autoimmune patients. Their toxicity and their reliance, so far, on living donors has prompted questions about how widespread the treatment can become.

Divide and conquer

Another way to thwart immune cells is to isolate them. A strategy called co-stimulatory blockade stops communication between specific immune receptors, which stud the surface of all sorts of immune cells and help govern their behavior, and the T cells on which particular receptors reside. Ideally, this prevents a defined subset of T cells from causing inflammation, while leaving everything else untouched. MGH's Sykes co-opted this approach when she added antibodies to her chimerism approach, but it can also be used alone.

One co-stimulatory blockade drug is anti-CD3, which interferes with so-called CD3 receptors and alters their ability to signal to T cells. The drug inactivates a subset of helper T cells thought to be involved in type I diabetes. These T cells apparently destroy insulin-producing islet cells in the pancreas. French scientists, led by Lucienne Chatenoud at the Necker Hospital in Paris, reported in 1997 that giving mice anti-CD3 cured diabetes, even after the drug was stopped. Now Kevan Herold of Columbia University, Jeff Bluestone of the University of California, San Francisco, and others are testing it in newly diagnosed diabetic patients, with the hope that such patients may still have islet cells left to save. Other antibodies are being explored for diseases ranging from psoriasis to MS to rheumatoid arthritis as well as kidney transplants.

Discouraging works

For tolerance researchers, safety issues loom large. In the past few years, a handful of trials have caused enough harm to be halted, and others, such as stem cell transplants on autoimmune patients, have recorded higher-than-expected mortality rates for reasons not understood, says Roland Martin, chief of the cellular immunology section at the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland.

Martin still does not understand exactly what went wrong in his MS trial, supported by Novartis in Basel, Switzerland, and the biotech firm Neurocrine Biosciences in San Diego, California. It ended disastrously in 2000, after three of the eight volunteers suffered exacerbated MS symptoms apparently linked to the peptide-targeting drug supposed to temper immune attacks. One patient began the trial with a few brain lesions and ended up with 91, and another exhibited large tumorlike lesions he'd never had before. It's still not clear what caused the lesions—which were successfully treated with standard MS drugs—although Martin theorizes that the dosing may have been too high, somehow sending immune cells into overdrive instead of quelling their activity.

"[Immune tolerance] is a matter of tipping the balance," says Elaine Collier, chief of the autoimmunity section at the National Institute of Allergy and Infectious Diseases in Bethesda. "We may be tipping one set of regulatory cells the way we want, and another set the way we don't want."

Fine distinctions in the immune system or among different diseases may help explain the startling variations in response to treatments, says Tyndall. Clues to what distinguishes subsets of patients could come from the tiny number of transplant patients who stopped taking immunosuppressants but somehow kept their organ. Kenneth Newell, a kidney and pancreas surgeon at Emory University in Atlanta, Georgia, is hoping to identify roughly 40 kidney patients in the United States and Europe who fit the bill; a group at the University of Pittsburgh in Pennsylvania is doing the same for liver recipients.

Fully "curing" disease by inducing true tolerance without the help of drugs remains the holy grail of the field. But those involved say that, given the mysteries that still surround the human immune system and the devastation it can produce, a more realistic, short-term goal may fall somewhere between broad immune suppression and total tolerance.

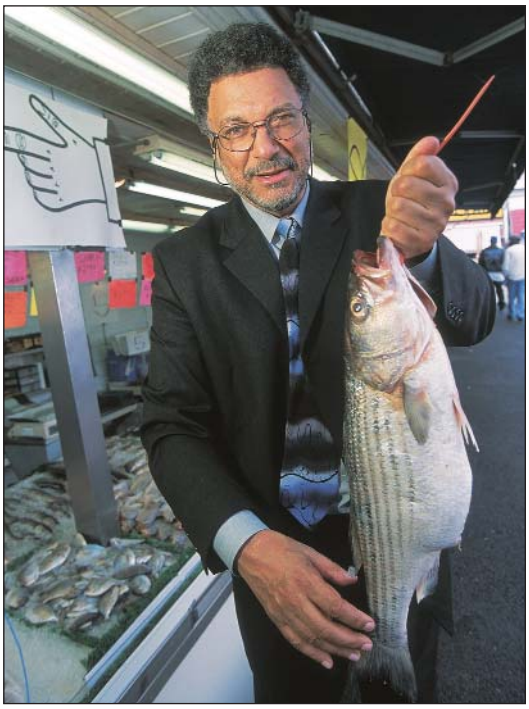
–JENNIFER COUZIN

PROFILE DANIEL PAULY

Going to the Edge to Protect the Sea

Fisheries biologist Daniel Pauly has carved out a colorful—and controversial—career with fresh and frank insights into marine fisheries

Daniel Pauly still remembers his youthful encounter 30 years ago with what he calls "the living papers." A graduate student in Germany, Pauly watched the field's royalty with awe at his first major fisheries conference. "Names I knew only from the literature were suddenly parading before me like kings," he recalls. "I was terrified."



