

In Rural China, a Genetic Mother Lode

By John Pomfret and Deborah Nelson
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Fourth of six articles

TOUTUO, China -- They came from distant farming villages and scattered rural shacks, trudging miles by foot across precipitous terrain and muddy green tea fields. Women left the open ditches where they washed the family clothes, dragging children along with them. The men joined in. Fifteen hundred people answered the call.

Among them was Wang Guangpu, 26, who makes \$36 a month cutting hair in a hut made out of reeds in the Toutuo town center, a 100-meter strip of crumbling structures on a rutted dirt road.

"We were told there would be free medical care," he said. "So of course everybody came out."

There was a catch, however: Residents had to give blood. Few in this impoverished community could afford a doctor otherwise, because economic reforms had gutted China's free health care system. So, one by one, they extended their arms.

This was no ordinary blood drive. It was genetic research, a pamphlet explained to participants. But many couldn't read, and few could have guessed at the tangle of scientific and business dreams that lay behind the project.

DNA from this region was coveted in the West. Researchers at Harvard University and its corporate sponsor, Millennium Pharmaceuticals, Inc., of Cambridge, Mass., believed the isolated population here and elsewhere in the mountainous Anhui province held a treasure of unpolluted genetic material that could yield medical breakthroughs and perhaps millions in biotech profits.

Because it was unusually homogenous and made medical research easier, the DNA in the local population's blood "was more valuable than gold," the lead Harvard researcher reportedly told colleagues. Ounce for ounce, that would prove a sound estimate.

Harvard ultimately reaped millions of dollars in federal grants and private investment for the university and the project's lead researcher because of its access to Anhui DNA. And Millennium was able to raise tens of millions of dollars from corporate investors.

Along the way, Harvard allied itself with researchers in China who sometimes used the coercive levers of the country's government to help round up volunteers. They recruited women for one reproductive genetics study through the controversial Chinese bureaucracy charged with limiting births. To encourage blood donations, they sometimes mobilized local cadres for "thought work."

Some Chinese who took part complain the bargain proved one-sided. In Toutuo and elsewhere in Anhui, people such as Wang Guangpu say promised medical treatment never materialized.

The story of Harvard's blood harvest in China highlights a question increasingly asked by medical ethicists as

U.S. academic and corporate researchers turn to poor countries to find large pools of willing human subjects: Are some populations too vulnerable for all but the most essential medical research?

Harvard and Millennium officials say their research adhered to strict ethical guidelines. They say Chinese participants volunteered freely and Harvard kept its commitments.

"We were very mindful of having the same standards applied to them as in the U.S.," said Harvard Provost Harvey V. Fineberg. "Every effort was made to assure that was the case."

The same standards may not provide the same protections, though.

In November, spurred in part by complaints about the Harvard-sponsored work in Anhui, the U.S. Embassy in Beijing issued an unusual advisory warning U.S. medical researchers against working in impoverished, rural areas of China where "health care is poor and people are unable to protect their rights."

On the Chinese side, Yang Huanming, the director of sequencing work for the Chinese Human Genome Project, who has worked with the United Nations on genetic research ethics, offered scathing criticism. "I hope that Harvard and the School of Public Health will understand that the [recruiting] methods they used in China are unacceptable to the Chinese," he said in an interview.

An Attractive Target

The China project was hatched in the office of Geoffrey Duyk, a Harvard geneticist who had one foot out the door to industry.

At the time, 1994, genetics seemed the next big thing in American medicine. Among those enamored was Scott Weiss, a prominent Harvard respiratory epidemiologist. Weiss had come to Duyk for help in launching a study into genetic causes of asthma and similar illnesses.

Duyk perked up when Weiss said he had a line on an unusually homogeneous population of 62 million people in Anhui province, a region isolated by geography and poverty for 2,000 years.

For researchers seeking genetic links to diseases and blockbuster drugs to treat them, DNA in such a place as Anhui offers a rare chance to study the human blueprint. Genetic deviations that may cause medical disorders are much easier to identify in a large DNA sample from a relatively uniform gene pool.

The research required thousands of volunteers, nearly impossible to obtain in such a remote place without an experienced guide. Weiss had just the person -- he had mentored a post-doctoral fellow, Xu Xiping, who came from Anhui and had conducted several public health studies there. Xu was an epidemiologist with no real expertise in genetics, but he had hometown connections and a proven aptitude for getting things done in China.

"Xiping had the skill to mobilize people," Duyk said. Duyk told Weiss that he was leaving Harvard to work for a biotech start-up, Millennium Pharmaceuticals, that might be interested in financing the Anhui project.

They picked asthma as the disease to study. It was common enough in the West to make it an attractive target for Millennium.

