Behavioral Genetics in Transition

A mass of evidence—animal and human—shows that genes influence behavior. But the attempt to pin down which genes influence which behaviors has proved frustratingly difficult

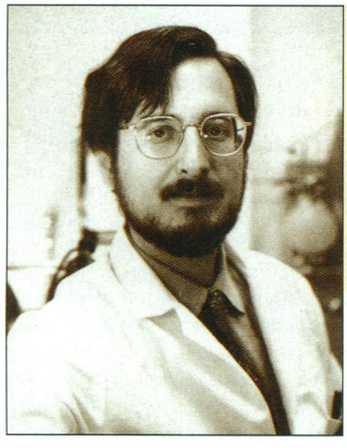
Exactly 70 years ago a German dermatologist named Hermann Siemens published the first complete description of a new method for determining whether scholastic achievement and other types of human behavior were inherited or due to some factor in the environment. He compared the school transcripts of identical twins, who have exactly the same genetic endowment, and fraternal twins, who are no more closely related genetically than any other siblings. More than three quarters of the pairs of identical twins received similar grades and comments from teachers, he found, whereas only a fifth of the fraternal twin pairs compiled such comparable records. The "similarities of body features and mental capacities," he wrote, demonstrate that both originate in "a hereditary pool."

Siemens published his twin experiment in 1924, when the eugenics movement was at its peak. In the United States, supporters of what Harvard University geneticist Edward M. East described as the mission "to cut off defective germ-plasm" included many prominent biologists, as well as political figures from radical Margaret Sanger to conservative Calvin Coolidge. ("Biological laws show...," the president believed, "that Nordics deteriorate when mixed with other races.") That same year Coolidge signed the Immigration Restriction Act, which blocked immigration from southern and eastern Europe to prevent supposedly inferior Latin and Slavic genes from swamping the United States. By 1930, 24 states had enacted laws to sterilize the "feeble-minded."

The Nazis' pseudoscientific justifications for anti-Semitism made eugenics so unrespectable that biologists fled the entire subject of genetics and behavior. Journals deleted "eugenics" from their titles; in 1965, the American Genetics Association changed its official credo from "the improvement of plants, animals, and human racial stocks" to the more neutral-sounding "improvement of plants, animals, and human welfare." Social scientists promoted a view of humankind as shaped almost exclusively by culture; human geneticists steered clear of behavior, even as they found gene after gene that was intimately involved in many other aspects of human metabolism and development.

Filling the gap, psychiatrists and psychologists launched a concerted scientific effort to make behavioral genetics respectable again. Today the *Archives of General Psychiatry* is filled with claims that heredity plays a role in everything from gregariousness and general cognitive ability to alcoholism and manic depression. Sensing a change in the Zeitgeist, molecular geneticists have begun to re-enter the field. Indeed, the pendulum has swung so far back that David Reiss, a psychiatrist at George Washington University in Washington, D.C., has declared that "the Cold War is over in the nature and nurture debate."

Not quite—behavioral genetics remains the subject of such bitter passions that anyone entering the field should "be prepared for a lot of abuse," says David E. Comings, a medical geneticist at the City of Hope National Medical Center in Duarte, California. In the best-known recent example of the opposition, a University of Maryland conference on the genetic aspects of violence was scuttled in 1992 after a protest led by Peter Breggin, director of the Center for the Study of Psychiatry in Bethesda, Maryland, and one of the most prominent critics of the field. "'Behavioral genetics' is the same old stuff in new clothes," Breggin says. "It's another way for a violent, racist society to say people's problems are their own fault, because they carry 'bad' genes."



"THERE DEFINITELY IS A GENETIC BASIS FOR MANY CONDITIONS, RANGING FROM TOURETTE'S SYNDROME TO ALCOHOLISM."

