gluten effects. It is debatable if within the former perspective, mean gluten effects on individual parameters could not be considered as "independent" observations, both because schizophrenia is clinically heterogenous and because in performing the ratings each dimension has to be regarded as separate and independent. It is certainly unlikely that the arguable relatedness of parameters could account for the probability of 1 in 10,000 obtained with the correlated t-test. The method Smith suggests deals with the second perspective. For that, the separate parameter-by-parameter analyses that we performed are to be preferred because the method of averaging across dimensions involves the unacceptable assumption of clinical equivalence of all parameters. He ignores the evidence from individual parameter analyses in concluding that the gluten hypothesis is not supported by our work.

The nonblind investigator (M.M.S.) interviewed patients only in the initial drug-free weeks to establish baseline pathology, but not in any of the periods relevant to the experiment.

The mean IQ of our sample (78.57) was not atypical when compared with the published figures from large samples indicating a mean IQ of 84.28 ± 16.6 for a diagnostic composition such as ours (*2*).

With the prevailing uncertainty about the syndrome called schizophrenia, our research decisions represented the best compromises we could devise between conflicting considerations, both practical and theoretical. After considering the criticisms, we remain convinced of the soundness of the decisions. Whether we are correct can only be determined by further research. One possibility is to test the wheat gluten effects in remitted, drug-free schizophrenics.

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Minimal Brain Dysfunction: Dopamine Depletion?

Shaywitz, Yager, and Klopper (*1*) propose that the hyperkinetic, or minimal-brain-dysfunction, syndrome in children may be due to a deficiency in the neural transmitter dopamine. As evidence, they demonstrate that rats selectively depleted of dopamine during infancy are significantly more active than normals during the 10- to 25-day range, and that they show learning deficits later in life. However, there are several difficulties with this analysis:

First, normal 10- to 25-day-old rats are "hyperactive" compared to older rats, apparently because certain adrenergic "activity" systems mature around age 10 days, while the cholinergic "inhibitory" systems, particularly the hippocampus and frontal cortex, approach maturity between ages 15 and 25 days (*2*). The hyperactivity produced by dopamine depletion was merely a moderate increase in the already-hyperactive behavior which is normal for this age. It disappeared at the same time that normal hyperactivity disappears, around age 25 days, presumably because of the maturation at this time of the cholinergic and perhaps also serotoninergic systems.

Second, Shaywitz *et al.* interpret the disappearance of hyperactivity in their rats at age 25 days as analogous to the amelioration of the hyperkinetic syndrome in children at age 10 to 12 years. However, age 25 days in a rat is merely the age of weaning. Puberty, corresponding to human age 10 to 12 years, occurs at about age 80 to 100 days in rats.

A more general hypothesis for hyperkinesis, which includes dopamine depletion as a special case, is that this syndrome is caused by a predominance of norepinephrine (NE) relative to other transmitters. Activity level and reward seem to depend on NE (*3*), and seem to be inhibited by acetylcholine (*4*), serotonin (*5*), and to a lesser extent dopamine (*6*). Rats with increased NE, or depletion of acetylcholine or serotonin, or damage to predominantly cholinergic structures, show high activity (*3–6*), deficits in habituation (*7*), difficulty with selective attention (*8*), and impaired punishment avoidance (*4, 9*). Adult human manics also show these four symptoms, plus euphoria (which is hard to demonstrate in rats); this parallel led to the now widely accepted theory that mania is due to an excessive level of NE relative to the other three transmitters (*8, 10*). The commonly reported characteristics of hyperkinetic children are, again, high activity, difficulty with selective attention, impaired punishment avoidance, and euphoria (*11*). One would suspect, therefore, that hyperkinetics, like manics, suffer from an excess of NE relative to the activity-inhibiting transmitters. (Curiously, mania is reportedly extremely rare in children, and hyperkinesis is unheard-of in adults.) Since the NE activating systems seem to mature before the cholinergic suppressive systems (*2*), any process which retarded the later periods of brain maturation would be expected to produce temporary dominance of the adrenergic systems, and therefore a hyperkinetic syndrome.

