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INVITED EDITORIAL
Outrageous Fortune: The Risk of Suicide in Genetic Testing for Huntington Disease

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Why do people kill themselves? In many cases we never know for certain, but it must usually mean that life has become unbearable. The "slings and arrows of outrageous fortune" can no longer be tolerated, and suicide becomes a means to "take arms against a sea of troubles and, by opposing, end them" (Shakespeare's *Hamlet,* act III, scene I). For some persons, Huntington disease (HD) becomes one of those unbearable burdens. In his original description of the disease, George Huntington (1872) himself referred to HD as "that form of insanity that leads to suicide" (p. 321). Although accurate figures are difficult to determine (Stenager and Stenager 1992), most investigators have concluded that Huntington was correct—suicide is indeed a more frequent cause of death among persons with HD than among the general population. In the literature, the range of HD deaths reported to be the result of suicide is 0.5%–12.7% (Harper 1996); the 5.7% rate found by Farrer (1986) is the most commonly quoted. This represents approximately four to five times the 1.0%–1.5% suicide rate for the general population of the United States (Roy 1995). This unfortunate phenomenon is not surprising, given the often agonizing clinical course of HD and the common occurrence of serious depression (9%–44%) in persons with the disorder (Harper 1996).

Prior to the development of DNA testing for HD, a study involving persons at risk for the disease revealed that ~75% would take advantage of accurate presymptomatic testing (Barette and Marsden 1979). Now that DNA testing is available, ~25% of persons at risk are apparently involved in genetic testing programs. What will be the emotional toll of such testing on this vulnerable population? Wexler (1985) elegantly reviewed the complex issues in this field at the beginning of the DNA testing era and asked the poignant question: Would this new genetic knowledge be life enriching or destructive?

Some colleagues argued that there was unnecessary anxiety over the potential consequences of DNA testing for HD. They pointed out that doctors give patients bad news every day (e.g., diagnoses of cancer, AIDS, or ALS). Conversely, it can be argued that HD is one of a small group of really dreadful diseases. The diagnosis of HD typically implies all of the following: (1) a progressive degenerative brain disorder in the prime of life, (2) a socially embarrassing and disabling movement disorder, (3) serious cognitive and behavioral changes, (4) no cure or even effective treatment, (5) shortened life span, and (6) a 50% risk of the same disorder for each child. Furthermore, asymptomatic persons are not told they have the "disease" but that they have inherited a mutation that will lead to the disease at some unknown future date: the prolongation of an already nearly intolerable ambiguity. Clearly, informing highly anxious, asymptomatic persons that they carry the gene for such a condition would have to be done with considerable trepidation.

Almqvist et al. (1999 [in this issue]) provide important new information on the emotional responses of persons undergoing genetic testing for HD. The authors surveyed 100 centers in 21 countries and gathered information on 4,527 individuals who had received predictive genetic testing for HD, through either linkage analysis (16.4%) or more-recent direct DNA testing (83.6%). In this population, the authors investigated psychiatric "catastrophic events," which they defined as suicide, attempted suicide, or acute hospitalization for psychiatric reasons. These catastrophic events might be viewed as the proverbial canary in the coal mine. That is, if the catastrophic event rate is too high (the canary loses consciousness), then genetic counselors and family members (the miners) need to abandon presymptomatic HD testing programs (the mine).

How dangerous is the HD genetic testing mine? The

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Almqvist et al. (1999) study addresses this question; the results can be briefly summarized. Of the 4,527 persons undergoing testing, there were 5 completed suicides, 20 suicide attempts, and 18 psychiatric hospitalizations, for an overall catastrophic event rate of 0.97%. Furthermore, 1,817 persons (40.1%) were confirmed to be at increased risk of developing HD. This group had a 2% rate of catastrophic events, and all five completed suicides were in this subpopulation. Most of the serious episodes occurred <18 mo after the individuals' receipt of the test results, and all five completed suicides occurred in persons who had subsequently developed clinical symptoms of the disease. Of interest, 7 (0.3%) of the 2,601 persons who were confirmed to be at decreased risk also experienced a catastrophic event.

