informed consent should focus on the process and substance of informing volunteers rather than on obtaining a signed document, and it suggests that some procedures should be exempt from routine consent requirements if the risks are truly "minimal."

The new report also could be the panel's swan song. Meslin says the commission has received no word on whether its charter, which expires in October, will be extended. Even if the NBAC report is ignored, however, the idea of a new oversight body has been embraced by the biomedical community. On 23 May a consortium of six university and research groups—including FASEB—announced the formation of the Association for the Accreditation of Human Research Protection Programs. The association will operate a voluntary national accreditation program to monitor clinical research carried out with either public or private funding.

–ELIOT MARSHALL

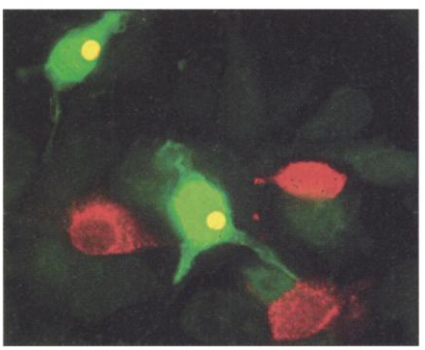
With reporting by Gretchen Vogel.

CELL BIOLOGY

Protein Clumps Hijack Cell's Clearance System

Although Parkinson's, Huntington's, amyotrophic lateral sclerosis, and other neurodegenerative diseases cause very different behavioral symptoms, inside the neuron they look a lot alike. All are marked by big intracellular clumps of protein that scar neurons targeted by the disease. But researchers haven't known whether these protein clumps cause neurological damage themselves or are mere byproducts of some other system gone awry.

Now a study on page 1552 suggests that protein aggregates can directly damage cells by hijacking a cellular quality control mechanism, the ubiquitin-proteasome system (UPS). Normally, the UPS seeks out and destroys misshapen proteins inside the cell—including those that tangle up into clumps in neurodegenerative disease. But in cells artificially induced to churn out clump-prone proteins, the system stalls. Protein tangles thus apparently "initiate a vicious cycle," says Susan Lindquist of the University of Chicago. "The study suggests very nicely that there is an interplay between the two: As proteins start to accumulate, they put stress on the UPS. This in turn causes more proteins to accumulate, which in turn puts more stress on the UPS."



CREDIT: N. F. BENCE *ET AL.*

Overwhelmed. Cells with clumps of proteins (yellow) can't clear an aberrant protein marker (green).

A stressed-out UPS spells trouble for the cell. As many as 80% of the proteins a cell produces don't fold correctly, points out Alfred Goldberg of Harvard Medical School in Boston; the UPS destroys them before they cause damage. Ubiquitin tags abnormal proteins for destruction, and the proteasomes chew up those ubiquitinated proteins. If proteasomes are stifled by inhibitors, even healthy cells accumulate abnormal proteins in thickets similar to those seen in neurodegenerative diseases. These cells can't reproduce, and they're likely to die.

Earlier research uncovered suggestive links between the UPS and neurodegenerative diseases. Mutations in UPS-related genes can cause early-onset forms of Parkinson's disease, for instance. And protein clumps inside diseased neurons are studded with both ubiquitin and proteasomes.

To test directly whether protein clumps can hobble the UPS, Ron Kopito and colleagues at Stanford University developed an easy-to-read tracer, composed of a fluorescent protein attached to a protein fragment that sends an "eat me" signal to the UPS. If the clearance system is working efficiently, it destroys the tracer and the cell's fluorescence quickly dims.

The researchers engineered cells to produce one of two proteins—one involved in cystic fibrosis and the other in Huntington's disease—both of which tend to aggregate. In cells with clumps of these proteins, the researchers found, the fluorescent tracer glowed robustly, indicating that the UPS was powerless to break it down.

Although they're not sure how tangled proteins shut down the UPS, one possibility is that "the proteasome is, as we put it, frustrated," says Kopito. Abnormal proteins are sucked into the proteasome through a small opening, like someone slurping a strand of spaghetti. If the protein is tangled into a clump, the proteasome can't pull it in. But, because the proteasome is a "possessive enzyme" that holds onto its prey, it also can't let go. "The proteasome is basically out of commission," says Kopito, which prevents it from chasing down new, badly built proteins, and the problem escalates. Either player in the drama—an excess of misfolded proteins or a glitch in the UPS—could trigger the cycle, Kopito says.