JOEL GELERNTER

Behavioral geneticists strongly disagree with that assessment. "There definitely is a genetic basis for many conditions, ranging from Tourette's syndrome to alcoholism," says Joel Gelernter, a psychiatrist at Yale University. "The evidence is overwhelming that something is there." Shelley D. Smith of the Boys Town Center for Hereditary Communication Disorders in Omaha, Nebraska, concurs: "There are clear genetic components to behavior," she says. "We just want to try to get at what the mechanisms are."

Moreover, those in the field say, the research is aimed at helping people—not stigmatizing them, as Breggin claims. Smith, for example, has been attempting to understand the genetic background to dyslexia. "It may be linked to a region on chromosome 6 that is involved with the immune system," she says. And if dyslexia turns out to be a hereditary disorder linked to the immune system, "that would tell us a great deal." That information, says Smith, might well lead to new and more effective treatments, or give hints about other, related disorders.

Indeed, in spite of the remaining contentiousness in this field, there are signs of a growing consensus that heredity plays *some* role in human behavior—a consensus that includes, however grudgingly, those most critical of behavioral genetics. Steven Rose of Britain's Open University, co-author of the anti-eugenics polemic *Not in Our Genes*, agrees that genetic influences "exist and are real"—the problem, he says, is society's tendency to translate this likelihood into what he calls "neurogenetic determinism," in which genes determine behavior rather than influencing it in concert with personality and the social environment. Even Breggin concedes genetics "may have some part" in the spectrum of human action, although he believes the search for subtle hereditary effects on behavior among the "incredibly oppressed and stressed" inhabitants of inner cities "is misguided, to say the least."

The increased acceptability of behavioral genetics has three main scientific causes, of which the first is the huge accumulation of data about hereditary influences in animal behavior (see story on page 1690). "Put a border collie puppy with a Newfoundland moments after being born," says University of California, Berkeley, geneticist Jasper Rine, "and the collie will still have 'eye'"—

SAM OGDEN

THE PURPOSE OF BEHAVIORAL GENETICS "IS NOT TO PUSH PEOPLE INTO TROUBLE BUT TO PULL THEM OUT."

XANDRA O. BREAKEFIELD

the ability, associated with border collies but otherwise unusual in dogs, to maintain eye contact with people and other animals. "Raise a Newfoundland with border collies, and it will never have 'eye.' These things are pure genetics, and they're absolutely uncontroversial—they've been known for almost 30 years."

A second cause is the appearance of larger and more sophisticated studies of human beings, most famously those of the Minnesota Center for Twin and Adoption Research in Minneapolis, captained by Thomas J. Bouchard. Since 1979, the project has intensively examined almost a thousand pairs of twins, identical and fraternal, of whom 128 pairs were reared in different homes—a fascinating natural experiment, as Siemens recognized in 1924. In huge numbers of traits, Bouchard says, identical twins resemble each other much more than their other relatives. Skeptics may quarrel with individual data points, says Bouchard, "but the arrows all point in the same way."

The third, and most important, cause is the growing understanding that the interaction of genes and environment is much more complicated than the simple "violence genes" and "intelligence genes" touted in the popular press. Indeed, renewed appreciation of environmental factors is one of the chief effects of the increased belief in genetics' effects on behavior. "Research into heritability is the best demonstration I know of the importance of the environment," says Robert Plomin, director of the Center for Developmental and Health Genetics at Pennsylvania State University. The same data that show the effects of genes also point to the enormous influence of non-genetic factors. "They build on each other," says Plomin.

Complex behavioral traits, says Dean Hamer of the National Cancer Institute, are the product of multiple genetic and environmental antecedents, with "environment" meaning not only the social environment but also such factors as the "flux of hormones during development, whether you were lying on your right or left side in the womb, and a whole parade of other things." If that picture were not complex enough, Hamer argues, the relationships among genes and environment "probably change from place to place. Genes might have a somewhat different effect on someone in Salt Lake City than if that person were growing up in New York City."

