RESEARCH ETHICS

Sweden Considers More Oversight of Research

STOCKHOLM—Swedish scientists may soon see radical changes in the way research proposals are evaluated. Last month, a committee of parliamentarians issued a sheaf of recommendations designed to increase public oversight of research. Their proposals would subject all academic research involving human subjects or tissue to ethical review, turn the peer review of grants on its head by giving applicants anonymity while revealing the identity of reviewers, and require all graduate students to attend courses in research ethics.

The committee was set up 20 months ago in response to several well-publicized cases of research fraud, studies indicating sex bias and nepotism in the awarding of grants in Sweden, and controversy over research such as the cloning of Dolly and experiments on human embryos. The suggested reforms aim to shore up public confidence in science by creating more of a dialogue between researchers and the public. "If we don't handle it right, the general public will lose trust in science," says committee chair Barbro Westerholm, a liberal party parliamentarian. The report is now being sent to research organizations across Sweden for comments, after which the government will decide whether to act on its recommendations.

The most significant proposal would require each university to establish an independent ethics committee—made up of equal numbers of laypeople and scientists—to review research involving humans or human tissue. Psychology and sociology studies, and any work that uses identifiable data from medical or scientific records, would be included. Currently, academic ethics committees review medical research conducted with public grants, but they are not required to look at privately funded studies.

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>
> **—Barbro Westerholm**

Most researchers have welcomed this proposal in principle, but there has been skirmishing over the details. For example, the report suggests that the committees' decisions should be made by consensus, but medical ethicist Birgitta Forsman of Göteborg University argues that "majority decisions are much better for controversial issues." The risk, she says, is that "people would vote to accomplish consensus in order not to appear too difficult instead of expressing their true opinion."

The report suggests that if researchers are not satisfied with a committee's decision, they could seek a second opinion from another independent ethics committee. But a minority of the parliamentarians argued that the ethics committees should be given clearer ground rules and that their decisions should be legally binding. "We already have a number of committees devoted to questions of ethics in human medical research. But what we still haven't seen is the legal regulation as to what principles the committees should work from," says lawyer Elisabeth Rynning of Uppsala University.

To counter scientific misconduct, the report urges the government to set up a central commission to deal with individual cases. It also says researchers should be required to document and file important scientific material for at least 10 years, and they should be obliged to reveal any industrial or financial interests in their research. And—stressing that prevention is better than cure—it suggests that all graduate students be required to take courses in research ethics.

Stellan Welin at the Center for Research Ethics in Göteborg argues that even these measures lack teeth. "It would be better if reporting of scientific misconduct was made obligatory by law," he says. But Forsman counters that obligatory whistle-blowing would create a legal minefield: "Because there is no exact definition of what scientific misconduct consists of, it is extremely difficult to create formal legislation."

As for peer review, the committee took note of recent studies indicating that the allocation of grants in Sweden is biased against women, young researchers, and workers in cross-disciplinary fields. One remedy, the committee says, is to appoint more women to evaluating committees. "Both women and men should be educated in techniques for gender-neutral evaluation," says immunologist Agnes Wold of Göteborg University. But it also has a more radical suggestion: Grant applicants should remain anonymous in the first stage of the review, while the reviewers should be named. And the results of peer review should be made publicly available so that applicants can debate the decisions with reviewers.

This idea is likely to be controversial. "In general, my experience is that the applicant and what they have already accomplished is a better indication that interesting science will result," says astrophysicist Bengt Gustafsson of Uppsala University. "Moreover, opening the reviews to public scrutiny will make them more conventional and polite, which is of no benefit to science."

Concerns like these are likely to get a thorough public airing over the next few months.

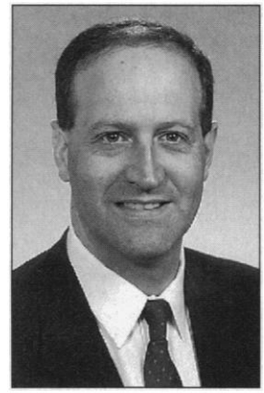
–JOANNA ROSE AND ANNIKA NILSSON

Rose and Nilsson are writers in Stockholm, Sweden.

