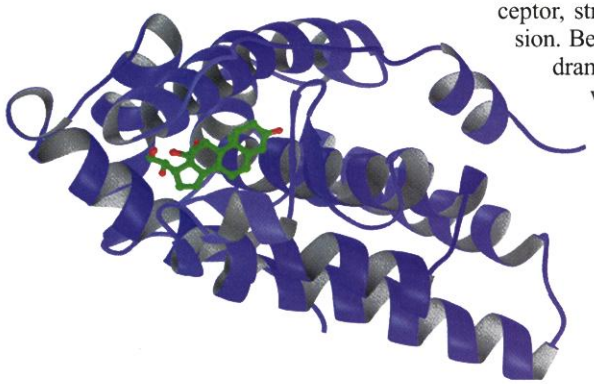
On page 119, the Yale group reports finding a new mutation in the so-called mineralocorticoid receptor, a protein in kidney cells that is involved in the body's handling of salt. The receptor has long been thought to play a role in regulating blood pressure, but this is the first work to demonstrate how alterations in it could give rise to hypertension. In particular, the findings may explain why some women experience a sharp rise in blood pressure during pregnancy. "It's a genuine tour de force," says nephrologist Friedrich Luft of the Max Delbrück Center for Molecular Medicine in Berlin, Germany. "It uncovers new and unexpected mechanisms for hypertension" in humans, he says, that could one day lead to better treatments and new diagnostic tools for the disorder.



Pressure point. Region of mineralocorticoid receptor binding to steroid (green). A mutation in the receptor results in high blood pressure.

Moreover, the work produced a major, unexpected bonus: The researchers discovered a key mechanism that the entire class of steroid hormones—such as estrogen and thyroid hormone—appears to use to trigger the receptors they dock into. That finding could aid the design of drugs for conditions from breast cancer to congestive heart failure. "It's a beautiful example of a clinical investigation taken to a molecular level," says molecular biologist Christopher Glass of the University of California, San Diego, School of Medicine.

That investigation began about 2 years ago, when the Yale team, led by geneticist Richard Lifton, began systematically screening patients with hypertension for variants in a suite of genes they had previously linked to blood pressure abnormalities in humans. As part of that study, Lifton's group analyzed blood from a 15-year-old boy with severe hypertension that had been shipped to them by doctors at Albert Einstein College of Medicine in New York City.

The boy, the Yale team discovered, had a mutation in the mineralocorticoid receptor. When activated by the steroid hormone aldosterone, this receptor normally triggers a cascade of molecular events that cause kidney cells to absorb salt and water for release back into the blood. This can help prevent dehydration on a hot summer day, but it also raises blood pressure.

Lifton, postdoc David Geller, and their colleagues then found that this boy's mutation—a single changed DNA base pair—caused hypertension before age 20 in all the boy's relatives who had inherited it. They went on to discover why: The researchers detected activity from the mutant receptor in cultured cells—which had been engineered to glow when the receptor was activated—even in the absence of aldosterone. It appeared to be permanently stuck in the "on" position.

To their surprise, they also found that progesterone, which gums up the normal receptor, strongly stimulated the mutant version. Because progesterone levels increase dramatically during pregnancy, Lifton wondered whether the hormone would exacerbate blood pressure problems in pregnant women who have this mutation. It seemed to: Worsening hypertension had plagued all five of the pregnancies of two women carrying the mutated receptor.

Although Lifton does not think this particular mutation will turn out to be common, he says the findings suggest that the salt recycling pathway in which the mutant receptor acts could be important in hypertension. They also suggest that hormones like progesterone might in some cases overstimulate the pathway. The Yale team is now working to identify milder mutations in the mineralocorticoid receptor, and in other proteins in the pathway, that might lead to more common forms of hypertension, including some brought on by pregnancy.

To determine why progesterone triggers the mutant receptor, Lifton's group teamed up with Yale structural biologist Paul Sigler to model the mineralocorticoid receptor on a computer, based on the known structure of the progesterone receptor, a close cousin. In the model, they confirmed that aldosterone interacted with its receptor using a precisely positioned hydroxyl group, which progesterone lacks. In its tête-à-tête with the mutant receptor, however, progesterone seemed to work by bringing two of the receptor's protein helices in contact with each other. "That suggested this interaction might be key to progesterone's ability to activate the receptor," Lifton says. His team then proved that's the case by altering the receptor to prevent its helices from touching: Progesterone could no longer activate it.

The Yale group then examined the crystal

CREDITS: (LEFT TO RIGHT) D. GELLER *ET AL.*; NRC

ScienceScope

Research Rescue After years of neglect, the Canadian government is giving the National Research Council (NRC) $75 million worth of attention as part of a $475 million helping hand to the country's beleaguered Atlantic provinces.

