Hanshin earthquake. "We only got this office up and running last July," he says. The Frontier research themes and the general priorities were set by STA staffers, he admits, after informal inquiries into potentially promising areas of research. In the future, he said, the office will draw on advice from two committees, one concerned with broad policy and another focusing on issues related to the observation networks. Inoue says a more rigorous review process will be used for future research, particularly work within the Frontier themes.

In addition to seeking outside advice, STA is opening up the program in another way: It plans to make all relevant observational data more accessible. At least 16 universities and agencies now operate observation networks, says Inoue, noting that "walls between the different agencies" have prevented data from being used outside the institution that collects it. Masayuki Kikuchi, a professor of physics at Yokohama City University who uses instrument data to study earthquake sources and mechanisms, says that it was quicker and simpler in the days after the Hanshin earthquake to get data from U.S. agencies, via the Internet, than from any source in Japan.

Even if he had succeeded in getting Japanese data, he might not have been able to use it because of the different methods of recording and digitizing the data. The result, Kikuchi says, is that "a lot of data are collected during an earthquake, but very little is ever used." A single database would allow Kikuchi and others to examine earthquake source mechanisms with greater precision and detail. "Instead of relying on global data, it would be better to get more detailed data from observation points close to the source," he says.

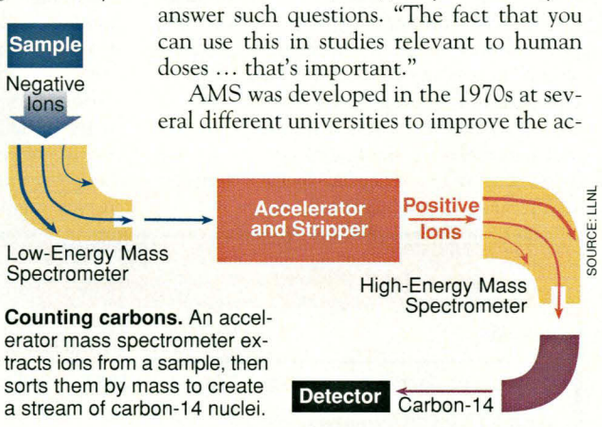
Given the level of seismic activity in Japan, opening up the databases is likely to provide him and other Japanese seismologists with plenty of useful information. And once these data are shared with researchers overseas, the entire world may be able to benefit from the lingering impact of the Great Hanshin Earthquake.

–Dennis Normile

TOXICOLOGY

AMS Adds Realism to Chemical Risk Assessment

Here's an alarming tale for readers who like their burgers well-done. In a study just completed at York University in England and the Lawrence Livermore National Laboratory (LLNL) in California, several cancer patients who were scheduled for colon surgery consumed trace amounts of radioactively tagged heterocyclic amines—compounds that form in cooked meat. After their surgery, the LLNL researchers analyzed the colon tissue, and so far the results show that even at these minute doses the substances bind to DNA in the tissue. The finding supports other evidence that well-done meat poses a cancer risk. And it's a striking demonstration of a new technique for testing potential carcinogens and other compounds, known as accelerator mass spectrometry (AMS).



Counting carbons. An accelerator mass spectrometer extracts ions from a sample, then sorts them by mass to create a stream of carbon-14 nuclei.

The technique's proponents at LLNL and elsewhere say AMS has the potential to do away with the time-honored tradition of administering massive doses of chemicals to rats and hoping for a response that has some relevance to human beings. Instead, AMS traces the fate of minute quantities of a compound tagged with radioactive carbon-14 (C^{14}) in tissues, cells, or even compartments within cells—generally in an experimental animal rather than a human subject. By literally counting C^{14} nuclei, the apparatus can follow just micrograms of a pesticide, a compound in food, or a potential drug through the body. And it may offer an answer to growing concerns about whether high-dose tests have any real usefulness in predicting human health hazards.

"It's a hot issue in risk assessment, dose relevance," notes Ken Turteltaub, an LLNL biochemist. "Is 5000 cans of Diet Coke fed to a mouse every day for life relevant to us?" AMS, says Richard Adamson, a former director of cancer etiology at the National Cancer Institute (NCI), may offer a way to answer such questions. "The fact that you can use this in studies relevant to human doses ... that's important."

