

ON HUMAN NATURE

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Sir John Everett Millais, *Ophelia*, 1852

Not to Be

For Hamlet, that slightly mad, too thoughtful hero (and possibly for Shakespeare, speaking through him), the central puzzle of human existence was whether “to be or not to be.” Certainly, that question strikes many of us as close to the heart of what it means to be human. Few, if any, nonhuman animals can *choose* not to be. When soldier ants sacrifice themselves for the good of the colony, their behavior is in some sense genetically mandated. Sociobiologists may say similar things about some self-destructive human behavior, that it is a form of self-sacrifice, produced by evolutionary forces much like those that act on the ants. The individual is lost, but the sacrifice saves others, some of whom are closely related; thus the genes contributing to the self-sacrificial tendency (however small that contribution may be) are carried forward by the surviving relatives.

It may seem to be stretching this argu-

ment to subsume suicide within it, but consider the kamikaze pilot of the Second World War, or today’s holy warrior for Islam and Khomeini. These men are heroic and suicidal both, and they certainly bring honor to their relatives. More ordinary suicides can also be rooted, at least partly, in the belief that someone close may benefit, and life insurance policies take this possibility into account.

Notwithstanding the validity of these arguments, the fact remains that some self-destructive human behavior, be it heroic or suicidal or even hedonistic, cannot benefit one’s kin, and this sort of human sacrifice the Darwinians can only call “maladaptive.” That is, it is being selected against; in theory, at least, the tides of phylogenetic time will finally wash it away. Until then, it remains an integral part of our range of choices, enlarging, at once, our sense of the world as a dangerous place and our deepest sense

of human freedom. In fact, in the post-Darwinian world, the hallmark of our species may be precisely this: we are the only animal that can consciously choose to be selected against. Perverse? Yes—but superbly and beautifully human.

Of course, to defy the logic of natural selection is not necessarily to defy the laws of biochemistry. Could it be that a question of such philosophic moment as Hamlet’s hinges ultimately on chemical interactions, perhaps on the presence or absence of a single molecule? Such speculation would be a foray into territory that has proved itself treacherous. One molecule thought to be a clue to schizophrenia turned out to shed light only on the food served at the hospital whose patients were under study. A naturally occurring LSD-like substance that seemed at first to shed light on mental illness could not be detected in subsequent studies. So even the most biochemically inclined of psy-

chiatrists—perhaps especially they—are skeptical of broad claims about the role of any one molecule. “Well,” one can almost hear them saying, “we’ll see whether it’s replicable. There might be a piece of the truth here, but only a piece. For diagnostic purposes, I’ll stick to the work-horses—symptoms, history, course of illness, possibly also drug response. As for a prognosis of something like suicide. . . .” The derisory smile would be sufficient to complete the sentence.

Yet some of the toughest-minded biologically inclined psychiatrists are beginning to take note of a molecule in the cerebrospinal fluid, which fills the spaces in and around the brain and spinal cord, cushioning against shock and serving as a receptacle for the brain’s secreted and excreted substances—the important products and incidental by-products of innumerable chemical reactions. The cerebrospinal fluid of people destined to take their lives, it appears, contains an unusually low concentration of a simple substance that goes by the delightfully rhythmic name five-hydroxy-indole acetic acid, or, to its friends, 5-HIAA.

For many years, 5-HIAA, studied by Marie Åsberg, of the Karolinska Institute, in Stockholm, and Frederick Goodwin, of the National Institute of Mental Health, among others, has been known as the major metabolite, or breakdown product, of serotonin—one of the first chemical transmitters proved to have a functional role in the brain. Serotonin (also called five-hydroxytryptamine) is synthesized in certain brain cells and secreted across the synapse—the gap between the cells and the neurons they stimulate or inhibit. The action of serotonin on the receiving neuron’s membrane is what causes the inhibition—hence the name neurotransmitter. Serotonin is thus a vital link in various neural circuits, circuits with both known and unknown functions.

As critical as it is to get that pulse of serotonin across the synapse, it is equally critical to remove it, and quickly. The precision of the nervous system’s function depends as much on the brevity of the pulse as on its existence; it would not do to have even as useful a molecule as serotonin indolently hanging around, causing inhibition not explicitly called for by the neurons that secreted it. So it is removed by an enzymatic reaction that, in the process, produces 5-HIAA; and 5-HIAA thus becomes an indirect indicator of serotonin turnover and of the level of activity of serotonin neurons.

