China: A Living Lab for Epidemiology

A large new epidemiological study tracks the changes that industrialization is bringing to disease patterns in China

TO THE STATUS-CONSCIOUS PEOPLE of China, animal products have a certain cachet. Someone clothed in a fur hat, wool coat, and leather shoes has higher prestige than his comrade swathed from head to toe in lowly cotton. But one area where the Chinese have not, by and large, been able to indulge their fascination with animal products is diet: meat has been scarce in their primarily agrarian society.

But that has begun to change in recent years, at least in some areas, with the advent of industrialization and the life-style changes it brings, such as increases in smoking and eating a diet richer in animal fats. And that makes China a remarkable laboratory, giving epidemiologists the opportunity to test firsthand the connections between diet and other life-style factors and disease.

Indeed, epidemiologists and medical researchers have already begun to make use of this enormous demographic laboratory. A collaborative group that includes U.S., British, and Chinese researchers is in the final stages of the most comprehensive survey of food, environment, social practices, and diseases ever made in China—and one of the largest epidemiological studies ever done anywhere. "China is the perfect place to do epidemiology," says cancer expert Bruce Ames of the University of California, Berkeley, who is following the research because of his interest in the relation between diet and cancer. "The study is unique in the world."

The study finds that in those few regions of China where meat consumption has begun to go up, it has been closely followed by the incidence of the "diseases of affluence," including heart attacks, cancer, and diabetes. "Once people start introducing animal products into their diet, that's when the mischief starts," says nutritional biochemist T. Colin Campbell of Cornell University, one of the leaders of the U.S. group.

But the Chinese study may have another virtue, beyond allowing epidemiologists to watch the effects that a changing diet has on disease rates as those changes actually occur, not after the fact, as is largely the case in the developed world. "It also offers great potential for improving the health of one-fifth of the world population," say Richard Peto of Oxford University, a British team member. If the Chinese apply the information coming out of the study, they may be able to ward off some of the more deleterious changes that come with industrialization.

The study also shows that international research collaborations can work, although perhaps not without strains—especially in their formative stages.

The idea for a collaborative study in China came up when Chen Junshi of the Chinese Academy of Preventive Medicine spent the 1980–81 academic year on sabbatical in Campbell's lab at Cornell. In the mid-1970s, Chen had surveyed mortality patterns in China and found that death rates from diseases such as cancer often varied dramatically from one geographic location to another. Such clusters, he hypothesized, might be associated with endemic factors, such as mineral deficiencies, social habits, or the effects of industrialization.

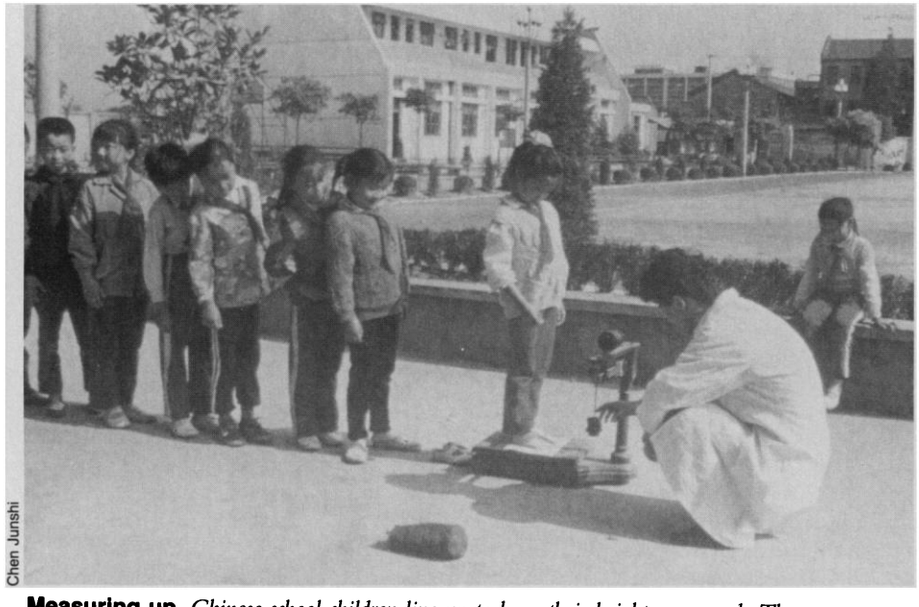
Chen and Campbell decided to pool their resources, following up on Chen's initial study and looking at the changes that come with industrialization. They were joined by another Chinese researcher, Li Junyao, then on temporary leave from the Chinese Academy of Medical Sciences to study epidemiology at the National Institutes of Health in Bethesda, Maryland, and by Oxford's Peto.

