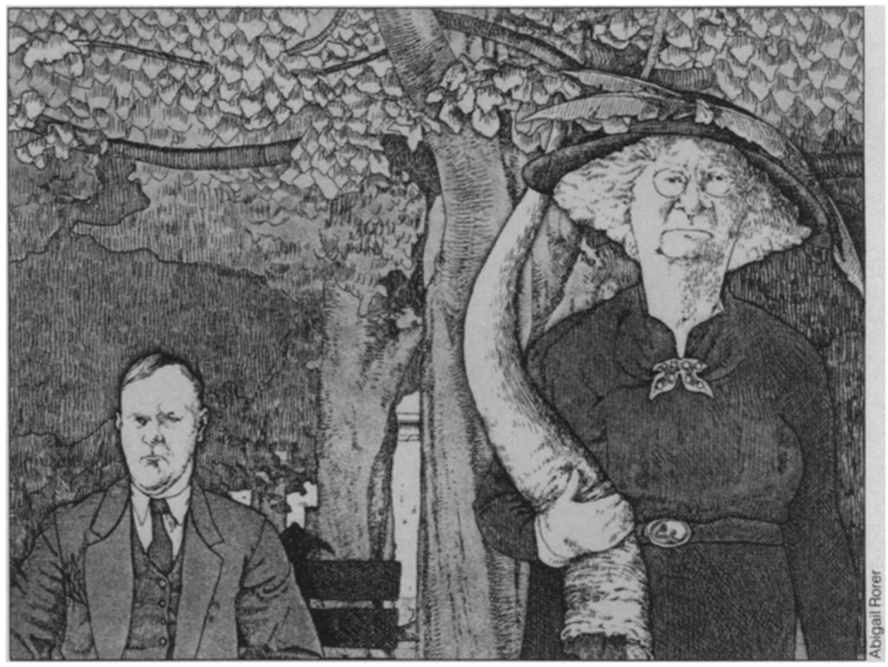

Melancholy Genes

BY WRAY HERBERT

Most researchers are convinced that serious depression is inherited, but the genetic workings remain a mystery. Behavioral scientists are now turning to recently developed gene-splicing technologies in their effort to isolate the depressive genes and see how they behave.

Suspicions about the hereditary origins of mood disorders — and specifically manic-depressive illness — can be traced back as far as the 19th century, when the German psychiatrist Emil Kraepelin referred to the hereditary "taint" of "circular insanity" in his famous classification of mental diseases. Nearly a century later, despite an immense amount of psychogenetic research, Kraepelin's suspicions remain unconfirmed. Scores of family studies, twin studies and, more recently, studies of adopted children have fortified the notion of inheritance, but even those who are convinced by those studies concede that they have no idea just how depression is transmitted from one generation to the next.

But research may now be entering a new stage. Scientists at the National Institute of Mental Health have recently embarked on a project aimed at uncovering the actual gene — or genes — that are responsible for manic-depressive illness. The creation of the new DNA laboratory — which is the first to use the new gene-splicing technology for behavioral research — signals the conviction of some psychiatrists that behavioral disorders must ultimately be investigated at the molecular level. And it may also reflect growing disappointment with reigning research strategies — especially the search for so-called "gene markers" — that some say have shed little, if any, light on the genetic mechanisms underlying mental illness.

Genetic marker research is primarily statistical research aimed to test whether or not patients with mental disorders typically show other characteristics as well — a particular blood type, a high level of certain enzymes — which are known to be dictated by the genes. The idea is that if manic-depression could be shown to accompany another genetic characteristic, however unrelated, it would be possible to assume that the gene for depression is linked to the known genetic site — located near it on the chromosomal map. But genetic marker studies have failed to reveal any such link, many psychogeneticists say. A recent research report by University of Rochester geneticist Lowell R. Weitkamp suggested that depression is linked to the gene for human leukocyte antigen (HLA) (SN: 12/5/81, p. 356). But though Weitkamp is optimistic about his results, other have already begun to seriously question his findings; HLA has been studied before with negative results. In fact, says psychiatrist John I. Nurnberger Jr. of NIMH, he and his colleagues have done marker studies for some 30 characteristics and have yet to discover a reliable linkage.

Similarly, the so-called "pedigree" studies — computer analyses of hereditary patterns in single multi-generation families — have been successful in producing only negative findings by and large. They have all but debunked the notion that depression is carried on the X chromosome — once a popular theory — and they have not turned up any useful connection with dominant or recessive genes. But they have also indicated that depression is not transmitted at random. In short, researchers say, the sum of psychogenetic study has made almost irresistible the idea that depression is in the genes, but it has yielded scant evidence about just where it is coded and how it manifests itself.

