frayed ends capped with hydroxyl groups. Trying to coax the stable CP-263,114 into a more unstable form proved very difficult. After numerous attempts, the team designed another cascade reaction, which finished the job. When the resulting compound passed muster in a structure-determining nuclear magnetic resonance machine, the climb was complete. Atop the mountain, says Scripps Ph.D. student Phil Baran, "it feels like a 200-ton anvil has lifted off my back."

Yet in some ways the work is just beginning. Now the hunt is on to come up with CP analogs that are more potent and simpler to make. The Scripps team is also launching studies of the detailed biological effects of CPs and their kin. Of course, the search is also on for new molecular mountains to climb.

–ROBERT F. SERVICE

BEHAVIORAL GENETICS

Fickle Mice Highlight Test Problems

Studying the genetics of behavior is often like riding a roller coaster. A standard way to look for the genetic basis of a behavior—anxiety, say, or aggression—is to knock out a suspect gene in a mouse strain and test the animals in the laboratory. But no sooner has one group of researchers tied a gene to a behavior when along comes the next study, proving that the link is spurious or even that the gene in question has exactly the opposite effect. Now, on page 1670, a study born in part out of frustration over this phenomenon shows how easily such discrepancies may arise.

Behavioral geneticists from three labs across North America applied the same battery of behavioral tests to the same strains of mice, under almost exactly the same circumstances—and yet they often got strikingly different results. This implies that almost undetectable environmental differences may have large behavioral consequences. The finding is bound to complicate efforts to pin down the genetic influences on behavior. "It's the kind of study that needs to be done, but nobody wants to be doing," says behavioral neuroscientist Elizabeth Simpson of the University of British Columbia in Vancouver. "You're looking into something that people would like to believe is not a problem."

The three labs, led by John Crabbe, a behavioral geneticist at the Veterans Affairs' Portland Alcohol Research Center and Oregon Health Sciences University, Douglas Wahlsten of the University of Alberta in Edmonton, Canada, and Bruce Dudek of the State University of New York, Albany, carefully standardized the tests. All three started on 20 April 1998 between 8:30 and 9:00 a.m. local time, and each used a total of 128 77-day-old mice from the same eight strains. Conditions in the three labs, from the light-dark cycle to the brand of mouse feed, were painstakingly equated, to the point of driving the researchers "nuts," says Crabbe. And yet, genetically identical mice often behaved differently, depending on where they were tested.

One puzzling result came from a standard test for anxiety, the so-called "elevated plus-maze." In this test, researchers place a mouse in the center of a big horizontal plus sign fixed about 1 meter above the floor and then measure how much time it spends in each of the four arms, two of which have transparent plastic walls, while the other two are open. Animals that prefer the safety of the walled arms are thought to be anxious, while the ones that venture onto the open arms, nosily peering over the cliffs, are deemed less inhibited. As it turned out, anxiety levels among mice of all strains were lowest in Edmonton. In addition, one strain, in which a receptor for the neurotransmitter molecule serotonin was knocked out, gave different results in all three cities: In Portland, it showed more activity on the maze than controls with intact serotonin receptors; in Albany, it was less active; and in Edmonton, lacking the receptor didn't seem to make any difference.

The same mutant also provided an unpleasant shock for Crabbe. In 1996, his team reported in *Nature Genetics* that the animals drank much more alcohol than control mice having the receptor—a major result, addiction researchers said, because it seemed to firmly nail the importance of the serotonin pathway in addiction. The team had replicated the finding four times. But this time, all three teams found that the animals were no fonder of drink than controls. "It was a bad surprise," says Crabbe, who is

Puzzling plus. Outcomes in the "elevated plus" anxiety test varied from lab to lab.

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ScienceScope

On the Move The headquarters of a global research collaboration aimed at eradicating malaria in Africa is moving to the National Institutes of Health (NIH) near Washington, D.C. The Multilateral Initiative on Malaria (MIM) will soon arrive at NIH's Fogarty International Center, with British advisors in tow, following an 18-month start-up run at the Wellcome Trust charity in London.

Though the Trust played a key role in launching MIM, it did not want permanent custody of the program, which coordinates a wide range of malaria-related research. The move, announced 26 May, is designed to prevent the effort from becoming firmly "embedded in any organization," says Trust official Catherine Davies. Officials are mum on whether other makeovers will accompany MIM's change of address.

Clear Skies? European radioastronomers have won greater protection from the electromagnetic smog produced by a flotilla of satellites. The European Science Foundation announced this week that Iridium, a company that last year turned on a globe-girdling communications network of 66 spacecraft, will limit interference that is drowning out radio whispers produced by galactic gas clouds.

Last year, Iridium signed similar agreements with U.S. and Indian astronomers, promising to silence its satellites for a few hours each night so that radiotelescopes could tune in to one prized signal (*Science*, 2 October 1998, p. 34). But European astronomers said those pacts didn't go far enough for them. The hard-nosed stance appears to have paid off, with Iridium promising clear skies over Europe about 50% of the time until 2006 under the new agreement. The company has already promised to completely eliminate its smog after 2006.

But interference caused by other satellites could continue to grow worse, says astronomer Jim Cohen of the U.K.'s Jodrell Bank Observatory. He and other researchers are organizing to defend key pieces of the radio spectrum at a May 2000 allocation conference in Geneva, Switzerland.

Contributors: David Malakoff, Jocelyn Kaiser, Eliot Marshall

now trying to find subtle genetic changes that may have caused the mutants to lose their taste for alcohol.

As for the other discrepancies, the researchers can only conclude, Crabbe says, that they are the result of very subtle differences in lab conditions, like the chemical composition of the water, or the way the researchers handled the animals, or even the way the scientists and technicians looked or smelled. In Edmonton, a research assistant was highly allergic to mice and wore a respirator. "That looks weird to us; it may look strange to a mouse, too," says Crabbe.

