Letters to the Editor

Schizophrenia and Binge-Eating Disorders

Sir: There are many reasons why people with schizophrenia may have problems with food and weight. However, few empirical studies have examined the potential comorbidity between eating disorders and schizophrenia. Recent advances in the pharmacotherapy of schizophrenia have altered the side effect profiles of patients taking the newer generation of atypical antipsychotic drugs compared with older, conventional drugs. The older concerns with motor side effects have been replaced by problems even more relevant than before with overeating, obesity, and type 2 diabetes mellitus and its associated complications.[1] Considering that overeating and obesity can be the features of eating disorders, knowledge of an association between schizophrenia and these disorders can lead to earlier identification of the comorbid conditions and prevention of other likely complications.

Method. We evaluated a sample of 31 outpatients (25 men with a mean ± SD age of 34.8 ± 9.2 years and 6 women with a mean ± SD age of 41.1 ± 10.1 years) after obtaining informed consent and institutional review board approval. All were diagnosed as having schizophrenia by experienced clinicians using the Structured Clinical Interview for DSM-IV.[2] Each of these subjects was administered the semistructured Binge Eating Clinical Interview (BEDCI)[3] to determine the presence or absence of binge-eating disorder. The diagnosis of bulimia nervosa was made by clinicians experienced in treating these conditions, again using the BEDCI. While we have suggested that the differentiation between binge-eating disorder and bulimia nervosa, nonpurging type (BN-NP), may be artificial,[4] for the purposes of this communication, we have relied on the existing classification system (DSM-IV). Additional assessment was performed with the Eating Disorders Inventory (EDI).[5] Data were gathered from September through December 2001.

Results. Most patients (71%; N = 22) were overweight as defined by a body mass index (BMI) of > 25. Sixty-two percent (N = 19) were obese as defined by a BMI of > 27. Five of the obese subjects (all males), representing 16% of the sample, were diagnosed with binge-eating disorder or BN-NP. Three of these patients developed binge eating after the onset of treatment with atypical antipsychotics. Specific items on the BEDCI and the EDI reflected the subjects' attitudes toward eating and weight. All 5 patients with binge-eating disorder/BN-NP and 5 other patients (32% of the entire sample) had scores indicating that weight and shape affected their self-esteem. The patients with binge-eating disorder displayed low drive for thinness and body dissatisfaction scores on the EDI, reflecting either an attitude of giving up on dieting and concerns with the body or never having been concerned with these issues; this attitude is not unusual for males.

The present study suggests an association between schizophrenia and bulimia nervosa or binge-eating disorder, but not anorexia nervosa. However, this study is limited by the small patient group size, and the specificity of the patient environment limits the ability to generalize these results to other settings.

Brewerton and Shannon[6] reported on the potential exacerbation of bulimia nervosa when patients were given clozapine, and clozapine therapy has been found to generate binge-eating episodes in some patients.[7] The potential association between schizophrenia and bulimia nervosa or binge-eating disorder has not been widely investigated, a result, perhaps, of the complicated relationship that has been described for these disorders.[8] From the few published case studies that are available on women with schizophrenia and reported bulimic disturbances, a reciprocal relationship appears to exist between these syndromes.[8] Specifically, binge and purge cycles have been found to emerge during periods of decreased psychotic symptoms, and, as the negative symptoms of schizophrenia have progressed, the drive to restrict or binge and purge has diminished as goal-directed behavior has become deficient.[8] In accordance with this evidence, Hugo and Lacey[9] hypothesized that bulimia nervosa may in fact protect against a psychotic state and help to alleviate a psychotic process.