There are several other points about the hyperkinetic syndrome which make sense if we attribute it to delayed maturation of the later-maturing parts of the brain. First, the syndrome is three or four times more common in boys than in girls (*11*), which correlates with the fact that girls mature faster than boys. Second, the amelioration of the condition with age may be attributed to the continued, though belated, maturation.

Hyperkinesis, therefore, could be caused by anything which produced NE dominance with delayed maturation of cholinergic systems being perhaps the most common mechanism. One otherwise paradoxical phenomenon of hyperkinetic children makes sense on the basis of NE dominance: the activity-reducing effect of amphetamine. As Shaywitz *et al.* insightfully suggested, this result can best be explained by assuming that amphetamine stimulates the activity-suppressing transmitters dopamine and 5-hydroxytryptamine (5-HT) (*6, 12*) as well as NE. The question, of course, is why amphetamine effects on dopamine and 5-HT should dominate in hyperkinetics, although the effect on NE is greatly predominant in normals. An attractive possibility is that amphetamine's effects on dopamine and 5-HT become evident only when NE levels are so high that further increases would be ineffective. Indeed, analogous phenomena have already been demonstrated in rats: After NE has been highly potentiated by high doses of imipramine or amitriptyline, amphetamine has less activity-facilitating effect than usual. Also, when operant response rates are very high (analogous to hyperkinesis), amphetamine decreases the response rate (*13*).

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13 February 1976

Shaywitz, Yager, and Klopper (*1*) reported that rats treated neonatally with 6-hydroxydopamine (6-OHDA) (intracisternally) exhibit learning defects as well as transitory activity increases. Shaywitz *et al.* attributed these behavioral characteristics to the depletion of brain dopamine that resulted from the neonatal injections. They then took a giant step to generalize their results to children, who are diagnosed as having minimal brain dysfunction (MBD). These children are characterized by learning disabilities and hyperactivity, with activity levels subsiding as adolescence is approached. While treatment of rat pups with 6-OHDA may ultimately prove to be an invaluable animal model for MBD, we feel this extrapolation is unwarranted for several reasons.

First, our research which preferentially depletes central norepinephrine (NE) to the exclusion of other neurotransmitters, also reports activity increases (*2*). It should be pointed out that we obtained activity increases without concommitant dopamine alterations.

Second, previous work with 6-OHDA, administered neonatally or in adulthood, usually reports hypophagia to some degree and a parallel weight loss (*3*, *4*). Body weight was not reported by Shaywitz *et al.*, but if the experimental animals were indeed lighter than controls, then the observer was not really "blind" as to which rats were treated or untreated. Further, reduced food intake in the experimental group would imply that these animals received too little nourishment during the critical developmental period and therefore there is no appropriate control. A "weight matched" control group could be produced by restricting intake to an amount equivalent to that eaten by the experimental group.

Third, previous studies in which 6-OHDA is administered to neonatal rats typically find severe and apparently permanent depletions of NE in peripheral structures (*4*, *5*). Treated rats are effectively partially sympathectomized. Shaywitz *et al.* fail to mention NE content in peripheral structures; however, if peripheral NE depletions did indeed occur, one could hardly attribute behavioral changes to central nervous system effects.

Fourth, the volume of the intracisternal injection appears extremely large for newborn rat pups. The 25-μl injection, in fact, is equivalent to that used for intracisternal injections of adult rats (*6*). One might expect an intracranial injection of this magnitude to raise intracerebral pressure significantly. This suggests that in addition to the vehicle group, a second, noninjected control group should have been employed.

