The Promise and Pitfalls of Molecular Genetics

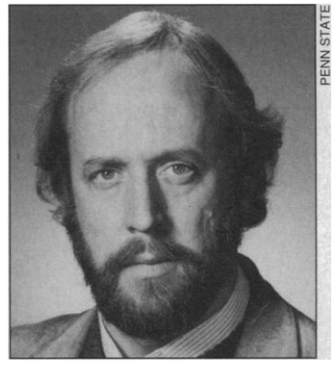
BERLIN—"There are colleagues who think I'm a racist, sexist, fascist pig," says psychologist Tom Bouchard with his usual affable smile. Bouchard's offense? The University of Minnesota researcher is a human behavioral geneticist—probably the best known in the world. By studying differences between identical twins reared apart, he's estimated the relative contributions of genes and environment in shaping traits like intelligence and personality (*Science*, 12 October 1990, p. 223). Along the way, he's attracted abuse from those who equate human behavioral genetics with eugenics and gained sufficient public attention to have his Minnesota Twins Project featured on the cover of *Newsweek*.

The traditional way. Nick Martin with experimental subjects.

But the controversy generated by Bouchard's past work could be just a warm-up for what's to come over the next decade or so. Not satisfied with assessing the overall influence of genes on human psychology, some behavioral geneticists are now beginning to turn to molecular genetics in an attempt to pinpoint the individual genes that are involved. At a recent Dahlem workshop,* many of the 45 attendees from 11 nations predicted that in a few years they will be routinely mapping and sequencing genes that influence intelligence, personality, and important psychiatric disorders like schizophrenia. Combining these techniques with twin studies should make it possible, participants said, to see how individual genes interact with environmental factors—including those in the prenatal environment (see box)—in influencing human psychology. In "perhaps 30 years time," says Nick Martin, a behavioral geneticist from the Queensland Institute of Medical Research in Brisbane, Australia, teachers could be designing classes for individual children based on their genetic makeup.

Sounds fanciful? Certainly. But already a team led by Robert Plomin from Pennsylvania State University has launched an effort to find genetic markers that correlate with high IQ, and researchers from the Univesity of Colorado recently identified two markers that they believe are linked to dyslexia. These efforts, in particular, left the Dahlem participants in no doubt that the shift to molecular genetics has begun. But, despite the enthusiasm among some behavioral geneticists for such work, there have been few major successes so far—even in the search for genes linked to mental illnesses, which should be a more manageable problem than tracking down genes associated with, say, intelligence. Indeed, much of the discussion at the workshop was about the pitfalls inherent in sensitive genetic association studies and the more traditional linkage studies now being used by human behavioral geneticists with a molecular bent.

Take the large-scale association study being conducted by Plomin at Penn State. Plomin's group has amassed data from a battery of cognitive tests given to 600 U.S. children aged 6–12. Now molecular geneticists are typing the children for more than 100 polymorphic genetic markers that are thought to be linked to neural function—among them are some of the cDNAs isolated from human brain tissue by Craig Venter, from the National Institute of Neurological Disorders and Stroke in Bethesda. Their goal: to identify alleles that are particularly common in children at the top end of the IQ scale. Plomin doesn't expect that any single gene will have a major effect on IQ. But with a large number of markers, he believes it should be possible to pick out numerous genes that appear to have small effects, making it possible for the first time to list individual genes affecting intelligence. The risk inherent in such studies, however, is that spurious associations may be picked up.



PENN STATE

The new way. Robert Plomin is looking for genetic markers associated with high IQ.

The most obvious source of error is stratification—the possibility that the population being studied contains a mix of different subgroups, which tend to mate among themselves. If, for whatever reason, these groups tend to score differently when tested for IQ, Plomin's study could throw up associations for alleles that just happen to be common in a particular subgroup but have little to do with IQ. "Given the number of tests they're doing, they're almost bound to find associations," says psychiatric geneticist David Pauls of Yale University. "But who knows what that means?"

Plomin's group remains optimistic. Peter McGuffin, a psychiatric geneticist from the University of Wales in Cardiff, who is a coinvestigator in Plomin's study, thinks that stratification won't be a major problem. By restricting the study to a sample of U.S. Caucasians, "we're selecting a sample which, at least on the face of it, is homogeneous," he says. Plomin also says he will replicate the study using a second sample before publishing the results.

Linkage limitations. The alternative is to go for a second approach—genetic linkage studies, which exploit the tendency for genes that are close neighbors on the same chromosome to be inherited together. Because linkage studies look within families for a correlation between the possession of marker genes and a phenotypic trait, they're not confounded by stratification effects. The method has its own drawback, however: Linkage analysis is much less sensitive, making it harder to detect genes that exert only a small influence on the trait being studied. That's no problem for medical geneticists trying to track down simple Mendelian disorders like cystic fibrosis, where the disease may be caused by a single mutant allele with a very major effect. But for a trait like IQ, which is probably influenced by tens—or even hundreds of genes—it's a major limitation.

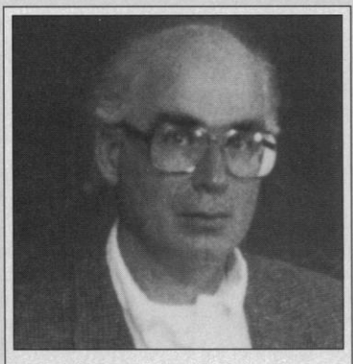
Even for psychiatric illnesses like schizophrenia and manic depression, which are thought to be influenced by at most a handful of genes, geneticists are having problems picking out individual genetic loci that may be important. There have already been some embarrassing setbacks: In 1987, for instance, Pauls' group at Yale published a paper in *Nature* indicating linkage between a genetic marker on chromosome 11 and manic depression. But when they followed up with a larger study, the apparent

*The Dahlem Workshop on "What are the mechanisms mediating the genetic and environmental determinants of behavior? Twins as a tool of behavioral genetics" was held in Berlin from 17 to 22 May. The results will be published by John Wiley & Sons Ltd., Chichester, England.

