to make a peptide that binds to the AIDS virus receptor. Since the binding data indicated that a naturally occurring neuropeptide binds to the receptor, they began by looking for such a peptide. To do this, they searched a computer data bank, looking for sequences shared by the AIDS virus and other known substances. The computer found an octapeptide from the viral coat which matched up with a segment of the coat of Epstein-Barr virus. They called this AIDS peptide peptide T because it contains four threonines. Then Edward Ginns of NIMH "thumbed through books" and found that the peptide also is part of vasoactive intestinal peptide, or VIP, a 28 amino acid peptide that acts on the gut and the central nervous system.

They then looked at the sequences of all known AIDS virus isolates and discovered that a pentapeptide within the original octapeptide remains constant. "It is a mini-constant region within a hypervariable region," says Pert. Moreover, they learned that this pentapeptide prevents the replication of the AIDS virus in lymphocytes, presumably by preventing the virus from entering cells. It also binds to brain—including monkey brain and human brain obtained after autopsy—in the same pattern as the antibodies against the AIDS virus receptor.

When the researchers gave peptide T to rats and monkeys, they found that it seemed nontoxic and that it entered the animals' brains. In fact, says Peter Bridge, they "never found an LD_{50}", which is the dose that kills 50% of the animals receiving the drug. Standard toxicological studies of drugs always include an LD_{50} as an indicator of a drug's lethal dose.

In Sweden, says Wetterberg, the AIDS patients who received peptide T had no ill effects. The only adverse effect occurred when a nurse doubled the rate at which a patient was being infused with the drug. The patient's blood pressure dropped from 120 to 90. The patient, however, "did not feel anything. He had no subjective side effects," Wetterberg says.

Although the Swedish study was not meant to be a scientific test of the drug, Wetterberg says he was encouraged by the way the patients improved when they took it. Their lymphocytes increased in number and the virus' effects on their brains, as measured by nuclear magnetic resonance, declined. One patient had a severe case of psoriasis as a result of his AIDS infection and his lesions cleared up entirely after four weeks of treatment. The psoriasis has now returned, Wetterberg says. The patients have been off the drug since the end of October.

If indeed peptide T is relatively nontoxic, its apparent safety seems paradoxical since it is derived from VIP, which has definite physiological effects. VIP in large doses causes an increase in blood pressure and also causes diarrhea, for example. But Michael Ruff and his colleagues from the NIMH speculate that these known effects of VIP may be caused by a different part of the molecule than peptide T.

When VIP was first sequenced, says Ruff, investigators noticed that it has a natural cleavage site about 13 or 14 amino acids from its carboxyl terminus. They suggested that perhaps VIP normally is split up and that the two sections of it have different actions. This hypothesis was not pursued, however, until the NIMH investigators came upon peptide T. Ruff, Ginns, and their colleagues are looking to see if a 12-amino acid fragment of VIP exists in nature and, if so, what it does. Although VIP apparently binds to the brain, no one has any idea what it does there.

Wetterberg speculates that the normal function of VIP in the brain may be a clue to the AIDS-associated dementia and other neurological problems. The AIDS virus, he says, may bind to VIP receptors in the brain and prevent VIP from acting as a neuropeptide. Peptide T may overcome this effect of the AIDS virus.

Although the Swedes are testing peptide T alone against placebo, they and the NIMH group think that if the drug is successful it may eventually be given along with an anti-viral agent, such as azidodeoxythymidine, or AZT. Peptide T does not kill the AIDS virus and patients may retain active viruses which may enter cells as soon as peptide T is withdrawn.

Of course, peptide T, promising as it looks, has not yet been scientifically tested in humans and it could still turn out to be a disappointment. Although the theory that led to the drug is attractive, the real test will be the clinical trials. ■ GINA KOLATA

ADDITIONAL READING

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Manic-Depression Gene Tied to Chromosome 11

A dominant gene causes this psychiatric disorder in 60 to 70% of those who inherit it

A group of researchers from the Massachusetts Institute of Technology, the University of Miami School of Medicine, and Yale University School of Medicine has found a genetic marker for manic-depression—a piece of DNA so near the manic-depression gene that it is inherited along with the disease-causing gene. This is the first genetic marker for a mental illness and the investigators stress that it is expected to lead to a new understanding of the biochemistry of manic-depression and also to new treatments. "We see this as a landmark study," says David Pauls, one of the study investigators.

At the same time, two other groups report that they have failed to find the marker in other populations of patients with manic-depression, indicating that there is more than one gene that predisposes to this mental illness. The three groups report their results in the 26 February issue of *Nature*.

The new study indicates that at least some cases of manic-depression are caused by a dominant gene on the tip of the short arm of chromosome 11. Although the researchers do not yet know what the manic-depression gene is, they are intrigued by the fact that at least one gene in this region of chromosome 11—the tyrosine hydroxylase gene—is involved in the synthesis of the neurotransmitter dopamine. Dopamine is thought to be involved in the genesis of manic-depression.

Yet, at least in the case of manic-depression, the gene is not necessarily destiny. Only 60 to 70% of those who inherit the gene get the disease, and investigators speculate that some as yet unknown environ-

mental factors may determine whether persons with the gene develop the illness.

The genetic marker occurs in the Old Order Amish—a group of over 12,000 people living in relative isolation in Lancaster County, Pennsylvania. Ten years ago, Janice Egeland of the University of Miami School of Medicine initiated an extensive genetic study of these people, including a study of the incidence and inheritance of manic-depression, which is also known as bipolar illness (*Science*, 2 May 1986, p. 575). It was this study that led to the current result.