"It's rather like high blood pressure and cholesterol," says Kenneth Kendler, a psychiatrist at the Medical College of Virginia in Richmond. "We know genes play some role, but there is also major environmental influence. You inherit the genes, but it also depends on whether you smoke and how many anchovy pizzas you eat. Eat enough pizza, and it doesn't matter what your genetic endowment is—you're at risk for a heart attack." On the other hand, he points out, if compulsive eating has a genetic component, then overindulgence in pizza might not be purely environmental. "Genes and environment," he says, "loop out into each other and feed back on each other in a complex way that we have just begun to understand."

Finding the genes proves difficult

Yet going from the general belief that genes and environment "loop out into each other and feed back on each other" to identifying specific genes tied to specific behaviors has been far more difficult than researchers initially hoped. They have had enormous success finding genes that lead to clearly identifiable behavioral phenotypes—those behavioral traits in which a population can easily be divided into people with a condition and people without it. An example is profound retardation, which is often accompanied by hyperactivity, autism, or repetitive involuntary motions. Scientists have found more than a hundred mutations that lead to this syndrome and in this way have repeatedly demonstrated the connection between individual genes and at least some types of behavior.

But the record is much worse for less clearly identifiable phenotypes, in which the population is not so easily split into those with and those without a particular trait. Depression and schizophrenia are examples. Although severe cases of both conditions can be readily identified, the dividing line between schizophrenics or depressives and the rest of the population is not absolutely precise. And the science is correspondingly more difficult. Time and time again, scientists have claimed that particular genes or chromosomal regions are associated with behavioral traits, only to withdraw their findings when they were not replicated. "Unfortunately," says Yale's Gelernter, "it's hard to come up with many" findings linking specific genes to complex human behaviors "that have been replicated." One exception he notes is the linkage of some inherited cases of Alzheimer's disease to genes on chromosomes 14, 19, and 21.

That record may improve as researchers develop more sophisticated models of the genetic influences on behavior and experimental techniques to test them. But the models and techniques of the past have not been sufficient. The troubles began in 1965, when a team of researchers suggested that men with an extra Y chromosome (XYY males) are more aggressive than men with the usual XY complement of sex chromosomes. After an avalanche of media coverage, other researchers attacked the data; a 1993 report from the National Academy of Sciences dismissed the link as unproven. The pattern continued into the 1980s, with scientific reports linking reading disability to genes on chromosome 15, schizophrenia to chromosome 5, psychosis to chromosome 11, and manic depression to chromosome 11 and the X chromosome (see story on page 1693). All were announced with great fanfare; all were greeted unskeptically in the popular press; all are now in disrepute.

More recently, a group of researchers led by Kenneth Blum at the University of Texas Health Science Center in San Antonio and Ernest P. Noble of the University of California, Los Angeles, School of Medicine announced in 1990 the discovery of a possible causal link between alcoholism and an allele of the D_2 dopamine receptor gene (DRD2), which is important to the chemical transmission of signals in the brain's "pleasure center." Afterward, Comings's team at City of Hope reported associations between DRD2 and autism, drug abuse, attention-deficit hyperactivity, post-traumatic stress disorder, pathological gambling, and Tourette's syndrome, as well as alcoholism. Because other groups have failed to replicate these findings, investigators are proceeding with caution (see story on page 1696).

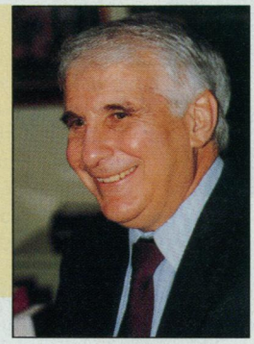
Behavioral geneticists were not discouraged, as demonstrated by two recent papers in *Science*. In the first, Dean Hamer and four colleagues at the National Cancer Institute reported last July that homosexuality may be associated with a region at the tip of the long arm of the X chromosome known as Xq28 (*Science*, 16 July 1993, p. 321). Because each

mother passes on to her male offspring just one of her two X chromosomes, the probability that two sons will receive the same Xq28 is 50 percent—20 out of every 40 randomly selected pairs of brothers. Hamer's group looked at 40 pairs of gay brothers and found that 33 had identical Xq28 markers, suggesting that this region may hold a gene that plays a role in male sexual orientation.

