In response to the suggestion that depression is becoming increasingly common, evidence is cited that shows it "appears to be shifting and concentrating in particular demographic groups, rather than increasing across the board." Changes in Earth's obliquity are suggested to provide an alternative explanation for the dramatic shifts in climate, including low-latitude glaciation invoked in the "snowball Earth" hypothesis, during the Archean and Proterozoic eons. And, the implications of a report on ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome are discussed.

Dialog on Depression

In her News Focus article "Global survey examines impact of depression" (7 Apr., p. 39), Constance Holden describes a 25-nation study by the World Health Organization to examine the social and economic effects of depression. From the survey being used for the study, researchers will be able to look for correlations of psychiatric depression with chronic physical problems. Ronald Kessler, an epidemiologist at Harvard Medical School who designed the study, is quoted as saying, "We don't know how many people with headache or fatigue are really suffering from depression in disguise."

But some research suggests almost the opposite—that the diagnostic syndrome of major depressive disorder may be chronic physical illness in disguise (*1*). It is many years since Kurt Schneider suggested that the core symptoms of depression might be the "vital" symptoms of depression, and that low mood was a secondary consequence of these physical changes (*2*). This view has received support from modern immunology and pharmacology (*3*).

The primary symptom cluster of classic depression is the malaise state known as "sickness behavior," which is also the behavioral component of the mammalian immune response to infection or inflammation (*4*). Malaise is an energy-conserving behavioral pattern designed to mount an acute and all-out attack on invading microbes. Physical malaise includes symptoms such as aches, pains, heaviness, fatigue, somnolence, slowing of thought and action (retardation), and the demotivating inability to feel pleasurable or rewarding emotions. These symptoms are probably produced by circulating immune active cytokines such as the interferons and interleukins (*3*). Low mood is a consequence of sustained malaise.

By this account, antidepressant drugs do not act on mood directly, but instead have analgesic properties to alleviate the malaise state. For example, tricyclic antidepressants are long-acting and powerful pain killers, used widely in internal medicine (*1*). So, the effect of antidepressants on mood may be akin to the effect of aspirin in treating a headache—aspirin does not "make" you happy, but by relieving pain and malaise, makes it much "easier" to be happy (*5*).

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Holden's article repeats the frequently heard assertion that depression is "increasingly common"— but where is the hard evidence for this statement? Previous research suggesting rates of depression are increasing was based on asking individuals to recall episodes of depression in the often distant past, and such memories may be unreliable.

The perhaps definitive study published recently on this issue (*1*) compares rates of depression among representative samples of adults in Atlantic Canada who were interviewed in 1952, 1970, and 1992. This methodology provides a population perspective over extended time, rendering long-term recall unnecessary. The results cast doubt on the view that depression is generally increasing, because the prevalence of depression remained steady at about 5% among successive samples of adults from 1952 to 1992. Although the data do not suggest depression is increasing, there is, however, strong evidence that its distribution is changing across the general population, with marked increases in younger women (the rate almost tripled in women under 45 between 1970 and 1992).

But the fact that depression appears to be shifting and concentrating in particular demographic groups, rather than increasing across the board, does have significance for speculations about etiology. Asking why some groups are more prone than others is likely to be more fruitful than pondering why depression should be generally increasing across the whole of society. Even if it were true, it would be odd for so many factors to combine in such a way as to produce a marked increase in whole populations in such an etiologically complex disorder. The danger, therefore, of statements that depression is generally increasing is to grossly simplify thinking about the causes of this important illness.

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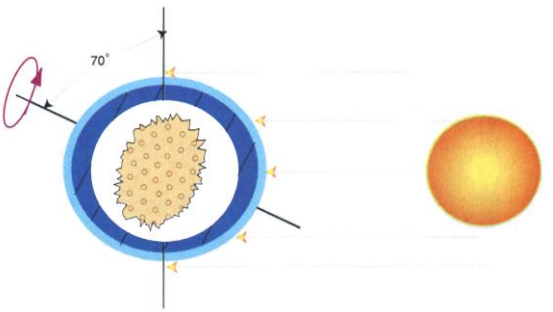
The "Snowball Earth" and Precambrian Climate

The "snowball Earth" hypothesis (*1*) is being considered an attractive solution to low-latitude glaciation, although numerous questions remain unresolved, as Richard A. Kerr discusses in his News Focus article "An appealing snowball Earth that's still hard to swallow" (10 Mar., p. 1734). For example, does low-latitude glaciation in the Proterozoic equate to a "snowball Earth"? It does if Earth's tilt (or more specifically, obliquity, the angle between the equatorial and orbital planes) was similar to the present-day tilt. However, if Earth's tilt was greater than 54°, then low latitudes would have received less solar energy on an annual basis then high latitudes (*2*), which would mean that glaciation could have been localized to low latitudes and not necessarily have been a global event (see the figure). Two recent global climate model studies have shown that cold, low-latitude conditions with extensive sea ice and snow could occur with high obliquity (*3, 4*).

Glacial deposits have been found in low latitudes that are from the early Proterozoic (~2.5 billion years ago) and late Proterozoic (700 and 600 million years ago). The underlying assumption of the snowball Earth hypothesis and our current understanding of Precambrian climate is that high levels of various



The migration of a large land mass into low latitudes initiates glaciation for a high-obliquity Earth. Solar energy is reduced in low latitudes with high obliquity.

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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