Finally, we question the statistical analysis of the activity data of Shaywitz *et al.* It is inappropriate to use the *t*-test to compare the experimental group to the control group on each trial or observation. Instead, a two-factor analysis of variance with repeated measures on one factor is required. Then, if the group-by-trials interaction were significant, one would be justified in comparing the two groups at each individual observation or trial with tests of simple effects. Further, one should note that systematic application of the *t*-test between groups at each observation greatly increases the probability of finding statistically significant differences.

In conclusion, we feel that the experimental model of neonatal injections with various neurotoxins provides valuable information about the functional significance of different neurotransmitter systems. However, it is only an experimental, not a clinical model. We feel it is a bit premature and perhaps ambitious to equate human behavioral disorders with the behaviors of rats that receive neonatal 6-OHDA.

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17 February 1976

Shaywitz *et al.* (*1*) presented a rat model of the minimal brain dysfunction syndrome (MBD). They injected 5-day-old rat pups intraperitoneally with desmethylimipramine (DMI) and then intracisternally with 6-hydroxydopamine (6-OHDA), producing permanent reduction of whole brain dopamine with no significant reduction in whole brain norepinephrine. In comparison to vehicle controls, these rats were significantly hyperactive from 15 to 22 days of age. The hyperactivity abated by 26 days of age, but a deficit in avoidance learning was observed at 27 days. Shaywitz *et al.* considered this profile to be analogous to the child with MBD who is hyperactive until 10 to 12 years of age. This hyperactivity subsides but is followed by other behavioral difficulties.

This proposed animal model is interesting because of the general utility of such models in deciphering the possible neurochemical bases of this and other syndromes such as Parkinson's disease. However, Shaywitz *et al.* failed to use the appropriate control groups which would permit them to relate their behavioral alterations only to the proposed critical pharmacological manipulation, the depletion of brain dopamine. No groups that had received only DMI or 6-OHDA were behaviorally tested. Thus Shaywitz *et al.* can only conclude that pharmacological manipulation, regardless of its specific nature, leads to the behavioral changes that they observed.

Behavioral alterations similar to those observed by Shaywitz *et al.* can in fact be observed after peripheral injections of 6-OHDA in the newborn rat. This treatment permanently destroys forebrain norepinephrine projections apparently originating in the locus coeruleus, while elevating pontine norepinephrine levels, but does not alter brain dopamine levels (*2*). These rats are hyperactive during infancy until about 25 days of age, and they also show a persisting behavioral deficit (*3*). Furthermore, neonatal injections of guanethidine induce hyperactivity during infancy but do not have a toxic effect upon brain catecholamine

Table 1. Mean (± standard deviation) height and weight for 23 hyperactive children (mean age, 9 years and 4 months) and two sets of age and sex appropriate norms. The t values were calculated by comparing height and weight scores to appropriate norms for each hyperactive child.

Data source	Height (cm)	Weight (kg)
Knights and Viets data (*7*)	132.8 ± 9.75	29.0 ± 5.78
McCammon norms (*9*)	135.8 ± 10.76 $t = -2.38, P < .025$*	31.1 ± 6.44 $t = -2.63, P < .01$*
Vaughan norms (*10*)	136.7 ± 10.36 $t = -3.27, P < .005$*	31.0 ± 5.80 $t = -2.97, P < .005$*

*Probabilities are one-tailed with d.f. = 22.

neurons (*3*). Thus the rat behavioral syndrome attributed by Shaywitz *et al.* to depleted brain dopamine is also observed after pharmacological manipulations which have no effect upon brain dopamine levels.

It also seems premature for Shaywitz *et al.* to causally relate behavioral change to one effect of a pharmacological manipulation when only two gross effects of the manipulation are measured. As administration of 6-OHDA or 6-hydroxydopa to the neonatal rat affects not only brain norepinephrine but also varying aspects of brain serotonin, histamine, and acetylcholine (*4*), so may intracisternal injection of 6-OHDA profoundly alter activity in other neurochemical systems not directly affected through the toxic mechanism of this drug.

