was 95% for duodenal ulcers and 74% for gastric ulcers.

In February of this year, Enno Hentschel and colleagues at the Hanusch Hospital and the University of Vienna School of Medicine provided supporting evidence, reporting in the *New England Journal of Medicine* that duodenal ulcers recurred in only 8% of patients treated with antibiotics—compared with 86% in patients receiving a placebo.

For many researchers this means that the case for a bacterial cause of most ulcers has been made unequivocally. "I don't think there's any question that *H. pylori* infection plays a critical role in all but a small percentage of cases of peptic ulcer disease," said Richard Galbraith, an ulcer specialist at Rockefeller University Medical Center. Gastroenterologists at some major medical centers also find the data compelling enough to prescribe antibiotics for ulcer patients. At the Mayo Clinic, for example, antibiotic therapy has become standard treatment. "Our view here is that if you get rid of the bacterium, you get rid of the ulcer once and for all," says Nicholas J. Talley, associate professor of medicine.

And the benefits of prescribing that kind of therapy might not be merely medical. According to findings presented at a European workshop on *H. pylori*, which will be published as a consensus report in an upcoming issue of *Lancet*, eradicating *H. pylori* has the potential to cut the cost of gastrointestinal medicine by 80% over the next 5 to 10 years.

But the clinical practitioners of gastroenterology aren't rushing to reap these potential benefits. Some gastroenterologists, while accepting the idea that bacteria are associated with the recurrence of ulcers, don't think they're the cause. Says Denis McCarthy, chief of gastroenterology at the University of New Mexico School of Medicine: "I don't think the evidence supports that *Helicobacter* is involved in the initial development of an ulcer. *H. pylori* is certainly part of the jigsaw puzzle, but there is probably some other insult that sets the stage for *Helicobacter* infection." Only 90 miles north of the Mayo Clinic, in Minneapolis, nobody at the University of Minnesota Hospital and Clinic prescribes antibiotics for ulcers. "The case isn't strong enough yet," according to a hospital spokesperson.

In other cases, however, it isn't a matter of skepticism, it's simply that word from the research community isn't filtering through to the clinician. "The majority of physicians are still treating ulcers as they have for the past 20 years," says Blaser. A gastroenterologist in private practice, who insisted on anonymity, described the growing support for treating ulcers with antibiotics as "news to me. Most of us in private practice depend on drug company literature to learn of new therapeutic approaches."

And the drug company literature isn't filled with news of antibiotic treatments partly because drug companies don't appear to be interested in developing them. Calls by *Science* to a variety of major drug companies revealed only two—Astra Pharmaceuticals and Abbott Laboratories—that acknowledged they were working on developing antibiotics for use in treating ulcer disease.

Perhaps even better than new antibiotics would be a vaccine, given early in childhood. "This is the only approach that will ultimately succeed, because the ability of *H. pylori* to mutate and swap DNA segments makes it unlikely that resistance will not develop," says McCarthy. At least two biotechnology firms, Orovax, in Cambridge, and Chiron, in Berkeley, are currently developing an *H. pylori* vaccine.

While it would certainly be exciting to have a vaccine against ulcers, the role of *H. pylori* in human disease may not end with that condition. Epidemiological and biopsy data suggest that *H. pylori* infection may be a crucial first step in the genesis of gastric carcinoma. "What the evidence seems to show is that once a person is infected with *Helicobacter*, they remain infected for life. In most people, nothing develops except perhaps for a mild inflammation of the stomach lining," said Blaser, who has accumulated some of the epidemiological data. "In some patients, *Helicobacter* infection leads to ulcers, and in a third group it produces chronic atrophic gastritis, which is a well-known precursor of gastric carcinoma."

It's not known what factors determine which of these three outcomes is realized. Nor do researchers have the answer to another key question: how the bacterium is transmitted. Epidemiological data showing that infection rate is highest where sanitation levels are lowest suggest that in developing countries oral-fecal transmission may be the most common route of infection. Those data, however, don't explain how transmission occurs in the United States and other developed countries.

