found that "there is too much reliance on a limited number of known individuals," and too few women and minorities are tapped early in their careers. Yet only eight of 128 people who responded to a question about expanding participation in NRC studies suggested adding minorities, women, or young researchers to council bodies. Despite some carping, volunteers seem pleased with how the NRC operates. A survey of nearly 1500 people found that 87% would serve again, and 92% were satisfied or very satisfied with the quality of the NRC work.

With regard to staff, Alberts says he will emphasize professional development and improving communication "so that help can be provided before things go wrong." The initial reaction to the proposals by staff seems positive. "People aren't jumping up and down," says one staffer who requested anonymity, "but we're optimistic." Colglazier says the plan will be finalized in November and implemented by the end of the year.

–ANDREW LAWLER

SCIENTIFIC PUBLISHING

Chemists Toy With the Preprint Future

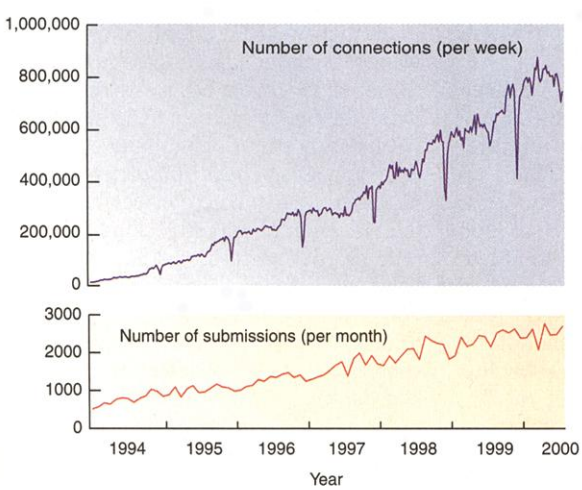
After watching their physics colleagues explore the digital landscape of electronic preprints over the past decade, chemists are sending out a survey party of their own. Last week, the giant publishing house Elsevier Science launched the first electronic archive for chemistry preprints through its ChemWeb subsidiary. The new site (http://preprint.chemweb.com) will be a common repository for reports on a wide range of chemistry topics and a forum for authors and readers to discuss the results. But ChemWeb could face an uphill battle in convincing authors to post their papers on the site, as many of the field's premier journals decline to accept papers that have already been posted on the Web.

ChemWeb's new preprint service is modeled closely on the physics preprint archive started in 1991 by Paul Ginsparg at Los Alamos National Laboratory in New Mexico, which today serves as a storehouse for some 146,000 articles. Although readers of the new chemistry preprints will be able to rank the papers, there will be no formal peer review, says ChemWeb's preprint manager James Weeks. The service is free to both authors and readers. (They need only register with ChemWeb, which is also free.) ChemWeb, says Weeks, hopes that its new service will generate enough Internet traffic to lure advertisers to fund the site.

For now, about all the site is attracting is heated debate. "A preprint server is highly controversial among chemists," said Daryle Busch, president of the American Chemical Society (ACS), speaking at the society's national meeting in Washington, D.C., last week. Busch, a chemist at the University of Kansas, Lawrence, says he and his colleagues are lured by the Web's speed, wide dissemination, and low cost of publishing new scientific results. But many researchers fear that the absence of peer review will reduce the quality of submissions and force readers to wade through electronic mounds of poor-quality results in search of tidbits of worthwhile science. Says Peter Stang, a chemist at the University of Utah, Salt Lake City, "It's a dilemma."

Apparently, it's one that a broad cross section of chemists are struggling with. According to Robert Bovenschulte, head of ACS publications, the association conducted a survey of some 8000 of its members last summer on the question of non–peer-reviewed electronic preprints. The results "are a very mixed bag," Bovenschulte says. "A lot of people were in favor of it. A lot of people were against it."

Nevertheless, the new preprint archive likely faces a tough future, because ACS journal editors themselves are lined up against it. ACS, the world's largest scientific membership organization, with 161,000 members, also publishes many of the premiere journals in the field including the flagship *Journal of the American Chemical Society*. But nearly all ACS journal editors consider posting results on the Web to constitute "prior publication," says Bovenschulte. (*Science* maintains the same policy.) As a result, Boven-



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Physics envy. Elsevier is hoping its chemistry preprint archive will prove as popular as the Los Alamos physics archive, use of which by U.S.-based users is shown above.

