

### Depression Is an Adaptation

**D**r Nesse, in raising the question, "Is Depression an Adaptation?"<sup>1</sup> has contributed greatly to understanding this poorly understood, unpredictable condition. He offers many possible functions for low mood and depression, but he stops short of firmly concluding that depression has adaptive significance.

A strong case for the phylogenetically adaptive significance of depressive symptoms can be made, however. Depression has a genetic component: parents of persons with major depressive disorder (MDD) are 2 to 3 times more likely to have had the disease themselves than parents of persons without depression.<sup>2</sup> Depression is also common. Lifetime prevalence of MDD is 15.8%.<sup>2</sup> The rate of spontaneous mutation in humans is 1 per 10000 to 1 per 1000.<sup>3</sup> Taking the conservative values of 1 in 10 for MDD and a mutation rate of 1 per 1000, depression is observed at more than 100 times the mutation rate. Depression must have had a definite selective advantage in the ancestors of modern humans; otherwise, it would be rare.

Not all modern depression is necessarily adaptive, of course. Depression consequent to hypothyroidism, for example, is clearly pathological. Also, even if some depression is strongly disadvantageous in modern conditions, the effect of negative selection on prevalence will not be apparent for many generations.

Knowing that depression was adaptive to our ancestors and may often still be adaptive as Nesse has shown, encourages a new view of this old disease. This evolutionary view implies that triggers of depression are likely to bear a recognizable relationship to situations in which depression would have improved fitness in ancestral conditions. Seasonal affective disorder, triggered by low light conditions<sup>4</sup> and enforcing reduced energy consumption at times when our ancestors would have suffered seasonal scarcity, may be an example of this.

The typical relapsing, noncontinuous course of depression may have increased fitness by enabling behaviors adapted to circumstances. Nesse, noting that repeated episodes of endogenous depression often seem unrelated to life events, argues that these depressive episodes are not defenses. If previous depressive episodes increase sensitivity to subsequent triggers, however, heightened reactions to triggers we do not yet recognize may explain the apparent absence of life events triggering recurrent endogenous depression.

In any case, we can say with confidence that depression is an adaptation—the result of eons of positive selection. As the origins, physiology, and adaptive significance of depressive symptoms become better under-

stood, it may become possible to predict and prevent depression in its more deleterious forms.

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### Sex Hormones, Darwinism, and Depression

**T**wo recent articles published in the same issue of the ARCHIVES<sup>1,2</sup> pose interesting questions regarding the evolutionary roots of depression and depression in women. We would like to propose a point of view that connects the two, and examine its practical implications.

**Depression in Women vs Men.** Women have an increased incidence of depression compared with men, by a ratio of 2:1.<sup>2</sup> Moreover, not only clinical depression, but also more subtle dysthymic traits have had a higher prevalence in women after the onset of puberty.<sup>3</sup> In evolutionary terms, if depression is viewed as conducive to staying out of danger in a sheltered place,<sup>1</sup> it may have made sense historically for women to manifest more of that trait than men. Women have traditionally been involved in child-bearing and child rearing, whereas men have traditionally been the providers of food, material resources, and protection. Dysthymic traits would have kept a woman sheltered from danger to bear and care for children; whereas a dysthymic man would have been impaired in performing his main role as a provider and protector. As such, traits predisposing to dysthymia may have been selected for in women, and selected against in men over time.

Sex hormones may be important mediators of these evolutionarily selected behavioral differences. It is interesting to note the antidepressant, novelty-seeking, and aggression-promoting effects of testosterone.<sup>4</sup> It is also interesting to note in a woman's life cycle, the increased incidence of first-trimester and postpartum depression.<sup>5,6</sup> Both are critical periods for the offspring, and a lower level of activity of the mother, keeping out of danger, may have been reproductively advantageous in times past.

