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NATHALIE T. GODART, M.D., PH.D.
ZOÉ REIN, M.SC.
FABIENNE PERDEREAU, M.D., M.SC.
FLORENCE CURT, M.D., PH.D.
PHILIPPE JEAMMET, M.D., PH.D.
Paris, France

Dr. Woodside Replies

TO THE EDITOR: I read with interest the letter by Dr. Godart et al. concerning the rates of premature termination of inpatient treatment for anorexia nervosa. This issue, studied minimally in adults, has been neglected in adolescents. I expect that some of the differences in the findings of the study by Dr. Godart et al. and ours can be explained by the nature of the patient population. I would also be interested in knowing how Dr. Godart et al. established a failure in a patient's therapeutic contract, given that the patients were all adolescents and receiving treatment at least partly at their parents' behest.

D. BLAKE WOODSIDE, M.D., F.R.C.P.C.
Toronto, Ont., Canada

Brain-Derived Neurotrophic Factor in Patients With Remitted Depression

TO THE EDITOR: We read with interest the article by Alexander Neumeister, M.D., and colleagues (1). The neurobiology of brain-derived neurotrophic factor (BDNF) is complex and influenced by a number of different hormonal systems, including the hypothalamic-pituitary-adrenal (HPA) axis, which is known to be dysfunctional in patients with severe mood disorders. Stress-responsive corticosteroids, which are the end products of the HPA axis, have been shown to have important effects on the expression of BDNF in preclinical studies (2). We have also recently shown an interaction between cortisol and serum levels of BDNF in patients with bipolar depression and schizophrenia (3). Furthermore, tryptophan depletion has been shown to lower cortisol levels in patients with mood disorders (4) as well as in healthy comparison subjects (5). Of interest, sham tryptophan depletion has also been reported to cause a significant decrease of plasma cortisol (4). Changes in cortisol levels may, therefore, account for the increases in BDNF following sham depletion observed by Dr. Neumeister and colleagues.

The data presented by Dr. Neumeister et al. may indeed suggest an intimate link between the serotonergic and neurotrophic systems, but in the absence of any data regarding HPA axis function in these patients (and healthy subjects), it remains a possibility that the observed changes of expression of BDNF are secondary to differences in cortisol production. We advocate that further studies of BDNF in mood disorders also investigate HPA axis function.

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PAUL MACKIN, M.B., B.S., PH.D., M.R.C.PSYCH.
PETER GALLAGHER, B.SC., M.PHIL.
Newcastle Upon Tyne, U.K.

Drs. Neumeister and Manji Reply

TO THE EDITOR: We read with interest the letter by Dr. Mackin and Mr. Gallagher in which they suggest interpreting the interactive effects of BDNF and serotonin in major depressive disorder in the context of HPA axis function. Preclinical studies (1) have suggested major functional interactions between knockout mice with genetically induced alterations in serotonin (5-HT) transporters and heterozygous BDNF knockout mice and have also shown that this leads to enhanced stress responses with altered HPA axis function. Notably, a decrease in BDNF concentrations does not appear sufficient to lower extracellular 5-HT; similarly, constitutional changes in extracellular 5-HT because of differences in 5-HT reuptake by 5-HT transporters do not affect BDNF protein levels. This adds to the importance of identifying additional parameters that may contribute to the interactive effects of 5-HT and BDNF in major depressive disorder. There is a wide range of evidence supporting the idea that glucocorticoids play a key role in acute and chronic stress responses. For example, stress and glucocorticoids impair hippocampal neurogenesis; furthermore, in addition to directly causing neuronal atrophy, stress and glucocorticoids also impair cellular resilience that together may lead to the well-established morphological alterations in major depressive disorder. Notably, BDNF and other