mentation, and yet others may remain untestable and useless to science. Scientists accept the unknowable and the differences of predictive knowledge and conjecture and are humbled by their limitations. Not so the humanists, who sense science's method as a threat to their untestable almagests. As a remedy humanists have been able to turn scientific illiteracy into a main advantage in an environment where a scientifically naïve public and media are easily drawn to the facile side of a debate.

Alarms have been sounded and enemies of science have been exposed (*2*), but it may be time for scientists to worry about Trojan horses in their midst. It should be apparent that equivocation has long been a part of what passes for legitimate science. Think of regulatory sciences, which like mystical persuasions are grounded on default assumptions; global climactic models forced on international deliberations as if factual; flimsy epidemiologic speculations proffered as established risks or remedies; or sociologic conjectures empowering massive social policies.

It does not help to ignore or belittle a war, for the future of science—and likely of humankind—may well hang in the balance. Scientific truth is problematic but has yielded objective worth. Contrived delusions are not a reasonable alternative.

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"Model" Behavior

In their report "Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity" (15 Jan. 1999, p. 397), Raul R. Gainetdinov *et al.* present their study, which indicates that, in mice in which the dopamine transporter (DAT) gene has been eliminated or "knocked out" (DAT-KO mice), and which therefore have elevated levels of extracellular dopamine, methylphenidate has clinical effects on hyperactivity without altering dopamine levels. They conclude, on the basis of other published work, that "the primary calming effect of psychostimulants in DAT-KO mice is mediated by the 5-HT system," although they did not measure 5-HT (serotonin) levels. They add that the DAT-KO model may be a valuable animal model for the study of attention-deficit hyperactivity disorder (ADHD) and for testing new therapies, and that it "may also provide insights into the basic mechanisms that underlie the etiology of this and other hyperkinetic disorders."

As a clinician working primarily with ADHD, I have two questions regarding Gainetdinov *et al.*'s conclusions. Is this phenotype a model of ADHD, or could it be a model of a different hyperkinetic syndrome? and, how can one apply this model to the study of ADHD when the presumed biological mechanisms in ADHD differ so much from those of the model?

Regarding the first question, the authors say that phenotypically DAT-KO mice resemble ADHD patients because the mice are hyperactive and are extremely poor learners. However, there are many presentations of hyperactivity, only one of which is ADHD. For example, the most severe clinical presentations of hyperactivity are often found in children with pervasive developmental disorders (PDDs). These children usually respond poorly to stimulant therapy, but they may derive some benefit from selective serotonin re-uptake inhibitors and dopamine antagonists. They also demonstrate a more profound inability to learn than is usually found in ADHD children. Although ADHD children may have impaired learning, they

do not usually demonstrate the almost total inability to learn that the DAT-KO mice presented. Most ADHD patients have no impairment in learning, if the saliency of the material is significant enough for them to pay attention. Given the saliency of food, most would expect an ADHD model mouse to learn the maze without great difficulty. The same would not be true of PDD. I am not suggesting that the DAT-KO model is a good model of PDD; only that, phenotypically, there are other clinical presentations that may match this mouse model more closely than ADHD.

Regarding the second question, DAT-KO mice, lacking a dopamine transporter, have elevated levels of extracellular dopamine. However, studies indicate that ADHD patients have low extracellular dopamine (*1, 2*). The mechanism of action of the stimulants is to inhibit the dopamine transporter, thereby raising levels of extracellular dopamine. N. Volkow *et al.* (*3*) reported that "methylphenidate is very effective in blocking dopamine transporters, and at the weight-adjusted dose used therapeutically, 0.3 to 0.6 mg/kg, it is likely to occupy more than 50% of dopamine transporters." Because inhibition of the dopamine transporter is impossible in this mouse model, as by definition the mouse lacks the dopamine transporter, I question whether the same mechanisms of action would apply in ADHD humans and thus that this model could be used to "study the basic mechanism" of ADHD, when the biological parameters are in such opposition.

Finally, many studies indicate that, in ADHD humans, there is underactivation of the frontal lobes. This would be consistent with low dopamine levels. A functional magnetic resonance imaging study by K. Rubia *et al.* (*4*) demonstrated hypofrontality in adolescents with ADHD during higher order motor control tasks.

In conclusion, I suggest that the DAT-KO mouse may be a poor animal model for ADHD; however, it may be suitable for another hyperkinetic syndrome.

