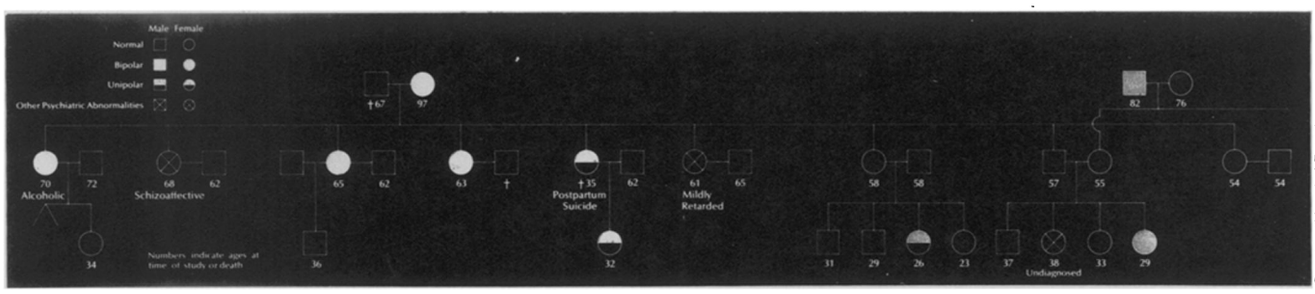
Inheriting Mental Illness: Nature & Nuture

Though much of it is circumstantial, evidence of a genetic component in certain emotional illness is growing steadily. Just how such conditions may be "transmitted," however, remains a mystery.

BY JOEL GREENBERG



Gershon/Hospital Practice

This strange-looking diagram might seem at first to be a psychiatrist's version of a sophisticated football play. Where split ends, tackles and linebackers should be among the Xs and Os are printed terms such as "alcoholic," "schizoaffective," "postpartum suicide" and "mildly retarded." Further inspection reveals, of course, that this is not a sketch of a fake to the alcoholic up the middle followed by a touchdown pass to the manic depressive; it is the pedigree, or "family tree," of three generations of an extraordinary New England family. It is meant to illustrate in the extreme how emotional illness — in this case depression-related afflictions — can run in families.

"Like several other serious mental diseases ... the affective disorders [primarily depression, manic depression and related conditions] have been shown to have a strong familial, and almost certainly inherited, component," says Elliot Gershon, chief of the section on psychogenetics at the National Institute of Mental Health. As Gershon suggests, there is growing evidence of genetic components in some schizophrenia, alcoholism and drug abuse, as well as depression. The federal Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) is currently spending more than $11 million in 115 research studies related to alcohol, drug and mental health problems.

Despite the investment and growing sophistication of such studies, the exact mechanisms of genetic transmission have yet to be discovered. The links between genes and behavior are still essentially hypothetical because little *physical* evidence of their existence has been uncovered. David E. Comings of the City of Hope National Medical Center in Duarte, Calif., has reported the discovery of "the major gene in depressive disease" (SN: 1/13/79, p. 20). But Comings's work and conclusions have been widely challenged, and so far the study has not been replicated.

As ADAMHA administrator Gerald L. Klerman suggests, the inheritability of certain mental conditions — unlike the single-gene transmission of a physical disease such as Huntington's chorea — probably involves "multiple genes or complex interactions" between biochemical/genetic factors and environmental ones, such as family upbringing. Patterns of behavior, some experts note, can be "inherited" non-genetically through early exposure. Says Theodore Reich of Washington University in St. Louis: "The human family is an extremely powerful mechanism for transmitting information."

To further cloud matters, recent evidence suggests that although a substantial percentage of schizophrenia and depression — about half, according to Harvard psychiatrist Seymour Kety — has a strong genetic factor, the remaining cases stem primarily from environmental causes. Acknowledging this probability, Gershon says of depressive patients, "We don't know which person is genetically ill or not genetically ill."

Some experts concede that such frustrations are to be expected in a field where, unlike physical medicine, one cannot "see" major afflictions; indeed, even diagnosing some emotional problems represents a sizeable hurdle. Nevertheless, the mass of "circumstantial" evidence pointing to the genetic susceptibility of certain individuals to serious mental health problems is growing increasingly impressive.