A malfunctioning UPS could be partly at

ScienceScope

Germany's Space Future For the first time in nearly 2 decades, Germany has an official space policy. The plan, approved by the cabinet last week, commits $3.8 billion to space R&D over the next 4 years. But some researchers worry that homegrown science will be squeezed to accommodate international projects.

The new policy will give Germany "the necessary planning security" to fund both national projects and long-term partnerships with the European Space Agency (ESA) and other nations, says Walter Kröll, chair of Germany's aerospace research center in Cologne. But critics note that the lion's share of the funds will go to ESA projects and the international space station, leaving just $150 million a year for domestic programs.

Astrophysicist Wolfgang Hillebrandt, a director of the Max Planck Institute for Astrophysics in Garching, says that greater levels of support are needed so that German researchers "can participate in the science that is part of the ESA missions."

Reducing the Mortgage The National Cancer Institute (NCI) is moving to rein in the explosive recent growth of its $1.7 billion grants portfolio. NCI chief Richard Klausner told an advisory board this week that the number and size of NCI's extramural grants has been growing faster than the agency's budget, prompting at least two new rules. One limits researchers applying for renewals of 3- or 4-year grants to no more than a 20% increase (and he predicts most will get substantially less). The other will require the growing number of scientists seeking especially large grants—$500,000 or more—to enter a separate competition for a specified pool of funds.

Klausner says the changes will help NCI, the largest member of the National Institutes of Health (NIH), make a smooth transition to the slower budget growth expected when Congress completes an NIH budget-doubling push in 2004. He noted that NCI's spending on grants grew 17% last year, compared to a 13.5% overall budget increase—growth that "cannot be sustained with anticipated funding," he says. "Eventually, the numbers come back to bite you."

Contributors: David Malakoff, Robert Koenig

fault in other neurological diseases as well. Alzheimer's disease is defined in part by protein tangles inside the cell similar to those modeled in the current study. But other protein clumps, amyloid plaques outside neurons, have received more attention lately (see following story). Kopito says it's possible an overloaded UPS or similar mechanism could allow plaques to form. He also suspects UPS overload in bovine spongiform encephalopathy, or "mad cow disease," and its human cousin, Creutzfeldt-Jakob disease, which are both characterized by clumps of abnormal protein fragments. If so, says Kopito, "this could be an explanation" for how these mysterious diseases kill neurons.

–LAURA HELMUTH

NEUROBIOLOGY

New Clue to the Cause of Alzheimer's

Alzheimer's disease sneaks up on its victims, robbing them first of short-term memory and then ultimately of all ability to think and reason. Like several other neurological diseases, Alzheimer's seems to be caused by abnormal protein deposits accumulating in the brain (see previous story). In Alzheimer's, the prime suspect is a small protein called amyloid beta (Aβ), which is a major component of the pathological plaques that stud the patients' brains. But what causes that protein to accumulate?

Alzheimer's suspect. The red staining shows the distribution of neprilysin in the normal mouse brain.

Most Alzheimer's researchers have focused on the enzymes that free Aβ from its precursor protein (*Science*, 29 September 2000, p. 2296). By releasing too much Aβ, overactive enzymes could lead to abnormal Aβ deposition in the brain. Recently, however, researchers have been approaching the problem from a different direction: looking for enzymes that degrade the peptide. If the enzymes are underactive, the result could also be Aβ buildup. "It's just as important to find the [Aβ] degradation pathway as the synthesis pathway," says Rudolph Tanzi, an Alzheimer's researcher at Massachusetts General Hospital in Boston.

On page 1550, a team led by Takaomi Saido of the RIKEN Brain Science Institute in Saitama, Japan, now provides direct evidence in mice that a protease called neprilysin could be a natural Aβ-degrading enzyme. "It might play an important role in clearing Aβ in the brain," says Alzheimer's researcher Sangram Sisodia of the University of Chicago Pritzker School of Medicine. But he and others caution that more work will be needed to confirm that neprilysin does indeed break down Aβ. Neprilysin is not the only candidate for that job, however.

