amined; however, we could not confirm the multiple endocrine neoplasia type 1 gene mutation and did not observe any endocrine disorders and psychiatric symptoms in these two descendants. On the contrary, her mother committed suicide under treatment for a gastrointestinal tumor.

Although the hypothesis of multiple endocrine neoplasia type 1 and schizophrenia comorbidity could not be ruled out completely, the patient's psychiatric symptoms differed from those typical of schizophrenia. These clinical features seemed to be one of the psychiatric manifestations of multiple endocrine neoplasia type 1. We concluded that the psychiatric manifestations of our patient could be linked with multiple endocrine neoplasia type 1.

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Liepmann's Phenomenon During Benzodiazepine Withdrawal

TO THE EDITOR: Liepmann's phenomenon has been described in the context of alcohol-related delirium (1). We present a case of Liepmann's phenomenon apparently occurring with excessive use of diazepines.

Mr. A, a 44-year-old man, was admitted to the gastroenterology unit of Kitasato University for general fatigue of 1 week's duration. He had been followed since he was 29 for ulcerative colitis and had undergone a total proctocolectomy with an ileal pouch and anastomosis at 37 years of age. On admission, he was alert, and the results of a physical examination, routine blood tests, and X-ray radiographs of his chest and abdomen were within normal limits. Brotizolam, 0.25 mg/day, was prescribed for insomnia.

On the second hospital day, a colorectal fiberscopy revealed no substantial worsening of the mucosal lesions. At 3:00 a.m. on the fourth day, Mr. A began to wander about the ward, saying, "Many strange little people are walking around," "I'm coming home," and "I must meet an appointed user now." His restlessness alternated with sleeping every few minutes. A diagnosis of delirium was made, and haloperidol, 5 mg, was injected intramuscularly at 5:30 a.m. and had little effect on him. At 11:00 a.m., when a consultant psychiatrist gently closed Mr. A's eyes and asked if he could see birds, Mr. A replied, "That's right, I can see birds (*Hontoda, tori ga mieru*)." He also exhibited Liepmann's phenomenon (1) in relation to a whale (i.e., he said that he could see a whale when the psychiatrist closed his eyes and asked if he could see a whale). A brain computed tomography scan revealed normal findings, and an EEG showed a low-voltage fast pattern with no paroxysmal discharges.

At 11:30 a.m., Mr. A's father informed his psychiatrist by telephone that Mr. A consumed "too much alcohol and hypnotics" every night, but later, the "too much alcohol" was confirmed to be 350 to 500 ml of beer. At the time, Mr. A was unable to answer when asked whether he used any hypnotics. At around 2:00 p.m., while exhibiting Liepmann's phenomenon in regard to an airplane, he repeated the names of the psychiatrists whom he usually consulted. The psychiatrists were contacted and informed us that Mr. A was taking 2.4 mg/day of alprazolam, 1.5 mg/day of etizolam, 0.5 mg/day of triazolam, 2 mg/day of estazolam, 0.25 mg/day of brotizolam, 2 mg/day of flurazepam, and 10 mg/day of zolpidem.

Oral diazepam, 20 mg over 24 hours, and drip infusion of flunitrazepam, 2 mg at night, was started. Since then, Mr. A has not exhibited Liepmann's phenomenon. This delirious episode resolved in 5 days. His dose of diazepam was reduced to zero in 8 weeks. The episode of delirium may have been attributable to withdrawal from excessive use of sedative drugs. Liepmann's phenomenon in Mr. A was observed exclusively during the delirium.

To our knowledge, few reports, other than the report by Miura et al. (2) on withdrawal from meprobamate (3000 mg/day) have described Liepmann's phenomenon in conditions besides alcoholism. However, this case clearly demonstrates that it is necessary to be alert to the "concealed" or possible use of excessive diazepines underlying Liepmann's phenomenon.

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Increase in Risperidone Plasma Level With Lamotrigine

TO THE EDITOR: A combination of clozapine and risperidone is effective in treating patients with schizophrenia who are unresponsive to other atypical antipsychotics or monotherapy with clozapine (1). Nevertheless, there are patients who respond only partially or even fail to respond to this combination. Saba et al. (2) and Dursun et al. (3) reported on patients who showed a substantial improvement of persistent positive symptoms when lamotrigine was added to clozapine therapy. There is evidence supporting the positive effects of lamotrigine based on its glutamate excess-release inhibition (4).