At first, the collaborators planned only to probe the relation between diet and cancer plus a few other diseases. But as the work progressed, that seemed too small a compass, and they decided to expand their efforts, considering habits in addition to dietary ones—and about 50 diseases besides cancer.

One reason for broadening the work was the realization that China provides such an excellent experimental system for broad epidemiological studies. The population is large, which makes it easier to gather enough data to achieve statistical significance than it would be in a smaller country. In addition, the Chinese people still lack mobility and choices at the marketplace. More than 90% of Chinese live and die in the province where they were born. And most people have to rely on the local food and water, helping to ensure that diets are relatively uniform within any given region—although they may vary dramatically from one region to another.

Moreover, the Chinese people themselves are generally genetically homogeneous within a region, although there is much ethnic heterogeneity from region to region. And, as Chen's first study showed, disease incidences may vary more than 100-fold from one locale to another, much more than they do in the West. All this makes it much easier to detect important associations between diseases and life-style factors.

But the size and complexity of China also present formidable obstacles to a project as massive as the one the collaborators were planning. For example, in order to carry out their first study, they had to train hundreds of local medical workers—doctors, paramedics, public health workers, and nurses—



Chen Junshi

Measuring up. *Chinese school children line up to have their heights measured. They were among nearly 15,000 people who participated in the epidemiological surveys.*

to collect blood and urine samples and help the study participants complete a health questionnaire. That survey was conducted in 1983 and 1984 among 6500 adults living in 130 villages, two in each of 65 counties located in 24 provinces.

Once the collaborators had shown that their approach was feasible, they undertook an even more ambitious survey of more than 8000 people living in 69 counties in 25 provinces. Once again the number of diseases went up—this time to 150. Sensitive socioeconomic data, including income and Communist party membership, were collected along with more mundane dietary information.

In both studies, cooperation from the villagers was extraordinary by Western standards, Chen says, even though much of the data for the second survey was collected in 1989 after the events of Tienanmen Square. Only one of the 69 counties failed to deliver the samples as directed, despite the civil disturbances. "It was surprising how well things worked," Peto says.

Perhaps the most surprising facet of the second study is that it included Taiwan, making it what Campbell describes as "the first research project between the two countries." Moreover, he continues, "Taiwan's involvement was a great benefit since the nutritional experience there is intermediate between that of China and the West." Taiwan can therefore serve as an epidemiological benchmark, effectively allowing the researchers to show a dose-response relation between incremental changes in diet and changes in disease incidences.

And meat was perhaps the most significant dietary contributor to disease that emerged when the massive amounts of data collected in the two studies were analyzed. In counties where meat consumption increased, the rate of cardiovascular disease also increased. In some cases the increase was a remarkable 50-fold over the rate in counties with more traditional Chinese diets, in which animal fat provides only 15% of the calories. (In a typical U.S. diet, animal fat provides 40 to 45% of the calories.)

The results also emphasized the role played by plasma cholesterol in heart attack mortality. Most people in China have cholesterol levels much lower than those of Westerners, and the study showed that mortality from coronary heart disease declines linearly with plasma cholesterol—with no sign of bottoming out, even at the lowest concentrations. "This observation suggests that there is no threshold of plasma cholesterol below which coronary heart disease mortality is constant," according to the researchers.

What's more, although a few studies of U.S. subjects have indicated that very low plasma cholesterol levels may be linked to a higher incidence of cancer, there was no evidence of such a link among the Chinese. Peto says he hopes the Chinese modify their diet in the direction taken by Japan—high in plant and fish proteins—rather than in the U.S.–U.K. mode: high in sugar and fat.