Crabbe doesn't have a clear solution yet to the problems that the study lays bare, but he is now planning experiments to find out if a combination of three or more different tests, designed to measure the same behavioral trait in different ways, would produce more reproducible results than a single test.

Meanwhile, he says, the field of behavioral genetics should at least standardize its tests and perform them just as attentively as, say, a DNA extraction. But because even that won't eliminate outcome differences, every result should be replicated with a new batch of mice within the same lab, and perhaps even elsewhere, before it's published.

–MARTIN ENSERINK

EXPERT TESTIMONY

Project Offers Judges Neutral Science Advice

Federal judges looking for impartial scientists to help sift through complex technical evidence will soon have an easy way to find them. Last week the American Association for the Advancement of Science (AAAS, publisher of *Science*) launched a 5-year pilot project to supply judges with lists of experts who can provide advice in complicated cases, such as claims of software patent infringement or illness from exposure to a toxic substance. The project is intended to cut through the legal confusion generated when expert witnesses hired by each side dispute the significance of such evidence. Pamela Ann Rymer, a judge with the U.S. Court of Appeals for the Ninth Circuit in Pasadena, California, and chair of the project's advisory committee, welcomes the arrival, "for the first time, [of] a single, independent, and neutral source for identifying potential experts."

Courting science. Judge Pamela Rymer lauds project to provide impartial experts.

The $500,000 project, with support from the Leland Fikes Foundation of Dallas and financier George Soros's Open Society Institute, grows out of a 9-year-old idea from a joint panel of AAAS and the American Bar Association. Its stock rose after a 1993 Supreme Court decision urged judges to act as "gatekeepers" for scientific evidence, disallowing expert testimony that doesn't meet accepted scientific standards. The court expanded the ruling earlier this year to include evidence involving the expertise of engineers and those in other technical fields (*Science*, 2 April, p. 21).

The Court Appointed Scientific Experts (CASE) project will rely on a panel of scientists, professional societies, and even the Internet "to help identify people respected in their field" in response to a request from a judge, says project manager Deborah Runkle. It will also develop guidelines for measuring potential conflicts of interest. A 1993 survey by the Federal Judicial Center (FJC) suggests that district judges would welcome input from an impartial expert, who might be involved in everything from tutoring judges and juries in computer codes to explaining the methodology underlying scientific testimony.

Why would a scientist want to get involved in a court case? "It's a service," says Runkle, just like testifying before Congress or serving on a blue-ribbon panel. Adds CASE advisory panel member Sheila Widnall, an aeronautics professor at the Massachusetts Institute of Technology, "It's extremely important for our society, as issues get more and more complicated, that there is a voice" from scientists. The FJC will evaluate the project's impact after 5 years.

Opening for business this fall, the project has already drawn criticism from trial lawyers, who fear that it could tip the balance in the current adversarial system. Ned Miltenberg of the Association of Trial Lawyers of America in Washington, D.C., says that scientists are deeply divided on such legal hot buttons as whether animal tests should be admitted as evidence of causation in toxic tort cases. Putting a stamp of approval on a witness, says Miltenberg, could easily lead "overawed" judges and juries to defer to the court-appointed expert's opinion.

But Runkle says "any good scientist" will acknowledge legitimate opposing views. Besides, she adds, conflicts "are going to exist whether we are here or not."

–JOCELYN KAISER

CELL BIOLOGY

New Leads to Cancer, Arthritis Therapies

Some enzymes get the glamorous jobs: repairing damaged DNA, for example, or shuttling other substances into and out of cells. Others pursue seemingly boring occupations. The enzymes known as metalloproteinases, for instance, simply chew up proteins. They are every bit as essential, however. By breaking down collagen and the other proteins that make up connective tissue, they remodel the entire body during embryonic development and help migrating cells, such as immune cells or the cells necessary for wound healing, move to where they are needed. And like their glamorous cousins, the protein-degrading molecules can cause serious problems when they become overactive, allowing cancers to spread or eroding joints in arthritis. Now, two new findings about the metalloproteinases could open the way to controlling the enzymes.

On page 1667, Karl Tryggvason and his colleagues at the Karolinska Institute in Stockholm, Sweden, describe for the first time the complete three-dimensional structure of a metalloproteinase. This enzyme, known as MMP-2 (for matrix metalloproteinase 2), is usually found only in the developing embryo and healing wounds. But it can also help cancer cells spread in the body and allow growing tumors to build new blood supply lines, and so researchers have been looking for drugs that inhibit its action—a quest that the new structure may aid.

And on page 1664, a team led by Elizabeth Arner at DuPont Pharmaceuticals Co. in Wilmington, Delaware, reports the cloning of a new metalloproteinase that seems to play a key role in the development of arthritis by breaking down a cartilage protein called aggrecan; it may thus be a target for antiarthritis drugs. "Everyone looking for arthritis targets is very excited, [because] understanding cartilage destruction had been on hold until the 'aggrecanase' activity was found. This will set the stage for a lot of activity," predicts arthritis expert John Sandy of the Shriners Hospital for Children in Tampa, Florida.

The MMPs, so named for the zinc ion in their catalytic centers, first appeared in the late 1960s when MMP-1, a collagen-degrading enzyme, was discovered. After a long gap, in 1980, Lance Liotta of the National Cancer Institute (NCI), working with Tryggvason, found that various tumor cell lines produce huge amounts of a related enzyme, MMP-2, and linked the enzyme to metastasis. "MMP-2 is not active in benign tumors; it only becomes activated once the tumors become invasive," Tryggvason ex-