The majority of evidence focused on understanding the comorbidity between schizophrenia and bulimia nervosa and binge-eating disorder points to the use of antipsychotic medication as the main reason for this association.[6] In our sample, 60% of the binge-eating disorder/bulimia nervosa group developed their eating symptoms after use of the new generation of neuroleptic drugs. The newer, atypical antipsychotics olanzapine and clozapine have been implicated in causing significant weight gain in 40% to 80% of patients who use these medications, and treatment with the medications can result in weight gain of 20% or more beyond ideal body weight.[10] This phenomenon seems to be due to an increase in body fat, caused by enhanced caloric intake without a subsequent increase in physical activity.[11,12] Theories concerning possible involvement with serotonergic, dopaminergic, and histaminic receptors have been suggested.[13]

Other hypotheses for the link between eating disorders and schizophrenia target the lifestyle of schizophrenia patients. For example, level of physical activity has been deemed low in this group. One study[12] found that patients spent less than 10 continuous minutes in moderate activity during the day despite encouragement from staff, which is much less activity than that reported for healthy individuals. In addition, there is a high level of unemployment in this population, leading to little exercise from work-related activities.[14] It may also be helpful to view the onset of eating disorders in schizophrenic patients within the context of lack of achievement in other life areas (e.g., academic or social). Dymek and le Grange[15] described the development of an eating disorder as a response to a feeling of success in weight loss. In addition, Ferguson and Damluji[16] suggested that an eating disorder appears in many ways to provide some semblance of value and organize the life of schizophrenic patients.

Probably the most important issue highlighted by this work is the need to develop weight control programs for patients with

schizophrenia. These should include lifestyle intervention programs that focus on diet, emphasize physical activity, and teach problem-solving skills specified for patients with schizophrenia.[10] Current evidence suggests that short-term weight loss is achievable in this population, but other strategies must be generated to target long-term weight loss[10] or the prevention of weight gain.

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The Effects of Newer Antidepressants on Low-Density Lipoprotein Cholesterol Levels

Sir: Nicholas et al.[1] must be commended for investigating a topic of major clinical importance, i.e., the effects of the newer antidepressants, such as mirtazapine, on serum levels of low-density lipoprotein cholesterol (LDL-C). Indeed, LDL-C levels are considered as an important predictor of cardiovascular events.[2] The authors showed a statistically nonsignificant increase of 3% in LDL-C in healthy controls after 4 weeks of mirtazapine treatment compared with placebo treatment and concluded that mirtazapine did not increase LDL-C levels. We believe that there may be methodological explanations for their neutral findings.

Lara et al.[3] have shown that 20 mg q.d. of paroxetine significantly increased LDL-C by 9 mg/dL (11.5%) after an 8-week treatment period in 18 male healthy controls, with LDL-C levels returning to baseline after discontinuation of paroxetine. Another study[4] showed that 12 and 28 weeks of treatment with venlafaxine in patients with generalized social phobia induced dose-related mean increases of LDL-C of 7.7 and 10.4 mg/dL, respectively, suggesting a dose- and duration-dependent increase in LDL-C. In a less-controlled and naturalistic, but long-term study[5] in which most patients were treated with sertraline, we found a mean increase of 39.9 mg/dL in LDL-C concentrations. Together, these data suggest that the 4-week study by Nicholas and colleagues was too short to assess whether mirtazapine induces an increase in LDL-C levels.

Nicholas et al.[1] included 10 men and 18 women in the mirtazapine group. In a recent study from our group that included 42 men and women, paroxetine-induced increase in LDL-C was limited to men and did not take place in women (M.C.A.; J.-M.L.; N. Lara, M.D.; et al.; unpublished data, October 2003). A dilution effect due to the absence of an impact of mirtazapine on LDL-C level in women (18 of 28 subjects in the mirtazapine group) may therefore have also contributed to the neutral findings. In this regard, a separate analysis by gender would be informative. A study with a longer duration of treatment and a greater male representation might be necessary to fully assess the effect of mirtazapine on lipids.

The mechanism of the effects of paroxetine, venlafaxine, sertraline, and possibly mirtazapine on LDL-C level remains to be determined, but these agents all cause an increase in firing of serotonergic neurons. The increase in LDL-C appears to be independent of the antidepressant/anxiolytic activity of these compounds since such an effect was also observed in healthy controls.