Finally, animal neurochemical models generally ought to closely match the behavioral and physical characteristics of the human syndrome. In this regard, it is important to note that heightened skeletal motor activity is a variable symptom in MBD children. Attempts to measure activity differences between MBD and normal children have produced inconclusive results (*5*). Furthermore, one striking effect of neonatal administration of DMI and 6-OHDA is a profound growth deficit (*6*). In this laboratory, intraventricular injections of 100 μg of 6-OHDA on days 5 and 6, preceded by intraperitoneal DMI, produced rats whose body weights at maturity were approximately 70 percent of the average weight of rats given vehicle or DMI only. It is not clear whether this reflects endocrinological or consummatory disturbances. Shaywitz *et al.* did not report body weight data. However, we assume they would also observe such an effect. Growth deficits of this magnitude are not obvious in children with MBD, although we were unable to find direct tests of this possibility. Reported mean height and weight data are close to the 50th percentile for normals of the same average age (*7*). We have statistically compared available height and weight data for a group of MBD children with the 50th percentile for two sets of age-matched height and weight norms (Table 1). While on all four tests, the MBD children were significantly below the 50th percentile, the mean differences were not large. Furthermore, the previous drug histories of these children were unknown, and recent reports (*8*) have indicated that stimulant therapy can cause slight growth deficits. These data provide only the weakest suggestion that MBD children are small for their age, and it seems unlikely that an obvious growth deficit, comparable to that observed in dopamine-depleted rats, would have escaped statistical and clinical detection this long.

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3 March 1976

In response to Kalat, the hyperactivity in children classified as having minimal brain dysfunction (MBD) is only slightly greater than activity in normal children. That this is so has been emphasized by many people who have evaluated children with MBD. Thus, our dopamine-depleted rat pups are significantly more hyperactive than their littermate controls to the same degree that hyperactive children are more active than children considered to be normal. I also take issue with his assumption that maturity in the rat does not occur until 80 to 100 days of age.

Histologically, the cerebral cortex of the rat has assumed all the features characteristic of the adult by 18 days of age, and these features become progressively more developed in the 24- and 30-day-old animals. Thus, by 30 days of age, axon density in cerebral cortex is 85 percent of mature cortex, and the dendritic branching index, a measure of the dendritic field of cortical pyramidal cells, is 80 percent of adult indices at 24 days and 85 percent by 30 days of age (*1*). Similarly, the electrical activity of the rat cortex attains an adult pattern within the first month of postnatal life. Auditory evoked responses mature by 14 days and visual evoked responses by 27 days (*2*). Neurochemical evidence indicates that the requirements for catecholaminergic neuronal transmission develop rapidly in the newborn rat. Both dopamine and norepinephrine are present in the brains of newborn rats in concentrations of 20 to 30 percent of adult animals (*3*, *4*). Dopamine concentration attains adult values by 50 days of age and norepinephrine by 40 days of age, with the greatest increase in brain concentration of monoamines occurring between 7 and 18 days of age (*5*).

Tyrosine hydroxylase (*6*), dopamine decarboxylase (*7*), and dopamine betahydroxylase (*8*), the enzymes involved in the synthesis of catecholamines, increase in a parallel fashion. Similarly, the enzymes concerned with the metabolism catecholamines, monoamine oxidase (*9*) and catechol *O*-methyltransferase (*10*), also increase in a fashion similar to the amines and their synthetic enzymes. Furthermore, both biochemical investigations (*11*) and morphologic studies utilizing the Falck-Hillarp fluorescence histochemical technique (*12*) have shown that monoaminergic neurons develop mechanisms for the synthesis, storage, and reuptake of amines prior to birth. These studies thus suggest that there is much to support our interpretation of 25 days of age in the rat as being close to maturity, that is, adoles-

cence. It is of course somewhat naive to attempt to too closely correlate age in an experimental animal with age in the human, a subject that has been discussed recently by Himwich (*13*).

