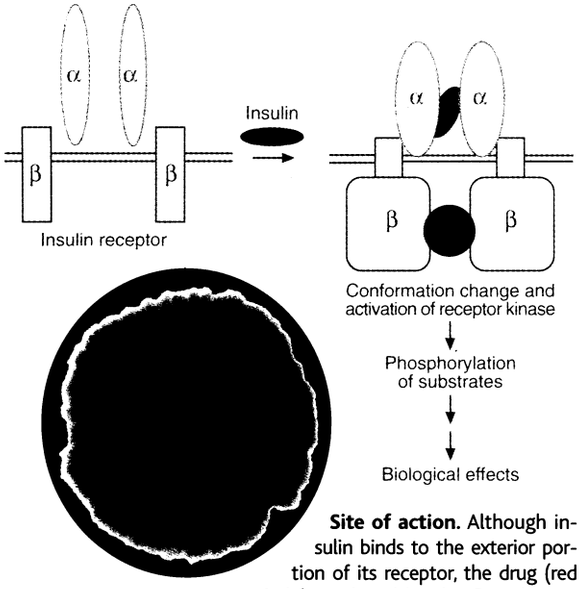
any misdeeds. "I couldn't believe that he could come up with such a story," Goeddel testified. And he denied that he used patented UC material as the basis of Genentech's discovery. Genentech's attorneys also spent a day attacking Seeburg's credibility, pointing out many inconsistencies in his testimony over the years. They reminded the jury that Seeburg—as co-inventor on the UC patent—stands to make a lot of money if UC wins this case.

Only about half the testimony has been presented so far in this trial, and there could be more surprises before the end. Barring an early settlement, this complicated dispute may go to the jury for a decision by the end of the month. **–ELIOT MARSHALL**

DIABETES RESEARCH

New Lead Found to a Possible 'Insulin Pill'

A lowly fungus that grows deep in the African forests near Kinshasa could soon be a pharmacological celebrity. Collected years ago and then analyzed by researchers from Merck Research Laboratories in Madrid, Spain, who hoped to find new drugs in rainforest flora, the fungus, called *Pseudomassaria*, attracted little notice at first. But now another Merck team, led by Bei Zhang and David Moller of the company's Rahway, New Jersey, laboratory, has found that *Pseudomassaria* produces a unique agent that could lead to a new type of antidiabetes pill. Such a treatment would be welcomed by the millions of diabetics who now must inject themselves with insulin or choose from a few orally administered drugs with serious side effects.



Site of action. Although insulin binds to the exterior portion of its receptor, the drug (red circle) produced by the *Pseudomassaria* fungus *(inset)* binds to the inner part.

In work reported on page 974, the team gave the compound, a small, five-ringed molecule of the quinone family, to mutant mice with symptoms similar to those of patients suffering from adult onset or type 2 diabetes. These include high blood sugar, defects in insulin production, and also a decreased ability of the tissues to respond to insulin. The agent reduced these symptoms in the animals, the researchers found, apparently by tweaking the same cellular receptor that insulin acts on. But, unlike insulin, the fungal compound is not a protein and, thus, could likely withstand the body's potent digestive juices. "This is an insulin mimetic molecule which could become a drug that may be able to be given by mouth," says endocrinologist Arthur Rubenstein, a diabetes expert at Mount Sinai Hospital in New York. "The potential is enormous."

To find the new compound, Zhang and Moller took advantage of the known activity of the insulin receptor, which is embedded in the cell membrane. The portion protruding to the exterior spots and attracts insulin molecules, while an inner portion is a kinase enzyme, which responds to insulin's nudging by tacking phosphate groups onto various proteins in the cell. This leads to changes in the activities of those proteins, which in turn allow cells to take up and use the sugar glucose, thereby lowering its blood levels. The insulin-triggered upswing in the receptor's phosphate-adding activity is also useful to researchers hunting for antidiabetes drugs, because they can use it to pinpoint chemicals that mimic insulin's effects.