Duyk could provide the genetics know-how, Weiss the pulmonary disease expertise. And Xu could gain access to Anhui's population.

They began a pilot study in China, and within a year, Millennium agreed to pay \$3 million for the DNA of thousands of Anhui residents to be collected through a collaborative effort among Harvard, Brigham and Women's Hospital -- a Harvard affiliate -- and Xu's alma mater, Anhui Medical University.

Millennium announced the deal in July 1995, one month after a controversial eugenics law took effect in China. The law, which attracted international condemnation, promoted sterilization or lifelong birth control for citizens with an unspecified "genetic disease of a serious nature." With such a harsh law in place, some Western scientists thought genetic research should no longer be carried out on China's population, particularly given the history of forced sterilization of mentally retarded people in some provinces.

Weiss and Duyk said the issue didn't come up in their discussions, and they plunged ahead.

The Millennium-Harvard asthma deal provided Harvard with seed money to launch an ambitious genetics research program.

The deal helped win a key early infusion of capital for Millennium. In December 1995, just five months later, Astra AB, a large Swedish pharmaceutical company, agreed to invest \$53 million in Millennium for genetic research into respiratory disease. Millennium and Harvard officials credited the Anhui project with securing the investment.

Millennium also received a \$70 million commitment from pharmaceutical giant Hoffmann-LaRoche for obesity and diabetes research, and then added \$500,000 to its Harvard collaboration for the DNA of 400 obese families in Anhui.

Anhui, where millions starved in a 1960s famine, might seem a peculiar place to search for answers to the affluent West's battle of the bulge. Yet Anhui's poverty increased the likelihood the rare family with a serious weight problem had bad genes rather than just a bad diet, researchers theorized.

"The Company believes that its access to these samples will facilitate the identification of the genetic components that underlie obesity," Millennium said in a document filed with the Securities and Exchange Commission in 1996. The filing announced the company's first public sale of stock. A prospectus described research projects targeted at six major diseases and twice highlighted company access to DNA from the "large, homogeneous population" of Anhui.

Millennium's public offering raised \$54 million on Wall Street.

Combing the Countryside

In the high-tech harvest of Anhui DNA, Xu's job was reaper.

Xu had spent the early 1970s in Anhui as a "barefoot doctor," one of the lay workers who provided medical care after the Cultural Revolution purged China of its professional classes. He earned a medical degree in 1982 at Anhui Medical University, a PhD in epidemiology in Japan in 1988 and a master's in biostatistics at Harvard in 1993, where he stayed on as a faculty member in the School of Public Health.

In the early 1990s, the slight, bespectacled native son returned to Anhui wearing the newly minted imprimatur of Harvard University. In a place where higher education is revered but access to it remains rare, Xu shone like a Dallas Cowboys quarterback returning to his Texas high school.

Xu said he wanted to study the causes of health problems common to Anhui and the West, with an eye toward prevention. He did non-genetic research into occupational and environmental ills and studied women working in textile mills.

When the opportunity arrived to work with Millennium, Xu said, he jumped at it.

"I thought it would be a win-win situation," he recalled. "It would help give me a track record in genetic research and advance the cause of genetic epidemiology. . . . The population was ideal for gene mapping, because there are no trains or planes. People don't move."

With the Millennium agreement in hand, Harvard established the Program for Population Genetics in 1996 for the China initiative. It named Xu director.

Xu proved able to operate with ease in China's authoritarian system, where the cooperation of government officials was essential and where volunteers lacked many of the freedoms and much of the information available to their Western counterparts.

His network of allies included provincial officials in the Chinese government; his alma mater, Anhui Medical University; and the regional Anqing Public Health Bureau, whose politically connected director was given co-investigator status on Xu's research. Xu helped set up genetic research centers at Anhui Medical University and in Anqing and became their director, his resume says. Local officials and health clinics were mobilized to comb the countryside for thousands of subjects who met the study criteria.

"It's different in a Communist state," said Karin Schmitt, who monitored the Anhui project for Millennium in 1997. "I think you always need to get in with the right groups. You need to see who can influence the people. We were working with the health minister of the province. He practically endorsed the study. Then he goes one level down, and the next one goes a level down."

In 1997, financial details about the Millennium-Harvard deal in Anhui leaked to the Chinese press and caused a storm of criticism. The idea of U.S. capitalists profiting from China's genetic heritage sparked such a fury that foreign genetic research stalled for a year as the Beijing government mulled new regulations.

But during this period, Xu said he got permission to take DNA out of China with the help of Anhui officials.

"They didn't listen to Beijing," he said.

Xu actually had support from Beijing, said Yang of the Chinese Genome Project. "We didn't agree with this decision but the Ministry of Health backed Xu," he said. "There was nothing we could do."

