tion deficit hyperactivity symptoms, as well as providing increased energy. Modafinil has not been evaluated in patients with a recent history of myocardial infarction or unstable angina (package insert). Further careful case reports and controlled studies are needed to more precisely correlate modafinil with cardiac arrhythmias, such as PVCs, and to elucidate the causal mechanism responsible.

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Risperidone-Induced Immunoallergic Hepatitis

TO THE EDITOR: Mechanisms of reported risperidone-induced hepatotoxicity remain unclear (1). We report a case of risperidone-induced cytolytic hepatitis, suggesting an immunoallergic reaction.

Mr. A, a 28-year-old Caucasian man with paranoid schizophrenia, was administered risperidone (titrated up to 8 mg/day within 5 weeks) because of a reappearance of auditory hallucinations and thought disorder after he had been free of all medications for 12 months.

After 7 weeks of outpatient risperidone monotherapy, elevated levels of serum aspartate aminotransferase (AST) (83 U/liter, normal=10–50) and alanine aminotransferase (ALT) (123 U/liter, normal=10–60) were observed. The results of cholestatic blood measurements, WBC and RBC counts, and coagulation tests were normal. Mr. A's medical history did not reveal autoimmune or allergic disease. There was no history of alcohol or substance abuse, except occasional hashish smoking. During Mr. A's previous hospitalization (4 years earlier), while he was receiving haloperidol, his serum transaminase levels had been normal.

His ALT and AST levels markedly increased during the 8th week of treatment (AST=139 U/liter, ALT=522 U/liter). Mr. A developed nausea, vomiting, and epigastric pain. Hospitalization was decided upon, and risperidone treatment was discontinued.

An abdominal ultrasound was normal. Serological markers for viral hepatitis A, B, and C were negative. Determinations of ceruloplasmin and copper in his serum were also normal. His WBC count showed eosinophilia (850 cells/mm^3, normal<500), and laboratory analyses for autoimmune diseases revealed high levels of anti-smooth-muscle antibodies (titer=1:640), without actin or vimentin specificity. Tests for anti-liver-kidney microsomal enzymes, antisoluble liver antigen, and antinuclear and antimitochondrial auto-antibodies were negative.

With treatment consisting only of loxapine (200 mg/day) and oxazepam (200 mg/day), Mr. A's AST and ALT levels returned to normal within 3 weeks. One month after risperidone discontinuation, his anti-smooth-muscle antibodies titer had decreased to 1:100, and his eosinophil level had returned to normal. Mr. A was then given haloperidol (20 mg/day), and his serum transaminase levels remained normal.

The temporal relationship between risperidone exposure and serum liver enzyme elevations, deterioration under continuing risperidone treatment, an immediate decrease in liver enzyme abnormalities after risperidone discontinuation, and the exclusion of other causes made us classify our case as probable risperidone-induced hepatotoxicity, according to the scale of Naranjo and colleagues (2).

Risperidone is metabolized to its active metabolite (9-OH-risperidone) by cytochrome P450 (CYP) 2D6 (3). In slow metabolizers of CYP2D6, marked differences in the pharmacokinetic profile of risperidone and 9-OH-risperidone might increase the risk of liver toxicity (1). In our patient, this hypothesis was not supported by the *CYP2D6* genotype (*CYP2D6*1/CYP2D6*5*), which corresponds to the CYP2D6 rapid metabolizer phenotype. However, a metabolic type of idiosyncratic toxicity resulting from rare CYP2D6 mutations other than *CYP2D6*3, CYP2D6*4,* and *CYP2D6*5* cannot be ruled out.

Eosinophilia and high levels of anti-smooth-muscle antibodies suggest a risperidone-induced immunoallergic reaction (4). The significant decreases in the patient's eosinophil count and anti-smooth-muscle antibodies levels after risperidone discontinuation support this hypothesis. The possibility of drug-induced immunoallergic hepatitis must therefore be kept in mind when initiating treatment with risperidone.

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An Update of Fast-Off Dopamine D_2 Atypical Antipsychotics

TO THE EDITOR: Older antipsychotics (chlorpromazine and haloperidol) elicit extrapyramidal signs and prolactinemia, compatible with the idea that these typical antipsychotics bind more tightly than dopamine itself to the dopamine D_2 receptor, with dissociation constants that are lower than those for dopamine (1). The newer atypical antipsychotics, such as quetiapine, clozapine, and remoxipride, bind more loosely than dopamine to the D_2 receptor, with dissociation constants that are higher than those for dopamine, thus minimizing extrapyramidal signs.

These data agree with the rates of antipsychotic dissociation from human cloned D_2 (1–3). For instance, haloperidol, chlorpromazine, and raclopride dissociate slowly over 30 minutes, whereas quetiapine, clozapine, remoxipride, and amisulpride dissociate rapidly, in less than 60 seconds (1). These data match brain imaging findings that show haloperidol remaining constantly bound to D_2 in humans undergoing two positron emission tomography scans 24 hours apart, whereas the occupation of D_2 by clozapine or quetiapine has mostly disappeared after 24 hours (reviewed in reference 1). Atypical antipsychotics, therefore, are helpful to patients by transiently occupying D_2 and then rapidly dissociating to al-

low dopamine neurotransmission. This keeps prolactin levels normal, spares cognition, and obviates extrapyramidal signs.