AMS was developed in the 1970s at several different universities to improve the accuracy of radiocarbon dating in archaeology and allow the use of smaller samples. Archaeologists traditionally measured the amount of C^{14} in an artifact—an indicator of age—by monitoring the radioactive decay of the isotope, an approach that requires several grams of sample material. AMS, in contrast, counts the C^{14} nuclei directly, allowing the use of as little as a milligram of material.

To perform this feat, the machine first extracts carbon atoms from the sample and ionizes them by adding an extra electron. The beam of negatively charged ions passes through a bending magnet, where ions of lighter carbon isotopes—carbon-12 and -13—bend more sharply than the heavier C^{14} and can be culled from the beam. An accelerator then propels the beam through a thin foil that removes the electrons and breaks up the remaining molecules before they pass through a second bending magnet. This step further purifies the beam before it reaches a final sorting bin, where the C^{14} nuclei can be detected individually.

The same apparatus can also detect other isotopes with much the same sensitivity—down to one part per quadrillion. As a result, AMS quickly spread beyond archaeology to other fields, including earth science and nuclear physics. The LLNL Center for Accelerator Mass Spectrometry (CAMS), for example, was originally designed to diagnose the fission products of U.S. atomic tests and monitor the spread of nuclear weapons to other countries by detecting telltale radioisotopes in samples of air, water, and soil. But those applications have been swamped by the more than 15,000 measurements a year performed at CAMS by the international research community.

A growing fraction of those outside users are biomedical researchers, who hope to study the biological activity of potential carcinogens and toxins at everyday levels. That's unprecedented, says Bruce Ames, director of the University of California, Berkeley's, environmental health sciences center and a leading critic of current animal studies. "Today, we find the level that will kill an animal, back off a little bit, then feed it that level for a lifetime. ... That's crazy." Ames has long argued that the toxic effects of such high doses spur rapid cell division, which in turn boosts the risk of cancer—whether or not the compound itself is carcinogenic at ordinary doses.

Not every biochemist shares Ames's views about existing tests, but they do agree on the need for a more sensitive test for suspect compounds. The first step is to label a compound with C^{14} and feed it to a laboratory animal. Then different bits of tissue—

chromosomes, cell membranes, cytoplasm—are run through the AMS to determine just where the compound wound up, how it was metabolized, and which macromolecules it interacted with. That kind of information offers no clear verdict on cancer risk, acknowledges Turteltaub: "We can't make the direct connection between a chemical and a tumor." But it does give a picture of how a chemical behaves in the body at doses 1000 times smaller than those traditionally administered to laboratory animals, says John Vogel, an LLNL physicist who pioneered the field of bio-AMS with Turteltaub in the late 1980s.

Data are pouring out of such studies, says Snorri Thorgesson, chief of NCI's laboratory for experimental carcinogenesis, and he adds that "at the technical level, there's no question [that] the data are valid." Among other things, the AMS has shown that even low levels of benzene bind to the proteins that form the scaffolding of chromosomes, suggesting that the compound may interfere with chromosomal replication, and that even the smallest detectable amounts of the pesticide malathion latch onto brain-cell DNA. "We are getting mind-boggling results," Vogel says, as he shuffles through a pile of yet-to-be-published data.

Pharmaceutical companies are also exploring AMS as a means of tracing how potential new drugs are metabolized. Chiron, of Emeryville, California, has just begun such a project with the LLNL group. Gavin Dollinger, Chiron's principal scientist on the project, gives an example of the technique's appeal: To see whether a compound crosses the cell membrane—a prerequisite for many drugs—he would ordinarily lace it with a highly radioactive tracer and feed it to a rat at high doses. If it didn't cross the membrane, he would alter it slightly and try again. "It's not only trial and error, but it's a very slow process with a lot of radioactivity and a lot of rats," Dollinger says.

AMS, in contrast, lets him test many compounds at once, because the doses can be much lower and the radioactive tags more subtle. The idea, Dollinger explains, is to give a rat, say, 100 C^{14}-tagged compounds that share a common trait like molecular weight. If the AMS analysis reveals that several different members of that group penetrate the cell membrane, the scientists will have some idea of the property responsible. By studying the behavior of other sets of compounds with other common properties, he and his colleagues are building up "personality profiles" of potential drugs.