Such mysteries will be unraveled some day, and if by then ulcers have gone the way of polio and smallpox, Marshall, nearly everyone agrees, deserves major credit. "Though he can certainly be on the outrageous side"—he once dosed himself with the bacterium to make his case—"he probably deserves a Nobel Prize for this work," says McCarthy. Marshall would no doubt not refuse the Nobel Prize, but he's not convinced his work is done. The main task, he says, is to get news of his conclusion to where doctor meets patient. "We need to do a better job getting this information into the hand of the practitioners outside of the major research institutions if this discovery is ever going to have a major effect on health care in America."

–Joseph Alper

EVOLUTION

Why Some Fishes Are Hotheads


JAMES D. WATT

A warm body. The yellowfin tuna...

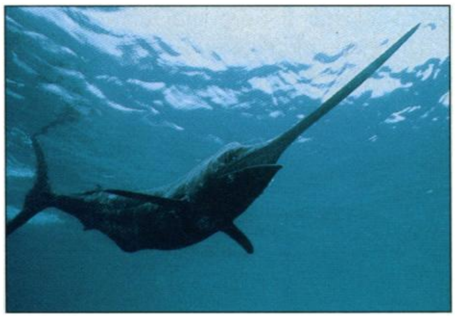
Anyone who has taken a swim in a cold lake knows how fast the water drains heat from your body. Fish have it worse; water not only surrounds their bodies but circulates across their gills as they breathe. No wonder most of the 30,000 species of bony fishes don't try to warm themselves: They are cold-blooded, their body temperature fluctuating with that of the water. But the tunas, the swordfish, and several dozen other fishes don't give in to the cold. To animal physiologist Barbara Block, how and why these fishes came to be warm in some parts of their bodies was an irresistible evolutionary puzzle. In this issue of *Science* (see p. 210), Block and her team at the University of Chicago provide what other biologists are hailing as some of the best evidence yet about what drove the evolution of endothermy, or internal warming, in these fishes—and insight, says Block, into how the trait evolved in other animals.

For years, researchers have debated two hypotheses about why animals first became endothermic: as a means of maintaining body warmth so that they could be active in habitats of varying temperature (the "niche expansion" hypothesis) or as a byproduct of the high metabolism needed to sustain an active lifestyle (the "aerobic capacity" hypothesis). Their fish studies, say Block and her students John Finnerty, Alexandre Stewart, and Jessica Kidd, give strong support to niche expansion as a driving force. By using the tools of molecular biology to probe evolutionary history, they found that the three different groups of endothermic fishes evolved the trait independently. And in each case the trait evolved as the fishes' ancestors expanded their ranges into colder waters.

Other evolutionary biologists are embracing that conclusion. "Before, what we had were 'Gee-whiz' observations about warm-blooded fish," says James Spotila, an endothermy expert at Drexel University. "Now, we have a whole new insight into [their] thermoregulatory strategies." But researchers are more cautious about what Block's work means for the evolution of other warm-blooded animals. Says Raymond Huey, an evolutionary physiologist at the University of Washington, "It remains to be seen whether her arguments will apply to birds and mammals. They may not, if only because the problems of heat transfer differ so radically between terrestrial and aquatic environments."

Biologists had known for 150 years that tunas are warm-blooded, but it was not until the 1980s that scientists learned that some other large fishes, including the billfishes (such as swordfish and marlin) and the butterfly mackerel, also keep parts of their bodies warm. Each of these three fish lineages keeps warm in its own way. Billfishes heat only their brain and eyes, doing so by passing blood through a special eye muscle—"a furnace made of muscle," as Block puts it. Block and her colleagues have found that the butterfly mackerel has a similar brain heater based on a different eye muscle. Tunas, by contrast, warm their brains by means of special vascular plumbing, which captures heat produced by their muscles before it is lost through their gills, and they also have similar heat exchangers for other parts of their bodies.

These varied mechanisms suggested to Block and other workers that endothermy might have originated more than once in fish. Though all three endothermic groups belong to the same suborder, the scombroid fishes, most scombroids are cold-blooded, and nobody knew just how the warm groups are related. If the warm fishes are more closely related to cold-blooded fishes than to each other, endothermy must have arisen three separate times. And if so, the researchers might be able to pin down the key selective force by looking for some common factor.


JAMES D. WATT

...and a hothead. The swordfish.