For their drug-fishing expedition, the Merck team used hamster ovary cells engineered to produce the human insulin receptor. Then, following a strategy frequently used to search for new drugs, the researchers set up a screening assay in which they divided the cells among thousands of miniature petri dishes. After trying some 50,000 mixes of synthetic chemicals and natural extracts on these cells, the investigators scored a major hit with an extract prepared from *Pseudomassaria* culture broth. Zhang and Moller then sent the extract to Merck chemist Gino Salituro, who set about purifying the active agent, a daunting task, as the fungal extract contained hundreds of compounds.

When Salituro finally pulled out the active ingredient, chemical analysis showed that it is a quinone. That was a surprise, Moller says, because none of the other antidiabetes drugs currently in use or under investigation belongs to that class of compounds. "From looking at its chemical structure, it does not have any obvious biological activity," he says. Yet in tests on cultured cells, the *Pseudomassaria* product, known as L-783,281, stimulated the phosphorylating activity of the insulin receptor by up to 100 times more than other natural compounds tested.

And its effects appear to be specific. L-783,281 does not spur the activity of receptors with similar protein-phosphorylating ability, including the receptors for epidermal growth factor, platelet-derived growth factor, and insulin-like growth factor. L-783,281 apparently diffuses through the cell membrane and binds directly to the kinase portion of the insulin receptor, activating it.

Achieving such specificity has always been "an elusive goal," says Zhang. Other antidiabetes drugs work in various ways, such as increasing insulin production by the pancreas or binding to the outer portion of the insulin receptor, but they may have other effects as well. This can lead to serious side effects such as excessively low blood sugar or blood pH, gastrointestinal problems, or in the case of the recently controversial antidiabetic agent Rezulin, liver failure.

Preliminary animal tests with L-783,281 also look promising. The Merck team tested the compound in two mutant mouse strains that have classic diabetes symptoms. In both strains it suppressed the skyrocketing blood sugar levels by up to 50%—comparable to the reduction seen with current oral antidiabetic therapies, Moller says. The compound also reduced the elevated insulin levels seen in one strain, presumably because blood sugar levels dropped, causing the pancreas to lower its insulin production.

If further animal trials confirm that L-783,281 or chemical variants resembling it are both effective in lowering blood sugar concentrations and safe, Merck says clinical trials might be feasible. People have been talking about making an insulin-replacement pill for a long time, Zhang says, and "now we have shown it's possible." **–TRISHA GURA**

Trisha Gura is a science writer in Cleveland, Ohio.

SWEDEN

Academics Applaud Renewed Support

STOCKHOLM—Think of Thomas Östros as the calm after the storm. Following years of turmoil and distrust between scientists and policy-makers, Sweden's youthful minister of education and science has spent his 7 months in office reassuring academic scientists that the government values their contribution and has no intention of letting outsiders call the shots. And that empathy, combined with the promise

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of a small spending boost, appears to be carrying the day. "It feels like we have come in from the cold," says molecular biologist Britt-Marie Sjöberg of Stockholm University.

An affable 34-year-old Social Democrat with graduate training in economics, Östros has been busy since last fall's election trying to formulate how the state, which funds less than one-third of all research done in the country, should interact with other sectors. The government's relationship with basic scientists has been especially touchy, as the amount of money going to universities and the basic research councils has decreased, despite an overall rise in R&D spending. Last fall, a committee of parliamentarians added new tensions with a report, called Research 2000. It called for a welcome increase in basic research but suggested scrapping the current system of funding research through a multitude of research councils and mission agencies. It also argued that politicians should control the management of independent foundations that focus on applied research (*Science*, 20 November 1998, p. 1401).

Warming trend. Science minister Thomas Östros sees "good climate" between scientists and government.

Last month, as part of his first official response to Research 2000, Östros announced that the government intends to boost the current $1 billion basic research budget by $8.4 million next year and by a total of $93 million by 2002. And in a 45-minute interview with *Science*, Östros made it clear that he is sympathetic to scientists' concerns over Research 2000. "Only researchers can guarantee the scientific quality of their work," he said. "We know that the free search for knowledge is important in the long term." Earlier this spring, in another conciliatory move, the government reestablished a scientific advisory group and appointed immunologist Hans Wigzell, head of the Karolinska Institute, as its science adviser.