Agoraphobia,<sup>7</sup> a condition related to depression and anxiety, has also been described in the postpartum period, as have sex differences in social anxiety disorder.<sup>8</sup> Depression and anxiety often coexist<sup>9</sup> clinically and genetically. It may well be that the dimensions of restraint and concern shared by both depression and anxiety<sup>10</sup> were evolutionarily advantageous to women in terms of child-bearing and child rearing.

**Depression and the Menstrual Cycle.** On a smaller time scale, the menstrual cycle has a phase leading to ovulation and a dysphoric phase following that. The initial euthymic phase leading to ovulation is conducive to mating and makes evolutionary sense. Following potential impregnation, a lower-energy dysthymic phase would make the women stay out of danger and provide more safety for the potential product of conception. Progesterone, the hormone that promotes pregnancy, as its name suggests, has been implicated in inducing dysthymia and overt depression in susceptible individuals.<sup>11</sup> It seems to be the driving force of premenstrual dysphoric disorder,<sup>12</sup> and it has been implicated in postpartum depression.<sup>13</sup>

**Practical Implications.** Natural selection has selected for different traits in men and women in terms of propensity to mood disorders, specifically dysthymia and depression. The propensity varies during the menstrual cycle and life cycle of a woman, and sex hormones seem to be powerful regulators. Understanding dysthymia and depression in women, not as an aberration, but as something that has a biological rationale, will have 2 practical implications. It will remove some of the ignorance and stigma surrounding “moodiness” in women, and more importantly, since the evolutionary reasons that led to this biological difference are not valid anymore in modern times, nature can and should be gently corrected. Using lifestyle changes, somatic therapies,<sup>14,15</sup> psychotherapy, and pharmacotherapy more proactively and in a prophylactic<sup>16,17</sup> fashion<sup>13,15,18,19</sup> at selective junctures in a woman’s life cycle may significantly improve their quality of life and minimize discomfort and morbidity.

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## Clinical Depression Is a Disease State, Not an Adaptation

In his recent ARCHIVES article, Nesse<sup>1</sup> discusses depression as a possible evolutionary adaptation. Dr Nesse presents some interesting arguments that in certain stressful situations, the symptoms of depression can help increase the likelihood of an individual’s survival. One cardinal symptom of depression that Dr Nesse fails to discuss, however, is suicidal behavior.

In Darwinian analyses, natural selection will tend to favor behavioral traits that will maximize an individual’s reproductive capacity.<sup>2</sup> It is hard to imagine a behavior that is less likely to maximize an individual’s contribution to his or her gene pool than suicide. There is no way that suicidal thoughts or behaviors can lead to a person’s surviving any situation. Even if suicidal behavior in an individual somehow conveyed an advantage to the species as a whole, genetically determined suicidal behavior would rapidly be selected against as individuals who displayed it killed themselves before being able to increase the frequency of these “suicidal” genes in the population by reproducing.

Suicide (and hence severe depression) can thus only be seen as a disease state that conveys no benefits to an individual. Fleeting suicidal thoughts (as opposed to actual suicide) are common even in mildly depressed individuals. Thus, the clinical depression that psychiatrists most often see and treat must be seen as primarily a disease state and not adaptation. The depression that Dr Nesse describes is part of an individual’s normal behavioral repertoire.

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## Ethical Dilemmas in Prescribing Antidepressants

In his thoughtful article, Nesse<sup>1</sup> provides a persuasive argument that depression has adaptive functions for some patients. But this paradigm leads to an additional question. If depression is adaptive, could its treatment be maladaptive? With the wide array of effective and relatively benign pharmacological treatments for depression, it has become almost a “knee-jerk” reaction among health care practitioners to prescribe antidepressant medication when patients have symptoms of severe depression. Given the distressing and disabling nature of depressive illness, many patients clearly benefit from this strategy. However, on those occasions when severe depression is serving an adaptive purpose for the patient, improvement in depressive symptoms results in overall net harm. The practitioner is then faced with the ethical dilemma of considering stopping the medication in the face of patient opposition. The following cases illustrate these points.