To trace the evolutionary history of the fishes, Block and her team constructed a phylogeny by comparing DNA sequences from the warm scombroids, their cold-blooded relatives, and several more distantly related fishes—32 species in all. The molecular data confirmed that all three endothermic groups are independent of one another in evolutionary terms. A look at the fishes' ecologies suggested the common factor: niche expansion. Each group of endothermic fish experiences a wider range of temperatures than its cold-blooded relatives. The swordfish, for example, swims from warm surface waters to chilly waters hundreds of meters down in pursuit of squid; the bluefin tuna migrates between the tropics and subpolar seas.

There's another reason to think that niche expansion, rather than higher aerobic capacity, was the critical selective factor, says Block: the fact that in the billfishes and the mackerel, the warming is restricted to the brain and eyes. That wouldn't do much for a fish's aerobic capacity. But it would offer a clear advantage to a species that was expanding its temperature range, says Block: protecting the temperature-sensitive brain and retina so that the fish could still spot and pursue prey.

If Block had had only one case in which endothermy came with a move to cold water, it could have been written off, says Huey. But because she showed that it happened three times, "it's more likely to be a law of nature."

Block draws some broader conclusions, however, that aren't being so readily accepted by other researchers. She and her colleagues think the different forms of internal heating in the three fish groups—some partial, some more complete—support a possibility raised for mammals more than a decade ago by Alfred Crompton and his colleagues at Harvard University: that animals may have become warm-blooded in steps. As Finnerty puts it, "Endothermy doesn't have to be an all-or-nothing thing." Possibly so, say some other researchers, but fish don't prove it. Says Albert Bennett, an evolutionary physiologist at the University of California, Irvine, and a leading proponent of the aerobic capacity theory: "I don't think [fish] can tell us anything" about the evolution of warm-bloodedness in birds and mammals.

To Block, though, fish provide one of the best places to turn for clues. All living mammals and birds are warm-blooded, after all, so it's not possible to unravel the evolution of warm-bloodedness—and the selective pressure that drove it—by comparing the history, anatomy, and ecology of warm and cold-blooded birds or mammals. And if you want to know why an animal would start warming its blood, where better to look than at the warm fishes, where the "cost" of being warm is especially high? After all, Block says, "it was hard to become warm in the water."

–Traci Watson

A Balancing Act in Predatory Fishes

At the other end of the scale from evolution's grand puzzles, such as why only a few dozen of fish species out of more than 30,000 are warm-blooded (see main text), are the exquisite miniatures that show natural selection in action. Take the scale-eating cichlid fishes. Just seven of the thousands of species of cichlids in the lakes of Africa's Rift Valley, the scale-eaters stand out with their toothy, lopsided grimaces and their peculiar feeding habits: ripping scales from other fish. Now there's another reason to take note. They provide the first example of an unusual evolutionary turnaround: a predator existing in different forms that are kept in balance by its prey.

In this week's issue of *Science* (see p. 216), Michio Hori, a biologist at the Wakayama Medical College in Japan, describes how the behavior of the scale-eaters' prey maintains a nearly perfect 1:1 ratio between the cichlid's two genetically determined forms, distinguished by mouths that twist either to the left or the right. Predators have often been shown to exert this kind of pressure—known as frequency-dependent selection—on their prey populations, says evolutionist Brian Clarke of the University of Nottingham, but this is "the first indirect evidence of frequency-dependent selection on predators by prey. It's rather a fascinating story."

Hori had been studying the grimacing fish in Lake Tanganyika for more than a decade when he tallied the ratio of left-mouthed to right-mouthed scale-eaters. He found that instead of varying as environmental factors change, as one might expect, the ratio held steady at almost exactly 1:1. Scientists had long suspected that having a mouth frozen open on one side makes the cichlid's attacks more efficient—but also restricts each fish to attacking from just one side. Hori confirmed that suspicion by dangling a live fish in the lake as a lure; he found that left-mouthed scale-eaters only attack the right side of their prey—and vice versa. And when he analyzed stomach contents from left-handed fish, Hori found mostly scales from their prey's right flanks.

That restriction, Hori believes, explains why the left- and right-handed populations stay in balance. If, for example, right-mouthed fish became more common, their prey would change their behavior, becoming more alert to activity on their left sides and thus fending off more attacks by right-mouthed fishes. Meanwhile, left-mouthed fish would gain the advantage, and the balance would be restored. The victims may lose a few scales—but not without leaving a mark of their own on their attackers.

–T.W.