clature based on a single molecular sequence difference "will only produce chaos and would not result in nomenclature stability" (*2*). A perceptive article by R. A. Lewin (*3*) illustrates why there is no benefit from adopting many proposed taxonomic rearrangements or name changes.

Schemes for revision of bacterial taxonomy and name changes based on limited "molecular trees" have become muddied by the discovery of widespread lateral gene transfer among bacterial species. Thus, neat-looking molecular trees have begun to anastomose and now resemble tangled masses of spaghetti. The complexities of bacterial evolution have been greatly underestimated by those who believe we can now trace billions of years of bacterial evolutionary history with a simple "molecular litmus test." We advise a moratorium on useless name changes pending more research on the course of evolution of microbial cells (in contrast to evolution of 16*S* RNA molecules).

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THE DEBATE BETWEEN THE SUPPORTERS OF PhyloCode and those of the traditional Linnaean classification system could benefit from the wisdom of Thomas Jefferson. Eighteenth-century scientists proposed a variety of nomenclatures. Jefferson accepted the importance and usefulness of such systems, but believed them to be inherently arbitrary (man's attempt to organize the units of nature) and subject to error. He reviewed the various nomenclatures first proposed by Ray, Klein, Brisson, and, finally, Linnaeus, which competed with the systems of Blumenbach and Cuvier.

After thoughtful analysis, Jefferson supported the Linnaean system for a number of reasons. More importantly, Jefferson reflected on the validity of nomenclature systems in general: "But to this objection every mode of classification must be liable, because the plan of creation is inscrutable to our limited faculties. Nature has not arranged her productions on a single and direct line. They branch at every step, and in every direction, and he who attempts to reduce them into departments, is left to do it by the lines of his own fancy" (*1*).

As PhyloCode proponents argue that their system would fix a fundamental flaw in the Linnaean system, they too must be reminded that Jefferson recommended caution before supporting novel systems, lest competing nomenclatures actually lead to confusion. The scientific community must be cautious in quickly accepting multiple systems, a situation that could lead to more, not less, organizational confusion.

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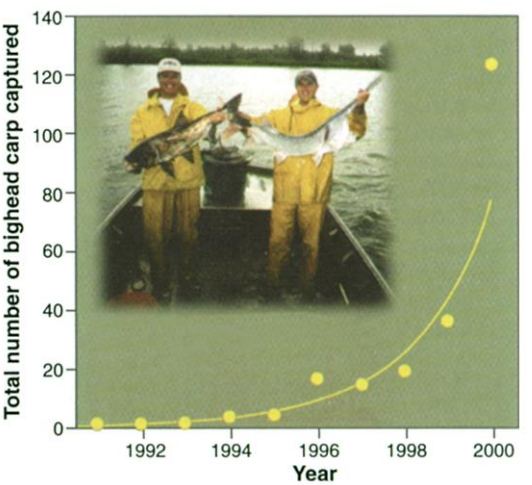
Invasive Carp in the Mississippi River Basin

BLACK CARP POSE A POTENTIAL THREAT TO the ecology of the Mississippi River Basin, as Dan Ferber warns in his News Focus article "Will black carp be the next zebra mussel?" (13 Apr., p. 203). Nevertheless, before black carp ever become a problem, the Mississippi Basin will have been contending with two other invasive Asian carp, bighead and silver carp, for several years. Both species were brought to the United States in the 1970s for use in aquaculture, escaped into the Mississippi River soon thereafter, and subsequently established reproducing populations in the Mississippi, Missouri, Ohio, and Illinois rivers (*1*). Recently, populations of these two species have increased dramatically in certain areas. For example, the bighead carp population in navigation pool 26 of the Mississippi River (near St. Louis, Missouri) appears to be increasing exponentially (see the figure). An exceptional year class of bighead carp was produced in the La Grange reach of the Illinois River (near Peoria, Illinois) in 2000, with the total number of carp captured increasing by two orders of magnitude compared with previous years (i.e., from less than 10 per year to more than 1100 captured in 2000).

Catch data from commercial fishers also show dramatic increases in recent years. From 1988 to 1992, the combined annual harvest of bighead and silver carp by Illinois commercial fishers in the Mississippi and Illinois rivers was less than 600 kilograms (*2*). Total harvest increased to more than 5000 kilograms in 1994 and has been greater than 50,000 kilograms since 1997.

Bighead and silver carp pose a threat to the ecology of the Mississippi River Basin and connecting aquatic ecosystems. Both species are filter feeders, consuming a variety of planktonic organisms, and are capable of significantly reducing zooplankton abundance in ponds and lakes (*3*). Because all fishes forage on planktonic organisms during their early life history stages, bighead and silver carp have the potential to adversely affect every species of fish in the Mississippi River Basin. Additionally, several fishes native to the Mississippi River Basin are filter feeders as adults, including paddlefish (listed as a species of special concern by the U.S. Fish and Wildlife Service), bigmouth buffalo, and gizzard shad. If nothing is done to halt the upstream spread of bighead and silver carp in the Illinois River, they will soon enter the Great Lakes, ecosystems already stressed by introductions of sea lamprey, zebra mussel, and the round goby.

Once a nonnative species successfully invades an ecosystem, it is often difficult or impossible to eradicate it (*4*). Extirpating populations of bighead and silver carp from the Mississippi River Basin will require detailed information about the biology of these species specific to this system, including their reproductive behavior and the habitats used by larvae and juveniles. Nevertheless, such information does not guarantee a workable solution will exist. These problems highlight the need to prevent introductions of non-native species through management and laws such as the National Invasive Species Act of 1996, which is up for reauthorization this year (*5*). Currently, an electric barrier is under construction on the Chicago Waterway to prevent the movement of round goby from Lake Michigan to the Upper Mississippi River System (*6*). Re-



Bighead, big problem. Researchers in the Long Term Resource Monitoring Program (*7*) sample fishes each year from June through October. Catch data for navigation pool 26 of the Mississippi River reveal an exponential increase in bighead carp (*8*). (Inset) A bighead carp (left) and a fellow filter feeder, a paddlefish, were caught in the same net in pool 26.

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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*).

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

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.

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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