ScienceScope

Animal Outrage A prominent biomedical research group wants to derail a possible agreement between the government and an animal rights group that it says would hamper research. The National Association for Biomedical Research (NABR) of Washington, D.C., this week said it will go to court to oppose a U.S. Department of Agriculture (USDA) bid to reach a settlement with groups pushing to have the agency regulate the use of laboratory mice, rats, and birds.

Mice, rats, and birds—which make up 95% of lab animals—are now exempt from the agency's Animal Welfare Act rules, which set caging and care practices. But in July the Alternatives Research & Development Foundation of Eden Prairie, Minnesota, won a key preliminary ruling in its suit to overturn the exemption (*Science*, 21 July, p. 377). On 25 August the two parties asked a federal judge for a 30-day time-out to reach a deal to phase in regulation of the animals.

NABR, however, "is absolutely opposed to these negotiations—it's an unacceptable way to make policy," says executive vice president Barbara Rich. The group, which represents more than 300 universities and hospitals, is worried that the new rules will burden researchers and that USDA doesn't have the budget to enforce them properly. USDA "is pandering to activists who oppose the use of lab animals," says Rich. "It's unbelievable."

Taking the Helm After nearly 6 weeks without a director-general, France's $2.2 billion basic research agency will apparently be led by a researcher with a taste for technology. Geneviève Berger, currently the research ministry's director of technology, was expected this week to be named to replace former CNRS chief Catherine Bréchignac, whose mandate expired in mid-July. A squabble between President Jacques Chirac and Prime Minister Lionel Jospin over whether Bréchignac should stay or go was apparently responsible for the delay (*Science*, 28 July, p. 523).

Berger, 45, has advanced degrees in physical sciences, human biology, and medicine. She is known for her work in applied medical research, especially new techniques for imaging. Such practical accomplishments made her attractive to the French government, which is pushing to make basic research serve the economy. Understanding science's impact on the bottom line is now "an essential qualification for being CNRS head," says one researcher.

schulte says, those ACS journals will not publish papers that appear first on ChemWeb's preprint server. And that, says Ralph Nuzzo, a chemist at the University of Illinois, Urbana-Champaign, would convince him and most of his colleagues not to post their articles on ChemWeb. "If I couldn't publish my paper [in a conventional journal], I probably wouldn't do it," Nuzzo says.

In an effort to find a compromise, Weeks says ChemWeb will remove the full text of papers from the site when they are published in a print journal, keeping an abstract and a link to the journal article. But Bovenschulte says ACS journals would still not consider such papers, because the results would already be public knowledge.

Not all journals are playing hardball. Ginsparg points out that American Physical Society journals, including the prominent *Physical Review Letters*, not only publish articles already posted on the Los Alamos preprint server, but even provide the electronic connections for authors to submit to the journals at the click of a button.

Elsevier's own journals will publish articles that appear first on ChemWeb. Indeed, Elsevier—which is ACS's chief competitor in the chemistry journal publishing business—may be counting on ChemWeb to give its journals an edge among some chemists. Elsevier officials may be hoping that researchers interested in distributing results quickly will then send their articles to Elsevier journals, says Bovenschulte. For Elsevier, he says, "this could be considered a cost of attracting the best authors."

Whatever the motivation, chemistry preprints are long overdue, says R. Stephen Berry, a chemist at the University of Chicago. The culture among chemists—with their history of close ties to industry—is more conservative than that among physicists, says Berry. Still, Berry believes that chemistry preprints have a shot. "We just have to wait and see if it works," he says. "But this is the kind of experiment we should be doing."

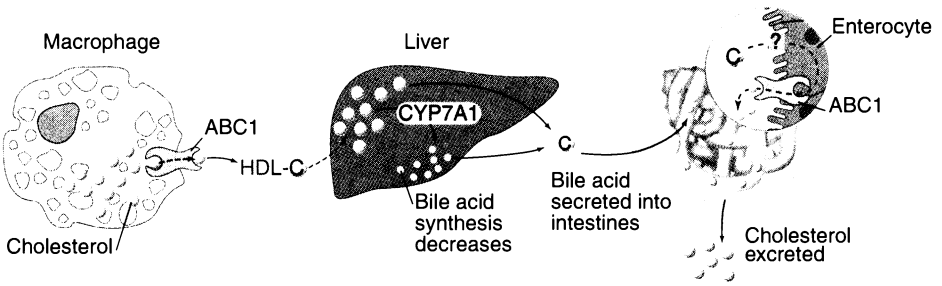
–ROBERT F. SERVICE

LIPID RESEARCH

Possible New Way to Lower Cholesterol

Clinicians may soon be able to mount a multipronged attack against cholesterol, the artery-clogging lipid whose buildup in the body is a major contributor to heart attacks and other cardiovascular diseases. Millions of people take drugs that lower cholesterol levels by blocking the body from making it. But we also consume the lipid in our diet, and today's drugs don't do much to keep our body from taking it in; nor do they take advantage of our body's ways of getting rid of excess cholesterol. New results could change that.