The next step for the pharmaceutical makers is to use AMS to test actual drug products, to see exactly how they fare within the cell. But Dollinger says that he and his colleagues won't be working with proprietary substances anytime soon. Even large pharmaceutical companies would likely balk at the cost of having their own AMS lab, at least for now, he says. "That to me is the biggest issue so far," Turteltaub concedes. "How do you move it out of Livermore?" The sprawling LLNL machine is already oversubscribed and running around the clock, and new AMS facilities don't come cheap, costing anywhere from $1 million to $4 million.

What's more, most of the roughly 35 AMS centers in the world have shunned biological research. The levels of C^{14} needed to trace compounds in biological tissues, while low, are still 10 to 1000 times higher than those typical of archaeological materials, and operators fear that residual C^{14} left from bio-AMS might confound later archaeological studies. Indeed, that happened after the very first published biological experiment on an AMS, done in 1988 at McMaster University in Hamilton, Ontario, in conjunction with LLNL biochemists. Says Vogel, "Everyone else is still making their money from carbon dating, and they're still terrified of us."

Still, there are signs that this nascent field of bio-AMS is beginning to catch on. One AMS maker, High Voltage Engineering Europa, is building a prototype AMS specifically for biological studies, while the U.K.'s Wellcome Trust recently purchased an NEC accelerator for Oxford University to study the link between aluminum and Alzheimer's disease. Japan now has six AMS centers, and at least one of them is planning to run biological experiments. And at Beijing University in China, a team is gearing up for bio-AMS studies, Vogel says. The Livermore work, boasts Ivan Proctor, the acting CAMS director, "is way in front of a wave that's just beginning to ripple."

–Jonathan Weisman

Jonathan Weisman is a science and defense writer at The Oakland Tribune.

HUMAN GENETICS

New U.K. Committee Draws Fire

LONDON—Last week the British government announced what it believes to be a world first: a new committee to advise it on genetic testing. But far from drawing praise, the announcement instantly prompted a storm of protest from the House of Commons' science and technology committee, the body that originally suggested a new commission. Members of Parliament (MPs) complained that the government had thoroughly diluted their proposals. "The government's response is very complacent, and there is unanimous disappointment among us," says Labour MP Lynne Jones.

Last year, the parliamentary committee carried out a wide-ranging inquiry into human genetics—the largest it has undertaken since being set up in 1992. The MPs urged the government to set up a Human Genetics Commission, with statutory powers, to cope with the impact of genetics research, which is likely to identify many important human disease genes by the end of the decade. "The scale of the potential problems is enormous, and the right structures are needed now," says Conservative MP Giles Shaw, chair of the committee. The proposed commission was to span issues from regulating genetic medicines to offering advice on screening, insurance, patenting, research, and public education. "It was well received by patient interest groups, medical researchers, and the pharmaceutical industry in this country and abroad," says Labour MP Jeremy Bray.

But the committee announced last week, to be chaired by physicist John Polkinghorne, president of Queen's College Cambridge and a member of the Church of England's doctrine commission, will only provide advice on developments in testing for genetic disorders, testing individuals, and establishing requirements for manufacturers of genetic tests. This limited scope means that many issues raised by the inquiry have not been dealt with, says Jones. "All sorts of concerns, including insurance and employment, are not there," says David Shapiro, secretary of the independent Nuffield Council on Bioethics, which has explored many issues raised by genetics research. Researchers are also unhappy. Clinical geneticist Peter Harper at University College Hospital in Cardiff says that it looked like a "thorough watering down" of the parliamentary committee's proposals.

The new committee will report to the Department of Health along with two other bodies, the Human Fertilisation and Embryology Authority and the Gene Therapy Advisory Committee. But, says Bray, the field is moving too fast for the strategy of setting up ad hoc committees as problems arise to be successful. "There's also real concern that it's linked to the Department of Health, when there are many concerns outside that department's remit," says Harper. The parliamentary committee now plans to recall key researchers and other experts who gave evidence to its original inquiry to consider its next moves.

Health Minister John Horam, announcing the new committee, said he was confident that its purpose would be widely understood and accepted and its work would be reviewed after 2 to 3 years. But pressure will now be on to widen its purview, says Shapiro: "The government may need to look at it much sooner."

–Nigel Williams