We do not believe that the increase in LDL-C observed after acute treatment with several antidepressants is a major concern for most medically healthy psychiatric patients, although monitoring of lipid levels during long-term administration of those antidepressants would appear prudent. The antidepressant-induced increase in LDL-C is a greater concern in the numerous patients with major depressive disorder who suffer from comorbid coronary heart disease, for whom even a small increase in LDL-C carries a significant cardiovascular risk. However, antidepressants with a positive impact on endothelium function and platelet activity are likely to induce beneficial cardiovascular effects that could offset the deleterious effect of the LDL-C increase.[6]

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Dr. Nicholas and Colleagues Reply

We appreciate Le Mellédo and colleagues' interest in our work. Their point is well taken: our 4-week study may not have detected changes in levels of low-density lipoprotein cholesterol (LDL-C) and other lipids that could have reached statistical significance only after 8 or more weeks of mirtazapine exposure. However, we deliberately chose to study healthy control subjects in order to avoid potential confounding effects of a psychiatric disease state per se in our investigation of the effects of mirtazapine. For practical and ethical considerations, we limited the exposure of these healthy subjects to 1 month. We believe that while it is possible that longer-term exposure might uncover a statistically significant effect, it is unlikely that the effect would be clinically meaningful, except possibly in patients who already have problematic elevations in LDL-C levels. It should be noted that there was a trend toward increases in high-density lipoprotein cholesterol levels following mirtazapine exposure as well, and this favorable effect may balance any negative consequences of elevated LDL-C.

We controlled for sex in our analyses, and the effect of the sex factor did not approach significance. However, since our groups were not balanced, it is still possible that there were confounding factors and that the absence of an LDL-C increase in our 18 women diluted the overall effect of a noteworthy LDL-C increase in our 10 men.

To further clarify the sex effect on LDL-C, we reanalyzed the study data by sex. Within the mirtazapine treatment group at week 4, the men showed a small mean LDL-C increase from baseline of 1.2 mg/dL, which was an increase of 0.8%, while the women showed a larger increase of 5.3 mg/dL, which was an increase of 6.2%. Since about the same proportion of men (6/10) and women (10/18) showed some increase, it is clear that the difference was due to larger increases among the women.

Closer inspection of the data reveals that only 6 of 18 women accounted for most of this effect. Among the 8 of 28 subjects with the largest increases in LDL-C (increase of more than 10%), 6 were women (only 2 were men); 4 of these women (no men) had increases of more than 25%, and 3 had increases in LDL-C of 30% from baseline. These results were not statistically misleading "outliers," since individual subjects' levels were generally quite variable, demonstrating moderate decreases, as well as some large increases, within both sexes; this large individual variability (pooled SD = 14%) works against finding statistical significance and may suggest the influence of some other unknown factor (e.g., diet, exercise).

We conclude that there could possibly be a noteworthy sex effect even though it was not significant in our sample. However, in contrast to the findings of Le Mellédo et al., our results show the most robust LDL-C increases in women rather than men. We thank Le Mellédo and colleagues for bringing these interesting and clinically important issues to our attention.

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Duloxetine's Role in the Treatment of Depression and Associated Painful Physical Symptoms

Sir: The recent letter by Leo[1] raises a number of questions concerning the role of antidepressants in the treatment of painful physical symptoms associated with depression and pain in nondepressed patients. The author focuses on published data for the antidepressant duloxetine and attempts to determine whether there is a role for duloxetine in chronic pain management. We wish to reply to points raised in the letter and add data that were not in the public domain at the time of the letter's submission.

These new results support the following conclusions: (1) duloxetine is an effective antidepressant that successfully treats painful physical symptoms in depressed patients; (2) alleviation of painful physical symptoms in depressed patients significantly increases their probability of achieving remission; (3) approximately 50% of duloxetine's effect on pain in depressed patients occurs independently of changes in core emotional depression symptoms; and (4) duloxetine effectively treats pain associated with diabetic neuropathy in nondepressed patients.

First and foremost, duloxetine is an effective antidepressant. While some studies have investigated the efficacy of duloxetine in pain states, the primary focus of our clinical development program has been the treatment of major depressive disorder (MDD). Results from double-blind, placebo-controlled studies[2–5] and a long-term, open-label study[6] have established duloxetine as a safe and effective treatment for MDD.

Duloxetine is a balanced and potent reuptake inhibitor of both serotonin and norepinephrine. In addition to their role in the neurobiology of depression, these neurotransmitters act as pain modulators in the descending inhibitory pain pathways of the spinal cord.[7] In placebo-controlled studies,[2–5] duloxetine has demonstrated efficacy in the treatment of painful physical symptoms in depressed patients, as assessed using visual analog scales for pain.

