BIOETHICS

U.S. Questions Harvard Research in China

BOSTON—Government investigators last week took Harvard University and two other U.S. institutions to task for their handling of research studies involving rural Chinese subjects. University officials insist they have already tightened their procedures, but the U.S. Department of Health and Human Services has asked for more information on whether researchers failed to obtain informed consent in advance, backdated documents, and misled investigators about the number of people involved in the studies.

Group activity. China's Anhui Province was the site for several studies under question.

The department's Office for Human Research Protections (OHRP) began its inquiry in 1999 after a Harvard School of Public Health researcher filed a complaint alleging that two occupational epidemiologists at the school, Xiping Xu and David Christiani, had taken advantage of Chinese subjects in rural Anhui Province, where they conducted a variety of genetic and environmental studies. The department's first public comment about its continuing probe appeared in the form of letters to Harvard, Brigham and Women's Hospital, and Massachusetts Mental Health Center, dated 28 March, that outline the government's concerns and ask for more information.

The letter to Harvard does not draw any conclusions but questions whether some subjects were enrolled in investigations before they signed informed consent documents. It also notes that "the handwriting for the dates next to the subject's signatures appear to be identical," indicating that either the subjects—even those who could write—did not do the dating or that the documents may have been backdated. The letter also cites a large discrepancy between a report to OHRP and a journal article on the number of women enrolled in one particular study. Harvard has until 10 May to respond.

OHRP notes that the institutions have made strides in correcting the apparent problems, and Xu says the investigation has "improved our protection of human subjects in China." A Harvard statement points to the "complex and difficult ... ethical and cross-cultural issues" in international research, adding that the university has beefed up its monitoring staff. It has also formally reprimanded Xu and Christiani and placed their work under greater scrutiny.

But others say the problems with the research involve more than lax record-keeping. "This is a blatant and massive institutional violation of the human rights of subjects," says Vera Hassner Sharav, director of the New York City–based Alliance of Human Research Protection, a private activist group that has followed the issue closely.

Harvard officials insist that OHRP has accepted its action plan and that the matter is largely laid to rest. But OHRP officials say the case remains open. Former Harvard researcher Gwendolyn Zahner, who brought the original complaint, says she is happy that OHRP has examined her allegations but chides it for not looking "beyond [the] paperwork." Investigators need to visit China, she says, to find out what really happened. **–ANDREW LAWLER**

PROTEIN STRUCTURE

Harmless Proteins Twist Into Troublemakers

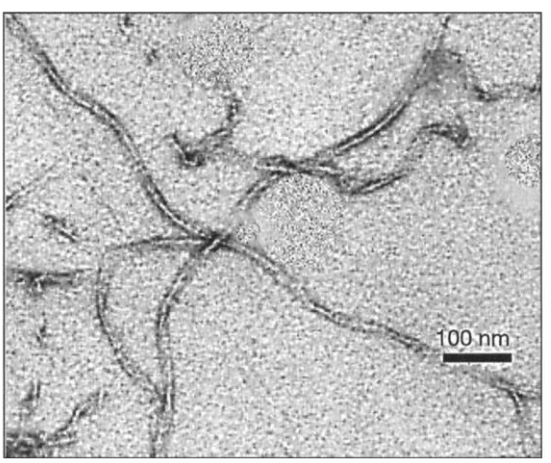
A select group of proteins are known contortionists; they bend and fold and stick together, contributing to neurodegenerative diseases such as Alzheimer's. Now researchers report the startling news that all sorts of proteins can perform the same devilish tricks in the lab. Furthermore, initial tests reveal that at least two of these normally benign proteins are toxic to cells when misfolded. The findings, discussed at a colloquium* in Washington, D.C., in late March and reported this week in *Nature*, hint that a certain type of misfolding may be common to all proteins, prompting theories that cells have evolved techniques to guard against such behavior. Scientists caution, however, that the work has been limited to test tubes and that the proteins were exposed to extreme conditions.

About 20 proteins share the ability to misfold and clump together to form distinctive "amyloid fibrils" found in Alzheimer's, Creutzfeldt-Jakob disease, and a variety of lesser-known disorders. The most famous of these proteins is β amyloid, which has been implicated in Alzheimer's.

Chris Dobson, a chemist and structural biologist at the University of Cambridge, U.K., suspected that a much broader range of proteins could form amyloid fibrils in test tubes. But the thesis sounded so implausible that Fabrizio Chiti, then a graduate student at Oxford and now at Cambridge, recalls trying to flee the project. Chiti quickly switched from skeptic to believer as protein after protein proved capable of forming fibrils when heated or immersed in a solution containing acid or a form of alcohol. Thus far, Dobson and a team at the University of Florence in Italy, led by biochemist Massimo Stefani, have experimented with roughly a dozen proteins with a variety of structures and functions. "We haven't yet got a protein we haven't been able to convert into fibrils," says Dobson.

The proteins the team tested are easily found in humans, plants, or yeast. Even the common oxygen transport protein myoglobin underwent a complete structural overhaul and adopted a fibrillar form. The amyloidlike fibrils the team induced had parallel structures and similar binding properties to those malformed proteins found in diseased brains. The research suggests that even in healthy organisms, "forming misfolded aggregates is an essential part of what proteins do," says Martin Karplus, a chemist at Harvard University and Louis Pasteur University in Strasbourg, France.

The lab-induced transformations may be as deadly as the misfolding of disease-related proteins. The researchers tested the effects of two of their manipulated proteins on mouse and rat cells. Products from an early stage of fibril formation were far more toxic to cells than the final, fibrillar form—just as some researchers suspect is the case



Tangled web. A normally harmless protein forms toxic amyloid fibrils when exposed to acid.