Earning his stripes. Daniel Pauly displays a professional interest in a Washington, D.C., fish market.

CREDIT: RICK KOZAK

These days, the 55-year-old Pauly—tall and graying—is a bit of a living paper himself. A professor at the University of British Columbia (UBC) in Vancouver, he is arguably the world's most prolific and widely cited living fisheries scientist, with recent headline-grabbing papers in *Science* and *Nature*. He's also an architect of a leading fish database and a popular ecological modeling program.

Despite these accomplishments, Pauly remains something of an outsider. His offbeat approach to the science is part of the reason. Whereas colleagues have built careers by using complex mathematics to crunch massive data sets, Pauly has worked mostly in data-deprived developing nations, and he says he can't stomach "enormous equations."

His irreverence is another factor. In a field marked by caution, Pauly has become an outspoken and often controversial critic of modern fishing practices. He's suggested that marine fishers will leave little but jellyfish for future generations to eat, and he has blamed the Chinese government for inflating fish catch statistics and helping obscure a global overfishing crisis. The industry, he says in a sonorous accent that hints at a globe-trotting life, "has acted like a terrible tenant who trashes their rental." Some colleagues are also uneasy about his close ties to

the Pew Charitable Trusts—an unabashed advocate for marine conservation (see sidebar) that has given him nearly $4 million.

But even opponents say Pauly is a valued foe. "[Pauly] is an immensely charismatic, articulate, big-picture guy in a science that tends to produce little-picture guys," says veteran fisheries biologist Ray Hilborn, a friend and sometime critic at the University of Washington, Seattle. "For better or worse, he's probably had a greater impact on the field than any member of his generation."

A difficult start

Pauly has always stood out from the crowd. The child of a French mother and an African-American father, he recalls a "difficult" childhood in Switzerland being raised by another family. A church-related job working with the disabled led to a scholarship to attend Germany's University of Kiel, where he chose fisheries science. "I wanted to find an applied way to help people," he says. He also wanted to travel. "I sometimes felt odd in Europe, so I thought I might blend in a little more" in the developing world.

In 1974, he got his chance, spending 2 years helping aid officials develop new fisheries in Indonesia. The experience led to his first big scientific hit: the "Pauly equation." It's a relatively simple formula that enables researchers in data-poor tropical nations to estimate the natural mortality of fish, a key measure needed to calculate sustainable catches. Traditional methods, he notes, were mostly devised to survey relatively homogeneous northern fish stocks, not diverse tropical schools, and depend on reams of technical information churned out by well-equipped labs.

Bent on finding simpler methods, Pauly mined the literature for the mortality, growth rates, and habitat temperatures of 175 types of fish. His goal was to use the well-documented species to predict the mortality of unstudied varieties living in similar habitats. Success would allow researchers to use a pocket calculator to crunch easily gathered numbers, such as fish lengths culled from local markets.

The mathematical product of Pauly's labors appeared in 1980 [*ICES Journal of Marine Science* **39** (3), 175-192] and the paper has become the most cited of his more than 400 publications. Its tally of 313 citations, as compiled by the Institute for Scientific Information in Philadelphia, Pennsylvania, is 16 times the norm.

The formula has also become a celebrated part of Pauly's professional persona. When Hilborn wrote a parody a few years ago comparing fisheries research to a priesthood, he dubbed Pauly "the Prophet Daniel, … a heretic" who had been exiled to "the lower regions, the hot places. Daniel must toil in infernal heat … armed only with a thermometer."

Today, researchers still debate the robustness of Pauly's equation. "It doesn't always give the right answers," says Ransom Myers of Dalhousie University in Halifax, Nova Scotia, "but it got people thinking about better ways." Pauly is self-deprecating: "The equation gets lots of citations. But half of them probably say, 'It's crap—but there is nothing else to use.' "

Career move

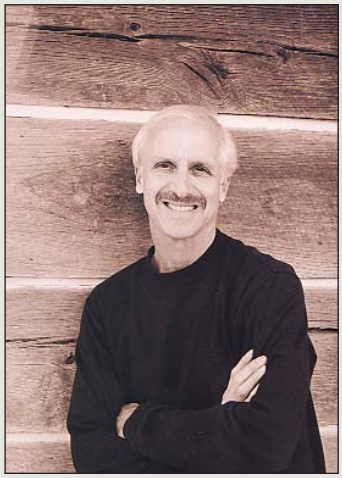
Armed with his doctorate, Pauly moved to the Philippines in 1979 for what became a 15-year stint at the International Center for Living Aquatic Resources Management (ICLARM) in Manila. A training ground for researchers from developing nations, ICLARM offered Pauly a bully pulpit as well as backing for two major projects that would raise his profile.