And in October a Dutch-American team led by Han Brunner of the Nijmegen University Hospital reported linking "a syndrome of borderline mental retardation and abnormal behavior," including "arson, attempted rape, and exhibitionism," to an apparently rare mutation of a gene on the X chromosome (*Science*, 22 October 1993, p. 578). The gene codes for the activity of monoamine oxidase A (MAOA), a compound that metabolizes dopamine, serotonin, and noradrenaline, which are in turn involved in the transmission of neural signals in the brain. In its mutated form, the gene doesn't work, and the affected individual lacks MAOA—which to the researchers suggested a relation between the gene and aggressive behavior.

BEHAVIORAL GENETICS IS "ANOTHER WAY FOR A VIOLENT, RACIST SOCIETY TO SAY PEOPLE'S PROBLEMS ARE THEIR OWN FAULT."

PETER BREGGIN



GINGER ROSS BREGGIN

Methodological troubles

Neither finding has yet been replicated, but even if they are, they are unlikely to mollify the critics of previous efforts to link specific genes to human behaviors. The critics' complaints about the previous work fall into four general areas: misuse of statistical methods, failure to define the trait under study, bias in the selection of cases and controls, and inadequate sample sizes. Arguments over statistics can be a morass, but one of many disputes involves "heritability," the measure usually quoted when researchers refer to a trait as being, say, "50% heritable."

Heritability is calculated by partitioning a trait into its genetic and environmental fractions—a procedure, argues Peter Schönemann, a psychologist at Purdue University in West Lafayette, Indiana, who is an outspoken critic of behavioral genetics, that "assumes the relationship between them is additive, which it isn't. So you're using a measure that embodies assumptions you know are wrong—it invites abuse." He adds, "Somehow it always seems that the crummier the test, the higher the heritability it produces."

These troubles are exacerbated by the tendency for behavioral traits to be inexactly defined, which means that researchers into the same subject cannot ensure that they are measuring the same phenomenon. Determination of mental illnesses, for example, is ruled by the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association. The APA has just issued the fourth edition in this constantly evolving series; one New York psychiatrist describes the changes as "reflecting the latest accumulation of knowledge, plus a fair dose of habit and prejudice." The potential for disrupting research, he says, is "obvious."

Third, some of the critics charge that researchers in behavioral genetics have not always controlled well enough for bias. "Typically," Kendler says, "studies of mental disorders have taken patients in the institutions researchers work at, which are usually university teaching hospitals. But the people who are referred there are not random." They may belong to a particular social class, he said, or have unrepresentative previous experience with mental illness. "There's any potential number of biases, and you're not in a strong position to extrapolate from them. It's a big problem."

Finally, even the most careful work can be undone by an inadequate sample size. Much behavioral genetics research has attempted to link traits to single genes that are passed on in a simple Mendelian manner from generation to generation. The model is the single gene on chromosome 4 that causes Huntington's disease, which was identified by looking for genetic markers in an extended family from Venezuela with the world's highest incidence of this dreadful condition.

Unfortunately, this attractive model is misleading for behavioral genetics, according to Brian K. Suarez, a psychiatrist at the Washington University School of Medicine in St. Louis. "We knew sickle-cell anemia and Huntington's were monogenic [caused by a single gene] for decades before we discovered which genes were affected," he says.

DARROW MONTGOMERY

"I don't believe that any of the psychiatric disorders are that simple. They probably involve multiple genes, which may interact in linear or nonlinear ways." Because of the fluctuations, a given gene might show its face in one small group of, say, schizophrenics, but not in a second—while still being a real contributor to the disease. As a result, confirming a discovery requires a sample large enough to capture its vacillating effects. How big is that? Suarez decided to find out.