"I feel that there is a good climate and an emerging dialogue [between scientists and the government]," Östros told *Science*. "It is not a goal in and of itself, but it's not good to live with conflicts for too long." The research community seems to agree. Zoologist Dan-E Nilsson of Lund University, the driving force behind a lobby group to support basic research called the "professors' council," says Östros's efforts to reach out to the community have eliminated the need for the informal council.

Not everyone is pleased with the increased emphasis on basic research, however. "A small country like Sweden cannot afford putting its money on basic research and hope to reap economic benefits of a breakthrough every 30 years," says Kurt Östlund, executive director of the Royal Academy of Engineering, adding that most economic growth has come from applied science. But Östros doesn't buy that argument. "If you look at research mostly as a way to support current economic activities," he says, "there is a risk that you only end up conserving those parts of industrial life that are doing well at the moment."

Östros declined during the interview to discuss how the mechanism for funding research should be reorganized, saying only that a working group will investigate different options and that the current discussion would feed into a new policy to be issued next year. But he seems to have accepted the criticism of Research 2000's plan to replace the current multitude of state funders of research with four discipline-oriented research councils, which would fund both basic and applied research. "I am in sympathy with the thought of joining mission-oriented and basic research," he said. "At the same time, there are strong opinions and worries, even within the government. I don't expect radical changes, but I do hope to simplify the system."

He also made it clear that he opposes the plan's suggestion to scrap the university's obligation to maintain strong links to society at large in addition to its duties of research and education. And he signaled his agreement with those who felt Research 2000 failed to acknowledge the importance of multidisciplinary research, pointing in particular to the need for greater understanding of environmental problems and for work "at the interface of people and technology."

Östros hopes to close the book on a largely political debate over management of the independent foundations that focus on applied research, saying he believes that scientists as well as policy-makers should be represented on their advisory boards. "It is important to bring the fight to an end," he says.

Although he doesn't promise to resolve the chronic problems of inadequate funding and squabbling over the share of grant money spent on overhead, Östros says he's looking forward to the give-and-take. "I like the dialogue with the research community, which is where I have my own roots," he says. "I think it's a fascinating world."

–ANNIKA NILSSON AND JOANNA ROSE

Nilsson and Rose are science writers in Stockholm, Sweden.

ScienceScope

Educational Payoff For years, the National Science Foundation (NSF) has been pushing research-intensive universities to place more emphasis on teaching in a drive to raise scientific literacy. Now, NSF director Rita Colwell wants to back this philosophy with some cold cash, by boosting the salaries of faculty members who are superstars in the classroom as well as in the lab. "The idea is to significantly reward those who teach intro courses as well as those recognized as exemplary teachers," says Colwell, who has broached the subject with professional societies and, last week, with Congress at a hearing on improving precollege science and math instruction.

Several schools already fatten faculty paychecks to reward teaching prowess. But Colwell says a similar NSF program could have a bigger payoff: By improving the quality of instruction given to nonscience undergrads, some of whom go on to become tomorrow's policy-makers, it could build public support for science. She's hoping to put something together later this year.

Land No! A new report from marine researchers has some practical advice for ship captains seeking to prevent exotic stowaways hidden in ballast tanks from invading U.S. waters: Flush those critters into the briny deep. The study, mandated by Congress and prepared by a government-appointed task force, tackles a growing ecological threat: introduced species that displace native organisms. In the United States, for instance, experts believe the Asian zebra mussel (above) slipped into the Great Lakes decades ago in ballast tanks. It has since caused billions of dollars in damage by clogging pipes, disrupting fisheries, and driving out native shellfish.

To prevent similar invasions, U.S. officials now ask captains to exchange their ballast waters in midocean, where they are unlikely to pick up organisms that can survive in harbor waters. But in case they don't, the report concludes that ships can safely flush their ballast tanks almost anywhere more than 200 kilometers offshore. Now it's up to captains to follow the advice.

Contributors: Jon Cohen, Jeffrey Mervis, David Malakoff