Last year, Dennis Selkoe's team at Harvard Medical School in Boston showed that a neuronal protein called insulin-degrading enzyme can break down the peptide in lab cultures. If a deficiency of either—or both—of these enzymes turns out to contribute to Alzheimer's, the enzymes could provide new targets for drugs to prevent or treat the disease, which afflicts 4 million people in the United States alone.

Saido's team identified neprilysin as a possible Aβ-degrading enzyme about a year ago. In that work, the team injected mouse brains with Aβ and also with a series of specific protease inhibitors to see which would reduce the breakdown of the peptide. This led the researchers to neprilysin and three related protein-destroying enzymes. Because neprilysin had the greatest activity against Aβ in test tube studies, the scientists collaborated with Craig Gerard's team at Harvard Medical School, which had knocked out the neprilysin gene in mice, to see how that affected the animals' ability to degrade the peptide.

When injected into the brains of normal animals, Aβ is broken down within about 30 minutes. But in the knockout mice, the researchers found, almost all of the peptide persisted. By crossing knockout mice with normal animals, the team produced mice that have just one active copy of the neprilysin gene. These animals yielded intermediate results: More of the injected Aβ persisted than in normal animals, but less than in the complete knockouts. That's important, Saido says, because it "indicates that even partial reduction of neprilysin activity, which could be caused by aging, will elevate Aβ and thus cause Alzheimer's."

The Saido team also found that natural Aβ levels in the knockout mice were highest in brain regions, such as the hippocampus and cortex, where Alzheimer's plaques are most prominent. This and recent findings from Patrick McGeer and his colleagues at the University of British Columbia in Vancouver are consistent with the possibility that neprilysin deficiency could contribute to Alzheimer's, says Saido. When McGeer's group analyzed neprilysin levels in the brains of patients who had died of the disease, they found the lowest levels in the high-plaque regions. "If you have adequate amounts of neprilysin, you never accumulate Aβ," McGeer concludes.

Despite the biochemical evidence suggesting that neprilysin deficiency could lead to Alzheimer's, to clinch the case researchers are waiting for two additional findings. One would be the demonstration that neprilysin deficiency increases plaque formation in an Alzheimer's mouse model—an experiment that Saido describes as the "top priority." The other is genetic evidence linking the neprilysin gene to human Alzheimer's.

Tanzi's group at Harvard has found hints of such a genetic linkage between human Alzheimer's and the region on chromosome 3 where the neprilysin gene is located. It was just short of statistical significance, however, and he hasn't published the work. But a neprilysin deficiency could be caused by a defect in the machinery needed for expressing the gene, as well as in the gene itself, Saido speculates.

Meanwhile, Selkoe and his colleagues are following up on the insulin-degrading enzyme. Among other experiments, they are knocking out the gene in mice to see whether that alters Aβ handling in the brain. If at least one of these enzymes proves to be a bona fide Aβ-degrading enzyme in the brain, Alzheimer's researchers will have an important new line of investigation to pursue in their efforts to tame this devastating disease.

–JEAN MARX

SOLID STATE PHYSICS

Rubbery Liquid Crystal Gives Lasers a Stretch

You won't find it in gumball machines, but Heino Finkelmann's stretchable laser may be the cutest example of elasticity since Silly Putty. Finkelmann, a physical chemist at the University of Freiburg, Germany, created a new type of artificial rubber with the light-altering properties of a liquid crystal display. Then, colleagues at Kent State University in Kent, Ohio, showed that it could be used as a new type of laser—one that emits light without mirrors or a cavity and that changes its wavelength when pulled like taffy.

Behind the fun lies serious physics. Finkelmann's rubber is a photonic bandgap material, one that can block light in a controlled way. Such materials are important as tiny light guides in the world of optical communications, but they are expensive and tricky to en-

CREDIT: S. FUKAMI, K. WATANABE, N. IWATA, AND T. C. SAIDO