**Report of Cases.** *Case 1.* A 35-year-old woman was referred by her internist. The patient experienced symptoms consistent with a major depressive episode of 1 year’s duration. The onset of these symptoms coincided with a worsening relationship with her boyfriend. He had become increasingly critical, controlling, and sometimes physically violent toward her. The patient realized that the relationship was devastating to her self-esteem and expressed a desire to leave it. She was amenable to psychotherapy and was given the telephone number of a clinical social worker. She was also administered paroxetine hydrochloride at 20 mg/d. At follow-up 4 weeks later, her depression was 50% better. She had made an appointment to see the therapist, but later canceled when her symptoms improved. During the subsequent 6 months of follow-up for medication management, her depression remained in partial remission, but she continued to maintain an abusive relationship with her boyfriend. She stated that she felt too frightened to leave the relationship, but would like to continue paroxetine.

*Case 2.* A 29-year-old man who had a history of alcohol dependence reported symptoms consistent with a major depressive episode for the previous 6 months following diagnosis of infection with the human immunodeficiency virus. He continued to drink a 12-pack of beer daily. The patient was warned of the depressive effects of alcohol and seemed amenable to entering an alcohol rehabilitation program. This was to be further discussed at the next visit, and in the meantime, he began a trial of fluoxetine hydrochloride at 20 mg/d. By the follow-up visit 6 weeks later, the patient’s depressive symptoms had largely remitted despite continued heavy alcohol use. He was no longer interested in rehabilitation, but he wished to continue the fluoxetine.

In one respect, these 2 cases seem to be treatment successes (ie, major depressive illness was correctly diagnosed, and treatment with medication resulted in substantial symptomatic improvement). On the other hand,

these patients continued to lead dysfunctional lives, and their motivation for major lifestyle changes seemed to decrease as depressive symptoms improved. In other words, would the 2 patients have been better off and made more definitive changes in their lives if treatment with antidepressants had been postponed? As physicians we try to respect patient autonomy in making such decisions. However, since we are responsible for writing the prescriptions, we are also bound by the ethic *primum non nocere*.<sup>2</sup>

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### In reply

I am glad to have an opportunity to reply to a few of the many letters received about my article.

Dr Longley is confident that depression is an adaptation because such a prevalent and costly genetic predisposition is difficult to explain in terms of mutation selection balance. While this principle makes sense in general, geneticists have so much trouble defining exactly when it applies<sup>1</sup> that I do not believe it offers strong support for the adaptive significance of depression. Wilson notes that evolutionary epidemiology can help us find new subcategories for depression.<sup>2</sup> I agree with this, and I look forward, in particular, to further studies investigating the personalities and reproductive success of individuals whose relatives have manic-depressive illness. While questions about genetic variation are of great interest, my article was restricted to the question as to why all humans seem to share a capacity for low mood (and perhaps depression). On another occasion, I will write about the very separate question as to why natural selection has not eliminated variation in susceptibility to depression. In general, I am impressed that most anxiety and depressive disorders occur in the 15% of people who are “sensitive.” I suspect that these people experience benefits as well as costs. If the benefits turn out to be related to their increased concern about the feelings of other people, this will be very important as we decide how to use our impending genetic knowledge.

Niculescu and Akiskal suggest that the sex difference in rates of depression may be an adaptation that reflects the increased vulnerability of women because of childbearing and child rearing. This is certainly plausible and somewhat supported by the hormonal mediators described, but it seems to me to be a better potential explanation for differences in anxiety rather than depression. A complementary possibility is that sensibly cautious men have had lower reproductive success than risk takers. From this viewpoint, it is not women who have excessive anxiety, but men who have too little. Regarding sex differences in depression vulnerability, I suspect that they arise, in part, from differences in emotional relationships. Backing up a moment, it is not yet certain that sex differences in depression arise directly from natural selection. For instance, it seems likely

that the evolved predispositions of men and women interact with the opportunities in many societies that result in many women having little power, less ability to extricate themselves from unsatisfactory situations because of this, and a resulting greater vulnerability to depression.<sup>3</sup>

