Body and Mind

BY MELVIN KONNER, M.D.

New Keys to the Mind

A dozen years ago, at the peak of the noisy controversy over sociobiology — a then-new science of the biology of behavior — it was common for critics to say there was no evidence of a direct link between a gene and any complex human behavior. Even then this was somewhat disingenuous.

The link between genes and behavior was, admittedly, not firm. And what was at stake was a view of human nature that had risky implications. Too many times in the past the genes-and-behavior argument had been misused politically, to support anti-Semitism, racism, sexism and other forms of bigotry and exploitation. Understandably, liberals — a category that includes many academics, including me — were prepared to be extremely skeptical.

But the book that caused the debate reviewed an impressive weight of evidence. It was Edward O. Wilson's "Sociobiology: The New Synthesis," and its contention was that the fullest understanding of animal and human behavior would be based on the fact that behavior had evolved genetically. Behavior, like anatomy, was a part of adaptation: a set of solutions to age-old problems posed by natural selection. And in its evolution and adaptation could be discerned the underlying truth that behavior, like height and weight, must, to an important extent, be coded in the genes.

Wilson was not alone. Decades of studies by psychologists had shown more similarities in various dispositions, abilities and psychiatric problems between identical twins than in twins with different genes; more similarities in biological parent-child pairs than adoptive ones (even when the biological children were separated from the parents at birth); and, in general, the more genes in common, the greater the psychological similarity. I was convinced. These studies, the critics said, showed only correlations that could have occurred for many other reasons.

Behavioral geneticists cited animal studies — resembling in many ways the classical genetics of Gregor Mendel and his pea plants — that were controlled experiments proving genetic effects: on timidity, for instance, or maze-running, in rats. The habit of exploring a strange environment, as opposed to cowering in a corner, can be passed from generation to generation. But these were only rats, of course. A reasonable person with no political agenda might conclude at that point — as I did — that there was sufficient evidence that genes influence behavior. But, understandably, even decades after World War II, memory of versions of this idea in Nazi propaganda cast a pall over discussion.

It's not that anyone ever claimed that genes are so important that environment could turn out to be unimportant. As I remove my spectacles to squeeze my nose and think, the computer screen blurs, and I am reminded for the thousandth time that partly genetic problems (in this case, myopia) can be solved by ingenious tinkering with the environment. Yet, going to the other extreme, the anti-gene critics repeated: "No conclusive evidence."

I used to listen wistfully to the debates, dreaming of a time when the direct links, which still seemed like science fiction, would be shown. Little did I know how soon powerful evidence would begin to present itself. Advances in the field are being made rapidly now as a result of the biotechnology revolution begun in the 1950's by Francis H. C. Crick and James D. Watson with their discovery of the chemical structure of DNA, the genetic material of plants and animals. By the early 1980's, the research keys created by this revolution had yet to be fitted to the brain.

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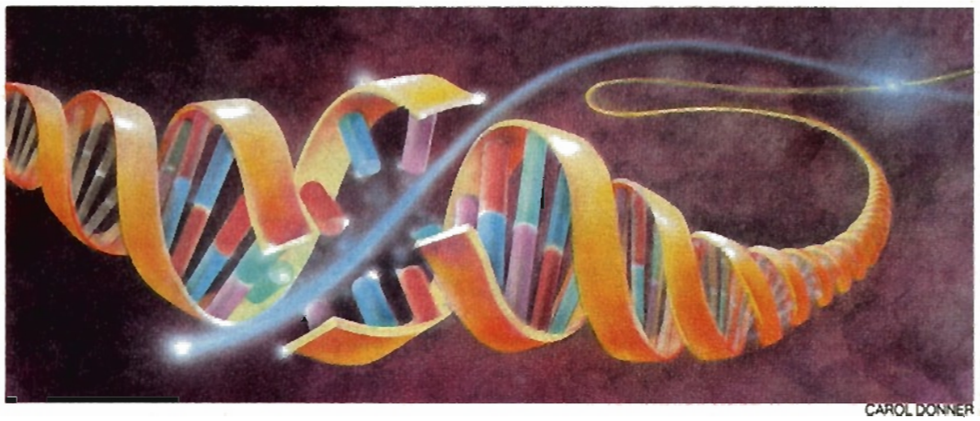

CAROL DONNER

Genes strung along the winding strands of human chromosomes contain codes for such traits as susceptibility to certain diseases. Can they also determine a person's emotional makeup?

But at that point, painstaking research was started with simple creatures like sea slugs — a sort of large snail without a shell — and fruit flies. Through what only seemed an incredible stroke of luck (more likely, as Pasteur put it, it was chance favoring the prepared mind) the first great breakthrough in understanding the molecular biology of the brain came in humans. A geneticist, James F. Gusella, now of the Massachusetts General Hospital, and a psychologist, Nancy S. Wexler, now of Columbia University College of Physicians and Surgeons, headed the study of a large Venezuelan family with Huntington's disease.