From the results of his own work, as well as other studies, Gershon states that "the weight of such evidence ... indicates that the familial component in affective disorders is largely genetic." Some of the most convincing research linking genes to depression and other behavioral illness involves studies of twins. Various studies

show that if one identical (monozygotic) twin suffers from affective disorder, the chance that the other twin will also be afflicted is 70 percent, according to Gershon. However, among non-identical twins or siblings, parents or children of the afflicted person, the risk drops radically, to about 15 percent; among "second-degree" relatives (uncles, aunts, grandparents, etc.), the rate drops to about half of that. This makes a strong case for genetic involvement, Gershon says, because monozygotic twins have all their genes in common, while dizygotic twins and first-degree relatives have half in common and second-degree relatives have less than half in common.

Perhaps even more dramatic are statistics from studies of children given up by their biological parents and adopted shortly after birth. A recent study by researchers at the University of Brussels and the New York State Psychiatric Institute found that among the biological parents of 22 adopted, manic-depressive patients, 7 percent had at some point suffered from the same disorder and 22 percent had exhibited diagnoseable depression. This compared with corresponding rates of 2 percent and 10 percent among the parents who were not biologically related to the youngsters, but who adopted and brought them up. This and other work indicates that relatives of manic-depressive, or "bipolar," individuals run a somewhat higher risk of affective disorder than do relatives of depressive, "unipolar" persons, Gershon says.

And among the most widely cited research is Kety's well-known study of adoptees in Denmark. He has reported a "significant concentration" of depression among biological, as opposed to adoptive, relatives of depressed persons. The apparent genetic factor is three times stronger in biological relatives of depressed patients than in their adopted families, according to Kety (SN: 10/7/78, p. 244).

Still, the inheritance factors reported in depression do not seem as strong as those that may be involved in schizophrenia — a term that has become almost synonymous with serious psychosis and that involves major disturbances in thought, mood and behavior, including some loss of touch with reality. Kety's study of 5,000 Greater Copenhagen residents reveals that the rate of schizophrenia among the biological parents, siblings and half-siblings of 33 schizophrenic subjects is nearly 4 times that of the biological relatives of a matched control group and about 5 times that of the schizophrenics' adopted families.

The bulk of family research indicates that the prevelance of schizophrenia among parents, brothers, sisters and children of schizophrenics is 8 to 10 times higher, and among more distant relatives 2 to 3 times higher, than in the general population, according to Seymour Kessler of the Genetic Counseling Program at the University of California at Berkeley. Kessler also notes that children in families where *both* parents are diagnosed as schizophrenics "show a rate of schizophrenia some 35 to 45 times higher than that of the population at large."

According to Kessler, "all" of the dozen major studies of twins and schizophrenia show that if one identical twin develops the disorder, there is a 40 percent to 50 percent chance that the other will as well; this compares with just a 10 percent risk among fraternal twins. "The overwhelming direction of the evidence supports the view that genetic factors are operative in schizophrenia," he says.

Similarly, "almost all [studies] have concluded that alcoholism is a strongly familial disorder," says Theodore Reich. While the risk of alcoholism in the United States is estimated at 9 to 15 percent for males and 2 to 4 percent for females, the risk for immediate male relatives of an alcoholic is 35 to 40 percent and for immediate female relatives is 12 to 15 percent. "Approximately one-half of the alcoholic population has an alcoholic parent and when a careful history is obtained, the majority of families which include one alcoholic member are found to have at least one other alcoholic," says Reich. In addition, studies of extended families of alcoholic individuals indicate that the problem often goes back three or four generations, according to the psychiatrist.

And as with depression and schizophrenia, results of adoption studies of alcoholics by U.S., Danish and Swedish researchers strongly suggest a genetic link. "Regardless of whether the adopting parents were alcoholic, biologic offspring of alcoholic males were [nearly 4 times] more likely to be alcoholic than biologic offspring of control subjects," says Reich, "a finding which strongly implicated a genetic factor in the familial aggregation of alcoholism."

The higher prevalence — up to 4 times higher — of alcoholism among males over females has led some to speculate that inherited characteristics may also be responsible for the varying susceptibility of the two sexes. Reich's current research results, however, "strongly suggest that sex effect can be eliminated when exposure to heavy drinking is controlled in a statistical fashion." He says, " ... the sex effect for alcoholism would likely disappear if women were as socially exposed to heavy drinking as [are] men."