Yang said he and others in the Chinese genetics community had grown uncomfortable with the scale and speed of Xu's projects. He said he expressed doubts to Xu that such a sizable effort could produce good science or guarantee that the participants were making informed choices. Yang said Xu responded that he had the backing of Harvard and China's leadership, and that Yang couldn't stop him. Asked about the conversation, Xu said it never took place, and that he didn't receive special treatment.

Using the Millennium project as a foothold, Xu expanded into other collaborations with Chinese researchers. He applied for and received grants from the National Institutes of Health and the March of Dimes for \$10 million in research projects. In his grant applications, Xu emphasized his access to Anhui DNA.

He analyzed the samples from Anhui through a variety of projects that would eventually include studies of asthma, diabetes, hypertension, human reproduction, nicotine addiction, obesity, osteoporosis, schizophrenia and twins.

Xu and his collaborators collected samples from thousands of people for Millennium and thousands more for his own research for Harvard and others. In all, by his count, 16,400 people gave DNA samples to the Harvard genetic bank, most from Anhui.

Xu also collected DNA from 1,000 Beijing women working in petrochemical plants who had received government permission to get pregnant for a study of human reproduction.

But most of Xu's work took place in rural Chinese areas that few of his U.S. funders ever visited. He reported extraordinarily high volunteer rates, "exceeding 95 percent for all of our genetic studies in the Anqing area," as he wrote in one grant application.

Andy Kuo worked in Xu's lab in Boston and helped him set up projects in Anhui from 1996 until 1998, before leaving Harvard for an industry job in the United States. Kuo described Xu as a talented and committed epidemiologist, but said Xu felt pressure to move quickly. They were moving so fast that they couldn't keep close tabs on recruitment or testing, and the data suffered from mishandling and mix-ups, Kuo said.

"I kept saying, 'Why not do smaller projects and do them well?' But he was under pressure from everybody -- Harvard, the private sector, Millennium," Kuo said. "I don't think Harvard did right to foster this."

In 1998, Xu set up a company in Massachusetts to coordinate private research ventures with the Meizhong Institute, according to incorporation papers, although Xu says that company never got off the ground. "He was always saying that we were all going to be rich," Kuo recalled. He said Xu compared DNA to gold.

Other colleagues recalled similar statements. But in an interview, Xu said, "I never described DNA as 'more valuable than gold,' a very childish statement, nor have I ever reported that I hoped to get rich from these research efforts."

He acknowledged some quality control problems but said they had been addressed by a recent decision to centralize testing.

"Throughout my scientific career and as a faculty member of Harvard University, I have always upheld myself to the highest standards," he said.

He said Harvard's collaborations in Anhui have provided valuable experience for Chinese researchers and may eventually yield important information about disease. For local hospitals and clinics, the collaborations were a "business opportunity" he said.

"An arrangement was made between the local hospital and the [Anhui] medical university. We gave a budget and we said this is the cost" for recruiting and examining study participants, he said. The clinics in turn used incentives like free exams and discounted health care to attract recruits and then hopefully retain their business, Xu said.

The research projects were also an opportunity for Anhui residents, he said.

"Very few of the people in the countryside ever get a health checkup," he said. "So when a team of doctors and researchers showed up there was a natural eagerness to participate."

Unkept Promises?

Toutuo Township is stranded in a mountainous region of Yuexi County, connected to the outside world by a lone dirt road. Families of ancient lineage are large and extremely poor. Illiteracy is high, particularly among women. One study by Xu put the illiteracy rate of his subjects at more than 70 percent.

Ten families from Toutuo (pronounced Toe-twaw) with a history of asthma took part in the Millennium study in 1996 and 1997, Xu said. During that time, Toutuo blood was also harvested from hundreds of residents for hypertension and pregnancy studies by Anhui Medical University and Xu.

Toutuo and Yuexi health officials and doctors were recruited to help find study volunteers. One of their initiatives left a bitter taste.

English teacher Chen Hong said local health officials told villagers they were collecting health data "to study disease related to genetics" for an "American" research project. Those who participated were to get a free exam, test results, follow-up care and a "health card" for a discount health care program, she said. The card was attached to a booklet that explained the physical exams were intended to "find scientific evidence for the effective prevention and treatment of chronic diseases from both genetic and environmental perspectives."

Volunteers underwent a battery of tests and gave blood, but the test results, follow-up care and health program never materialized -- meaning many of the medical problems identified in the physicals went untreated.

Wang Mengfeng was among 1,500 people who turned out to give blood. He had been suffering from a worsening stomach ailment, according to his wife, Hu Nanxia. He volunteered with hopes of getting it diagnosed and treated, she said.