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Response

ADHD is characterized by differing degrees of hyperactivity, impulsivity, and inattention. The etiology of the disorder is unknown; however, several investigators have attributed the condition to a dysregulation of dopamine neurotransmission (*1, 2*). From the perspective of pharmacotherapeutics (*2, 3*), it has been inferred that the dopamine transporter may be involved in this disorder. To test this hypothesis, we examined DAT-KO mice in several behavioral and pharmacological paradigms. These mice are hyperactive relative to their wild-type littermates, and psychostimulants attenuate the hyperlocomotion of the mutants, whereas the same treatment augments the activity of the controls. Besides hyperactivity, the DAT-KO animals also exhibit deficits in learning and memory processes, and analyses of perseverative errors suggest that the mutants may be less able than the controls to inhibit inappropriate responses. More recent unpublished studies from our lab have confirmed and extended our original findings by showing that the DAT-KO mice may be impulsive and inattentive. Because the results indicate that the DAT-KO mice have many of the same symptoms as human ADHD patients, we have suggested that these mice might serve as a useful animal model for the disorder.

Sarkis proposes that the phenotype of the DAT-KO mice might be more similar to the symptoms presented in PDD than

in ADHD. PDDs are characterized by impairments in several areas of development that include social interaction, communication skills, or the presence of stereotyped activities, interests, or behaviors (*4*). Some of the disorders under this heading include autistic, Rett's, childhood disintegrative, and Asperger's disorders, as well as PDD not otherwise specified. These disorders are often recognized during the first years of life and are associated with some degree of mental retardation. We feel that the DAT-KO mice do not display these phenotypes because they socially interact with their littermates, appear to be coordinated in their movements, and show no loss of skills over time, and both males and females are affected. Additionally, although the DAT-KO mice show impaired performance in the radial-arm maze, they are not debilitated. Occasionally, individual mutant mice could solve the maze. Importantly, psychostimulants served to attenuate the hyperlocomotion of the DAT-KO mice. As Sarkis notes, children diagnosed with PDD respond poorly to these drugs.

Another issue that Sarkis mentions is that the neurochemistries of the DAT-KO mice and human ADHD patients may not be congruent. He says that "repeated studies have indicated that ADHD patients have low extracellular dopamine"; however, comparisons between ADHD patients and normal control individuals in terms of urine, plasma, cerebrospinal fluid, or platelet levels of monoamines and their metabolites have yielded inconsistent results (*5*). None of these approaches can assess extracellular dopamine levels directly in humans. In our initial studies with the DAT-KO mice (*6*, *7*), we reported that although extracellular levels of dopamine were high, striatal tissue stores were low. Additionally, levels of the dopamine Dl and D2 receptors were significantly reduced in striata from these animals. More recent evidence from our lab confirms that dopamine autoreceptor function is down-regulated or may be completely lost in these mutants (*8*). In this context, the attenuation or loss of dopamine receptor function and the low tissue stores of dopamine in the DAT-KO mice could be interpreted as a presumed dopaminergic hypofunctioning that Sarkis attributes to ADHD patients.

Another point is that psychostimulants do not exert their actions only through the dopamine transporter. Dextroamphetamine and methylphenidate can bind not only to the dopamine transporter, but also to the norepinephrine and serotonin transporters, as discussed in our report. Because ADHD patients may display a range of behaviors associated with this condition, and because at least 25% of these patients do not respond to psychostimulants, it is likely that more than one neurotransmitter system may contribute to the disorder.

In conclusion, despite our reservations that the phenotype of DAT-KO mice may not precisely recapitulate all symptomotologies of ADHD patients, we do think that these mice may help us to better understand the basic mechanisms that contribute to the etiology and manifestation of the disorder (*9*).

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CORRECTIONS AND CLARIFICATIONS

News Focus: "On the hunt for a wolf in sheep's clothing" by Michael Balter (17 Mar., p. 1906). In the table in the sidebar (p. 1907), the sheep polymorphism VRQ should have been labeled "most vulnerable," and ARR "least vulnerable."

Special Issue News article: "Can old cells learn new tricks?" by Gretchen Vogel, (25 Feb., p. 1418). The credit for the image on p. 1418 should have read as follows: G. C. Kopen *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 10711 (1999).

ScienceScope: "Still connected" by Jeffrey Mervis (18 Feb., p. 1181). The employment status of Luther Williams, former Assistant Director for Education and Human Resources at the National Science Foundation, was incorrect. He retired from NSF at the end of 1999.

News of the Week: "Shadow and shine offer glimpses of otherworldly Jupiters" by Mark Sincell (3 Dec., p. 1822). The description of Jupiter's density in the second paragraph was incorrect. It should have read "one-third greater than the density of water."