searchers with the Illinois Natural History Survey are investigating the effectiveness of this barrier in limiting movement of native fishes, but studies are needed that specifically address whether such a barrier could prevent bighead and silver carp from entering Lake Michigan.

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7. The Great Rivers Field Station and the Illinois River Biological Station are part of the Long Term Resource Monitoring Program for the Upper Mississippi River System (UMRS). This program is funded by the U.S. Army Corps of Engineers, and administered by the U.S. Geological Survey–Biological Resources Division in cooperation with the five UMRS states of Illinois, Iowa, Minnesota, Missouri, and Wisconsin. More information is available at http://www.umesc.usgs.gov/ltrmp.html.
8. Regression analysis of the catch data shown in the plot indicates an exponential curve of the form Total Catch = $0.35 \cdot e^{0.54 \cdot Year}$ fit these data significantly (correlation coefficient = 0.97, degrees of freedom = 9, $P = 0.0001$).

Clioquinol's Return: Cautions from Japan

IN HER ARTICLE "AN ANTIBIOTIC TO TREAT Alzheimer's?" Laura Helmuth reports on clioquinol, a chelating antibiotic, that Ashley Bush and colleagues have found dissolves amyloid plaques in postmortem brain tissue from Alzheimer's patients and also dissolves Alzheimer's-like plaques in living mice (News of the Week, 17 Nov., p. 1273). The drug is in phase II clinical trials.

This drug, however, caused a tragic disease, subacute myelo-optico-neuropathy (SMON), in the 1960s in Japan. Patients showed subacute onset of visual loss, muscle weakness, numbness, and a tingling sensation in their lower extremities. Autopsies revealed degeneration of the optic tract and of the lateral and dorsal columns of the spinal cord. Neurologists noted that patients had green tongues and green urine, and analytical chemists concluded that this was due to chelated iron from treatment with clioquinol (*1*). Rats and mice did not develop the disease, but dogs developed a similar condition when treated with this drug (*2*). It has also been found that a chelate of clioquinol with zinc is toxic to mitochondria (*3*). Our epidemiological study revealed that those individuals who received 1.2 grams per day of chinoform containing clioquinol for more than 2 weeks developed SMON (*4*).

The use of clioquinol was banned in 1970 in Japan. Many patients still suffer residual effects from their treatment with this drug. Clioquinol might be found to help to relieve the symptoms of Alzheimer's disease, but it has the potential to cause a dreadful condition.

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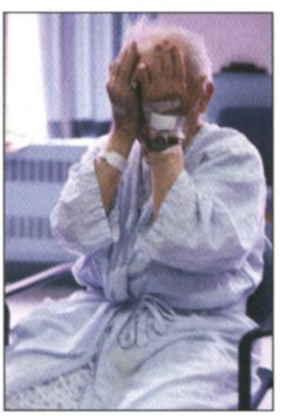
Response

WE APPRECIATE TABIRA'S CONCERN about clioquinol (CQ), a copper/zinc chelating antibiotic that markedly inhibits amyloid pathology in a transgenic animal model for Alzheimer's disease (*1*). The proof of principle of this approach in transgenic mice was achieved against a background of extensive in vitro data from our laboratories, which have defined the β amyloid protein of Alzheimer's disease as a metalloprotein with structural features similar to Cu/Zn superoxide dismutase (*2*).

Clioquinol earned an unfavorable reputation in Japan in the 1960s. It was used extensively for 20 years before the first case of SMON was described. Before its retirement, the drug was used for 500 million patient days as an antibiotic with a very favorable safety profile. As Tabira describes, in the 1960s Japan suffered an epidemic of this syndrome, and CQ was implicated in the pathogenesis. Because of the relatively low benefit of the drug as an antibiotic, its manufacturer, Ciba, withdrew it from the world marketplace rather than try to defend it. However, a causal relation between CQ and SMON was never proven (*3*).

In examining the drug's history, we found a number of facts that argue against CQ being the true and only cause of SMON. For example, the per capita consumption of CQ was higher in several other countries than the per capita consumption in Japan. Yet, at the time the drug was withdrawn, there were 10,000 cases of SMON in Japan, whereas there were only 220 cases identified in the rest of the world. Also, no clear relation has been identified between CQ dose and the risk for SMON. Six cases of encephalopathy (but not SMON) induced by acute overdoses in excess of 7.5 grams have been reported (*4*). Most importantly, 25% of patients with the diagnosis of SMON (in a sample of 2465 from Japan) had never taken CQ (*5*). Tabira cites one paper that shows that CQ is toxic to mitochondria in vitro. However, most antibiotics at high concentrations are toxic to mitochondria, and in medicine, antibiotics are dosed to avoid mitochondrial toxicity.