The link between 5-HIAA and suicide—now confirmed by a number of studies—could provide a much needed tool in the assessment of suicide risk. All psychiatric patients who suffer from mood disorders, who become periodically depressed and perhaps periodically man-

ic, are considered to be at significant risk of committing suicide. The clinical signs of depression, particularly if they include suicidal ideas, suffice to justify at least some precautions. But patients do not always tell doctors what they are thinking; moreover, conscious mental activity does not necessarily reflect all of the brain’s inner workings. So a biochemical indicator may be more telling than the most heartfelt revelation.

Åsberg’s initial discovery was that those depressed patients with high levels of 5-HIAA in their cerebrospinal fluid—whatever their clinical symptoms—were not really at risk of suicide; but if a patient was destined to commit suicide during the next year, the level of 5-HIAA was almost certain to be low. For example, in one of Åsberg’s study groups, consisting of forty-six patients who had previously attempted suicide, six patients took their lives within a year. All six belonged to a subgroup of thirty patients whose 5-HIAA levels were below the average. For patients with 5-HIAA levels above the average, the risk of death within a year was zero, and it has been very near that in other, similar studies. (Some of these patients *attempted* suicide, but by drug overdose, a method known to have a much lower success rate than do violent methods and, it has been speculated, one often employed by patients whose true intent is something other than suicide.)

Never has a biochemical measurement in psychiatry had anything like this degree of discriminatory power. If future studies show it to be reliable, it will have immense practical value, permitting the effective management of an important source of human suffering and sparing those not really at risk the annoying and unnecessary precautions. (Checks by nurses every five minutes and the prohibition of sharp objects are not only indignities but legally sanctioned infringements on freedom as well, and they may interfere with some forms of treatment.) Scientifically and philosophically, the implications are enormous: here is a molecule so small that it is dwarfed by even a single base pair of DNA, yet it may spell the difference between life and death.

The question, of course, is how. Subsequent studies have provided some clues. For example, individuals who do not have pronounced mood fluctuations but are at risk of suicide because of personality disorders—chronic maladaptations, as opposed to bouts of depression—can be divided into the same two groups: those with low 5-HIAA levels who are at high risk of committing suicide, and those with high levels who are not. This suggests that the significance of 5-HIAA relates fundamentally and directly to suicide rather than to any one type of depres-

sion that may in turn lead to suicide.

The biochemical mechanism underlying this relationship is not yet clear; however, there is evidence that supports the obvious interpretation—that serotonin neurons are for some reason less active in people inclined toward suicide. The brains of suicide victims, for example, have yielded evidence of low serotonin levels. In light of such findings, established facts about serotonin become more interesting: a high serotonin level makes an animal more tolerant of pain, and a level artificially lowered—say, through a diet deficient in serotonin precursors—makes it more sensitive. More subtle in its implications, though equally intriguing, is the fact that high serotonin levels are associated with normal sleep. Sleep disorders frequently accompany psychiatric illnesses, and psychiatrists have speculated that the problem goes beyond the insomnia that naturally accompanies unusually persistent anxieties and fears; the idea is that sleep disturbances are a basic and revealing characteristic of such illnesses rather than a consequence of them. If so, it is tempting to wonder whether those who, like Hamlet, are drawn to “that sleep of death” may have had a troubled sleep in life.

But this is far afield, and undoubtedly what we have here is only a piece of the truth. Still, such a piece can become a handle on a larger truth. It turns out, for instance, that individuals with low levels of 5-HIAA (again, whether they are depressed or not) are more likely to commit not only suicide but also nonsuicidal acts of violence. This suggests that, as psychodynamic theorists have often claimed, inwardly and outwardly directed violence are two sides of the same coin, separate expressions of a single aggressive urge—Freud’s death instinct, which, turned inside out, becomes homicide.

This brings us back to *Hamlet*—a play that, somewhat contrary to its most famous soliloquy, is not really about whether “to be or not to be” so much as whether to act or not to act. It is a deed of outward violence that the hero is headed for; the notion of finding in his breast a sheath for his own “bare bodkin” is only a brief byway. It may be that some utterly simple brain process involving a certain small molecule determines whether we will “take arms against a sea of troubles / and by opposing end them,” yet leaves open the question of whether to direct those arms against ourselves or against others. ●

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