Dr. Leo relates that reductions in pain severity ratings are often regarded as artifacts of improvements in mood observed when depressed patients are effectively treated. In contrast, results obtained during duloxetine clinical trials[8,9] support its direct effect on pain in both depressed and nondepressed patients and demonstrate the importance of effective treatment of painful physical symptoms associated with depression.

Statistical analyses, e.g., path analysis, can help demonstrate the independence of the effects of antidepressants on mood versus pain. We performed a path analysis on pooled data from 2 MDD clinical trials of duloxetine (60 mg q.d.) and demonstrated that approximately 50% of the decrease in pain severity in depressed patients is directly attributable to duloxetine treatment and occurs *independently* of improvement in depressive symptoms.[8]

If painful physical symptoms truly represent an important component of MDD, it may be expected that the alleviation of these symptoms should contribute to a patient's recovery from depressive illness and thereby influence the probability that a patient will achieve remission.[10] To further investigate this concept, we analyzed pooled data from 2 clinical studies of duloxetine (60 mg q.d.). The results demonstrated that improvement in pain severity was associated with an increased probability of achieving remission even after accounting for improvement in core emotional symptoms of depression.[11] These data are clearly inconsistent with Dr. Leo's statement that "as depression is alleviated, so too is the amplification of somatic symptoms reduced."[1(p1270)]

Dr. Leo also states, "Given the experimental paradigms employed to date, it would be erroneous to assume that duloxetine has a direct pain-relieving effect."[1(p1270)] He proposes the need for "compelling data . . . from studies demonstrating efficacy in pain patients with clear, identifiable disorders who are not depressed."[1(p1270)] Such study results were presented recently.[9] In a 12-week, double-blind, placebo-controlled study of 457 patients with painful diabetic neuropathy, duloxetine doses of 60 mg either q.d. or b.i.d. were significantly superior to placebo in alleviating diabetic neuropathic pain in *nondepressed* patients. Efficacy was demonstrated on both the primary measure (the weekly mean of the 24-Hour Average Pain Score) and several secondary measures (including Brief Pain Inventory pain severity and interference items).

We hope that the additional information discussed in this letter will clarify the role of duloxetine in the treatment of MDD and the painful physical symptoms associated with depression. Furthermore, while Dr. Leo asserts that the role of duloxetine in pain relief has yet to be elucidated, the results described here provide compelling evidence that duloxetine demonstrates efficacy in the treatment of pain symptoms in both depressed and nondepressed patients.

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Metyrapone for Delirium Due to Cushing's Syndrome Induced by Occult Ectopic Adrenocorticotropic Hormone Secretion

Sir: Cushing's syndrome secondary to ectopic adrenocorticotropic hormone (ACTH) syndrome is rare. Ectopic ACTH-dependent Cushing's syndrome is encountered in 2 forms, the classic overt ectopic ACTH syndrome and "occult" ectopic ACTH-secreting tumors.[1] Occult ectopic ACTH-secreting tumors are often small, and their detection requires meticulous examination. Despite recent technological advances, including inferior petrosal sinus sampling and the corticotropin-releasing hormone (CRH) stimulation test, localization of the tumor remains difficult.[1–3] We report a case of psychiatric manifestations that were caused by Cushing's syndrome induced by occult ectopic ACTH secretion and that have been controlled by metyrapone, an 11β-hydroxylase inhibitor.

Case report. Ms. A, a 53-year-old woman, was admitted to the hospital for evaluation of general fatigue and headache. She also presented with hirsutism and a recent weight gain of 7 kg (16 lb), and 3 months before her admission in April 2001, she had developed truncal obesity, "moon face," and general fatigue. Biochemical testing showed hypokalemia and hypercorti-

solemia (cortisol level = 125.3 μg/dL; normal range, 4.0–18.3 μg/dL), with failure of suppression following high-dose dexamethasone administration. Ms. A's ACTH level was 400 pg/mL (normal range, 9–52 pg/mL). In addition, the ovine CRH stimulation test showed no apparent change in plasma ACTH or cortisol levels. Inferior petrosal sinus sampling failed to detect a central/peripheral gradient of ACTH concentrations (maximal ratio = 1.6). Results of pituitary magnetic resonance imaging of the head were normal. Computed tomography of the patient's thorax and abdomen revealed no abnormalities except for hyperplastic adrenal glands with no adenoma. These findings suggested an ectopic ACTH source.