I would like to reassure McLean *et al.* on their concerns over methodology. The 25-μl injection is appropriate for a 5-day-old rat pup, as described by Breese and associates (*5, 14*). We have used this procedure now on almost 100 litters of rat pups and have injected approximately 1000 animals. Our mortality is very low, and it is unusual for us to have any rats succumb solely to the injection of the 25 μl of 6-hydroxydopamine or the 25 μl of saline given to controls intracisternally.

The body weight of dopamine-depleted rats is indeed less than that of controls. However, the differences are not so great as to be discerned at a distance of 8 feet (2.4 m) that we used in the time sample measures of activity described in our report. We are now utilizing a continuous video tape monitoring of activity. With this latter method the activity is scored via a camera mounted above the cages, a procedure that precludes possible bias by animal weight. Our results with this more sophisticated method are in complete agreement with those reported earlier. We routinely utilize analysis of variance in our statistical interpretations. Once this has been done we then apply *t*-tests to individual comparisons in question.

In response to the comments of Pappas *et al.*, we have done experiments utilizing only desmethylimipramine (DMI) and find no change in activity compared to controls. Since the duration of action of DMI, administered in a single dose, is relatively short, we were not surprised that we did not see any long-term effects from the injection. It must be emphasized also that one should not administer 6-hydroxydopamine alone intracisternally if one is attempting to deplete dopamine selectively, since administration of 6-hydroxydopamine without DMI results in depletion of *both* dopamine and norepinephrine. This is described well by Breese and Traylor (*5*), and experiments by us have confirmed the finding.

All investigators have recognized the difficulty in extrapolating from animal models to human disease states, and such problems have been discussed in detail by Dobbing (*15*) and Plaut (*16*). It is also apparent that the production of an animal model of MBD would provide a valuable technique to explore in depth those factors influencing particular cardinal symptoms of the disorder. In order to be considered a suitable model for MBD, however, certain criteria should be satisfied:

1) Specified cardinal features of the MBD syndrome must be replicated in the animal model. Such features may include hyperactivity, cognitive difficulties, attentional difficulties, and difficulty habituating to a new environment.

2) The pathogenesis of the MBD syndrome in the animal model must bear some relationship to what we believe to be the pathogenesis of the disorder in children.

3) Most importantly, the MBD syndrome in the animal model must be produced in the developing animal, not solely in the mature nervous system of the adult animal, and must follow the same developmental course in the animal model as found in the human counterpart. For example, the hyperactivity so frequently found in children with MBD decreases in frequency and severity as the children approach adolescence, and, in fact, hyperactivity per se is not a common symptom in youngsters with MBD who have matured. The production of persistent hyperactivity in an adult animal then would not parallel the symptom as seen in children with MBD.

4) Finally, response to medications in the animal model must parallel the response seen clinically in MBD in children. Administration of stimulant medications (for example, amphetamine, methylphenidate, or pemoline) must produce what is termed a "paradoxical" response in MBD. Instead of increasing activity and altering performance, these agents in doses similar to those used clinically should reduce hyperactivity and improve attention. Results of our investigations (*17*) indicate that the behavior of rat pups treated with 6-hydroxydopamine is strikingly similar to that observed in the clinical syndrome of MBD and satisfies the criteria for an experimental model of MBD.

We believe that the exploration of an experimental animal model has great potential in elucidating the underlying biochemical abnormalities in neuropsychiatric disorders such as MBD. By using an animal model we should be able to examine the relationships between cardinal symptoms of MBD and specific neurotransmitters. Through such an approach we are not limited by methodological restrictions imposed by human investigations and are free to exploit the most sophisticated available pharmacological techniques to explore in depth each step in the life cycle of catecholamine metabolism and its relationship to behavioral parameters of the investigator's choice. Whether such an approach will ultimately unravel as perplexing a disorder as MBD awaits future investigations.

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15 July 1976