Beyond statistical evidence, a growing number of biochemical study results are pointing toward genetic involvement in these mental health related areas. In the drug abuse field, perhaps the first direct observation of genetic damage caused by heroin has been reported by Arthur Falek, director of the Human and Behavioral Genetics Research Laboratory in Atlanta (SN: 12/8/79, p. 390). In their study of chromosomes in the white blood cells of heroin addicts, Falek and his colleagues found that addicts not only had "more DNA damage" than did control subjects, but also displayed significantly lower ability than controls to repair DNA damaged by heroin or experimentally by ultraviolet radiation. However, withdrawal from heroin or diversion to methadone treatment appears to reverse the damage and boost the addict's capacity to self-repair damaged genetic material, Falek says. The results suggest that active heroin addicts may be capable of passing on to their offspring such chromosomal defects, Falek indicates. As yet, though, no increase in birth defects among infants of addicts has been discovered.

Among alcoholics, Reich says there are several biochemical indicators of possible genetic factors:

- An abnormal requirement for the enzyme transketolase and at the same time a dietary deficiency of the vitamin thiamine, which transketolase requires for functioning.
- Unusually high levels of metabolites of aldehydes (substances derived from alcohol) in the blood following ingestion of alcohol. This has been seen in the sons of alcoholics, as well as in alcoholics themselves.
- An overabundance of certain white blood cell groups.

Perhaps the greatest recent influx of chemical evidence in any of these areas has been in the fields of schizophrenia and depression, where brain chemistry changes have been strongly associated with both schizophrenia and major depression. Numerous studies have linked schizophrenia to an overactivity of the neurotransmitter dopamine while depression appears to be accompanied by fluctuations in the neurochemicals norepinephrine and serotonin, as well as in the recently discovered "natural opiates" — enkephalins and endorphins (SN: 11/25/78, pp. 362-367).

In his work, Gershon found that while some sets of twins responded to doses of d-amphetamine with characteristic excitation, others appeared to be "immune" to the stimulant and showed no such response. Moreover, the finding that, in most cases, identical twins had the same response "implies that the response is under genetic control," Gershon says. "We found the excitement response to be independent of the plasma concentration of amphetamine. This suggests that the differences between twin pairs were related to genetic differences in the catecholamine neurotransmitter systems [with which the drug interacts in the brain] and not to differences in drug metabolism."

Despite these and other pieces of evidence favoring genetic involvement, it seems equally apparent that a significant proportion of these conditions is not due primarily to inheritance but to environment. Kety, for example, reports that half of the schizophrenic adoptees in his Denmark study show no biological family his-

tory of the disorder. This means, he says, "there must be two forms of schizophrenia: that which is primarily genetic and that which is primarily environmental." He speculates that environmental contributors might include birth trauma or perhaps even some form of virus.

Kessler cautions that while schizophrenia appears, statistically, to run in families, "it must also be remembered that divorce and wealth runs in families ... family studies themselves do not provide definitive evidence of a genetic contribution to the causes of schizophrenia," he says. "... fifty percent of identical co-twins do not [both] develop schizophrenia in spite of having identical genes." Similar problems permeate the field of depression and manic-depression. "At the present time there is no blood test or other procedure that can detect an affective disorder prospectively," Gershon states in the March HOSPITAL PRACTICE. Gershon perhaps best capsulizes the frustrations of trying to pin down genetic factors in the nebulous area of mental illness: "... even a precise answer to the question ... of how affective diseases are inherited ... would probably be of little practical value. It would still not enable us to single out those individuals within a given family who are at maximum risk of developing affective disorders," he says.

Nevertheless, Gershon indicates he may not be opposed to genetic counseling of people from "high risk" familial backgrounds who are contemplating marriage or having children. This view was at least partially prompted by a recent survey in which Gershon found that most spouses of manic-depressive husbands or wives revealed that if they had it to do over again, they would not have married the afflicted person. The survey also showed that about half of those surveyed said if given another chance they would refrain from having children. Gershon terms the survey's findings "sad."

Behavioral scientists appear to be far less in agreement, however, on the morally treacherous issue of genetic counseling than they are on the belief that genetics figure prominently in a significant number of cases of mental illness, alcoholism and drug abuse. Before any type of formal, widespread genetic counseling programs could even be speculated upon, according to some researchers, knowledge of behavior-related genetics must be greatly expanded. The road to that goal may be built through "genetic modeling studies," which would create new models of the genetics process to help explain how the role of inheritance in mental processes differs from its involvement in physical processes. Reich and others have already begun to work on such models. For now, Kessler advises his colleagues, "the counselor should make people aware of the risk [of an existing predisposition to a behavioral disorder] but should not tell them what to do." ☐