This dreaded condition, which killed folk singer Woody Guthrie, strikes young adults, usually in their 30's and 40's, but results from the action of just a single gene, inherited way back at the union of sperm and egg. This much was known from classical genetic studies of families: if you had a parent with the disease, your chance of getting it was 50-50. Although the long-term course of the disease was a relentless degeneration of movement centers in the brain, with the ultimate outcome death, sometimes the first symptoms were emotional. In some sense at least, this was a mental disease.

The Venezuelan family afforded an extraordinary opportunity for what are called linkage studies. In this work, maps are made of genes and the order in which they lie together on strands of chromosomes. Where certain sequences appear, chemical enzymes can now be used to cut through the chromosomes and genes (or, to use their chemical term, the deoxyribonucleic acid — the DNA) to isolate, identify and find them. Compare a map made of North America in the 12th century, after the Vikings touched down in North America, to the maps made after the great voyages of discovery of the 16th century. That's what new knowledge supplied from DNA technology is doing for gene mapping. The number of genes — that is, the "genetic markers," or signposts for inherited traits — that can be located and identified has increased enormously.

The Gusella-Wexler team found a marker close to the gene for Huntington's disease; family members who had that gene usually had the disease. Most chromosomes have two arms, short and long; the Huntington's disease gene was situated in a specifiable part of the short arm of chromosome 4 (there are, in all, 46 human chromosomes in 23 pairs; all except the X and Y chromosomes, which specify sex, are identified arbitrarily by number). This was the first human disease of any kind to be mapped using only the new methods. With it, a powerful new approach to brain genetics was born.

Huntington's disease had always been studied from the brain down. Autopsies had shown that certain brain regions

The revolution in molecular biology now offers powerful evidence in the debate over the link between genes and complex human behavior.

were affected most, and chemical measurements had been made throughout the 70's to investigate how the brain had gone awry. Such studies remain promising, but the new genetics may be preparing an end run around them. Current map makers are "walking" toward the gene on chromosome 4 — narrowing the search to the precise section where it must be. When that section is small enough, then it will be practical to anaylyze it chemically. From the chemical sequence, the protein produced by the guilty gene will be identified. It is this protein that must in some way be responsible for Huntington's disease. Hence, it may be the key to treatment.

Nor are other genetic mappers idle. Great excitement was generated last year by researchers studying a group of Amish relatives. Led by Janice A. Egeland of the University of Miami Medical School, the research team found that a form of manic depression is linked to a marker on chromosome 11. This illness causes severe mood swings, often including reckless or even psychotic actions at one extreme and incapacitating depression at the other. When manic, a person may talk fast, pile up speeding tickets, plan outrageous business ventures, make love to many strangers; when depressed, the world may seem so dark that getting up from a chair is almost impossible, and suicide may follow. Lithium has provided significant help, though suicides still occur.

Near that marker linked to manic depression is the gene for an enzyme called tyrosine hydroxylase, which is crucial in the brain's manufacture of certain, small molecules that affect mood changes. Antidepressant drugs work by retaining these molecules in the brain. We may be approaching an understanding of the cause of dangerous mood swings, beginning with a gene on a known place on a chromosome, going through an enzyme crucial to brain chemistry, and ending with a better explanation than we have now for a vastly complex pattern of human behavior.

Meanwhile, animal studies proceed apace. Trusty drosophila, the fruit fly relied on by geneticists since the turn of the century, has enabled investigators in the last few years to find the genes for ion channels. These are key functional units of the membrane, or skin, of the nerve cell. The brain's ability to regulate the flow of ions — charged particles like sodium and potassium — in and out of the cell is crucial to electrical impulses that make it work. Such channels are made up of proteins, coded by genes. As these genes are mapped and sequenced, we will zero in on one of the keys to brain function and behavior.

Similarly, studies of mouse brains using the new genetic methods have revealed the structures of the proteins that make up certain brain receptors — for instance, the receptor for the messenger molecule known as GABA. GABA's release from certain brain cells and attachment to receptors on adjacent cells inhibits anxiety. Valium and many other anti-anxiety drugs act by promoting that attachment. Now that we have unraveled the sequence of the receptor protein itself and of the gene that makes it — in effect, a gene for the inhibition of fear — perhaps we will identify a gene for fear itself. Is it inconceivable that we could then one day increase our measure of control over it?

How much longer will it be legitimate to say, "There is no conclusive evidence for a direct link between a gene and a complex behavior?" According to my guess, no more than a few years. And where will we stand when that step has been taken? On the shore of a great ocean, much vaster and more forbidding than any mere geographic explorers have viewed. Pity the soul that is not stirred by such a prospect. Are there dangers? What a question; since when was exploration supposed to be as safe as a parlor game? Will we relinquish all control of our bodies and our minds, becoming deterministic puppets dangled at the end of genetic strings?

I take off my glasses and squeeze my nose to think. The screen blurs — my largely genetic defect. I put the glasses on again. The words come clear. ■