modern marine biomass, disappear locally at the El Kef section. Perhaps even more so. The El Kef blind test was not designed to resolve various interpretations of the trans–K-T biotic record, but rather to determine the observational pattern of planktic foraminiferal extinctions at this single locality. Smit says he *observed* all Cretaceous species, save one survivor, extending to the boundary and then disappearing together, while Keller says she *observed* disappearances occurring before, at, and after the boundary horizon. The results of both investigators show substantial numbers of extinctions occurring at the boundary in this section. All four blind-test investigators confirmed Keller's general pattern. None confirmed Smit's, whose post hoc attempt to reconcile Keller's pattern with his own "model" of K-T extinctions, by means of unsubstantiated appeals to the Signor-Lipps effect, should be seen for what it is.

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Response: As I reported, each of the four blind testers, to one degree or another, found the same pattern of foram extinction as Keller did. But that does not rule out a sampling problem. In fact, the Signor-Lipps effect predicts that abrupt extinctions will look gradual if some rarer species are missed by a search of the fossil record; but the more intensive the search, the more abrupt the extinction event will appear. By combining the efforts of all four blind testers, Smit intensified the search until all of Keller's gradually disappearing species were found to persist up to but not beyond the impact.

The apparent gradualness of the K-T foram extinctions at El Kef thus shows every sign of being an artifact. On the other hand, the blind test cannot address the question of which forams survived the impact. Many presentations at the meeting addressed this controversial area using a variety of approaches, without any clear resolution.

Keller's recollection of Donald Lowe's remarks differs from my notes taken during that session. Lowe concluded that the Mexican K-T deposits were laid down by "high-energy, pulsating, and probably short-lived events" consistent with the succession of waves from an impact; he added that sedimentologists do not yet fully understand deposits from such huge waves. He specified that he was summarizing the impressions of the half-dozen sedimentologists invited on the trip, not those of all the participants. Of the five sedimentologists on the trip other than Lowe whom I interviewed for the story, four of them agreed that the deposit is consistent with waves from an impact and that no proposed alternative, including that of Wolfgang Stinnesbeck and Keller, can reasonably explain the deposit. Only one reserved judgment until further study.

—Richard A. Kerr

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Psychopharmacologic Drugs: Mechanisms of Action

Samuel H. Barondes (Perspective, 25 Feb., p. 1102) discusses the changes in psychiatric practice that have occurred with the widespread use of Prozac and comments on its possible mechanisms of action. The mechanisms of action are considered in terms of synaptic information transmission. Other than the conceptual limitations imposed by the present synaptic-dominated model of brain function, however, there is no reason to consider that Prozac or any of the drugs used in psychopharmacology operates exclusively by means of synaptic mechanisms. Accumulating evidence, in

fact, suggests the contrary (*1*) (M. Barinaga, News, 28 Jan., p. 466); the primary mechanisms may be types of nonsynaptic diffusion neurotransmission (NDN).

Beaudet and Descarries in 1978 suggested that the biogenic amines released from nonsynaptic varicosities in the brain might act not only on adjacent postsynaptic surfaces, but also in tissue of more distant receptor elements (*2*); more recent studies support this suggestion (*3*). Serotonin (Barondes points out that the mechanism of action of Prozac is in the serotonergic system) is among the most highly nonsynaptic monoamines in the central nervous system; it may be as much as 96% nonsynaptic in some systems (*4*).

Many functions may require combinations of both types of neurotransmission. The demonstration by Bonhoeffer, Staiger, and Aertsen (*5*) of spreading potentiation, recently extended by Schuman and Madison (*6*), strongly suggests that principal mechanisms of brain plasticity (long-term potentiation) may be both selective synaptic changes and distributed potentiation by means of diffusion, possibly of nitric oxide (NO), to nearby cells.

Mood is a mass-sustained function (*7*); in this regard it is more comparable to hunger, pain, and sleep than it is to visual perception and fine motor movements, which require synaptic activity [but which also have important NDN components at all levels (*8*)]. Thus, disorders of mood (and other psychiatric disorders) may be disorders of NDN mechanisms.

Vizi (*9*) has noted that drugs have difficulty reaching the receptors intrasynaptically. The sensitivity of nonsynaptic receptors is higher, and they are much more accessible to drugs. Receptors located presynaptically or prejunctionally (and thus, by definition, outside of the synaptic cleft) must be reached by means of diffusion through the extracellular fluid. Vizi suggests that diffusion neurotransmission may be the primary means of activation of receptors by externally applied or administered drugs.

Thus, concepts of the effects of drugs on the central nervous system have progressed from a consideration of the effects of specific agents on "the brain," to a consideration of their differential effects on specific regions of the brain (*10*), to an understanding of their effects on specific neurotransmitter systems, to knowledge of their specific intra- and extracellular mechanisms. An understanding of the mechanisms of transport within the brain and activation of synaptic and extrasynaptic receptors [as well as intracellular activation after diffusion across membranes (*11*)] should aid in the development and evaluation of the mechanisms of action of drugs that are used to treat psychiatric disorders.

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References and Notes

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5. T. Bonhoeffer, V. Staiger, A. Aertsen, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 8113 (1989).
6. E. M. Schuman and D. V. Madison, *Science* **263**, 532 (1994).
7. P. Bach-y-Rita, in (*3*), pp. 489–496.
8. ———, *Neurochem. Int.* **23**, 297 (1993).
9. E. S. Vizi, in (*3*), pp. 89–96.
10. J. Olds, K. F. Killam, P. Bach-y-Rita, *Science* **124**, 265 (1956).
11. Such as by NO; Soloman Snyder has referred to NO as "one of the main neurotransmitters in the brain" [*Nature* **364**, 577 (1993)].

Response: Bach-y-Rita correctly points out that when neurons release serotonin in the brain, the neurotransmitter may activate not only receptors at classical synapses, but also other receptors after diffusion to more distant neuronal sites. Such neurotransmission after relatively distant diffusion could be especially relevant to the action of drugs such as Prozac that block serotonin's reuptake, allowing released serotonin molecules to remain extracellular for longer periods of time. In addition to increasing the duration of the action of serotonin at classical synapses, this would also allow more time for diffusion to even more distant receptors. But this further complication in Prozac's actions on brain physiology in no way alters the clinical and societal issues I briefly addressed, which are already complicated enough.

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Corrections and Clarifications

In the report, "High performance photorefractive polymers" by M. Liphardt *et al.* (21 Jan., p. 367), equation 2 on page 368 was incorrect. It should have read

$$g = \frac{2\pi n_0^3}{\lambda \cos\theta'} r_{eff} \frac{1}{m} E_{sc}$$

Consequently, the value of the effective electrooptic response derived from equation 2, as reported in the second paragraph on page 369, should have been $n_0^3 r_{eff} = 3 \pm 0.5$ pm/V.

The chart on page 675 of the Perspective "Molecular genetics of neurological diseases" by Joseph B. Martin (29 Oct., p. 674) should have stated that the chromosome locus for spinobulbar muscular atrophy is Xq12 (not Xq21.3) and that the length of the CAG repeat in the androgen receptor gene in patient samples is 40–62 (not 30–62). In the discussion on page 676 of Alzheimer's disease among families of Volga-German descent, the exclusion chromosome numbers should have been 14, 19, and 21 (not 20).

The Random Sample item "The brain behind that happy face" (15 Oct., p. 336) refers to a paper by Paul Ekman and Richard Davidson. That paper appeared in the September 1993 issue of *Psychological Science*, a journal of the American Psychological Society.