greenhouse gases [carbon dioxide, methane (CH_4)] persisted during the first 3.5 billion years of Earth's history and counterbalanced a lower solar constant. When greenhouse gas concentrations fell below a critical threshold, however, snow and sea ice migrated toward the equator, producing the snowball Earth. The assumption of high atmospheric CO_2 has recently been challenged for the early Proterozoic (*5*). Consequently, CH_4 may have been considerably higher throughout much of the Archean (*6*). The earliest glacial deposits may reflect cold global climatic conditions caused by a reduction in CH_4 concentrations. Yet, the warm period that followed for nearly 1 billion years presents a new dilemma. High values of atmospheric CO_2 would be responsible for ending the snowball Earth conditions of the early Proterozoic and producing warm middle Proterozoic conditions. Even if CO_2 levels were high after the first glacial period, it seems likely that elevated atmospheric CO_2 would have been removed by weathering in the presence of land. Estimates of CO_2 concentrations during the middle Proterozoic through paleosol analysis would resolve this issue.

On the other hand, high obliquity in combination with considerably lower greenhouse gas concentrations can explain the warm Archean, the glacial periods of early Proterozoic, the warm periods of the middle Proterozoic, and the return to glacial conditions at the end of the Proterozoic (*4*). If Earth's high obliquity returned to near present-day values at the end of the Proterozoic through oblateness-obliquity feedback (*7*), then it could provide insight on rapid diversity and complexity of life at the end of the Proterozoic. Furthermore, it explains why low-latitude glaciation did not occur in the Phanerozoic.

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Induced Damage in the Developing Brain

The report "Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome" by C. Ikonomidou *et al.* (11 Feb., p. 1056) provides needed information on the possible mechanisms of neurodegeneration that lead to fetal alcohol syndrome in humans. In their conclusion, the authors point to applied issues in humans, on the basis of their studies in rats, when they say, "it is important to recognize that both NMDA antagonists and $GABA_A$ agonists are frequently used as sedatives, tranquilizers, anticonvulsants, or anesthetics in pediatric and/or obstetric medicine." These findings, when viewed in conjunction with research demonstrating that human brain growth continues for several years after birth (*1*), raise the issue of potential serious damage being caused not only by drug-abusing pregnant women but by the exposure of infants and toddlers to these agents through prescription practices by physicians.

Ikonomidou *et al.*'s research on possible mechanisms of action resulting in significant neurodegeneration should be viewed in conjunction with Zito *et al.*'s recent article (*2*) that reports on the increase in off-label use (*3*) of psychotropic medications for preschool children in two state Medicaid programs and one group health maintenance organization during the 1990s. Zito and colleagues document a significant increase in the off-label prescription of psychoactive medications in very young children (between

2 and 4 years old) for modification of behavioral disorders. Stimulant treatment alone reportedly about tripled during the period examined; however, increases were not limited to stimulants such as Ritalin or methylphenidate [frequently used as treatment for attention problems such as attention-deficit/hyperactivity disorder (ADHD) in children and adults], but included clonidine, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs).

Zito *et al.* conclude that "[u]nresolved questions involve the long-term safety of psychotropic medications, particularly in light of earlier ages of initiation and longer durations of treatment," and Ikonomidou *et al.* point out that "depending on the timing of exposure, different combinations of neuronal groups will be deleted." Taken together, these comments indicate that the National Institutes of Health and other public health organizations need to redirect some of the attention on prevention of fetal alcohol syndrome and other preventable neurological conditions to the study of the effects of prescription practices among physicians. At the very least, these articles should give practicing physicians pause in their increasing reliance on medication for management of behavior disorders in very young children.

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3. Off-label use refers to the use of a drug to treat a particular condition for which the drug has not been shown to be effective and for which there is no U.S. Food and Drug Administration–approved information in the product package insert labeling regarding the use of the drug for such treatments.