CREDITS: (TOP TO BOTTOM) CHARLES HUTZLER/AP; M. BUCCIANTINI *ET AL.*, *NATURE* 416, 507 (2002)

* "Self-Perpetuating Structural States in Biology, Disease and Genetics," sponsored by the National Academy of Sciences, 22–24 March.

for early stages of protein misfolding in Alzheimer's disease.

What this all means is yet to be determined. In people, as opposed to the test tube, "this doesn't happen to every protein," says Jeffery Kelly, a chemist at the Scripps Research Institute in La Jolla, California. No one knows what qualities, if any, are unique to the 20 proteins known to form amyloid fibrils in humans, or whether most proteins have evolved properties to prevent certain kinds of misfolding.

A small but growing cohort of scientists suspects that if this style of misfolding is a generic property of proteins, it's likely to play a still-hidden but useful role in normal biology. "My view is that there are some cases where these kinds of transitions are beneficial," says Susan Lindquist, a molecular biologist and director of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. Her work suggests that this applies to yeast, sometimes moderating gene expression in helpful ways; other researchers are examining whether this is also true in other organisms, including humans.

–JENNIFER COUZIN

Early bird? Blue tits use information from past years to synchronize their nesting with peak insect abundance.

CREDIT: DAVE WATTS

ANIMAL BEHAVIOR

Last Year's Food Guides This Year's Brood

Timing is everything for some breeding birds. They must hatch their young in time to exploit a brief springtime abundance of food. Seasonal cues such as day length help birds calibrate their breeding. But now a study on page 136 shows that some birds adjust their efforts according to lessons they learned the previous year. The finding implies that such birds might be able to accommodate some environmental changes spurred by global warming, but scientists caution that such adjustments may be limited.

As oak trees leaf out in European woodlands each spring, caterpillars hatch and devour fresh young foliage before the trees pump too many noxious tannins into the leaves. The 2-week burst of caterpillars provides blue tits, small birds akin to chickadees, the food they need to satisfy a nest full of clamoring little mouths.

Birds likely use a host of cues to sense that spring is in the air, such as temperature, young leaves, or hatching caterpillars. But some researchers have suggested that birds breeding too late or too early one year might learn from their mistake and adjust their timing the next. Indeed, a few studies have suggested that past experience can guide other reproductive decisions. For example, collared flycatchers adjust their clutch size, and great tits decide whether to stick with the same mate, based on past breeding success. Now, Fabrizio Grieco, Arie J. van Noordwijk, and Marcel E. Visser of the Center for Terrestrial Ecology in Heteren, the Netherlands, provide the first experimental evidence that experience can influence reproductive timing.

The group monitored pairs of blue tits as they bred in nest boxes for two consecutive years. In the first year, the team supplied half the pairs with caterpillars and mealworms as they tended their broods. The researchers took advantage of the birds' tendency to nest later than the natural caterpillar peak during their first year of breeding, due to inexperience, unfamiliarity with their territories, and the challenges of finding a mate. Thus, most unfed control birds bred late in the first year, then advanced their breeding to match the caterpillar peak in the second. But the pairs given food did not move up their breeding time in the second year. In fact, they delayed it, apparently because the first year's supplemental feeding led them to expect that food abundance would peak later.

The results show that timing reproduction "is more complex than we previously thought," says ornithologist Ruedi Nager of the University of Glasgow, U.K. Although past experience may be only one among many cues, others say, it is probably important for a species that returns to the same territory year after year and would benefit from learning the idiosyncrasies of its real estate.

But in another way, the blue tit seems to be an unlikely candidate for long-term

ScienceScope

Interim Quartet Health and Human Services Secretary Tommy Thompson last week appointed a four-member team heavy on bioterrorism expertise to temporarily lead the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta. The quartet succeeds Jeffrey Koplan, who will become a vice president at Atlanta's Emory University (*Science*, 1 March, p. 1624).

CDC deputy director David Fleming leads the new crew, with James Hughes and Julie Gerberding, the director and acting deputy director of CDC's National Center for Infectious Diseases, fronting bioterrorism efforts. The fourth member is bioterrorism guru Michael Osterholm of the University of Minnesota, Twin Cities, who will be Thompson's "representative" to CDC until a new chief is found.

Agency watchers say Osterholm's slot is designed to give Thompson greater control over CDC, which was criticized for its handling of the anthrax crisis. Margaret Hamburg, a bioterrorism expert at the Nuclear Threat Initiative in Washington, D.C., says the pick "reflects Thompson's desire to have someone he knows and trusts on the team."

Pick Six The National Science Foundation (NSF) has chosen six new Science and Technology Centers (STCs) for its long-running and once-controversial experiment in large, collaborative research. The new centers—which will be formally unveiled this summer—could receive up to $40 million each over 10 years to explore everything from space weather to new cancer-detection technologies.

Then–NSF director Erich Bloch started the STC program in 1987 as an attempt to move the agency beyond its traditional emphasis on small grants to single investigators. Many scientists feared that the centers would focus on applied science and drain support for basic research, but outside reviewers have since endorsed the concept.

The six new centers, chosen from 143 applications, will join five existing centers created in 2000 (23 others have finished their runs). Another competition is scheduled to begin later this year. All the new centers have multiple partners—the University of California, Berkeley, for example, is involved in four new STCs. The winners are now negotiating their budgets and marching orders with NSF. (For a list, see sciencenow.sciencemag.org/feature/data/stc.shtml.)

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