Discussion

Neurobiology and Genetics of Suicide Risk

Dr. DePaulo: Genetics research on bipolar disorder has been frustrating. With all the promise of the molecular genetic methods, it looked as though we were going to be able to identify loci or genes of major impact on the illness. We scanned the genome in a sizeable number of families, in 2 or 3 different studies. We found that the genes we thought would be related to these clinical phenotypes were genes of small effect, effects much smaller than the effect sizes shown in studies more directly related to neurobiology. The effect size of the genes we found for bipolar disorder is extremely small. The biology of the behavior, as shown by the elegant work of Dr. Mann and others, may in fact be much more useful to researchers than the genetics of the behavior.

The association between affective disorders and suicidal behavior has been apparent to all clinical researchers for a long time. The most powerful predictor of suicide over the years has been severe depression and particularly bipolar depression. How do we put the disorder back into the equation? Other studies show connections between suicide and conditions such as being alone in life, not going to church, or drinking too much coffee.

Dr. Mann: Effect sizes are smaller in some of the genetic models than in the biological studies because the biological studies are looking at a consequence of genetic, environmental, and rearing factors. We know, for example, from primate studies done by J.D. Higley and Markku Linnoila and others of evidence that altering rearing experiences in a fashion that persists into adult life can affect serotonergic activity. Other environmental factors, perhaps such as cholesterol intake, can affect serotonergic function. It is not surprising that one would see a bigger effect size when one looks at serotonin function or another biological index than when one looks at genetics. Suicidal behavior offers the opportunity to integrate social, biological, genetic, familial, and other factors into a model in which each one has a small but meaningful contribution to risk prediction. It would be dangerous to single out any one of these factors.

Dr. Roy: Studies that relate early personality to completed suicide as an adult are also very interesting *[Allebeck P, Allgulander C, Fisher LD. BMJ 1988;297: 176–178]*. The factors that epidemiologists code, such as church attendance, employment, and marital status, have some personality determinants. There are large genetic determinants to personality, and extraversion has been shown to predict levels of social support *[Kendler KS. Am J Psychiatry 1997;154:1398–1404]*. One study by Caspi et al. *[Caspi A, Moffitt TE, Newman DL, et al. Arch Gen Psychiatry 1996;53:1033–1039]* found that behaviors that were exhibited at ages as young as 3 or 4 years predicted later attempts at suicide—e.g., how social one was, how many friends one had, and whether conduct disorder was exhibited. There are studies *[Thomas CB. Johns Hopkins Medical Journal 1971;129:190–201]* assessing the personalities of incoming medical students who were followed up in cohorts of Johns Hopkins medical students. Among those who ultimately committed suicide, there were significant predictors of later suicide in their personality assessments at intake into medical school. There are ways that epidemiology, personality, suicide, and genetics can be partly tied together.

Dr. Baldessarini: What are the mediating phenomena that the biological and genetic factors seem to bring to the risk or the event of suicide? Major mood disorders are factors but not strong ones. At the trait level, impulsivity may play a role. The Danish adoption studies *[Wender PH, Kety SS, Rosenthal D, et al. Arch Gen Psychiatry 1986;43:923–929]* failed to make a case for an adoptive factor in depression in the families under study. The relationship between adoption and suicide, however, was quite compelling.

Dr. Roy: The Danish studies of depressed adoptees who appeared in the psychiatric case registers by virtue of having been treated for depression found that, in biological relatives who had committed suicide, the depressive diagnosis most strongly related to suicide was not unipolar depression or bipolar depression but rather a condition called affect reaction, which Scandinavian colleagues describe as a patient who turns up in an emergency room after an impulsive suicide attempt; many of these patients have a personality disorder and a scattering of affective symptoms .

Dr. Goodwin: One can make a case that a serotonergic link in bipolar disorder may override a subtle distinction between a patient who commits suicide and one who does not. Bellivier et al. *[Bellivier F, Leboyer M, Courtet P, et al. Arch Gen Psychiatry 1998;55:33–37]* found an association between bipolar disorder and the tryptophan hydroxylase allele but failed to find a similar association between the allele and violence or suicide. Also, the subtlety of environmental inputs in monkey studies is striking. One study found a blunted serotonin response to fenfluramine in adolescent monkeys whose mothers had been exposed to a period of several weeks of infrequent or irregular feeding. Adolescent monkeys whose mothers had not been

exposed to this brief period of infrequent feeding did not evince blunted serotonin response to fenfluramine. This brief and subtle stressor had a very profound effect many years later on blunted serotonin response to fenfluramine. There is also literature showing that children with conduct disorder have significantly lower measures of serotonin, whether measures of endocrine or 5-HIAA are used.

Dr. Shaffer: In my and my colleagues' epidemiologic study *[Shaffer D, Gould MS, Fisher P, et al. Arch Gen Psychiatry 1996;53:339–348]* of adolescents who committed suicide, we found moderately high rates of conduct disorder, both in those who had committed suicide and in controls, and the difference was not significant. However, the excessive alcohol abuse in older teenage males who had committed suicide was significant. We also found a good deal of comorbid depression and alcohol abuse in the older teenage males, but not in female suicides or controls. Alcohol abuse might explain the age and gender distribution of suicide during the teenage years. Suicide becomes increasingly prevalent through adolescence, with about half of all teenage suicides occurring at ages 18 and 19. There are between 4 and 5 times as many male suicides as female suicides at this age. Over two thirds of the male suicide victims aged 17 to 19 years fulfilled diagnostic criteria for alcohol abuse.

