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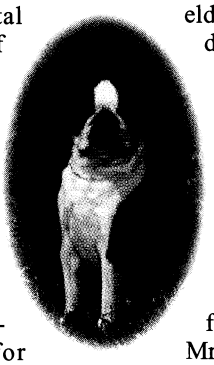
References and Notes
1. Information on the Protocol to the Biological and Toxin Weapons Convention is available at http://www.brad.ac.uk/acad/sbtwcl
2. UNSCOM report S/1999/94 on status of disarmament and monitoring of Iraq's proscribed weapons, 29 January 1999, available at http://www.un.org/depts/unscom/s99-94.htm

First Words

THIS REJOINDER COULD BE TITLED, "GET cause before effect." The Random Samples item "Walk before you talk" (29 Jun., p. 2429) briefly describes the work of Robert Provine, a developmental neuroscientist at the University of Maryland, Baltimore County, who has concluded that bipedality, which allowed "the redirection of breathing in the service of soundmaking," is "the key event in human evolution necessary for the emergence of speech." This conclusion, however, is eminently disputable.



Out of the mouths of...dogs?

First, what payoff that has anything to do with breathing for speech could have changed quadrapeds into bipeds when even the precursors to speech had not yet evolved? More to the point, most if not all quadrapedal animals make sounds. To invoke bipedality as "the key event in human evolution necessary for the emergence of speech" misses the pivotal point for evolution of speech.

If such "key events" were the case, consider a recording I made of Mr. Lucky, a Boston terrier, howling, in his quadrapedal stance, "I want my momma!" I played this recording for four decades to students of phonetics and speech physiology. Some thought it was a cerebral-palsied child. Not one suspected it was an animal, such as a parrot, let alone a dog. His owner was an elderly woman who unintentionally did what a mother teaching her child speech would do. She discovered her accomplishment when she left Mr. Lucky in her backyard while shopping. When she returned, her neighbor told her that someone had been calling for her. It was her dog. Why didn't Mr. Lucky, with his head start, develop speech? He did learn several other phrases by rote conditioning; none, however, were cognitive expressions of an idea.

My nomination for the key evolutionary event that opened the door to speech would not be soundmaking ability. After all, sign language does not require sounds, and of the almost 300 sounds used in all various languages, no language uses more than a small fraction. The key element has to be the cognitive capacity to linguistically convert thoughts into speech. What event could lead evolution in this direction? Probably the discovery that abstract sounds can symbolize objects and conditions. In sum, events and facts require a theory in which they are pivotal in a causal explanation before they can be tested for importance, let alone key importance.

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Effects of Lead Exposure

THE RANDOM SAMPLES ITEM "NO BENEFIT from lowering lead" (25 May, p. 1483) and a paper by Rogan *et al.* in *The New England Journal of Medicine* (*1*) that is the topic of discussion both start by saying that low levels of lead exposure cause cognitive deficits and other developmental problems.

CREDIT: ROBERT PEARCY/ANIMALS/ANIMALS

The large clinical trial conducted by Rogan *et al.* assessed whether reducing blood lead levels with a chelating agent in children with moderate levels of lead exposure (20 to 44 micrograms per deciliter) would result in improved scores on measures of intelligence and other abilities. Contrary to hypothesis, children randomized to treatment did not differ significantly from children in a placebo control group in follow-up psychometric evaluations 3 years after treatment. Several interpretations can be made of this finding.

First, it is possible that the damage was already done. This interpretation relies on an unusual assumption, that is, that the effect was capped at or before the age of recruitment (12 to 33 months), so the two groups went through the trial with no increment in effect for either. Second, as suggested by Rogan *et al.*, the changes in lead level resulting from chelation might not have been sufficient to demonstrate a difference in test scores.

The third possibility is that there might not be an adverse effect at this moderate level of exposure. A number of studies support this inference, but this remains a matter of controversy. The findings of some studies suggest a decrease of 2 to 3 IQ points associated with an increase of lead from 10 to 20 micrograms per deciliter (*2*). (This is an association which is not necessarily causal.) A few authors report larger associations. However, design problems, including limited control of confounding biases in selection and attrition and even deliberate misrepresentation of procedures and findings, complicate the interpretation of this research.

