(NSF), was that the agencies are encouraging grant proposals submitted to them jointly. Goldin argued that because of the colossally high energies at play in the big bang, the neighborhood of black holes, and within neutron stars, these astrophysical phenomena should be regarded as physics experiments that dwarf anything that can be done on Earth. NASA satellites, he said, could exploit those natural experiments by collecting radiation or particles, insuring that physicists would no longer be "victims of the last [terrestrial] machine you built."

Goldin's reference to scientists who focus on "the next bigger machine based on yesterday's technology," however, ruffled some scientists at Fermilab, which was just four days away from dedicating its latest particle accelerator, the $260 million Main Injector. Physicist and DOE Under Secretary Ernest Moniz, who was seated next to Goldin, interjected politely that physicists can look forward to "important advances, as well, in accelerator-based experiments."

A subsequent speech by Goldin during a conference here had been purged of disparaging references to standard particle accelerators that appeared in earlier drafts and received generally positive reviews. "Dan Goldin's inspiring set of things to do was really spectacular, I thought," said Leon Lederman, a Fermilab Nobel laureate in particle physics. "That's a grand vision," added Scott Burles, an astronomer at the University of Chicago, although "you're going to have to be very clever to come up with [actual] missions."

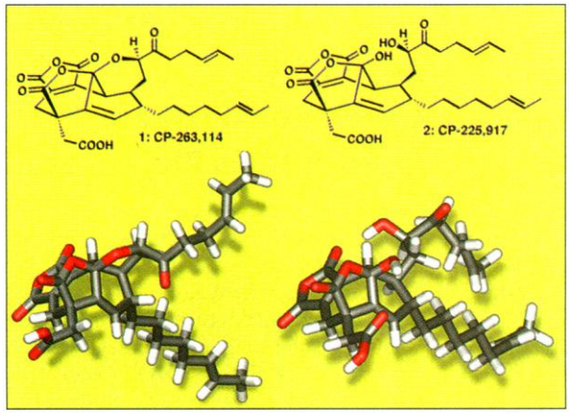
Goldin was short on specifics, and Moniz, at the press conference, stipulated that no new advisory body would be formed to guide the effort, whose direction would instead be determined by individual proposals that passed peer review. Nor was there any mention of new money to fund the initiative. In his speech, however, Goldin said that several years ago, when he first proposed NASA's "Origins" program to study the origins of life in the cosmos, "we didn't have a nickel in the budget" for it, but funding materialized as his vision got fleshed out.

In response to a question at the press conference, Goldin did show some interest in a concrete proposal by Saul Perlmutter of Lawrence Berkeley National Laboratory to build a telescopic satellite that would vastly expand both the quantity and precision of observations of distant supernovae, which have suggested that space is filled with a strange form of energy that counteracts gravity on large scales (see *Science*, 18 December 1998, p. 2156). The satellite would rely on new charge-coupled device light-sensing technology developed at the DOE lab. "I think it's very exciting," said David Spergel, a Princeton University cosmologist who is familiar with Perlmutter's concept. If NASA and DOE can get in the same flight pattern, particle physics may yet go where it has never gone before. —JAMES GLANZ

SYNTHETIC CHEMISTRY

40 Steps to a Chemical Synthesis Summit

Like mountaineers who set off to scale ever more challenging peaks, organic chemists over the past half-century have tested the limits of their skills by attempting to synthesize increasingly complicated natural molecules, such as antibiotics and steroid hormones. The most fiendishly complex targets have taken synthesis labs a decade or more to conquer. With the completion of each new project, labs scan the horizon for even higher peaks. And in the past 2 years, few mountaintops were more tantalizing than a pair of jellyfish-shaped molecules found in 1997 in a fungus.



Molecular mountains. Two years of chemical finesse went into mimicking these natural molecules.

