurons in a complex interactive network has received considerable attention in neurobiological research. Findings from neurobiological research may thus be useful for understanding gene regulation.

What can we learn from neurobiology?

Since the nineteenth century, neurobiologists have debated whether particular functions can be identified with particular regions of the brain. It is now recognized that particular sets of neurons and connections amongst neurons do serve particular functions. However, the functions they serve do not necessarily correspond to categories of behavioral function for which we have names. Also, within a given small region of the nervous system, one may find neurons that are involved in different functions. If one region of the brain is damaged, particularly in children, functions formerly subserved by that region may not be disrupted seriously or permanently; remaining neurons may continue to mediate the functions reasonably well, and other regions may gradually take over the functions of the damaged region. These insights have led to the concept of a distributed network to describe the nervous system. I suggest that the regulation of protein production from genes, and thus genetic effects on behavior, may also be mediated by a distributed network.

Some of the most popular targets for research on genes affecting mental characteristics are genes that code for neurotransmitter receptors. Neurotransmitters are the substances that mediate communication between neurons. Released by an excited neuron, the neurotransmitter produces an electrical signal in a recipient neuron by altering the structure of neurotransmitter receptors, which in turn prevent or allow positively or negatively charged molecules to enter or leave the neuron. Drugs that affect cognition or behavior, including drugs that are used to treat depression and schizophrenia, produce their effects by attaching to specific neurotransmitter receptors.

The reported genetic linkage to alcoholism, by Blum and colleagues in 1990, claimed linkage to a candidate gene that was a form of the gene for a particular receptor of the neurotransmitter dopamine. It would not be surprising if alterations in a neurotransmitter receptor had widespread effects on the nervous system, but how likely is it that a particular neurotransmitter or neurotransmitter receptor can be identified with one of our categories of human mental and behavioral characteristics?

Each neurotransmitter is used by a large number of neurons that are distributed over much of the nervous system. Neurons that commu-

nicate using one neurotransmitter are often interspersed with neurons that use others. There are generally several types of neurotransmitter receptors for a given neurotransmitter; each type can confer distinct electrical properties on the neurons that house them.

Even just a single type of receptor for a single neurotransmitter is generally distributed over much of the nervous system, in a complex but consistent pattern. Such patterns do not appear to delimit the set of neurons that participate in any single function that we can name. Instead, it now appears likely that each neurotransmitter receptor is like a component of an electrical circuit. Different types of components are useful for different electrical purposes. For example, one neurotransmitter receptor, called the NMDA receptor, has special properties that produce an electrical signal only when multiple, associated events occur simultaneously; in this case, the electrical signal lasts for an especially long time. Each cognitive or behavioral process probably involves a variety of such specific components deployed as needed in different portions of what can be considered to be its circuit.

Neurobiologists have tried to understand the roles played by particular neurons or connections among neurons in distributed networks. They have found that even after a network of interactions has been almost completely described, it is difficult to define the role of any single element. Such detailed knowledge of a network is currently available only for small neural systems, such as one responsible for swimming in the marine mollusk *Tritonia* and another responsible for digestion in lobsters and crabs. Researchers have drawn the equivalents of circuit diagrams of these systems, but examination of these diagrams, in which each neuron is connected to several other neurons, has not revealed what each neuron does during operation of the circuit.

Even these relatively simple systems involve interactions that are too complex for human understanding to assimilate directly. Instead, researchers have found it useful to create computer-based models of these networks, in which they can easily alter just one neuron or one interaction and see what outcome the network then produces, which can be surprising.

For example, physiological experiments revealed a set of neurons that are active during swimming in *Tritonia*, but it was not clear how their interaction could produce swimming or whether these neurons alone are sufficient to generate swimming. Some of the connections among these neurons are complex, involving both inhibition and excitation of each recipient neuron, each with a distinct time course. A computer simulation of this network showed that this set of neurons could produce an output similar to swimming and that the network created swimming by effectively alternating between two patterns of neuronal connectivity on each cycle of swimming (Getting 1983). Computer experiments like these gradually increase understanding of the role of each neuron and each interaction.

This line of research may provide a lesson for the study of gene regulation. Understanding the full behavioral effect of altering a particular gene may require knowledge of all the interactions that involve that gene and their functional consequences. Even then, the effects of a gene may not correspond to a particular category of function.

We may find that a network of interactions, rather than a gene, can be more accurately identified with a particular function. In other words, there may be emergent properties of the network that are not evident in the effects of most single genes or single proteins on their own. In such cases, the same gene may have different effects on a behavior depending on the context, which may include important environmental influences.

In addition, the same gene may have effects on multiple types of behavior or cognitive function. Thus, even if a genuine genetic link to manic depression, for example, is someday found, it might turn out that a variation in the gene can exacerbate certain symptoms of manic depression, but only if combined with other factors, and that the form of the gene also can have effects on individuals who are not categorized as manic-depressive. In such a situation, the notion that the gene's effect is to cause manic depression could be misleading.