The NRC funding will go toward a new NRC Institute of e-Business/Connectivity in New Brunswick; an expansion of offshore oil and aquaculture engineering research at the existing NRC Institute of Marine Dynamics (right) in Newfoundland; and magnetic resonance imaging research at a new brain repair center at Dalhousie University in Halifax, Nova Scotia.

"It's a good start ... and it will, I hope, remove some of the doom and gloom we had earlier in the year," says NRC president Arthur Carty. "If we can make this work, the government should jump at the opportunity to help us do it elsewhere."

The Atlantic development strategy also includes $205 million for universities and research institutes to meet matching requirements under the federal research infrastructure and research chairs programs.

Rays of Hope French physicists may soon have their most fervent wish granted. *Science* has learned that Research Minister Roger-Gérard Schwartzenberg is expected to announce shortly that France will build a new, third-generation synchrotron radiation facility either in the Paris suburbs or in Lille to the north. The facility would replace one that the previous government cancelled more than a year ago when it decided to throw in with the British on a new synchrotron near Oxford (*Science*, 17 March, p. 1899).

Ironically, British officials are expected to be on the dais with Schwartzenberg, who took office in March, to announce their intention to share the cost of the $200 million, 2.5-GeV machine. Spain and Belgium are also interested in becoming partners.

Although Schwartzenberg has been lobbied by regional officials from all over France, a scientist close to the French-British negotiations puts his money on Lille. "It would be a lot easier for [the British] to get to," he says.

In the Slammer Jacques Crozemarie, the former head of the French Association for Cancer Research, was jailed in Toulon on 1 July after losing an appeal of his 4-year sentence for dipping into the charity's coffers (*Science*, 22 October 1999, p. 655). The court said Crozemarie, 74, was a flight risk.

structures of other steroid hormone receptors. They saw interplay of the two protein helices in activated forms of every member of the family, including the estrogen and glucocorticoid receptors, suggesting that this point of contact has broad functional significance. The researchers are now trying to block this interplay in each steroid receptor to see if that does indeed prevent the receptor from being activated. If so, the insight might help researchers design drugs to block aberrant effects of any or all of these hormones. In particular, the mineralocorticoid receptor is considered a hot target for novel congestive heart failure treatments as well as new blood pressure drugs.

And if the work helps pinpoint causes for common forms of high blood pressure, it might eventually lead to earlier identification of people at risk for the disorder, enabling preventive measures to be taken. Genetic insights might also help doctors make more informed choices when prescribing from the "Chinese menu" of blood pressure drugs, Lifton says: "In the long run, we'd like to tailor our medications to the specific underlying abnormality of each patient."

–INGRID WICKELGREN

SPACE SCIENCE

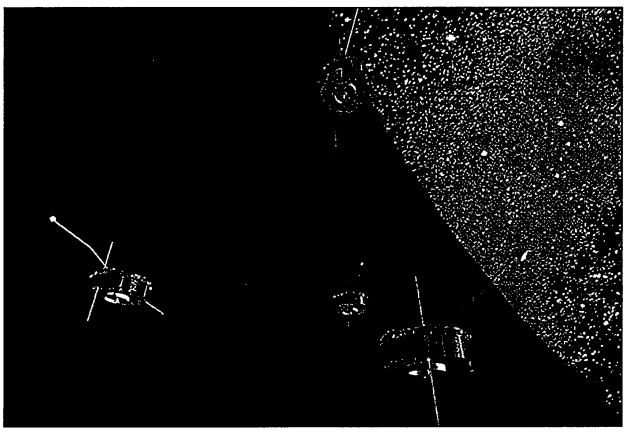
'Cluster' Prepares to Make a New Stand

Scientists who were at the Kourou space center on 4 June 1996 will never forget watching Cluster die. One moment, the mission—four identical satellites carrying 11 instruments designed to produce the first three-dimensional (3D) maps of the magnetic fields and plasmas surrounding Earth—was lofting skyward over French Guyana. Then the rocket carrying it exploded, turning one of the European Space Agency's (ESA's) most ambitious scientific projects into fireworks. "We were in shock," recalls principal investigator Nicole Cornilleau-Wehrlin of the Centre d'Étude des Environnements Terrestre et Planétaires in Vélizy, France (*Science*, 14 June 1996, p. 1579).

Dismayed scientists doubted whether ESA could muster the will, or the funds, to start over (*Science*, 28 June 1996, p. 1866). But Cluster is poised to fly again. If all goes well, four Cluster II spacecraft, built entirely from scratch, will reach orbit two at a time in mid-July and early August.

"I applaud ESA's determination to fly it again," says Cluster co-investigator Patricia Reiff of Rice University in Houston. "This is science that is not being done in any other mission before or in planning."