In work reported on page 1524, a team led by molecular pharmacologist David Mangelsdorf of the University of Texas Southwestern Medical Center in Dallas has pinpointed a biological master switch in mice that controls three pathways that work together to both rid the body of excess cholesterol and prevent its absorption from the intestine. "This is a real tour de force," says Steve Kliewer, senior research investigator at Glaxo Wellcome Inc. in Research Triangle Park, North Carolina. "It's exciting because it suggests an entirely new mechanism for reducing cholesterol." This might be done, for example, with drugs that turn up the activity of the master switch, a protein known as the retinoid X receptor (RXR).



Three ways to go. The drug LG268 fosters cholesterol elimination from the body by stimulating ABC1-mediated export of the lipid from macrophages and intestinal cells and also by inhibiting CYP7A1, a key enzyme needed for bile acid formation by liver cells.

The findings are a serendipitous outgrowth of previous test tube experiments by several groups showing that RXR teams up with any of several other proteins to turn on genes involved in cholesterol metabolism. For example, the Texas team found 3 years ago that RXR and a protein called the liver X receptor (LXR) work together to activate genes whose protein products are needed in the liver to break down cholesterol to bile acids, which are then excreted into the gut. This suggested that drugs that boost the activity of LXR might help the body rid itself of cholesterol.

To test this idea, postdoc Joyce Repa turned to a drug called LG268, which is a so-called rexinoid. These drugs bind to, and activate, RXR, which then teams up with its partner proteins, including LXR. Thus, the researchers expected that LG268 would boost LXR activity and stimulate bile acid formation.

To test that expectation in mice, Repa gave the drug to animals fed a high-cholesterol diet, which would ordinarily cause cholesterol accumulation in the liver. Sure enough, LG268 reduced these high liver cholesterol levels. But the researchers got a surprise when they conducted a second test. They redid the experiments on mice that cannot make LXR, expecting to see cholesterol pile up in the liver. Instead, the cholesterol content of the animals' livers plummeted. "We couldn't figure out why that was happening," Mangelsdorf says.

Further tests pointed to the explanation: Rather than speeding cholesterol breakdown to bile acids, LG268 exerts a powerful block on cholesterol absorption from the gut. At first, the researchers had no idea how the drug does this. They tested its effects on about 100 different genes involved in various aspects of lipid metabolism, but the experiments came up empty. Then, about a year ago, a clue appeared.

Other researchers discovered that people with Tangier disease, a rare hereditary condition that causes high blood cholesterol concentrations and severe atherosclerosis, have a defect in a protein called ABC1. They also have very low levels of high-density lipoprotein, which helps rid the body of cholesterol by carrying it back to the liver, the organ where most cholesterol breakdown occurs. "It was just like a light went on," Mangelsdorf recalls. "Bingo! Maybe [ABC1] was sitting in the intestinal cell and pumping [the cholesterol] back out" so that it wasn't absorbed into the blood, and LG268 was assisting in that process.

That's exactly what seems to be happening. The researchers found that LG268 ups production of ABC1 in cells of the intestinal wall, causing the lipid to pass right through the intestine without being absorbed. What's more, the drug turned out to activate cholesterol transport out of immune cells called macrophages. That's important, because cholesterol-laden macrophages help trigger the formation of artery-blocking atherosclerotic plaques. Activating ABC1 might thus help reverse the early steps of plaque formation, Mangelsdorf says.

The Texas group also found that LG268 stimulates ABC1 production by specifically boosting the activity of RXR-LXR pairs, and it has another surprising effect as well. The drug also boosts the activity of RXR paired with a protein called FXR, a partnership that reduces the production of bile acids by the liver. That should also help inhibit cholesterol absorption, because the bile acids dissolve

ILLUSTRATION: C. CAIN