Dr. Mann: Above and beyond having a high incidence of major depression, adult patients with a history of suicide attempts have an exceedingly elevated rate of past alcoholism or substance abuse or current smoking. A recently published study by Cornelius et al. *[Cornelius JR, Salloum IM, Day NL, et al. Alcohol Clin Exp Res 1996;20:1451–1455]* showed a high rate of lifetime history of suicide attempts—over 40%—in individuals who had depression with comorbid alcoholism. Alcoholism is associated with reduced serotonergic function, which may be involved in the pathogenesis of alcoholism. There is no animal model of suicidal behavior, but the mouse generated by Rocha et al. *[Rocha BR, Ator R, Emmett-Oglesby MW, et al. Pharmacol Biochem Behav 1997;57:407–412]* with the 5-HT_{1B} gene knockout is characterized by excessive and impulsive aggression, inappropriate impulsive sexual activity, and increased alcohol and cocaine intake. Only the suicidal component is missing—all as a result of knocking out only the 5-HT_{1B} gene. This is further evidence of how profoundly behavior can be affected by what appears to be a relatively subtle genetic modification in the serotonergic system. These behaviors are part of the classical disinhibitory syndrome described more than 20 years ago in relation to prefrontal cortical injury, the so-called disinhibitory psychopathology syndrome. We see parts of this syndrome aggregating in these different clinical populations.

Dr. Goodwin: Some of the confusion in the alcohol literature stems from failing to make the distinction between early and late onset. All of the associations between alcoholism and serotonin that my colleagues and I demonstrated in 1979 *[Ballenger JC, Goodwin FK, Major LF, et al. Arch Gen Psychiatry 1979;36:224–227]* and the associations between alcoholism and affective disorder are found in early-onset alcoholism, not late-onset alcoholism. The alcohol literature, most of which has been drawn from Veterans Administration hospitals, deals with late-onset alcoholism. Accordingly, some of these early-onset findings showing a high correlation between affective disorder, particularly bipolar disorder, and alcoholism or a high correlation between aggression and low serotonin measures are not considered in these studies. A 20-year-old alcoholic person seeking entrance into the armed services is likely to be rejected; the whole literature is distorted by that fact.

Dr. Müller-Oerlinghausen: Suicidal behavior is very complex, and we have to take psychological factors into account in order to make useful predictions and to reach useful correlations between, for example, the biological data and other data. Although we have made progress in using sophisticated tools to measure the biological factors, we still approach the psychological level in a simplistic manner. We have made little progress in concepts of impulsivity and aggression, despite much discussion. We would make progress by differentiating personality and other psychological factors in our assessments. Understanding the construct of anger might help extend our current simplistic construct of impulsivity in an interesting way. When we introduce more subtly shaded psychological parameters, we suddenly find meaningful associations and correlations with biological data assessed in a sophisticated and comprehensive way. Some promising classification systems of suicide attempts are not well known internationally. For instance, Felber et al. *[Felber W, Israel M, Winiecki P, et al. Münch Med Wschr 1998;140:43–46]* has published a quite sophisticated system of classifying suicide attempts, well validated by methods such as cluster analysis. Using such a system achieves more meaningful results. We need to make greater efforts in this area.

There is some overlap between constructs of aggression or impulsivity and anger, but anger is different. Try to imagine how a suicide attempt comes about. What happens in such a patient? When you ask patients why they reacted by attempting suicide, they often can't say. Their scores on scales such as the Buss-Durkee Hostility Inventory often do not reveal aggressiveness or anger. The validity of the scores on these scales in suicidal patients is not very high, since these scales were developed for other patients, such as criminals and arsonists, not this suicidal population. Still, suicidal patients talk about something like anger. We could profitably invest more time studying the connection between anger and aggression or impulsivity.

Dr. Jamison: Agitation and perturbance are clearly related states, yet there is very little way of assessing them objectively. How does Felber classify suicide attempts?

Dr. Müller-Oerlinghausen: Felber's classification is based not only on intentionality but on a multivariate analysis of factors such as severity, intentionality, psychiatric nosology, addictive behavior, and personality; he characterizes 4 different types of patients who attempt suicide.

Dr. Goodwin: He separates 1- and 5-year predictors and depressive turmoil in the collaborative study. Depressive turmoil is a very powerful predictor that is not easily measured by existing clinical scales.

Dr. Jamison: Depressive turmoil, often described as anxiety, is a distinct subjective phenomenon.

Dr. Sackeim: One of the difficulties I have had with standard modeling and its emphasis on linking impulsivity to aspects of the serotonin system is the issue of the individuals who attempt or complete suicide in a highly obsessive, highly planned, long-term fashion. The standard approaches describe suicide as an impulsive act, but in many cases it appears to be a highly considered act.

Dr. Jamison: Often suicide is both. Patients may be very obsessive and plan an attempt, but the timing of the attempt or its completion is a result of impulsivity—a combination of factors.

Dr. Baldessarini: When the last model is established, we may find out that suicidal behavior, like most constructs in psychiatry, is a phenotype, a syndrome that probably subsumes many different phenomena, causes, and types, each with a distinct biology and treatment pattern. We are far from that ultimate model at this point.