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

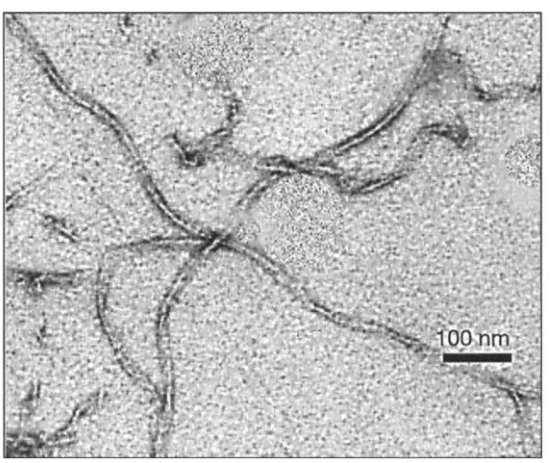
A select group of proteins are known contortionists; they bend and fold and stick together, contributing to neurodegenerative diseases such as Alzheimer's. Now researchers report the startling news that all sorts of proteins can perform the same devilish tricks in the lab. Furthermore, initial tests 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)

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