This information, incomplete though it may be, is critical to our assessment of the present state of HD genetic testing and crucial to our planning for the future. Like all good studies, the study by Almqvist et al. (1999) is informative but also provocative, raising many additional issues and questions. Given the international nature of the study, the investigators made a commendable attempt at relatively complete ascertainment. Their follow-up study of 47 initially nonparticipating centers revealed no evidence for unexpected biases in the original data. It can be argued that the testing centers are so cautious in their protocols that diffusion of such genetic testing into the broader, less methodical medical community will result in a higher incidence of adverse events. Of course, this may not necessarily be true. In fact, some individuals resent what they view as an excessively conservative, paternalistic attitude of academic centers toward testing.

There is also undoubtedly a self-selection of persons undergoing testing. What characteristics currently compel a minority of HD family members to pursue genetic testing? Are those who pursue testing more, or less, likely to have catastrophic events? What will happen if reluctant family members who have elected not to undergo testing begin to do so? Will they have a greater or lesser risk of catastrophic events?

The psychiatric outcome is unknown for 119 participants in the Almqvist et al. (1999) study, because these persons were lost to follow-up. The results of the study would be significantly different if a large proportion of this group experienced catastrophic events, but there is no way to determine how this missing information would have affected the study.

Most of the persons in this study were followed up for only 1–2 years (59% for ≤1 year). Will the rate of catastrophic events increase or decrease as time passes? Thus far, the results of this study suggest that the event rate is stable over time (0.44%/year). Furthermore, as the gap between learning the test results and a catastrophic event increases, the likelihood that there is a direct correlation between the results and the event decreases. The subsequent realization that symptoms of the disease are appearing may be more important than the initial test results.

To continue the coal-mine analogy, it is important to recognize that toxic fumes are not the only hazards in a mine. Likewise, suicide attempts and psychiatric hospitalizations are only a small fraction of the potential adverse results of genetic testing for HD. Such events are clearly only the tip of the iceberg. The effect of test results on a wide variety of other factors—marriage and other personal relationships, employment, insurance, family planning, and other mental and physical measures of well-being—need to be considered. It is instructive that a small number of persons in this study who received negative (i.e., decreased risk) results also experienced catastrophic events. Learning that one has not inherited the gene for HD clearly does not erase the burdens from the lives of these apparently fortunate persons—nor are those at risk for the disease the only ones affected by the test results. When we conducted a local study of suicide in HD families, we were sobered to find a spouse who had killed herself after struggling with the illness in her husband and all three of their children (Hans and Koeppen 1980; Lipe, et al. 1993). The distress of HD testing can also have a direct impact on the emotional well-being of health care providers who end up being the bearers of bad news. Sometimes the counselors need counseling.

How should we interpret the major findings of this study? How do we put these results in perspective? Is there a control group for such an investigation? Is the suicide rate average or high, good or bad, changeable or fixed? There were five completed suicides in the 1,817 individuals who received a positive (i.e., increased risk) test result. This equates to ~275 suicides per 100,000 persons. Because most of the suicides occurred ≤2 years after testing, we can extrapolate a completed suicide rate of 138/100,000 persons per year. The suicide rate among the general US population is reported to be ~12–13 per 100,000 persons (Roy 1995); the suicide rate reported by Almqvist et al. (1999) is therefore 10 times the US rate. These figures seem to confirm, or at least coincide with, the suicide rates previously reported for symptomatic patients with HD, which varied from 7 to 10 times the US average (Harper 1996). But this was an international study, and suicide rates vary among countries. The rate varies from <10/100,000 persons in Ireland to >30/100,000 persons in Hungary (Roy 1995). The suicide rate reported by Almqvist et al. (1999) is ~6.6 times that of the average rate in Sweden, which is 21/100,000 persons.