The new DNA project departs most significantly from past research by exploring not linkages but the genes that are actually suspected as causes of depression. It is an approach that could not have been taken without the recombinant DNA techniques developed over the past decade, according to psychiatrist Elliot S. Gershon, chief of the section on psychogenetics, and biochemist Prabhakara Choudary, its chief scientist. The inaugural experiment, for example, is designed to determine whether or not neurotransmitters in the brains of manic-depressives — in this particular case, beta-endorphin — might be genetically defective. It is known that the opiate systems of manic-depressives are often different from those of normal subjects — manic-depressives are less sensitive to physical pain — but it is very difficult to study beta-endorphin and other transmitters in human subjects. Peptides cannot be extracted from the brain of a living subject, and the scarce amounts that can be extracted from plasma have been so altered that they are difficult to study.

Gene-splicing technology allows the researchers to bypass this obstacle. Because the genetic code is known for pro-opio melano cortin — a precursor of beta-endorphin — it is now possible, using enzymes, to slice off the small segment of DNA that controls that substance alone. These tiny pieces of DNA are then spliced to plasmid DNA in bacteria, which grow quickly, thus producing a large quantity of the specific DNA fragment needed for research.

Such fragments of DNA, which are known to code specifically for brain peptides, can then be treated radioactively and used as "probes" of human DNA. A subject's DNA is sliced up chemically and spread out on an electrophoretic gel, in which each gene will migrate to a certain spot, depending on its character — its molecular weight and charge. The single-stranded probe will always bind with the complementary sequence of bases — its code — thus identifying the gene for beta-endorphin in the subject's own genetic material. The gene's location in the electrophoretic field reveals its nature.

What the researchers hope to find is what they call a "polymorphism" — variance in the gene's character. Just as another gene is known to produce variance in human eye color, for example, this gene is suspected of causing variation in brain peptides — an elevated level of beta-endorphin in some people perhaps, or beta-endorphin with a slightly altered nature. If it can be determined that the beta-endorphin gene in manic-depressive patients is consistently different from the same gene in normal subjects, it may become possible for the first time to identify people at risk for depression — or for having children at high risk. Genetic counseling — which psychiatrists have found extraordinarily difficult, because they are unable to tell their patients anything with certainty — could become quite simple, much as it is now with sickle cell anemia. Ultimately, Choudary says, it may be possible to correct genetic abnormalities in the laboratory.

Such clinical applications are probably far off, Gershon emphasizes. He and Choudary are guessing that beta-endorphin is implicated in affective disorders, but it may turn out that there is no significant variance in the gene or that the variance has no clinical significance; the first results should be available in six months. If they discover nothing, they will have to begin again with other suspect proteins. They already have plans to study the beta-adrenergic receptor (the receptor for beta-endorphin, which becomes less receptive under the influence of antidepressant drugs). But unlike the genetic code for beta-endorphin, which is known, the code for the receptor protein has not yet been figured out; thus the DNA fragments cannot be cloned for research. A fundamental task in the enterprise will be to decode the genes for various substances related to brain function and mood.

Psychogeneticists who have heard of Gershon's project see it as an interesting and bold, if slightly premature, endeavor. Depression is such a heterogeneous grouping, some note, that until a subgroup is found in which the disorder is strongly genetic it will be very difficult to detect any reliable connections; it is the same problem that has confounded much genetic marker research. Others say that the beta-endorphin hypothesis is a shot in the dark, that there are many brain chemicals implicated in mental illness with very little known about how they affect — or are affected by — mental disorder. Genetic marker research is at least based on some known facts about gene sites, some psychiatrists argue, and if the research has not paid off yet, it might, with more and more sophisticated statistical models, eventually do so.

Psychiatrist William Bunney Jr. of the University of California at Irvine — formerly chief of the biological psychiatry laboratory at NIMH — agrees that, following a half-decade of research on opiates and mental illness, no hypothesis implicating a specific neurotransmitter — including beta-endorphin — is particularly compelling. "The DNA research will have a guaranteed theoretical payoff," he says. "Whether or not we're in the right decade for a practical payoff is difficult to tell."

Gershon agrees that the project is ambitious and, while he is cautious about its promise, says that it is the only way to even begin exploring the causes of inherited psychiatric disorder. "The linkage studies, if they are successful — and we have serious doubts that they will show us anything — can tell you where the gene is that is transmitting the disorder," he says. "But they can never tell you the nature of the actual gene. This has the hope of telling us that." □

By isolating and studying fragments of genetic material responsible for the production of beta-endorphin, a neurochemical transmitter, scientists hope to discover if the DNA of manic-depressives is consistently abnormal in character.