AIDS VACCINES

Nabel to Head NIH Vaccine Research Center

After searching for more than a year, the National Institutes of Health (NIH) has finally found a scientist to head its nascent Vaccine Research Center (VRC): Gary Nabel, a gene therapy expert at the University of Michigan, Ann Arbor. Donna Shalala, secretary of the U.S. Department of Health and Human Services, announced on 11 March that Nabel has agreed to run the vaguely defined VRC, which will focus initially on searching for an AIDS vaccine.



New territory. Nabel's initial focus will be new AIDS vaccines.

President Clinton announced that NIH would build the new center—which will have a budget of $16.5 million this year—in a landmark speech on 18 May 1997, in which he challenged scientists to develop an AIDS vaccine by 2007. The leading AIDS vaccine advocacy groups have criticized NIH for taking so long to find a suitable scientist to head the venture. But Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases, says difficult jobs take longer to fill. Fauci, who had a say in the final selection, did acknowledge, however, that NIH had offered the job to a few other scientists who turned it down.

NIH originally wanted a candidate who had worked in industry, which Nabel has not. "If we could get an excellent person—scientifically a heavyweight—who had industrial experience, we would have gravitated toward it," allows Fauci. Failing that, he says, "we'd rather have a heavyweight than someone from industry." Nabel emerged as the leading candidate earlier this year (*Science*, 1 January, p. 17), but a deal took several months to close. It was finalized when his wife, Elizabeth, a prominent cardiologist, secured a top job at the National

CREDIT: HOWARD HUGHES MEDICAL INSTITUTE

Heart, Lung, and Blood Institute.

Nabel has worked on gene therapy for AIDS, therapeutic cancer vaccines, and a candidate Ebola vaccine, but he is a relative newcomer to AIDS vaccine work. He says, however, that his experience prepares him well for his new job, and he jokes that his limited AIDS vaccine research "should be an advantage because I'm not invested in old ideas that didn't work."

Nabel's background sits fine with Nobel laureate David Baltimore, head of NIH's AIDS Vaccine Advisory Committee—and Nabel's former postdoctoral adviser. "I have high hopes that Gary will be a great leader," says Baltimore, noting that Nabel is an "excellent manager" who is "widely knowledgeable in immunology and virology, giving him the perfect perspective for taking on this role."

One aim of the VRC—an idea first proposed by NIH immunologist William Paul—is to move fundamental research results more aggressively into clinical trials. But beyond that, its agenda is still largely up in the air. "It depends a lot on how Gary wants to build it," says Fauci. "We decided early on that we're going to put a lot of flexibility in the hands of the director."

A five-story building to house 100 VRC scientists is now going up at NIH's Bethesda, Maryland, campus. "The assumption is that the majority of the people are going to be brought in from the outside," says Fauci. Nabel, who starts his new job next month, plans to keep his Michigan lab running until the building is ready for occupants, by the middle of 2000. **–JON COHEN**

CANCER RESEARCH

A Surprising Partner For Angiostatin

The proteins angiostatin and endostatin have generated a lot of excitement in the past year or two because of reports that they can stop or slow cancer growth in mice, apparently by preventing the birth of new blood vessels needed to nourish growing tumors. But as potential therapies, they have a built-in drawback: Protein drugs can be fragile and hard to produce, as the pharmaceutical company Bristol-Myers Squibb acknowledged last month when it announced that it was giving up work on angiostatin. Efforts to get around those problems by developing small molecules that would mimic the effects of these proteins have been handicapped because little is known about how they act. Now, a research team at Duke University Medical Center seems to have solved part of that puzzle, at least for angiostatin.

The team, led by Salvatore Pizzo, reports in the 16 March issue of the *Proceedings of the National Academy of Sciences* that angiostatin binds to a surprising target on the surface of the endothelial cells responsible for blood vessel growth: an enzyme called adenosine triphosphate (ATP) synthase, never before found on the outer membranes of normal cells. The team can't say if this is angiostatin's only target on the cells, but they have evidence that the binding is necessary for angiostatin's antigrowth effects.