Suicide rates also vary with several other factors, including sex, socioeconomic status, and age (Roy 1995). The suicide rate is higher in individuals with other se-

rious mental and physical diseases, such as schizophrenia, depression, panic disorder, cancer, multiple sclerosis (MS), and AIDS (Weissman et al. 1989; Westermeyer, et al. 1991; Coté et al. 1992; Stenager et al. 1992; Storm et al. 1992). Furthermore, debate continues over whether suicide is ever a "rational" decision by a person seemingly facing an overwhelming sea of troubles and an unbearable life. Jack Kevorkian's first assisted suicide was a woman in the early stages of Alzheimer disease, and persons with ALS and MS have been prominent among his subsequent cases (Rohde et al. 1995). Rationality is a "multidimensional construct," as noted by Conwell and Caine (1991): "The presence of depression does not imply that a patient's choice is irrational, nor does the absence of mental illness imply rationality.... We must be better able to distinguish between people whose suicidal intent is clearly conceived and free of distorting mental disturbances, and people who are in need of psychiatric care" (p. 1102).

Almqvist et al. (1999) have made a valuable contribution by assembling and analyzing this important information about HD testing. We may conclude that they have presented us with good news and bad news. The good news is that at least half the people undergoing HD genetic testing receive negative results, and even those receiving a positive result do not show a rate of suicide higher than that of the general symptomatic HD population. Nor is the rate out of proportion to that of other groups with serious, progressive diseases; the resilience and strength of many persons receiving grave disappointment can be impressive and even inspiring. The majority of persons receiving an increased risk of HD appear to cope remarkably well with this new information. The bad news is that, within 2 years of receiving the test results, 2% of this increased risk group experiences serious catastrophic psychiatric events, including completed suicide. We must strive to reduce the rate of catastrophic events among this population.

In our role as physicians and counselors committed to the relief of suffering, what can we do to reduce this catastrophic event rate? One option would be to terminate presymptomatic genetic testing for HD. This would fly in the face of an important historical trend in medical care, which has been to provide available knowledge about an individual's health when the individual chooses to receive it and feels there are compelling and cogent reasons to obtain it. A critical factor in counseling such persons is careful education prior to any testing: education not just about the test, but about the disease, about the option not to proceed with testing, and about the possible psychosocial implications of learning test results (knowing full well that we do not know all the implications). Many clinics offer detailed printed information about HD testing, including a booklet published by our program (Bennett 1996). It is important that as geneticists we do not appear to be promoting or advocating presymptomatic DNA testing for everyone at risk. Most persons seeking DNA testing have strong hopes that the result will be negative. They must be encouraged to give careful thought to the possibility of a positive test result, how they might react to a positive result, and the ways in which it could change their lives.

The Almqvist et al. (1999) study provides some guidance for recognition of individuals who may be especially vulnerable for serious negative outcomes after HD testing. The results of the study suggest that the person at greatest risk for suicide is an unemployed woman who receives a positive result, develops early symptoms <1 year after the test, and has a history of psychiatric illness. This profile becomes less helpful when we consider that more women than men elect to be tested, the study's definition of "unemployed" included homemakers, and the majority of catastrophic events were not associated with a history of psychiatric illness. It should also be noted that, in our local study, all the completed suicides were in men (Lipe et al. 1993). Clearly, all persons undergoing HD testing require careful evaluation in the pretesting stage.

Depression should be recognized and treated prior to testing. Persons with depression or a history of psychiatric illness should be evaluated by a psychiatrist or clinical psychologist knowledgeable about HD. Testing can be postponed until both patient and counselor agree to proceed. Because use of firearms is the most common method of suicide in this country, encouraging HD families to remove guns from their homes can be another important precaution (Kellermann et al. 1992). Most important, every person undergoing HD testing must have careful and compassionate support in the weeks and months after the test. The availability of an identified and trusted support person who accompanies the at-risk individual through the entire testing process cannot be overemphasized. The thousands of persons undergoing HD testing, and the even greater number of individuals undergoing genetic testing for other similar diseases, will require an extensive, expensive, and labor-intensive counseling network. Such a network does not now exist. Who will develop it? Who will be trained to work within it? Who will pay for it? Society has only begun to struggle with these questions. As members of the American Society of Human Genetics, we are obligated to help answer these questions. I believe we should continue to provide HD genetic testing, but the process needs ongoing monitoring, refinement, and support. We need to keep a wary eye on all available warning canaries in the HD testing mine. The study by Almqvist et al. (1999) is a valuable step in that direction.

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