Five days after Ms. A's admission, her mental state deteriorated dramatically. Because the patient developed visual hallucinations, paranoid delusions, psychomotor excitement, and disorientation, she was referred to our department (Psychiatry) for further management. She was diagnosed with delirium due to Cushing's syndrome according to DSM-IV criteria and was begun on haloperidol treatment titrated to a maximum dose of 20 mg/day. After 3 weeks, she was less agitated but was very confused.

On the 37th day of the patient's hospitalization, haloperidol was discontinued, and metyrapone treatment was begun at 500 mg/day. Ms. A's cortisol level dropped rapidly to within normal limits (10.2 μg/dL), and her visual hallucinations, paranoid delusions, psychomotor excitement, and disorientation decreased during the next 2 weeks. The improvement persisted through the remaining month of her hospitalization. Cushing's syndrome and its psychiatric manifestations have been controlled with metyrapone, 1250 mg/day, for more than 20 months after the patient's discharge. Ms. A's cortisol level has been maintained within the normal range, and her ACTH level has been stabilized at around 200 pg/mL for more than 20 months. Regular follow-up has not yet located an ACTH-secreting tumor.

While delirium related to Cushing's syndrome was diagnosed in this case, an obvious underlying tumor was not present. An interesting feature of the case is the remission that occurred following metyrapone therapy. Although the patient's long-term, relatively high-dose neuroleptic prescription might have been partly responsible for providing a beneficial treatment response, metyrapone therapy led to a dramatic and sustained improvement in the patient's mental state.

Metyrapone reduces the production of cortisol by inhibiting the final step in adrenal steroid production, which is the conversion of biologically inactive 11-deoxycortisol to cortisol; metyrapone cannot inhibit production of ACTH directly.[4] Starkman and Schteingart[5] reported a significant relationship between the severity of neuropsychiatric disability and plasma levels of both cortisol and ACTH in patients with Cushing's syndrome. They also found that patients with adrenal adenomas with high cortisol but low ACTH levels had less severe neuropsychiatric disability than those with high ACTH levels, indicating that ACTH might contribute to the psychiatric manifestations of patients with Cushing's syndrome. On the other hand, psychiatric complications of exogenous corticosteroid administration have been recognized, although the suppression of ACTH production occurs.[6] In the present case, the patient's cortisol level rapidly normalized, while her high ACTH level has remained the same after metyrapone therapy. Therefore, psychiatric manifestations due to ectopic ACTH syndrome might result from a high level of cortisol rather than ACTH.

Most studies indicate that 50% to 80% of patients with Cushing's syndrome will experience mild to severe depressive symptoms, while psychosis and delirium are rarely reported.[7] To the authors' knowledge, the differences in psychiatric presentations between ectopic ACTH syndrome and pituitary overproduction of ACTH have not yet been investigated systematically.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Beneficial Effects of Gonadotropin-Releasing Hormone Analogue Treatment on Positive and Negative Symptoms of Schizophrenia: A Case Report

Sir: This letter reports a patient with chronic treatment-resistant schizophrenia and deviant sexual behavior who showed clinical improvement after treatment with the depot gonadotropin-releasing hormone (GnRH) analogue buserelin acetate. The patient's clinical improvement included decrease in positive (hallucinations, disorganization) as well as negative (social withdrawal, academic interest) symptoms. The possible therapeutic and theoretical implications of the putative role of hormones in schizophrenia are briefly discussed.

Case report. Mr. A, a 24-year-old married Orthodox Jew from a low socioeconomic status, presented in June 1999 with a history suggestive of a diagnosis of DSM-IV schizophrenia. At 20 years of age, Mr. A experienced his first psychotic episode, which lasted for more than a year. During this period, he had

delusions of influence and possible command hallucinations that ordered him to touch and fondle his best friend's small children. In addition, he had recurrent intrusive homosexual fantasies. In the following years, Mr. A experienced at least 3 relapse periods, each lasting more than 6 months. A marked deterioration of social and academic functioning was observed, and he ceased studying in the yeshiva. Symptoms of deviant sexual behavior and severely impaired judgment had become a significant problem and included several attempts to touch and fondle minors, as well as socially inappropriate behaviors. In addition, Mr. A had reported recurrent suicidal ideation, without a specific plan. Initially, standard doses of risperidone, olanzapine, haloperidol, sulpiride, and perphenazine monotherapy were administered. However, only partial response to the typical and atypical neuroleptics was observed. In addition, augmentation with valproic acid and lithium failed to improve the patient's condition. Clozapine therapy was not administered because of the patient's refusal.