Credit for squeezing the Cluster II project into ESA's already tight science budget belongs to ESA's science director, Roger Bonnet, says principal investigator Donald Gurnett, a space scientist at the University of Iowa in Iowa City. "Bonnet really did a great job in convincing the European Community that they should be falling in," Gurnett says. John Ellwood, Cluster's project manager at the European Space Research and Technology Centre (ESTEC) in Noordwijk, the Netherlands, agrees. "We didn't have the money initially," he says. "It took us a year to get the mission going again."



Lofty pyramid. Cluster II satellites will orbit in tetrahedral formation to make 3D maps of Earth's magnetosphere.

To come up with 318 million euros needed for Cluster II, ESA siphoned some funds from the operations budget of the first mission, rescheduled other missions, and took advantage of improved technology. Higher capacity memory chips alone saved millions of euros, Ellwood says, by enabling the new satellites to download data to one ground station instead of two. To economize on launch costs, ESA teamed up with STARSEM, a joint venture between Arianespace and the Russian Space Agency, which will launch the quartet of Cluster II satellites on two Soyuz rockets from the Baikonur Space Center in Kazakhstan. Soyuz, the old workhorse of the Soviet Union, is considered the most reliable launcher available, with a success rate of over 98.5% in 1600 launches. At 30 million euros per launch, it is also a bargain. "Two Soyuz cost less than an Ariane 4," says Philippe Escoubet, Cluster's project scientist at ESTEC.

During their planned 2 years of operation, the satellites will fly in a tetrahedral formation—the optimal configuration for 3D imaging. Ground controllers will vary the distances among the satellites in order to observe different parts of the magnetosphere, such as the polar cusps and the magnetotail. "If we have a perfect injection into orbit by Soyuz, some fuel will be left over, and we will be able to extend the project for a third year," Escoubet says. One benefit of the delay is that the mission will be active when the sun reaches maximum activity later this year or next year.

Among scientists, expectations are high. Says principal investigator Hugo Alleyne of the University of Sheffield in the United Kingdom: "In terms of understanding the solar wind, magnetospheric boundaries, and interactions, it will be a quantum jump."

–ALEXANDER HELLEMANS

Alexander Hellemans writes from Naples, Italy.

PLANT SCIENCE

New European Group Lobbies for Support

COPENHAGEN—Reeling from budget cuts and public doubts about genetically modified foods, European plant scientists are mounting an ambitious effort to persuade European Union (E.U.) officials to plow more money into their field. But their blueprint for change, intended to prevent them from falling farther behind their global counterparts, has so far failed to win any promises from E.U. commissioner and science chief Phillippe Busquin.

The plan was drawn up by the fledgling European Plant Science Organization (EPSO), an independent body that represents 30 leading labs from 20 European countries. The group was set up in February, and last month it presented Busquin with the 10-year plan. "There is an acute need to organize the research effort and to increase funding for plant science if Europe wants to stay competitive in this field," says the group's chair, plant geneticist Marc Zabeau of the University of Ghent in Belgium.

EPSO's top priorities include boosting funding for basic plant science and co-

Speaking up. Belgium's Marc Zabeau says European plant science is imperiled by funding cuts.

CREDIT: (TOP) ESA

ordinating research activities on both national and E.U. levels. The fundamental studies would eventually translate into new ways to raise yields and slash pesticide use. "If science is to tackle these challenges, there is a dire need for more integration," says plant geneticist Michael Bevan of the United Kingdom's John Innes Center. Zabeau sees parallel national initiatives in plant genomics in Germany and France as examples of unnecessary competition for scarce resources. At the same time, he acknowledges that collaborative research also faces many obstacles. "We have networks in place, but we need significant funding and an infrastructure that allows us to come together in practice," says Zabeau.

Under Framework 5—the E.U.'s research portfolio for 1999 through 2003—plant science no longer has its own pot of money but must compete with microbial and animal research. One result is a two-thirds reduction in the number of successful proposals (seven in the first round) compared with the previous Framework program. Among the casualties is a plan to complete work on the well-studied mustard, *Arabidopsis thaliana*. After the E.U. put up $20 million toward an international sequencing effort, "all funding was denied for the final phase," says EPSO coordinator Karin Metzlaff.

National funding for plant research has also declined, with Denmark and the Netherlands particularly hard hit. Dutch authorities are in the midst of implementing a 30% cut over 5 years and have ended funding for all collaborative projects. All Danish programs in plant biotechnology will expire by 2002, and no new initiatives are planned.

That alarms industry, which relies upon a strong public-sector commitment to basic research, says Georges Freyssinet, head of global genomics research at Aventis CropScience in Lyons, France. "The next 5 to 10 years will be essential," he says, warning that now is the worst possible time to be reducing government support for plant research. European companies may need to move research operations elsewhere if the political culture surrounding genetically modified foods does not improve, he adds.