The study by Rogan *et al.* is curious in that they did not present analyses relating initial lead level with scores on cognitive measures at that time or at the 3-year follow-up. Given the available research, the most we can say is that if there is an effect on cognitive function at this moderate exposure level, the effect is small. Nevertheless, the study is important. On the basis of the findings, chelation treatment for children with lead levels in the 20 to 44 microgram per deciliter range is not justified. It is still good practice to investigate the environments of these children to identify and remove sources. Even if there is not an adverse effect at this level, an active exploring child can access a source that could result in serious poisoning.

Fortunately, the prevalence of even moderately elevated lead exposure has decreased dramatically in the last several decades. Other risks associated with sociodemographic disadvantage have a greater impact on children and should command the attention that is still devoted to low-level lead exposure.

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References and Notes
1. W. J. Rogan *et al.*, *N. Engl. J. Med.* **344**, 1421 (2001).
2. S. J. Pocock, M. Smith, P. Baghurst, *Br. Med. J.* **309**, 1189 (1994).

Response

WE APPRECIATE ERNHART'S INTEREST IN OUR paper (*1*) and her support of our conclusions. We disagree, though, with three of her points. The first is her characterization as "unusual" the idea that children whose blood lead levels were once high might have sustained damage that could not be repaired later. The concept that damage done at a critical period cannot be repaired later is familiar to all who work with children. This is the idea behind screening for neonatal hypothyroidism to prevent irreversible cretinism, treating neonatal hyperbilirubinemia to prevent kernicterus, and the early diagnosis and treatment of phenylketonuria, to name a few examples.

The second point of disagreement regards the state of the literature about early exposure to lead and subsequent cognitive

development. Lead at high doses kills children by causing an encephalopathy, so the question is not whether lead is toxic to the brain, but at what dose the toxicity is measurable. Lead is the best studied of the environmental chemical agents thought to damage the brains of children at relatively low levels of exposure. Because lead poisoning occurs in environments that offer other challenges to the families, isolation of that effect has been difficult. Responsible reviewers, though, including the authors of the meta-analysis Ernhart cites (*2*), have taken confounding factors into account and judged it to be more likely than not that lead causes the defects. Claims of deliberate misrepresentation have not been verified (*3*); moreover, such claims were directed at a specific investigator and would not in any case affect interpretation of the weight of the literature. From our point of view, causality was sufficiently established so that we and our advisors thought that a trial, testing whether such damage could be prevented or reduced, was justified.

Finally, it is hardly "curious" that we do not report associations between lead level and IQ from trial data. Therapeutic trials and observational studies of etiology are designed very differently. In order that we could best make comparisons between children given the active drug and children given placebo, we selected children from a relatively high, narrow range of blood lead levels and, of course, we treated them, both of which factors make the trial data less suitable for studying etiology. There have been many other studies designed specifically to do that, as noted above (*2*).

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References and Notes

1. W. J. Rogan *et al., N. Engl. J. Med.* **344**, 1421 (2001).
2. S. J. Pocock, M. Smith, P. Baghurst, *Br. Med. J.* **309**, 1189 (1994).
3. J. Palca, *Science* **256**, 1389 (1992).
4. The authors note the passing of our senior colleague, J. Julian Chisolm Jr., a month after the appearance of our paper. His intellectual contribution to the study continued until the end, and we will miss him.

CORRECTIONS AND CLARIFICATIONS

PERSPECTIVES: "One for all?" by B. E. Ellis and G. P. Miles (15 Jun., p. 2022). Reference 5 [S. Plakidou-Dymock *et al.*, *Curr. Biol.* **8**, 315 (1998)] has been corrected by its authors. In the 3 April 2001 issue of *Current Biology* (p. 535) Kanyuka, Couch, and Hooley stated that their claim of a connection between the GCPR in *Arabidopsis* and the cytokinin response is wrong; a mutation independent of the antisense construct for the seven-trans-membrane receptor GCR1 caused this phenotype. Therefore, the function of GCR1 remains an open question. The main thrust of the Perspective is unaffected by this situation.

REPORTS: "Differentiation of embryonic stem cells to insulin-secreting structures similar to pancreatic islets" by N. Lumelsky *et al.* (18 May, p. 1389). In the first line at the top of page 1392, the average protein content of a cell is given as about 20 pg. It should have been given as about 200 pg per cell.