

patients and comparison subjects (1). They concluded that postsynaptic serotonergic receptors that are mCPP-responsive may be "relatively intact in depression." There are a number of flaws in this study that make the drawing of any conclusions impossible.

First, the menstrual cycle phase of female subjects in either group was not taken into account. There is a stepwise increase in serotonergic-mediated prolactin release throughout the menstrual cycle (2). In addition, GH responses were only blunted in male depressed subjects. By using a variety of GH-releasing probes, a number of investigators have shown that gonadal steroids, at either a somatotrope or pituitary level, influence GH secretion (3-5). In this study, phase of menstrual cycle was not taken into account, and the confounding effect of gonadal steroids on prolactin and GH release remains undetermined.

Second, the doses of mCPP that were used, while producing meaningful neuroendocrine responses, also led to various adverse effects in both groups. These included feeling less calm and more nervous and anxious. Furthermore, no mention was made as to how long before mCPP administration were the baseline samples taken. Prolactin is acutely sensitive to stress, be it caused by venipuncture or related to an adverse event (6). Both of these factors may have contributed to a release of prolactin through mechanisms other than the serotonergic system, which would thereby obscure any putative serotonergic deficit observed in depression.

Last but not least, mCPP is not a "clean" probe, since it also has dopaminergic agonist activity and α_2 -adrenoreceptor activity; actions at either of these catecholaminergic sites may have resulted in the observed neuroendocrine profile (7). By the authors' own admission, mCPP's effects on serotonin (5-HT) receptor sensitivity are complex: mCPP acts as an agonist at the 5-HT_{1C} site and has mixed properties at the 5-HT₂ site. Both of these receptors are subtypes of the 5-HT₂ receptor class, and mCPP's mixed actions may well explain the lack of any differences in prolactin secretion between the two groups studied.

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TO THE EDITOR: In their excellent article, Dr. Anand et al. showed that in comparison to normal subjects, depressed patients had a blunted GH response to mCPP, a direct 5-HT agonist, whereas cortisol and prolactin stimulation did not differ between the two groups. In conclusion, they suggested the possibility of a primary defect in GH production in depression. Indeed, blunted GH stimulation in response to various provocative agents, such as clonidine, desipramine, apomorphine, GH-releasing hormone, or 5-HT precursors, is consistently observed in depression. However, in a recent study, we failed to confirm this hypothesis of an intrinsic abnormality in the hypothalamic-GH-somatomedin axis in depression (1).

Recently, we developed a new serotonergic neuroendocrine challenge with flesinoxan, a highly potent and selective 5-HT_{1A} agonist (2). In a double-blind, placebo-controlled study, single intravenous doses of 0.5 mg and 1 mg were given over 10 minutes to 12 healthy male volunteers at 1-week intervals. Temperature and hormonal responses (ACTH, cortisol, prolactin, GH) were measured 30 minutes before, at, and 15, 30, 60, 90, and 120 minutes after administration. Flesinoxan induced a marked and dose-dependent increase in ACTH, cortisol, prolactin, and GH and a decrease in body temperature. The subjects' tolerance of flesinoxan was excellent; flesinoxan was associated with a pleasant feeling of relaxation and a slight drowsiness without substantial gastrointestinal side effects. In a second step, GH responses to 1 mg of flesinoxan were measured in a group of 12 male inpatients who met DSM-III-R criteria for major depression and 12 male comparison subjects (1). The patients had been drug free for at least 3 weeks before the neuroendocrine procedure. The two groups did not differ in the change in GH peak responses: mean=4.83 ng/ml (SD=5.24) for depressed subjects and mean=3.58 ng/ml (SD=4.13) for comparison subjects ($F=0.14$, $df=2, 21$, $p=0.70$). This finding shows that the hypothalamic-GH-somatomedin axis seems to be intact in depression. Therefore, a blunted GH response to 5-HT stimulation in depression could be considered as an indirect index that supports the hypothesis of a reduced sensitivity of postsynaptic 5-HT receptors in mediating GH release.

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Dr. Price and Colleagues Reply

TO THE EDITOR: We disagree with Dr. Thakore's assertion that there are major flaws in our study. We did not control for menstrual cycle phase because we had no reason to think that this variable would be nonrandomly distributed between patients and comparison subjects and would thus constitute a source of systematic bias. Moreover, controlling for this fac-

tor would have further delayed the initiation of treatment in our patients, who had not taken psychotropic medication for at least 3 weeks at the time of testing. In any case, reanalysis of the data by using days from last menstrual period as a covariate does not alter our original finding of no difference between healthy and depressed women in responses of GH ($F=2.19$, $df=5, 75$, n.s.), prolactin ($F=1.99$, $df=7, 91$, n.s.), or cortisol ($F=1.36$, $df=7, 91$, n.s.) to mCPP administration.