E.U. officials have already begun to plan for the sixth Framework Program, which starts in 2004. And although Busquin confesses that the plant science community has his ear, he says that "risk assessment and ethical aspects are important issues that have to be addressed." The research chief also doesn't want to be seen as catering to a particular discipline: It is "impossible at this point to promise more funds for individual fields," he says. **–LONE FRANK**

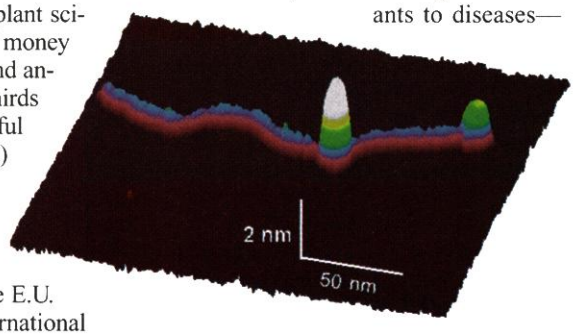
Lone Frank writes from Copenhagen.

CREDITS: (LEFT TO RIGHT) A. T. WOOLLEY AND C. M. LIEBER/HARVARD UNIVERSITY; NASA

DNA IMAGING

Getting a Feel for Genetic Variations

Even before last week's news of the near-completion of the human genome sequence, researchers had set about the arduous task of figuring out just how the sequence differs among individuals—and how those variations may predispose people to various illnesses. Current genetics technologies make it relatively straightforward to determine where such differences lie on a given chromosome, say, chromosome 11. But determining which of the two copies of that chromosome the change resides on—a necessary first step toward linking those variants to diseases—has proved challenging indeed. Now a team of researchers at Harvard University and the Massachusetts Institute of Technology (MIT) has come up with a novel atomic imaging microscope that may dramatically speed this task.



Fingered. A microscope easily spots a specially tagged site along DNA.

The microscope is a modification of the popular atomic force microscope (AFM), which uses an ultrasharp tip to map surfaces of everything from computer chips to DNA at the atomic level. The new version caps a conventional silicon tip with a carbon nanotube, an ultrathin, strawlike network of carbon atoms a mere nanometer or so across. By using this molecule-sized tip, the researchers —led by Harvard chemist Charles Lieber and MIT geneticist David Housman—were able to get their AFM to march down a strand of DNA and identify uniquely shaped reporter molecules engineered to tag the genetic variations. In this case, these variations are sites along a chromosome that harbor a one-letter difference in spelling called a single-nucleotide polymorphism (SNP).

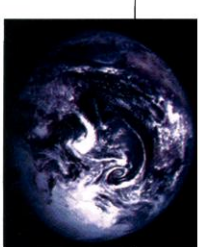
As they describe in the July issue of *Nature Biotechnology*, the Harvard/MIT group—which includes postdoc Adam Woolley, then-postdoc Chantal Guillemette, and grad student Chin Li Cheung—was able to feel its way around one of the most vexing problems in genetics: haplotyping. Haplotyping is the task of figuring out exactly

ScienceScope

Preventive Medicine Top U.S. research universities can do a far better job of protecting human subjects, says a new report by the Association of American Universities (AAU). The report (www.tulane.edu/~aau) urges the AAU's 61 member schools to beef up their Institutional Review Boards, which oversee clinical studies, by seeking outside accreditation and enrolling more nonscientists. AAU President Nils Hasselmo says that such changes could make redundant proposed legislation that would broaden federal oversight of clinical research (*Science*, 16 June, p. 1949). The report also proposes that the government help foot the bill.

Space Squabble Relations between the Administration and Representative James Sensenbrenner (R–WI), who chairs the House Science Committee, are strained on a good day. But his NASA authorization bill has added a new layer of stress.

The bill, H.R. 1654, would kill Triana, a pet project of Vice President Al Gore to beam satellite images of Earth (below). It also orders NASA to get a refund from the Russians for any space station delays and blocks the agency's ability to keep revenue from commercial deals. After the Administration threatened a veto, Sensenbrenner offered a "grand compromise" that would save Triana. But last week, at an inconclusive conference between House and Senate members, Democrats complained that some of Sensenbrenner's demands were not in the original bill approved by the House and that their suggestions were ignored.



Capitol Hill observers say that the way Sensenbrenner handles the squabble could affect his bid to chair the Judiciary Committee in the next session. "If he wants to show that he can be conciliatory, this is not the way to do it," harrumphs one Democratic aide.

Short Leash Energy Secretary Bill Richardson has given new security czar James Gordon until 5 September to work out a new arrangement with the University of California (UC) for its management of the nation's nuclear weapons labs. The UC contract runs until 2002, but Richardson says its performance "is unacceptable and must be addressed immediately." UC officials say they "welcome the opportunity to work with [the Department of Energy]."

Contributors: Wayne Kondro, Michael Balter, Eliot Marshall, Andrew Lawler