Geneticists call such multiple-gene effects "polygenic" (caused by many genes) or "oligogenic" (caused by a small group of genes), and have developed mathematical models to estimate the conditions necessary to observe polygenic or oligogenic genes. In one such simulation, Suarez modeled a disorder which affected 10% of the population and was associated with six genes. "I asked, if I determined one of them, how long would it take to replicate the finding? And the answer is, it takes a lot longer to replicate a true finding than it does to discover it for the first time."

Suarez projected that if the trait was 50% heritable and each family in the study had 10 members (4 grandparents, 2 parents, and 4 children), detecting one of the genes would require studying 175 families—that is, almost 2000 people. Replicating that finding would require studying 781 families—another 8000 people. To find and confirm each additional gene, researchers would need to go through the whole business again. "Suddenly you're talking about tens of thousands of people and years of work and millions of dollars."

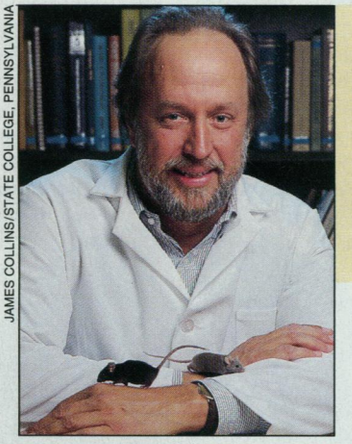
In an effort to get around these obstacles, behavioral geneticists like Comings, and Plomin at Penn State, are employing a more sensitive assay technique called "linkage disequilibrium." Instead of looking for a simple association between, say, depression and a genetic marker, linkage disequilibrium statistically compares the prevalence of the marker in depressives to its prevalence in the population at large. Used in the right circumstances, linkage disequilibrium can detect even tiny genetic contributions.

THE "ENVIRONMENT" INCLUDES "WHETHER YOU WERE LYING ON YOUR RIGHT OR LEFT SIDE IN THE WOMB, AND A WHOLE PARADE OF OTHER THINGS."

DEAN HAMER

Plomin's team is using this approach to study *g*, a measure of general cognitive ability that has the advantages of apparently being highly heritable and certainly being less inflammatory-sounding than "intelligence quotient," to which it is almost identical. "As soon as you mention intelligence or, God forbid, IQ, people go ballistic," Plomin says. The hypothesis is that *g* is connected to a group of genes, most of which make minuscule contributions.

Plomin hopes to pluck out what might be called the "biggest little effects"—the few genes that contribute as much as a few percent to *g*. His team has extracted blood samples from 63 Caucasian children with low, medium, and high IQs, measured the prevalence of more than 60 genetic markers, and compared their prevalence with those in controls. To avoid spurious leads, the group then recompared all positive correlations with those from a second, smaller group of 44 children with extremely high or low IQ scores. At present, Plomin says, he has one "interesting" candidate allele that his team is putting to further study. "We're going to keep replicating it until it's incontrovertible," he says.



JAMES COLLINS/STATE COLLEGE, PENNSYLVANIA

"RESEARCH INTO HERITABILITY IS THE BEST DEMONSTRATION I KNOW OF THE IMPORTANCE OF THE ENVIRONMENT."

ROBERT PLOMIN

Yet even Plomin believes that this probably will not be enough. Behavioral geneticists "have made plenty of mistakes in the past," he concedes, but the field "has a learning curve." Researchers have "improved" their methods, though he believes it unlikely that the techniques available today will be able in many cases to identify the genes that make small contributions to behavioral patterns. "If I were a betting person," he says, "I'd bet on a totally different technique" emerging in the next few years.

Societal implications

Behavioral genetics is clearly in transition. Mounting evidence from animal and human studies shows that genetics has a role in human behavior, though scientists are still struggling to identify the specific genes responsible for that role. As researchers grope for more successful methods, different groups continue to dispute the societal implications of their findings. For every Steven Rose who fears that "neurogenetic determinism" will erode human dignity, there are other researchers who believe these discoveries may help individuals with mental and physical problems.