Dr. Thakore also alludes to the adverse effects caused by mCPP and the possibility that stresses associated with the test procedure itself (e.g., the initial venipuncture for catheter placement) may have obscured important findings. We would not view subjective mood responses to mCPP as adverse effects but rather as meaningful effects that provide important information as to how the neuropharmacologic actions of this compound are transduced into behavior. As to the issue of test-related stress responses, it should be evident from the pattern of neuroendocrine responses on the placebo test days that neither patients nor comparison subjects exhibited such responses. This may partly have reflected the fact that the two baseline blood samples were obtained at least 45 and 60 minutes after intravenous catheter placement (at 15 minutes and 0.5 minute before the mCPP infusion, as stated in the Method section).

Finally, Dr. Thakore observes that mCPP is not a "clean" probe of the 5-HT system. We fully agree with this and made the same point in our report and used deliberate caution in drawing inferences from our findings. However, Dr. Thakore overstates mCPP's dopaminergic effects, which are weak (1), while its actions at the α_2 -adrenoreceptor have little significance in humans (2). There is strong evidence that mCPP's effects on cortisol and prolactin are mediated, at least in part, through 5-HT_{2A/2C} receptors (3).

In this regard, the findings of Dr. Pitchot et al. are particularly interesting in demonstrating the normal GH responses of depressed patients to the 5-HT_{1A} agonist flesinoxan. However, given the continuing ambiguity as to the mediation of mCPP's effects on GH, we stand by our cautionary statement regarding the interpretation of the blunted GH response observed in our patients.

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Freud and Music

TO THE EDITOR: Dr. Anthony Storr, in his book review (1), has perpetuated an ancient canard about Freud—that he

"hated music." What Freud actually described was a relative insensitivity to music as compared with literature. In fact, he enjoyed Mozart operas and, in a letter to Wilhelm Fliess, spoke of having "had a remarkable and pleasurable experience in [Richard Wagner's] *Die Meistersinger*" (2). It is true that in this letter he spoke of the story of the opera, rather than the music itself, but it would certainly be inaccurate to suggest that he "hated" the music; at worst, he may have been indifferent to it, captivated as he was by the theme of dream interpretation. He concluded, notably, by saying, "In no other opera . . . are real thoughts set to music, emotive sounds which dwell in the mind." Scarcely Philistine, and certainly not a token of hatred!

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TO THE EDITOR: In his review, Dr. Storr states, too categorically I think, that "the idea that Rossini's retirement from operatic composition was prompted by the death of his mother . . . has long been discredited" and says that Martin Nass's statement to the contrary is in error.

Storr does not make it clear precisely what has been discredited. Is it that Rossini's mother's death was *one* factor in what is often called his "Great Renunciation"? Or is it that Rossini's mother's death was *the only* factor in that renunciation?

We shall probably never know exactly why Rossini developed one of the more severe creative blocks of all time and gave up writing opera completely. There seem to have been many reasons for his abdication. As Francis Toye, a Rossini biographer, puts it, "No single reason . . . suffices to account for [it but] several causes . . . combined to bring it about" (1). In other words, Rossini's symptom, writer's block, was, like most writers' blocks in specific and most symptoms in general, of "multidetermined" origin.

We do not know if Rossini was grieving. And if he was, his grief was almost certainly not the only factor to cause his block. But I cannot imagine that the death of his mother would most assuredly *not* cause grief, and grief *not* be one of the factors in his blockage. If Storr meant to suggest that grief was absent, or not a factor, and that this has been proved beyond a shadow of doubt, then I think Storr, not Nass, is making the error.

The annals of writer's block are, in fact, replete with instances of block as a symptom of uncomplicated bereavement. For example, Ravel wrote nothing for 3 years after his mother died. Perhaps Agatha Christie said it most simply and directly in her autobiography: "Ever since my mother's death I had been unable to write a word" (2).

When analyzing dead artists we are often warned not to use biographical data lightly to prove our own favorite theories. For example, Frosch stated that "psychobiography has, until recently, been the haunt of amateurs . . . seriously marred by . . . mistranslation of the primary datum . . . [with psychobiographers] led astray by their reliance on secondary and tertiary sources" (3).

I would like to add a warning of my own. Just as we should