Because of these interesting reports, we decided to supplement the clozapine-risperidone combination of Ms. A, a 26-year-old inpatient who suffers from therapy-resistant schizophrenia with imperative auditory hallucinations, with lamotrigine. She had been taking clozapine, 550 mg/day, for 5 years and risperidone, 8 mg/day, for 4 weeks and had only responded partially. Her plasma levels of ris-

peridone (55–70 ng/ml) and clozapine (800–1100 ng/ml) were stable. Her lamotrigine dose was titrated up to 250 mg/day in steps of 25 mg per week. After Ms. A had been taking 175 mg/day of lamotrigine for 5 days, her plasma level was 5 mg/liter, and her risperidone plasma level was 69 ng/ml. We further increased her dose of lamotrigine to 200 mg/day. Her risperidone level rose to 284 ng/ml, and in follow-up measures, it showed a value of 263 ng/ml. Her clozapine level rose to 1300 ng/ml. Ms. A did not have any intoxication symptoms. Because we did not assume any connection of increased plasma level of risperidone with lamotrigine, we heightened the dose to 225 mg/day. The next measurement of both plasma levels indicated an exorbitant increase of risperidone plasma level, up to 412 ng/ml. Ms. A complained of dizziness and tiredness. We quickly reduced the dose of risperidone to 2 mg/day and withdrew the drug 1 week later. An overdose of risperidone was unlikely since it was taken under supervision.

Metabolism of risperidone occurs mainly in the liver and is dependent mostly on cytochrome P450 isoenzyme CYP 2D6. Lamotrigine does not inhibit CYP 2D6. It is eliminated by the kidneys after glucuronidation in the liver. Until now, we have had no explanation for the increase of the risperidone plasma level during concomitant therapy with clozapine and lamotrigine. Clinicians should be aware of this effect.

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Neuroleptic Malignant Syndrome Induced by Quetiapine and Fluvoxamine

TO THE EDITOR: Neuroleptic malignant syndrome is induced less by atypical antipsychotics than by conventional antipsychotics, and one particular atypical antipsychotic, quetiapine, rarely causes neuroleptic malignant syndrome (1). Selective serotonin reuptake inhibitors (SSRIs) are prescribed worldwide for the treatment of depression, and SSRIs and atypical antipsychotics are often prescribed together as augmentation therapy for depression. Here, we describe a male patient who suffered from severe neuroleptic malignant syndrome induced by concomitant administration of quetiapine, 150 mg/day, and fluvoxamine, 100 mg/day, although he had not shown any side effects with monotherapy with quetiapine, 150 mg/day, or fluvoxamine, 150 mg/day.

Mr. A, a 57-year-old man who was diagnosed with major depression at age 56, according to DSM-IV criteria, had been treated with fluvoxamine, 150 mg/day, for 1 year. During the year of treatment, no remarkable side effects were apparent, and after his condition had fully remitted, fluvoxamine was tapered off. Five months later, he presented with irritation and agitation, and risperidone was prescribed for these symptoms. Because of drug-induced extrapyramidal symptoms, risperidone was subsequently replaced by quetiapine, 150 mg/day, which was effective for his irritation and left him free of extrapyramidal symptoms. However, 2 months later, he increasingly developed a depressive mood and inhibition. Thus, fluvoxamine, 50 mg/day, was prescribed, in addition to quetiapine, and fluvoxamine was increased to 100 mg/day 1 week later. On the 10th day of concomitant administration of quetiapine and fluvoxamine, Mr. A stopped eating and drinking and developed muscle rigidity. On day 13, he was admitted to our hospital. At this time, he had a high temperature, severe extrapyramidal symptoms, high blood pressure, and tachycardia and was falling into a stupor. Laboratory tests showed elevation of his creatinine phosphokinase (7,500 IU/liter) and leukocyte (1.3×10^{10}/liter) levels. We stopped all psychotropic drugs and immediately started infusion of dantrolene, under a diagnosis of neuroleptic malignant syndrome, and Mr. A's symptoms improved gradually. However, on the fourth day of admission, he developed complications with acute pneumonia and respiratory failure and was transported to the intensive care unit and was treated with infusions of dantrolene and antibiotics. Three weeks later, he recovered from respiratory failure and neuroleptic malignant syndrome, and his laboratory measurements returned to normal.

In this case, concomitant administration of quetiapine and fluvoxamine caused neuroleptic malignant syndrome, although each drug alone did not cause any side effects. Since the doses of quetiapine and fluvoxamine were relatively low and these drugs are metabolized by different cytochrome P450 subtypes (2), induction of neuroleptic malignant syndrome was probably not due to an increase in the quetiapine and/or fluvoxamine concentrations. Hence, in this case, neuroleptic malignant syndrome may have been caused by a dopamine-serotonin disequilibrium (3), which was induced by concomitant quetiapine and fluvoxamine.

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