Delving into the data. *Chen Junshi and Colin Campbell have voluminous data to analyze.*

Nor did the high fiber content of the Chinese diet—they eat a mean of 35 grams of fiber daily, three times what most Americans eat—appear to compromise their nutritional well-being. That finding disputes a hypothesis that very high fiber intake may cause intestinal distress and impair the uptake of minerals such as iron, which is needed to make hemoglobin, the oxygen-carrying protein of blood. "In fact, hemoglobin levels, which depend partly on iron intake and absorption, are significantly higher when dietary fiber intake is higher," the researchers say.

In addition to driving home the effects of diet on disease, the study also documented the devastating impact of smoking on the country's health. When the Chinese Communists came to power in 1949, they promised "all essentials and a few luxuries." For many, the luxury turned out to be cigarettes. Within the last 20 years, smoking has increased so rapidly that 80% of Chinese men now smoke, and there is a boom in smoking-related diseases and premature deaths.

Until these data on smoking were gathered, the "Chinese [government] never thought about it," says Peto. "We helped change their perspective on disease control, particularly as it relates to tobacco, and we helped the Chinese to plan preventive strategies." In particular, laws have been recently drafted to restrict smoking in public places and to put health warnings on cigarette packs, much as is now done in the United States.

The participants in the collaborative study are gratified by the wealth of data gleaned from their work in China, and by the prospect that the information might be used to improve the health of the people there. But they also remember the hurdles they had to get over to obtain those data. In organizing the collaboration, politics were as important as science. "There were a lot of detractors," says Campbell.

One challenge was building credibility—on both sides of the Pacific. American and British scientists wanted assurance that the quality of the staff and diagnostic tools in China was adequate. In China, on the other hand, there were fears that the raw samples and data sent to the U.S. might not be handled appropriately. In particular, Chinese officials feared that the blood and urine samples would be analyzed for items other than those described in the experimental protocol, such as opium and the AIDS virus.

"The Chinese had a stormy meeting on whether the [blood and urine] samples should be sent out of the country," says Campbell, "and when they [the samples] eventually arrived at Cornell, they were accompanied by staff guarding the samples. The Chinese were not about to be used."

Several factors ultimately contributed to the Chinese having confidence in the project, Campbell says. For one thing, the Western researchers took great pains to ensure that all the data were returned to the Chinese. The study results have now been organized so that individual counties can retrieve data from their own area and receive an overview of the nationwide study and a commentary on regional concerns, such as the need to halt smoking or to encourage immunization.

Tact also played a part, according to Carl Taylor, a long-time UNICEF representative to China and professor emeritus of interna-

tional health at Johns Hopkins University. "Each side was willing to give credit, to make the extra effort, and to keep up communication," he says. "The American and British groups had a gentle and sensitive approach to accommodating [the Chinese] and their way of doing things. They maintained the posture that the ultimate decision rests with Chinese."

Taylor adds that several serendipitous events also helped. The first of the two studies began when the Chinese government initiated the "four modernizations" campaign, which stressed the idea of using science to solve problems. At the same time the relevance of good nutrition to good health was gaining visibility in China.

The process of building trust "is still evolving," Colin Campbell says. Meanwhile, he has been advising Chinese authorities and officials at the World Bank, one of the agencies supporting the study, that it is not advisable to encourage the growth of a livestock industry, and that the Chinese need not make a radical change in agricultural development. "This study," says Campbell, "offers the Chinese an opportunity to learn from our mistakes."

■ **ANNE SIMON MOFFAT**

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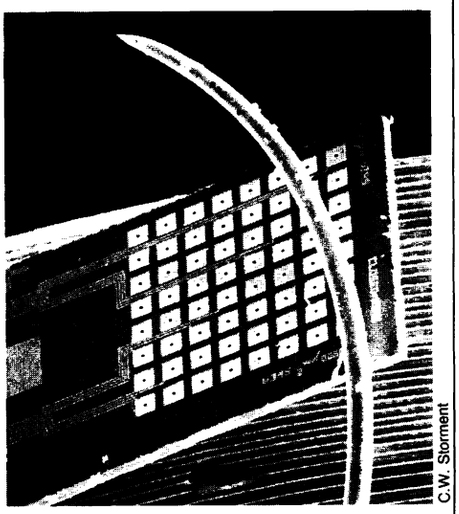
Tapping into Nerve Conversations

For several months a group of electrical engineers and physicians at Stanford University has been able to tap directly into the electrical conversations of individual neurons in a rat's leg. Their listening device is a tiny microchip, designed to withstand the corrosive environment inside living tissue, that they implanted between the severed ends of a bundle of nerves.