One was FishBase, a global database now packed with information on more than 26,000 species of fish (www.fishbase.org). As a student, Pauly was inspired by Walter Fischer, a biologist with the United Nations Food and Agriculture Organization (FAO), who cajoled colleagues into assembling fact sheets on thousands of economically important fin- and shellfish. The personal computer seemed like a natural extension, and in 1989, FAO and ICLARM joined forces to create FishBase, with Pauly and Rainer Froese, a German computer expert, running the show. After several false starts, FishBase now boasts of more than 3 million hits a month. "It may end up as [Pauly's] most lasting contribution," says Serge Garcia, a biologist with FAO in Rome, Italy.

The other high-profile project enhanced an ecosystem-modeling program called Ecopath. Traditional techniques that treated each fish stock separately had failed to grasp the messy world of marine ecosystems, and Pauly saw new possibilities in Ecopath, a little-known model for estimating biomass changes along coral reefs that was first developed by Jeffrey Polovina of the U.S. National Marine Fisheries Service. "I took it and tweaked it," says Pauly, incorporating an array of information on fish habitats and life histories that allows researchers to predict how populations might respond to various pressures. As with FishBase, he also recruited savvy partners, no-

Science Helps Pew Push Its Oceans Agenda

From scientific conferences to Congress and the courtroom, the Pew Charitable Trusts has emerged as a major force in marine fisheries research and conservation. Over the last 4 years, the $4.3 billion philanthropy, based in Philadelphia, Pennsylvania, has channeled more than $12 million to Daniel Pauly and other marine scientists to study the impact of human activities—in particular fishing—on the seas. The findings have fueled landmark lawsuits, sparked policy changes, and raised awareness of the precarious state of the world's oceans.



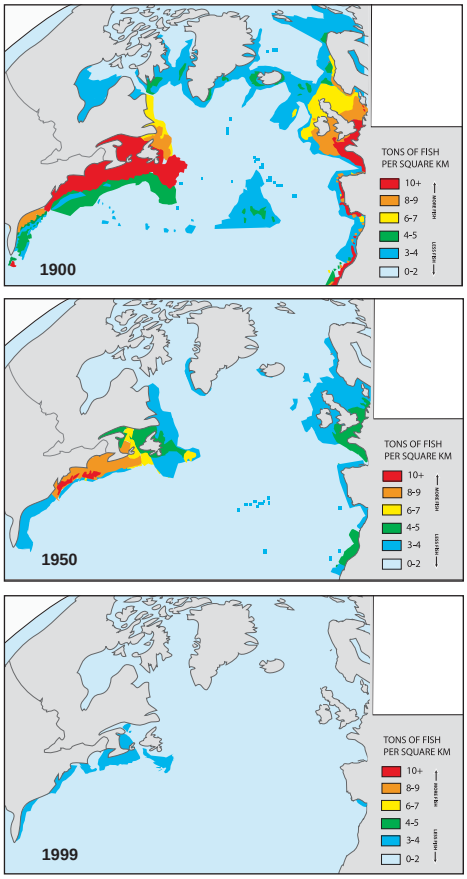
Angling for influence. Pew's Reichert wants to document human impacts.

Pew relishes its reputation as a results-oriented, hands-on funder. But Josh Reichert, head of Pew's $45-million-a-year environment program, rejects the whispers among some scientists that Pew is looking for predetermined results. "There is no contradiction between our pursuit of conservation goals and sound science," says Reichert. "We have a bias, but we never dictate results."

That bias can be seen in its research portfolio. Pauly's $4 million project stems from Reichert's interest in how fishing is influencing ocean ecosystems. Another team of researchers, led by Larry Crowder of Duke University in Durham, North Carolina, and Ransom Myers of Dalhousie University in Halifax, Nova Scotia, are studying the impact of "long line" fisheries on nontarget species, such as turtles and sea birds. Other researchers are studying how other types of fishing gear, such as bottom-dragging nets, affect sea habitats.

The results of these studies "can't solve problems by themselves," says Reichert, who will disburse about $12 million to marine-related efforts this year. But they provide ammunition to a growing network of Pew-molded advocacy groups, including the education-oriented SeaWeb and the newly created Oceana, a "supergroup" that will pursue litigation, lobbying, and media coverage. **–D.M.**

CREDIT: PEW CHARITABLE TRUSTS



Bye-bye biomass. Pauly's team has documented a sharp decline in North Atlantic table fish over the last century.

CREDITS: (MAP IMAGING) JONAH SACHS/FREE RANGE GRAPHICS, (MAP DATA) R. WATSON, V. CHRISTENSEN, D. PAULY/OCEANA; RICK KOZAK

tably Danish biologist and software wizard Villy Christensen, and used training workshops to spread the gospel.