It would be interesting to extend the work of Ikonomidou *et al.* on ethanol- and phenobarbital-induced neuronal apoptosis to include antiepileptic drugs (AEDs) that affect voltage-gated Na^+ channels. Phenobarbital is itself an AED that acts by increasing the mean Cl^- channel opening time. Like ethanol, the established AEDs phenytoin, carbamazepine, and valproate cause neurotoxic effects ranging from neural tube defects to reduced brain mass and neurobehavioral disturbances (*1*). These drugs act by limiting repetitive firing of action potentials in depolarized neurons through voltage- and use-dependent blockade of voltage-gated Na^+ channels (*2*). The interaction between Na^+ and K^+ conductances is a key feature of action potentials. The efflux of K^+ is involved in neuronal apoptosis (*3*). Considering this information, and the overlapping characteristics of fetal alcohol, fetal barbiturate, fetal hydantoin, fetal valproate, and fetal carbamazepine syndromes, investigating the effect of Na^+ channel–acting AEDs on apoptotic neurodegeneration would seem to be important. This is all the more important with the recognition of these drugs as a class of major human teratogens (causing abnormal fetal development), second only to ethanol (*4*).

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Response

In our report, which focused primarily on the deleterious effects of ethanol on the developing rat brain, we presented evidence that during a critical period in development (synaptogenesis, also known as the brain growth spurt period), drugs that block *N*-methyl-D-aspartate (NMDA) glutamate receptors or that excessively activate γ-aminobutyric acid type A ($GABA_A$) receptors have the potential to trigger extensive apoptotic neurodegeneration in the devel-

oping brain. Although this can explain why ethanol, which has both NMDA antagonist and $GABA_A$-activating properties, deletes large numbers of neurons from the developing brain, it also suggests the need for studies to clarify the potential risk associated with the use of NMDA antagonists and GABA-activating drugs in pediatric medicine. For example, effective management of pediatric seizure disorders often requires treatment with large doses of GABA-containing agents. In addition, neonatal infants, including premature infants, sometimes require major surgery that must be performed under general anesthesia. This is potentially problematic because the only drugs available for performing general anesthesia are either NMDA antagonists or $GABA_A$ activators, and the current practice is to use a combination of agents from both of these categories. It has generally been assumed that there is a wide margin of safety for the use of either or both of these classes of agents for anesthetizing pediatric patients. However, in light of our findings, it will be important to ascertain for drugs in these categories how the blood concentrations required for achieving therapeutic goals in pediatric medicine compare with the blood concentrations that cause neurons to die in the infant animal brain.

Montgomery cites our findings pertaining to drugs that interact with NMDA or $GABA_A$ receptors as basis for concern about other classes of psychoactive drugs being administered to young children for various neuropsychiatric disorders. However, the drugs he mentions cannot be indicted as brain-damaging agents on the basis of our evidence, or any other evidence we are aware of. At doses used in child psychiatry, these drugs do not block NMDA receptors nor activate $GABA_A$ receptors. Ritalin, the most widely used and most controversial of these drugs, was found in a large National Institutes of Health–sponsored multicenter study (*1*) to produce only minor side effects while providing more effective therapy for ADHD than was observed for unmedicated patients receiving various forms of behavioral therapy alone. Although we consider it imprudent to overprescribe drugs of any kind for children, we believe that some children do suffer from disabling neuropsychiatric disorders that, if not ameliorated by therapeutically effective drugs, are likely to have long-term deleterious consequences that are more serious than the side effects typically associated with such drugs. Of course, if it can be shown that a specific drug or class of drugs has the potential to cause permanent damage to the developing brain, the risk/benefit ratio for using such drugs in pediatric neuropsychiatry would have to be carefully reevaluated.

Regarding the letter by Sharma and Kumar, they suggest that another class of AEDs—agents that block voltage-gated Na^+ channels—warrant testing to determine whether they might also trigger apoptosis. They cite evidence that agents in this class, including phenytoin, carbamazepine, and valproate, are becoming recognized as major human neuroteratogens, second only to ethanol. We agree with Sharma and Kumar, and have performed preliminary studies (*2, 3*) showing that at least two of the agents they mention do trigger extensive apoptotic neurodegeneration in the developing rat brain.

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