The device itself is an impressive piece of engineering, but it is only a crude prototype of what the researchers eventually hope to develop: a computer chip that can be used to link an artificial hand directly to an amputee's nervous system so that the hand can be controlled by the individual's brain, much as a natural hand is.

The device was described at the annual plastic surgeons' meeting in Washington, D.C., this month by Gregory Kovacs, a student of electrical engineering and of medicine at Stanford University. Kovacs reported that he and his colleagues, Joseph Rosen and Bernard Widrow of Stanford University and Chris Storment of the Department of Veterans Affairs, have shown that their latest model chip can both record and stimulate the activity of individual nerve cells in the rat's leg. This is the first time such work has been done with a chip implanted for the long term. "Since our last presentation [at the 1988 plastic surgery meeting] we've shown we can actually communicate with the device," says plastic surgeon Rosen.

To make the chip, Kovacs' group resurrected an old method of stenciling electrodes onto silicon and used it to arrange one of the most stubborn of metals—iridium—in a precise array of square electrodes on the chip's surface. Then, with a laser, they riddled the chip with 1024 tiny holes, each centered on an iridium square. Finally, the chip was coated with silicon nitride to protect it from the destructive effects of body fluids.



C.W. Storment

Early Chip. *This chip has 64 iridium microelectrodes. The current model has 1024.*

When the chip was implanted between the severed ends of the rat's nerves, it not only survived inside the animal for 400 days, but individual regenerating nerve cells grew through the holes. That accomplishment, says Robert White, one of Kovacs' former professors of electrical engineering, was a major breakthrough. Though other researchers have been able to get regenerating nerves to grow through latticework, none have achieved such neural resolution.

Moreover, as the nerves grew through the holes, they made electrical contact with the chip's circuitry, creating a direct link between the peripheral nervous system and the chip. By applying probes to the chip, the Kovacs team could record neural signals as they passed through. The researchers could also stimulate the nerves leading to the animal's foot, which twitched in response.

After hearing Kovacs describe these results, Court Cutting, a plastic surgeon from New York University, described the talk as "one of the most exciting I've seen in my 15 years of coming to this conference."

But the Kovacs team still has a long way to go to achieve its ultimate goal. In the current work, external probes had to be applied to the chip to record and transmit the electrical signals. The next step, Kovacs says, will be to design a chip capable of communicating, through an implanted radio transceiver, with the outside world and, eventually, with an artificial hand.

Implanted processors used with an artificial hand would also have to convert neural impulses into commands. Widrow says the processors, called neural networks, could learn to interpret the thousands of electrical signals. Perhaps most difficult to build would be a device that can restore an amputated limb's sensory linkage to the brain—giving a sense of touch, heat, and position in space. But Kovacs says 40 chips implanted from the elbow on down could provide "every little bit of sensory perception and function" for an artificial hand, although the hand would probably have a limited repertoire of at most 100 movements.

Other experts on artificial limbs are skeptical about these claims, however. William Sauter, the head of a prosthetic team at the Hugh MacMillan Medical Center in Toronto, is "a bit wary of implants." When they fail, he says,"a patient must go into surgery again, and I think most amputees don't like to be opened up." Citing also the risk of infection, the expense of such a device, and the tendency a chip implant might have to migrate under the skin, Sauter says that great advances must be made, and that they will require decades of development, before Kovacs' device will be practical.

Another researcher in prosthetics, Robert Scott, director of the Institute of Biomedical Engineering at the University of New Brunswick, also has doubts about the feasibility of an artificial nervous system. The most difficult task will be to ensure that neurons attach to the electrodes within the chips and remain attached for an extended period of time without decay. This has not been demonstrated. But "the idea is wonderful," he says.

Kovacs remains confident, however, and is moving on to the next hurdle: the design of the "active" chip that will use a radio transceiver to send and receive information between a rat's nervous system and an external data processor. "By the middle of next year the chip will be made," Kovacs says with assurance, and the next cycle of testing and debugging will begin. ■ **SARAH WILLIAMS**

Sarah Williams is a Science *intern.*