This letter provides data on the off-rates of additional newer atypical antipsychotics, using methods similar to those reported for the human cloned D_2Long receptor in tissue culture cells (1, 2) and drug concentrations found in the spinal fluid of patients (4). The times for 50% dissociation from D_2 were the following: 42 seconds for 4 nM S-(-)-amisulpride, 66 seconds for 40 nM amoxapine, 52 seconds for 10 nM aripiprazole, 30 minutes for 1.5 nM chlorpromazine, 15 seconds for 200 nM clozapine, 38 seconds for 1 nM domperidone, 38 minutes for 2 nM haloperidol, 16 minutes for 20 nM loxapine, 17 minutes for 5 nM olanzapine, 24 seconds for 140 nM perlapine, 16 seconds for 200 nM quetiapine, 23 minutes for 4 nM raclopride, 13 seconds for 5 nM remoxipride, 27 minutes for 2 nM risperidone, and 60 seconds for 2 nM paliperidone (9-hydroxy-risperidone).

The data for the rapidly dissociating antipsychotics (amoxapine, aripiprazole, clozapine, perlapine, quetiapine, remoxipride, and paliperidone) are compatible with their low extrapyramidal signs. The extent of risperidone-associated extrapyramidal signs may depend on the proportions of risperidone and its metabolite, paliperidone, in the patient. Olanzapine has a slow off-rate from D_2, compatible with its dose-dependent incidence of extrapyramidal signs; however, the potent anticholinergic action of olanzapine (its dissociation constant of 2.1 nM matches that of benztropine at the muscarinic receptor) provides an effective anti-extrapyramidal-sign mechanism (1).

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Research Paradigms of Psychiatric Genetics

TO THE EDITOR: In his article, Kenneth S. Kendler, M.D. (1), identified "four major research paradigms," consisting of 1) "basic genetic epidemiology," 2) "advanced genetic epidemiology," 3) "gene finding methods," and 4) "molecular genetics." Dr. Kendler argued that although "a substantial portion" of gene association claims "do not survive the test of replication," family, twin, and adoption studies have found "genetic risk factors… for every psychiatric and drug use disorder that has ever been the subject of serious study" (p. 6). Moreover, "Unless there are strong and consistent methodologic biases operating across study designs, this growing body of work indicates that genetic risk factors are of substantial etiologic importance for all major psychiatric and drug use disorders" (p. 6).

However, as I argued in detail in my recent book (2), family, twin, and adoption studies do indeed suffer from "strong and consistent methodologic biases operating across study designs," not the least of which is the twin method's questionable "equal-environment assumption."

Dr. Kendler noted that the "low" replication level for linkage findings "contrasts strikingly with the high level of consistency seen in the results of genetic epidemiologic studies—for example, the results of family and twin studies of schizophrenia" (p. 7). In fact, there is no "striking contrast" between these results if they are viewed as evidence supporting a purely environmental etiology for psychiatric disorders. Environmental theories predict 1) familial clustering, 2) a higher concordance of identical versus fraternal twins, and 3) a failure to find genes, and this is what we find (2, 3). Rather than consider a purely environmental explanation as a competing paradigm, Dr. Kendler argued that linkage and association studies cannot be used to test "whether a twin or adoption study was correct in its conclusion that disorder X is heritable" (p. 8). I agree, but negative results could at least compel researchers to take a second look at these methods. Although Dr. Kendler views his four strategies as "competing paradigms," all four are components of the same biological/genetic paradigm, in contrast to what we might call the "environment/treatment/stress" paradigm.

Finally, Dr. Kendler called for integrating his four "paradigms," which would "require an appreciation of the complementary sources of information obtained by genetic epidemiologic and gene identification approaches" (p. 9). Thus, a "striking contrast" was transformed into "complimentary sources of information" in the space of three pages. Dr. Kendler called his synthesis "explanatory pluralism" (p. 10), but what this means in practice is falling back on family, twin, and adoption results to explain the unexpected failure to find genes. Far better, in my view, would be a reexamination of the assumptions and biases of twin and adoption studies (Dr. Kendler's paradigms 1 and 2) in the context of considering the possibility that genes for the major psychiatric disorders do not exist.

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Dr. Kendler Replies

TO THE EDITOR: In this brief letter, I cannot respond fully to the issues raised by Dr. Joseph or provide detailed references to support my position. Dr. Joseph and I disagree in four ways in the interpretation of the accumulating literature in psychiatric genetics. First, in examining family twin and adoption studies of the major psychiatric disorders, I concluded in my article that the evidence strongly supports the hypothesis that genetic factors play a significant role in the etiology of these conditions. I did not assert that individual studies are free