As many as 1 to 2 million Americans suffer from manic-depression, a disorder characterized by extreme mood swings. During the mania phase, patients are elated or are irritable. They say that thoughts race through their minds. The patients exhibit "increased activity and talkativeness," says James Sussex, one of the study investigators from the University of Miami. "They have poor judgment and behavioral excesses with sometimes catastrophic economic and social consequences." At other times, the patients are clinically depressed. They have, according to Sussex, "feelings of hopelessness and helplessness and changes in their sleep patterns and appetite. They may have suicidal thoughts and actions."

In between these periods of mania and depression, the patients are essentially normal. Although there are drugs that usually relieve the symptoms of manic-depression, the disorder can be a tragedy for patients and their families. "There are millions of people in the United States whose lives are essentially ruined by psychiatric disorders—schizophrenia and manic-depression are among the most severe," says Elliott Gershon of the mental health institute.

For years, mental health researchers have suspected that a predisposition to manic-depression is inherited. Their evidence, however, has been indirect—it has not been the sort to lead them immediately to a gene or genes causing the illness. For example, they knew that if one identical twin has the disease, the other has about an 80% chance of having it also. Among adopted persons with manic-depression, only 2% of the adoptive parents had the disease, but 30% of the biological parents did.

To find a genetic marker for the manic-depression gene, the researchers needed data from large families in which the disease is inherited. The idea is to trace the inheritance of the disease and to look for a DNA segment that is inherited along with a predisposition to develop manic-depression. This now-standard technique has been used to find markers for several inherited diseases, including Alzheimer's disease and Huntington's disease.

The advantage of studying manic-depression in the Amish is that they tend to have large families and good genealogies. Moreover, the genetics is simplified because few Amish enter or leave the community. The entire population is descended from about 50 couples who emigrated from Germany between 1720 and 1750.

Another advantage is that manic-depression is relatively easy to detect in the Amish because they do not use drugs or alcohol, which can mask the psychiatric symptoms. In addition, it is easier to ascertain the increased death rate from suicide that is attributable to the disorder because there are virtually no crimes or acts of violence in the Amish community.

"For the first time molecular genetics has entered the arena of psychiatric disorders."

But because there is, inevitably, a degree of subjectiveness in psychiatric diagnoses, the researchers studying the Amish attempted to be scrupulously strict in their diagnostic criteria. They enlisted a team of four independent psychiatrists to diagnose suspected cases of mental illness in the population and only when there was a complete consensus was a person included as a case of manic-depression.

When they agreed that individuals did have the disease, they sent samples of their white blood cells to David Housman of the Massachusetts Institute of Technology and Daniela Gerhard, who is now at Washington University in St. Louis, where the two looked for evidence of genetic linkages.

As soon as the chromosome 11 linkage became known, a group of researchers at the University of London, Oxford University, the Centre National de la Recherche Scientifique in France, and Brogaspitalinn in Iceland began looking for the linkage in three Icelandic families in whom manic-depression appears to be inherited through a dominant gene. The group, headed by Stephen Hodgkinson of the University of London, reports no linkage to genes at the tip of chromosome 11. In addition, Gershon and his colleagues at the National Institute of Mental Health looked at three North American families in whom the disorder appears to be inherited through a dominant gene. They, too, found no chromosome 11 linkage.

These findings do not cast doubt on the Amish results. What they mean, say the investigators, is that more than one gene may cause manic-depression. "I think we have a *major* answer [to what causes manic-depression]," says Kidd. "But it is not the only answer. It is very common to find that in different families what appears to clinicians as the same disease is caused by different genes."

The results also by no means indicate that the Amish alone have the particular manic-depression gene that is on chromosome 11. "There is no reason a priori to believe that the Amish are genetically unique," says Kidd. "From a genetic point of view, they're the same as other European families."

The significance of the Amish finding, for now, is that it opens up new research areas. Among the first questions being addressed is, Is it some defect in the tyrosine hydroxylase gene on chromosome 11 that causes manic-depression? Karen O'Malley of Washington University in St. Louis has cloned the rat tyrosine hydroxylase gene and, using her gene as a probe, Edward Gibbs, Brian Martin, and John Kelsoe of NIMH fished out the normal human tyrosine hydroxylase gene. They are now sequencing it. At the same time, they are isolating the gene from Amish who do not have the manic-depression marker, from Amish who have one copy of the manic-depression gene, and from Amish who have two copies of the manic-depression gene. Within a few months, according to Gibbs, they should know if tyrosine hydroxylase is abnormal in Amish patients with the manic-depression gene.

If the tyrosine hydroxylase work pans out, it could lead to a new understanding of the biochemistry of manic-depression. But even if it does not show that the enzyme is the culprit, the researchers at least have a good idea of where to look for the gene. They also can start investigating why as many as 30 to 40% of those with the gene never get the disease. As a result, they may learn new strategies to prevent manic-depression.

Even before this research begins, the marker for manic-depression is expected to have social consequences. By showing that this psychiatric disorder is genetic in nature, the investigators hope they have removed the stigma of manic-depression. They have shown, says Egeland, that "these swings in mood and energy are not necessarily things that people can control."

Now that the manic-depression genetic marker has been found, mental illness research has taken a new turn. "For the first time, molecular genetics has entered the arena of psychiatric disorders," says Housman. But no one expects it to be the last time."I think this is a strategy that will be extremely useful in studying other mental illnesses," says Paul. ■ **GINA KOLATA**