At presentation, Mr. A's last medication regimen included valproic acid (1000 mg/day divided into 2 doses), perphenazine (single daily dose of 4 mg), and clonazepam (3 mg/day divided into 3 doses of 1 mg). Paroxetine (30 mg/day) had also been added in the hope of ameliorating his intrusive sexual thoughts, with no significant behavioral effect. Therefore, sustained release GnRH analogue therapy was initiated in addition to the existing regimen. The patient was given buserelin acetate, a synthetic peptide GnRH analogue, in an intramuscular injection of 9.9 mg for a 3-month sustained release. For the initial 10 days, to overcome testicular stimulation, 50 mg b.i.d. of cyproterone acetate was added.[1] While no immediate reduction of symptoms was observed, behavioral change was first evident 10 days after this initial dose of buserelin acetate. The first symptom to improve was the patient's suicidal ideation, followed by gradual attenuation of his sexual impulses and improvement of his judgment over the next month. During this period, the patient reported mild sedation and impotence and marked improvement in overall mood.

Despite his improvement, the patient skipped the next scheduled injection. Four months later, he had experienced another relapse with identical symptomatology that again failed to respond to standard doses of valproic acid and perphenazine. Following administration of buserelin acetate depot, a similar course of gradual improvement of both positive and negative symptomatology occurred. Again, suicidal ideation was the first symptom to ameliorate, followed by the disappearance of command hallucinations around days 7 to 9. During that time, the patient reported significant decrease of his sexual impulses, with no external reports of further sexual behaviors. This behavioral change paralleled a gradual and continuous improvement in his judgment and decision making. The patient reported a significantly increased ability to initiate academic activities, supported by external reports that he had resumed attendance at his local synagogue. Currently, 2 months after the second injection, the patient shows no evidence of delusional ideations and reports continuous improved social communication and increased academic and religious interest. The patient has also reported a lack of compulsive sexual behaviors and recurrent sexual fantasies, to the extent of loss of libido and impotence.

In this case, GnRH analogue therapy was attempted due to refusal of clozapine combined with deviant, potentially hazardous sexual behavior. In addition to their role in reproductive endocrinology and treatment of prostate cancer,[1] GnRH analogues induce selective and reversible suppression of the pituitary-gonadal axis. This suppression results in chemical castration[2] that is helpful for the treatment of paraphilias and sexually deviant impulsiveness.[3,4] In addition, there is evidence to suggest that gonadal hormones may be involved in the pathophysiology of schizophrenia.[5] For example, gender differences in the onset and course of schizophrenia have been attributed to protective estrogen effects.[5] Furthermore, the administration of anabolic androgens is probably associated with increased rates of psychosis and mania.[6] A single case report[7] described amelioration of bizarre sexual behavior in an adolescent girl following administration of leuprolide acetate depot. However, there is some evidence that hormonal interventions in schizophrenia may have gender-specific effects.[5]

To the best of our knowledge, there are no prior reports of treatment of positive and negative schizophrenia symptoms with long-acting GnRH analogues in males. Since long-term GnRH administration in chronic mental disorders may result in hypogonadism-induced osteoporosis, they should be considered together with other added therapies (e.g., alendronate sodium). Additional adverse effects that cause specific concern in schizophrenia patients are loss of libido and sexual activity, both considered prominent negative symptoms in this disorder. At this preliminary stage, GnRH administration should be considered only in selected cases of psychosis combined with uncontrollable sexual impulses. However, other schizophrenia patients may also benefit from GnRH treatment. Therefore, more case reports and clinical trials are needed in order to assess the possible contribution of GnRH analogues to the treatment of schizophrenia patients.

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