Today, Ecopath and its offshoots are widely used. But like Pauly's equation, it is often reviled as too simplistic. "It's useful but still a work in progress," believes ecologist Stuart Pimm of Columbia University in New York City. Dalhousie's Myers agrees but says Pauly's team "almost single-handedly brought ecosystem approaches back to life."

In 1994, after a management shakeup at ICLARM, Pauly moved to Vancouver to become a tenured professor. He arrived in academia just as collapsing fisheries sent shock waves around the world, and he quickly adopted a bolder stance toward conservation. The result was a burst of provocative papers.

The first two are already minor classics. In the 16 March 1995 issue of *Nature*, Pauly and Christensen took aim at the idea that the sea is so fertile that humans haven't yet fully tapped its potential as a source of food. Earlier estimates, the pair noted, suggested that humans exploited fisheries that used just 2% of the globe's aquatic "primary production," leaving room to enhance catches. But the real take is at least 8% of primary production, the pair calculated, and up to 40% in key fishing grounds. Those numbers suggest that humans already claim a lion's share of the sea's accessible wealth.

In the second paper, published in the October 1995 issue of *Trends in Ecology & Evolution*, Pauly railed against "shifting baseline syndrome." Young biologists, he wrote, often failed to become outraged over the collapse of once-teeming fish stocks because they couldn't quantify—or didn't believe—anecdotes about immense past catches. As a result, "each generation … accepts as a baseline the stock size and species composition that occurred at the beginning of their careers," producing ever-shrinking expectations of what a fishery should look like. "It was an idea that was floating around at the time, and I just put a name on it," says Pauly.

Independence day

Such concerns eventually brought him together with marine conservation advocates at a fisheries meeting in 1995. "It was my declaration of independence," he says. "I ceased seeing myself as servicing government fisheries departments and the industry," he says, although some colleagues call it "an act of betrayal."

Two years later, Pauly met Josh Reichert, head of Pew's $45 million environmental program. At Reichert's invitation, Pauly floated a grand global vision, describing how Ecopath-like software, FishBase, and regional catch statistics could be combined to produce a portrait of the state of the world's fisheries. Although half a dozen prominent researchers predicted it would fail, Reichert says, "we took a chance anyway."

The $4 million investment paid quick returns. A year later, Pauly's team—many plucked from ICLARM—scored again with a paper (*Science*, 6 February 1998, p. 860) that analyzed world catch data. It argued that fishers had systematically overfished larger, more valuable predatory fish, such as cod and groupers, forcing them to shift to less desirable species lower on the food chain. This "fishing down the food web," Pauly said, would eventually leave people with a diet of "jellyfish and plankton soup."

Such hyperbole, and the statistical gyrations of Pauly's team, drew groans from some colleagues. FAO staff argued that Pauly had skewed their data to make his case (*Science*, 20 November 1998, p. 1383). In response, Pauly's team said that FAO's suggested corrections—such as accounting for aquaculture—only made the trend worse.

A similar exchange followed a recent *Nature* paper (29 November 2001) with UBC colleague Reg Watson that suggested that China had intentionally inflated its catch statistics to match its economic targets. The reality, Watson and Pauly found by comparing the claims with the fish-producing capacity of Chinese waters, was that China's overblown numbers had masked a slight decline in FAO's global catch estimates.

In a lengthy response (www.fao.org/fi/statist/nature_china/30jan02.asp), FAO researchers noted—accurately—that they had long ago asked China to correct the problem. And they decried press suggestions that they had intentionally fudged data to hide fisheries problems. "We welcome efforts to improve the accuracy of our data," says Richard Grainger, FAO's fisheries chief. "That's why we've worked hard to make it available to researchers such as [Pauly]."

Both papers "put FAO in a very difficult spot," says Andrew Rosenberg, dean of life sciences at the University of New Hampshire, Durham, and the former top U.S. fisheries biologist. "Some people may [already] have known these things. But [Pauly] puts them together in a way that makes sense."

Pauly's notoriety has generated a flood of speaking invitations and helped attract a publisher for a long-planned volume called *Darwin's Fishes*. The title is a play on Darwin's famous finches, although Pauly says, "Darwin actually wrote far more about fish." Being a celebrity is like hanging onto the side of a fast boat, he remarks: "It's nice to talk to the waves, but it's dangerous as hell."

Mr. Pauly goes to Washington. The researcher briefs congressional staff on fisheries issues.

Still, Pauly seems incapable of staying away from the edge. In recent speeches, he's told fisheries biologists that they need to win over the public—or else. "If fisheries science doesn't consummate a marriage with conservation," he says, his discipline—and the oceans—will suffer.

–DAVID MALAKOFF