Both viewpoints can draw support from the Dutch-American team's discovery of the mutation in the gene for MAOA that has been linked to some types of aggressive behavior. The mutation is simple—a single cytosine base has been switched with a single thymine base. But the interpretation is not. To Peter Breggin, the readiness to jump from "good lab technique" to "sweeping generalizations about human behavior" is an example of the dangers posed by this kind of research. "These individuals are mildly retarded," he says. "There they are in the middle of families of unaffected people—is it any wonder that they are full of frustration and anger? The prisons are full of mildly retarded people. Should we jail the rest of them?"

Group member Xandra O. Breakefield of Massachusetts General Hospital says she "wouldn't disagree" with Breggin's dismay. After the article was published, she was "stunned" to receive phone calls from lawyers who wanted to test their clients on death row for MAOA deficiency, hoping that it might exculpate them; equally bad were the talk-radio hosts who suggested sterilizing people who carry what one journalist called "the mean gene." Although Breakefield faults some of the language used by her team in preparing their reports, she also believes that neither side wished to grapple with the complexity of the interaction between genes and environment. "People reacted strongly in the most knee-jerk type of way," she says.

MAOA deficiency, in her view, does not automatically lead to violence, or indeed any other kind of behavior. "Even in this particular type of syndrome," Breakefield says, "which has major metabolic consequences, we have people who are happily married with children. They had the right type of support." Everyone needs support, she says, and the purpose of this kind of research is to discover what that support is, and who needs it. "The idea is not to push people into trouble but to pull them out. With a little intervention, you can be fine."

Breakefield points out that MAOA deficiency has many effects, including the inability to metabolize wine, cheese, and many types of Chinese foods—a severe reaction that can lead to cardiac failure. "Why should we deny these people help?" she asks. "With many of these deficiencies, if you don't change the diet within the first year, it's too late. Doesn't that mean we should look for this problem early? If we take the position that the ethical implications of this are something we can't deal with, then we'll never be able to help people like this." She adds, "It all should be done carefully, though. How could we do it in the right way, ethically? I'm not sure I know."

Comings furnishes the example of Tourette's syndrome, a highly heritable disorder which causes its victims to move and speak uncontrollably. "Having taken care of over 2500 Tourette's patients," he says, "I can tell you they exhibit a lot of disinhibitive sexual behavior. I had one boy who had Tourette's and kept grabbing himself in the crotch publicly. The school authorities turned him in, of course, and the father was accused of sexual abuse. He lost his wife and his family, but if we'd understood this was a hereditary disorder that was highly treatable, this family would have survived."

To people like Comings, Tourette's should be regarded in the same way as mild diabetes—a hereditary inconvenience that is no reason to discriminate against anyone. But others, like Harvard geneticist Jonathan Beckwith, regard this as the counsel of Pollyanna. "We are creating a new class of the 'asymptomatic ill,'" he says. "Health insurance and life insurance companies are already stigmatizing people with supposedly bad genes who show no symptoms. One wonders why it should be assumed the process will stop with insurance companies."

On both sides, one area of agreement is clear. "Our society handles this issue illogically and inconsistently," says Richard J. Herrnstein, a Harvard psychologist who has just completed a book with the conservative scholar Charles Murray on the policy implications of differences in IQ. "On the one hand, the conventional wisdom rushes out to embrace shaky studies that argue that alcoholism is genetically determined, but the idea that intelligence has a genetic component is pure anathema."

Herrnstein believes "there is less willingness at the public policy level or the level of the educational establishment to look at individual differences than there was in the hot days of 1969 or 1970. There's a taboo on this subject. It's not because the subject is not on people's minds—quite the reverse." He laughs. "It's on people's minds, all right."

–Charles C. Mann

Charles C. Mann is a frequent contributor to Science.