The allure of simple genetic explanations

Given the complex interactions that appear to mediate the development and operation of human cognitive and behavioral functions, why do some scientists and journalists apparently search for simple genetic explanations? The search for a gene for each category of experience and behavior may partly be a result of the culture of modern science. Scientists generally seek to reduce complex phenomena to simple descriptions. Such simplification has proven to be extremely useful in devising experiments that are likely to give clear and informative results. Scientists often choose an object for study (e.g., a particular function in a particular organism) because it is simple and thus more tractable. Such choices have facilitated remarkable progress in understanding principles of function. However, in the desire to extrapolate findings from simple systems to the most sophisticated functions of human beings, it is sometimes forgotten that different or additional principles may apply to the most complex systems.

Some simplification is also key to any understanding of a phenomenon. In providing any scientific explanation, scientists define the essential factors at work, extracting them from a morass of detail, much of which is unimportant for the questions at hand. But the type of explanation that provides us with the most understanding is not necessarily the simplest. The reductionism that most scientists espouse leads to descriptions in terms of progressively simpler and usually smaller elements. But many phenomena have emergent properties that cannot be observed or appreciated in descriptions of the smallest components.

Instead, explanations that describe processes at a level of organization not too distant from the phenomenon itself often provide the most understanding. For example, an explanation of a human behavior

that includes a description of how certain networks of neurons are active during the behavior may provide greater understanding of how the behavior is produced than an explanation solely at the level of genes or smaller components. If we had a complete description of alcoholism in terms of subatomic particles alone, would you believe that you now understood alcoholism?

There is also a danger of oversimplification by omission or inaccurate portrayal of factors that are crucial to research objectives. Scientists are often schooled to provide the most parsimonious explanations of phenomena, on the grounds that a complicated explanation should not be put forward if the evidence supports a simple scheme just as well. The problem is that the desire for parsimony can sometimes lead researchers to choose a simple explanation even when the evidence actually points to a more complicated scheme. For example, it has been known for some time that concordances (the odds that two individuals will either both have or both not have a given trait) for schizophrenia are very much higher for identical twins (39%–46%) and for children of two schizophrenic parents (34%–43%) than for first-degree relatives (4%–12%). This situation is incompatible with single-gene causation of schizophrenia independent of the environment, yet that is exactly what many investigators sought (Cloninger 1994).

An additional misinterpretation of studies claiming linkage between a gene and a human behavior is the notion that the behavior is therefore destined. There is a widespread and yet completely false notion that if something has a genetic cause, it is unalterable, but if it has an environmental cause, it is alterable. Some people respond to new claims of linkage between a gene and a certain characteristic—for example, alcoholism or homosexuality—by arguing that this linkage proves that the characteristic was fixed from birth.

Such an explanation may seem attractive if one wishes to deny that either personal choice or societal conditions contribute to the characteristic. For example, in a recent report on the mouse *obese* gene (Monmaney 1995, p. 21), the *Los Angeles Times* stated: "An important social implication of the obesity gene research, researchers say, is that it shows that obesity is not a weakness or a failure of willpower. In that sense, this high-tech lab work may help erase some of the stigma of being fat."

In fact, some conditions known to be caused by genes alone can be prevented or reversed by nongenetic means, such as providing a phenylalanine-free diet to children who have the genetic disorder, phenylketonuria. On the other hand, some environmental events, such as alcohol abuse by pregnant women, can often have permanent effects (Spohr et al. 1993).

The idea that our genes make us who we are has been so successful that even scientists occasionally mistake evidence of a biological correlate of a mental or emotional characteristic for evidence that the characteristic is determined genetically. For example, when a group of researchers reported in 1994 that they had isolated the mouse *obese* gene, they introduced their work by stating, "[a]lthough obesity is often considered to be a psychological problem, there is evidence that body weight is physiologically regulated" (Zhang et al. 1994, p. 425). In fact, psychological influences are necessarily mediated by physiological mechanisms.

A discovery of a biological correlate addresses neither the role of genes nor the role of nongenetic factors. The notion that *biological* implies genetic seems to assume that nongenetic events affect us without affecting our bodies and in particular our brains. Within a scientific world view, at least, such a view is untenable. One expects all effects on cognition or behavior to be mediated by changes in the body, usually in the nervous system. This notion says nothing about the original cause of the change or our responsibility for it.

Research into gene regulation and neurobiology has revealed intricate interactions among genes, proteins, hormones, food, and life experiences. These findings suggest that lasting explanations of most human mental and behavioral characteristics are not likely to be simple and are likely to arise only gradually. A real understanding of the causation of complex characteristics may require us to come to terms with the emergent properties of multiple interactions. In the meantime, pronouncements of simple genetic causation should be met with a critical eye and with questions about exactly what has and has not been demonstrated.

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