Twin Studies Go Back to the Womb

Even if research into the genetic control of human psychology is sewn up by molecular biology (see main story), twin researchers will still be left with a major puzzle: Just what are the environmental variables that account for the substantial nongenetic variance in human psychological traits? Robert Plomin from Penn State believes that future twin studies "will have at least as much to say about the environment as about genetics."

By studying twins, behavioral geneticists can divide the total variance in a psychological trait between three components—one due to genetics and the other two due to subtly different environmental influences: the shared and nonshared environments. The shared environment refers to influences experienced by both members of a pair of identical twins raised together, while the nonshared environment refers to experiences that are specific to individuals—including twins. In a situation where only one of a pair of identical twins develops schizophrenia, for example, the difference between the twins must be due to some factor in the nonshared environment.



UNIVERSITY OF MINNESOTA

Twin pioneer. Tom Bouchard urges study of prenatal environment.

Contrary to the "socialization" theories espoused by many psychologists, twin studies have revealed that the shared family environment exerts little influence on traits like IQ and personality: Differences between individuals in one family are generally larger than predicted by socialization theories. But so far, attempts to identify variables to explain the more influential nonshared environment have borne little fruit.

That may just reflect a lack of imagination among researchers. But Tom Bouchard from the University of Minnesota has an alternative explanation: Researchers may simply be focusing on possible environmental influences that occur too late in development. "Some nonshared environmental effects are prenatal," he asserts. For example, chance variation in the embryos' precise positioning in the uterus can result in differences in fetal nutrition, he says.

One recent study suggests that Bouchard may have a point. At the University of Southern California, Laura Baker and colleagues have been studying the concentration of the sex hormones estradiol and progesterone in blood sampled from the umbilical cords of newborn twins. (Neonatal levels of sex steroids have been found to correlate with later measures of behavior.) The team, which published its findings in the February issue of *Developmental Psychobiology*, wasn't surprised to find a strong genetic component to the variance in hormone levels. "But we were amazed to find little effect of the common [uterine] environment," says Baker: Some nonshared factor in the uterine environment apparently caused the nongenetic variance in neonatal hormone levels, resulting in differences within pairs of twins.

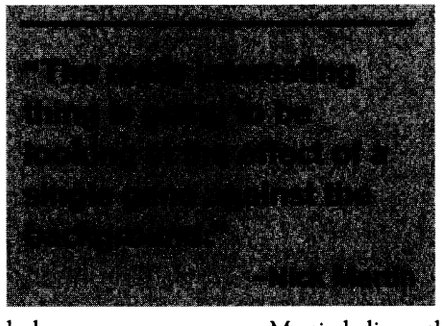
It seems that there's good reason for twin researchers to head back to the womb, in search of at least part of that elusive nonshared environment.

–P.A.

linkage disappeared. "We're still not quite sure what happened," says Pauls. All he can surmise is that the positive finding was one of the occasional chance significant results that affect all research relying on statistical probability testing.

Larger scale attempts to trace loci involved in psychiatric diseases using linkage are also experiencing tough going. Eighteen centers in Europe are now almost 2 years into a European Science Foundation project to look for loci associated with schizophrenia and manic depression, using some 150 genetic markers spread throughout the human genome. Although it's still in its early days—the project is expected to continue beyond 1995—the researchers have so far failed to discover any convincing linkages. "All those guys are starting to get depressed themselves," says Queensland's Martin. "Maybe there aren't any genes of really major effect."

But at least one recent study is keeping alive the confidence that such efforts will eventually pay off. A team led by the University of Colorado's David Fulker, working with Shelley Smith from the Boys Town National Research Hospital in Omaha, has found two separate loci, linked to different genetic markers on chromosome 15, that influence reading ability in children. Fulker's team looked at a sample at the extreme end of the distribution for the trait, focusing on families with dyslexic children. "You can get power from selected samples," he says. Although the paper appeared in an obscure publication, *Reading and Writing: An Interdisciplinary Journal*, several behavioral geneticists say that it could prove a landmark study. Andrew Heath, from Washington University, St. Louis, says that researchers who had begun to despair of ever identifying the genes that influence normal variation in human psychology are now saying: "Maybe there is hope for us."



If similar studies identify other genes influencing traits like IQ and personality, says Queensland's Martin, "the really interesting thing is going to be looking at the effect of a single gene against the background—both the genetic background, and the environmental." Identical twins present an ideal model in which to look for interactions between individual genes and the environment. Martin points to a study by the Norwegian geneticist Käre Berg, who in the early 1980s looked at the influence of the *MN* blood group genes on serum cholesterol.

Berg found that, within pairs, identical twins who possessed the M allele had very similar blood cholesterol counts, while those who carried only the *N* allele often gave widely differing readings. His conclusion: The M allele doesn't seem to interact strongly with the environment—in this case diet—in determining blood cholesterol level, while the *N* allele's effect on the trait can be pushed around strongly by environmental influences.

Martin believes the same approach could be used with genes for IQ and personality. "I can't wait to get into it," he says. And although a practical application for such research is now a "pie in the sky," says Martin, it is exactly the kind of work that could lead to such *Brave New World* activities as measuring the precise genetic makeup of children so that the teaching environment could be tailored to shape their development efficiently.

One thing's for sure: If you're looking for a quiet life away from controversy, behavioral genetics isn't going to be the field to join.

–Peter Aldhous