So why were the Japanese so severely affected by the syndrome? We believe that local demographic factors prevalent in Japan at the time might have predisposed this population to develop SMON. This disease resembles an accelerated form of subacute combined degeneration due to vitamin B-12 deficiency, and administration of CQ to normal mice has been reported to deplete brain and serum levels of vitamin B-12 (*6*). One possibility is that the Japanese were endemically B-12 deficient as a consequence of their diet in the postwar years, and that this was the predisposing factor to SMON. CQ was commonly used to treat gastrointestinal symptoms in an unregulated manner in Japan in that era, and SMON usually begins with symptoms of abdominal pain and diarrhea; therefore, overdosing in a B-12–deficient population might have exaggerated the incidence of SMON in Japan.



Alzheimer's disease affects about 4 million people in the United States.

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In light of this possible explanation for the association of CQ with SMON, co-administration of vitamin B-12 is part of the phase II clinical trial that is in progress. Nevertheless, we are sensitive to the possibility of neurological side-effects in our trial, and we have kept the doses of the drug to a fraction of what the dose was when it was used as an antibiotic (*7*). Taking this into account, we, and two other scientific bodies (*7*), believe that CQ might be safely used again as a drug. However, we agree that we must remain alert to the possibility that it might cause this syndrome, and safeguards are in place to monitor for SMON in the clinical trials.

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7. We have carefully reviewed the literature on the association between CQ and SMON. A summary of our findings on the matter forms the basis of a discussion in (*1*), which is the basis for our discussion here. The institutional review board of the Royal Melbourne Hospital (responsible for overseeing the phase II clinical trial that is under way) has reviewed and accepted our argument for why CQ, at low doses, would be safe to administer to patients in the trial. Similarly, scientific reviewers of the Alzheimer's Association of America have examined the evidence and the clinical trial protocol, and they have supported this trial. Our study participants are also reviewed by neurologists at regular intervals, and they have regular tests to identify subclinical signs of SMON, including nerve conduction studies. The clinical trial is sponsored in part by Prana Biotechnology Ltd., in which both authors are shareholders and consultants.

SCIENCE'S COMPASS

Forum for Agricultural Biotechnology Debates

THE STATEMENT THAT THE STANDING committee on agricultural biotechnology of the National Academy of Sciences "is expected to launch a study of the ecological risks of trees, grasses, and ornamental shrubs" in Jocelyn Kaiser's News Focus article "Words (and axes) fly over transgenic trees" (6 Apr., p. 34) is incorrect. Although issues raised by the development of transgenic trees are of great interest to the Committee on Agricultural Biotechnology, Health and the Environment (CABHE), we are not on the verge of launching such a study and could not pursue such issues until appropriate new resources are identified.

CABHE is a relatively new standing committee of the National Research Council. Composed of experts in biological and social sciences and in public policy, CABHE has been formed to address several important aspects of agricultural biotechnology, such as health-related and environmental consequences of using biotechnology for production of fiber and food (both plant and animal). Thus far, with support from the U.S. Department of Agriculture and the Food and Drug Administration, CABHE has been involved in planning and overseeing studies of animal biotechnology and of environmental risk assessment for transgenic crops, attempting to bring a diversity of viewpoints to the polarized debates about these issues. Summaries of CABHE activities appear on the project's Web site at http://www.nationalacademies.org/agbiotech.

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CORRECTIONS AND CLARIFICATIONS

LETTERS: "Human origins and ancient human DNA" by A. Cooper *et al.*, Response by G. J. Adcock *et al.* (1 Jun., p. 1655). In their letter, Cooper *et al.* described an error in a table in G. J. Adcock et al., *Proc. Natl. Acad. Sci. U.S.A.* **98**, 537 (2001). This information, however, was received too late in the publication process to include a response by Adcock *et al.* Their response is as follows: "Cooper *et al.* correctly point out that column 199 in out Table 1 is incorrectly marked as parsimoniously informative. This error is due to a copy-and-paste error and does not affect the remaining phylogenetic analyses."