One enticement was the anticancer and cholesterol-lowering properties of the natural compounds, called CP molecules. The other was their complexity. The molecules' compact structure, crammed with chemical groups, made them "diabolical" targets, says K. C. Nicolaou, an organic chemist at The Scripps Research Institute in La Jolla and the University of California, San Diego. But in the 1 June issue of *Angewandte Chemie*, Nicolaou and his colleagues report having scaled that demonic peak: They have performed the first-ever complete synthesis of the CP molecules.

"It's an extremely impressive accomplishment," says Samuel Danishefsky, whose own group at Columbia University in New York City was closing in on the same goal. Other recently synthesized molecules have been more than four times the size of the CPs, which have 31 carbon atoms each. But Danishefsky says the CP molecules require particular finesse. "The functional groups bump into each other so that it's difficult to work on one portion of the molecule without affecting another part," he says.

The CP molecules originally attracted attention when researchers at the pharmaceutical giant Pfizer showed that they inhibited the work of a cancer-causing gene known as *Ras*, which is overactive in up to 80% of human cancers. CPs, it turns out, block the addition of a chemical group known as a farnesyl group onto the *Ras* gene, a key step in its activation. Other more potent farnesyl blockers have been discovered, says Takushi Kaneko, a medicinal chemist at Pfizer's research center in Groton, Connecticut, who helped nail down the CP molecules' structure. But the new synthesis work could still prove vital, he says, by allowing chemists to manufacture CP analogs that may prove even more potent and also easier to produce than the CPs themselves.

Getting this far was a nearly 2-year slog. In all, it took more than 40 chemical steps and many grams of starting materials to make milligrams of the molecules, which consist of a core ring of nine carbon atoms bearing three more carbon-oxygen rings. And twice the group had progressed to key intermediate compounds along the way, only to find that although they were only a few bonds away from the complete structure, they could not forge the final links.

The final attempt that got them to the summit took three key steps. First, the researchers had to convert a linear hydrocarbon precursor molecule into the nine-membered ring at the core of each CP molecule. They turned to a well-known ring-forming process known as an intramolecular Diels-Alder reaction and tweaked the reaction conditions to coax the precursor to adopt the correct ring-shaped structure.

For the next step, the Scripps researchers developed a set of novel "cascade" reactions. Cascade reactions run through a staccato of intermediate steps—each one automatically producing the right materials and conditions for the next—before ending up at a final product. The researchers used two of their cascade reactions to fuse two additional five-membered carbon and oxygen rings to opposite sides of the core. A final summit push, consisting of a flurry of reactions, provided them with one of the CPs, called CP-263,114, the more stable of the pair.

But they also wanted to make its partner, CP-225,917, which differs only in that one of the three attached rings is broken, the

CREDIT: NICOLAS WINSSINGER

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

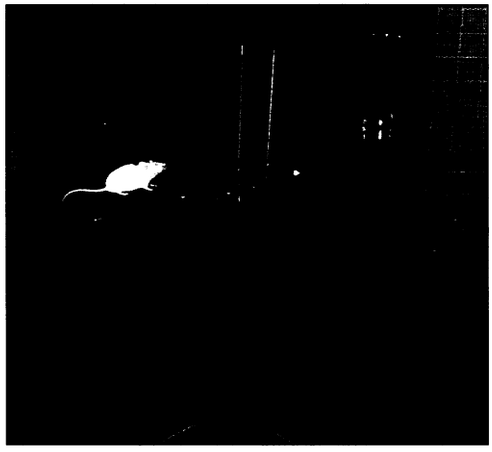
Studying the genetics of behavior is often like riding a roller coaster. A standard way to look for the genetic basis of a behavior—anxiety, say, or aggression—is to knock out a suspect gene in a mouse strain and test the animals in the laboratory. But no sooner has one group of researchers tied a gene 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.

CREDITS: (TOP TO BOTTOM) RICHARD NOWITZ/PHOTOTAKE/PNI; BRUCE DUDEK/ SUNY

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.

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