"This paper is important because of all of its implications," says Judah Folkman of Harvard Medical School in Boston, in whose lab angiostatin was discovered. For one, it may provide an explanation for endothelial cells' ability to grow in very low oxygen environments such as tumors. ATP synthase manufactures the energy-rich molecule ATP and thus may be providing endothelial cells with an extra energy source. If angiostatin's binding to the enzyme blocks its activity, that could be the means by which the protein prevents blood vessel growth. What's more, the work suggests that small molecules tailored to block ATP synthase might mimic angiostatin's effects and be useful as anticancer drugs. The paper "is sure to be very provocative," says ATP synthase researcher Gordon Hammes of Duke University.

Energized. Fluorescently labeled antibodies (red) to ATP synthase show the presence of the enzyme on human endothelial cells.

CREDIT: T. L. MOSER *ET AL.*, *PNAS* 96, 2811 (1999)

Tammy Moser, an associate researcher in Pizzo's lab, uncovered the enzyme in a search for endothelial cell proteins that bind angiostatin that she undertook on the assumption that such proteins help angiostatin stop cell growth. From a preparation of endothelial cell membranes, she fished out an angiostatin-binding protein and sent it to Peter Højrup at Odense University in Denmark. Using mass spectrometry, Højrup determined that what Moser had found was actually two proteins, the α and β subunits of ATP synthase. Because that enzyme was thought to be present only in the energy-producing organelles of higher cells, "our reaction was shock," Pizzo recalls.

By probing endothelial cells with antibodies that bind to the α subunit of the ATP synthase, the researchers soon confirmed, however, that it is indeed on the endothelial cell surface. They also found that the antibodies decreased angiostatin binding to the cells by more than 50%. This in turn led to an 80% decrease in angiostatin's ability to inhibit endothelial cell growth, which suggests that angiostatin works at least in part by binding to the ATP synthase. The Pizzo team recently acquired antibodies to the enzyme's β subunit and plans to see whether those block any of the remaining effects.

The ATP synthase could play a key role in the survival of endothelial cells, which live, Folkman notes, "in the lowest oxygen of all cells." Those in the capillary beds that drain tissues are bathed in blood that has been depleted of oxygen by the oxygen-hungry tissues. In tumors, which tend to compress their blood vessels, oxygen levels are even lower, but nevertheless, "you can see tumor vessels coursing through an environment where all the other cells are necrotic" from lack of oxygen, says Duke University tumor biologist Mark Dewhirst.

Normally, oxygen-deprived cells have trouble synthesizing enough ATP to survive. But the ATP synthase in the endothelial cells' outer membranes might produce ATP in a process that doesn't require oxygen. During energy generation in the mitochondria, the enzyme is driven by a gradient of protons across a membrane, produced by the organelle's oxygen-burning metabolism. But in endothelial cells, the gradient could result from the lack of oxygen, which tends to acidify the inside of cells compared to the outside. Endothelial cells could also have a plentiful supply of adenosine diphosphate (ADP) for conversion to ATP, Pizzo notes, because red blood cells release lots of ADP in low-oxygen conditions.

Hammes calls the hypothesis "speculative, but very intriguing." ATP synthase is a large enzyme, made up of many subunits, and the Pizzo team hasn't yet shown whether the whole enzyme is present and functioning in the endothelial cell membrane. The researchers are joining forces with biochemist Richard McCarty, who studies ATP synthase at Johns Hopkins University, to explore that issue. They will also look to see how angiostatin affects the enzyme.

If angiostatin does achieve its effects by inhibiting the enzyme, as Pizzo suspects, drug developers will likely start searching for small molecules that do the same thing. They might work as angiogenesis inhibitors that could be administered by mouth. "If I were a pharmaceutical company," says Folkman, "that's what I would do."

–MARCIA BARINAGA