Feder notes the huge fitness costs of suicide, and concludes that severe depression must, therefore, be a disease state. I did not discuss suicide because it overlaps only partly with depression, and because bringing up the issue would have required an assessment of the problematic theory that suicide could be an adaptation that has been shaped to benefit kin when resources are scarce.<sup>4,5</sup> Thus, while the increased risk of suicide does indeed suggest strong selection against predisposing genes, this does not provide definitive evidence about the adaptive significance of depression. Fawcett suggests that genes that predispose to depression could be selected for because of benefits to others in the group. Group selection is now recognized as a non-viable evolutionary explanation, but kin selection can, as he suggests, shape costly traits that benefit relatives.

Finally, Gregory and Jindal wonder if the adaptive significance of depression should influence our prescribing habits. They cite 2 cases in which pharmacological relief of depression may have inhibited motivation to escape bad life situations. This certainly happens, and it is one good reason why high-quality pharmacological treatment requires substantial psychological expertise. However, drug treatment can also increase confidence and initiative in ways that allow some individuals to get out of bad situations. We need controlled studies to determine the frequency of these responses. Meanwhile, it seems likely that the intensity and duration of low mood, like pain and the signals from smoke detectors, is often far in excess of what is needed, thus making it possible to use drugs to block it safely in many instances.<sup>6</sup>

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## Is Depression Adaptive for the Human Species?

While Nesse<sup>1</sup> enumerates the possible ways in which low mood and/or depression may be adaptive for an individual, another possibility is that depression, with its known increase in morbidity and mortality, may be maladaptive to the indi-

vidual, but adaptive to the species. Cyranowski et al<sup>2</sup> point out the increase in depression and sensitivity to loss of relationships in females during childbearing years.

It may be that in small bands of ancestral human hunter-gatherers, when a member lost her or his mate, the survival of the tribe was enhanced by the reduced food intake of the remaining member of the pair via depression or ultimately death, leaving more food for those who were successfully reproducing. The genes enhancing a depressive reaction to loss would be carried by the close kin of a depressed individual, and the enhanced survival of these kin would promote the increase of depressogenic genes in the population. A similar mechanism has been postulated for increasing the frequency of genes for "altruistic" behavior.

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## Depression Is an Adaptation

The article by Dr Nesse is a fine recap of issues as to possible adaptive aspects of depression.<sup>1</sup> It heralds to a large audience that there is more to come as evolutionary science continues to reform and integrate studies in psychopathology. Nesse, who has already done so much to foster the fruition of darwinian psychology and medicine, has done us another good turn.<sup>2,3</sup> Yet, for all the growth of "evolutionary psychology" thus far, it has yet to come to grips with genetic science.<sup>4</sup> In this context, the lack of reference to evolutionary epidemiology as an operationalized mode for precise assessments is a regrettable omission.<sup>4</sup>

As presently conceived, the indistinct nosological meaning of "depression" cannot constitute a proper unit of analysis since depression is likely a syndromic composite of homologous genetic traits, phenocopies, and proximal mechanisms.<sup>4</sup> However, family risk, twin and adoptee data, and *DSM-IV* definitions of major depression approaches a good degree of naturalistic and genetic validity.<sup>5,6</sup> Hence, it is clear that several distinct naturalistic epigenes are likely embedded in the broad and fungible term "depression." That genes linked to depression arose as heuristic population polymorphisms evolved in phylogeny is a point elaborated on elsewhere.<sup>4</sup>

With this in mind, application of Professor Ernst Mayr's cogent algorithm for answering evolutionary questions helps frame the issues more clearly.<sup>7</sup> An essential point is that, in evolutionary analysis, "whether" questions should be answered before questions of "how, when, where, and why." This promotes a less speculative and more falsifiable approach to questions concerning adaptation and polymorphisms.

It is clear, however, that some underlying genotype of depression is altogether too common to not have

been selected. So, the question (“Is depression an adaptation?”) has an affirmative answer. How else to account for all these genes in the human genome?

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