The medical team told Wang he had gastritis, she said. They drew his blood and gave him a health card. Afterward, the local clinic wouldn't honor it, because the staff said they had not received the promised outside funding for the program, she said. So Hu and Wang borrowed money that soon ran out, and his condition deteriorated until he died last year at 34.

"He was a good man," she said.

The director of the Toutuo Health Station was Zheng Guanghu, who is now the director of the Yuexi County Hospital administrative office. He said the health care initiative was a success. He described it as a joint effort to recruit volunteers for Xu's genetic research and drum up business for a low-cost health care program promoted by Anhui Medical University.

Zheng said he shipped 1,500 blood samples to Xu's Meizhong Institute, as did Baimao, a township in an isolated western valley of Anhui, and "every other county in Anhui."

But when Xu was asked about the failed initiative, he said he was not officially involved. He said he offered advice and reviewed the data they collected, but found it too unreliable to be useful for his research. He did not receive any blood from it, he said.

"Maybe some people fell through the cracks. Maybe some promises were broken," Xu said. "I didn't have anything to do with that."

Zheng subsequently faxed a statement to The Post saying Xu wasn't involved. According to a second faxed statement, this one from Anhui Medical University, Toutuo residents were questioned about The Post's "unauthorized" visit and none complained about the research initiative.

"All the subjects were satisfied about this project and were grateful to the local health agencies for their concern about their health," the second fax stated.

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Mining the Riches of Rural DNA

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'Thought Work'

Huaining County is another remote, rural district that Xu and his Anhui collaborators targeted for genetic research into several diseases, including hypertension and asthma. Here, too, participants say promises were not kept.

In 1996, with Xu's permission, a team of social scientists interviewed asthma volunteers for a U.N.-funded public health study. Several refused to cooperate, because of bad experiences with Xu's project, according to the field researcher's study diary.

"Had a refusal yesterday. . . . Complained had been subjected to a check-up and never told result. Felt used and tricked," one entry said. Said another: "The woman refused to have anything to do with us under any conditions, even if a gun was held to her head."

The field researcher, Leslyn Hall, recalled the encounter with the angry woman. "She was very, very upset," Hall said in an interview. "Her son was 8 or 10. A minor. She had a disagreement with her husband over participation that she felt led to divorce. The boy passed out during their taking blood. He was with the asthma group. She sought follow-up care for him and never got it."

The study was canceled because Xu's database of volunteers turned out to be too problematic, said Robert Weller, a Boston University anthropologist involved in the study. According to grant documents, Xu and his research team gave differing accounts of how they recruited volunteers.

Xu said he wasn't aware of any complaints from asthma families. After learning of the issue from The Post, he said he dispatched two researchers to visit 10 participants. None recalled any promises of follow-up health care, he said.

However, Kuo said that recruits were told that they would get medical care. At one point, doctors at Haikou Hospital in Huaining County sought the lab results from Xu for thousands of study recruits so they could be treated, Kuo said. But none were provided, according to the hospital's medical staff.

"Promises were made," said one doctor. "Participants were told they would get free medical care and reduced-cost care, but the research project never gave us the funds to do it."

The experience poisoned relations between local doctors and their community. "It used to be like this," said another doctor, clasping his two hands together. "Now it is very tense."

Volunteers are recruited through township health stations, the doctors said, but now people are reluctant to participate. So the hospital has been tasked with working with Communist Party officials to find volunteers.

"If they don't want to participate," said one doctor, "officials go down to the villages and do thought work and move them to participate."

"Thought work" involves meetings with local government and party officials and can involve both subtle and blatant forms of pressure. If officials are having trouble rounding up test subjects, residents said, thought work can become heavy-handed, even coercive. Residents rely on the Communist Party and local government for many favors involving taxes and the division of land. Families who are not cooperative could suffer, residents said.

When asked about the doctors' complaints last spring, Xu said, "I would be surprised if [the test results] were not returned."

He said the doctors did not know they were talking to a reporter, and Anhui's public security department has since issued a province-wide circular warning people involved in the research not to talk to outsiders. In a later e-mail, Xu said the hospital staff had been questioned about their complaints and confessed to lying about Xu promising medical care for volunteers.

"These doctors now regret any untruthful answer they may have naively offered," Xu wrote.

Asked about the "thought work" allegation, Xu answered through Harvard spokeswoman Robin Herman. "Dr. Xu has never heard of authorities demanding 'thought work' from recruited subjects," she said. "More importantly from Harvard's perspective, Dr. Xu or other Harvard researchers were never involved in such an effort."

Sponsors at Millennium said they didn't know how Xu recruited participants. "We left it up to [him]," said Schmitt, who oversaw the asthma study. "And we were happy with his progress."

Duyk said he assumed residents participated for the medical attention and, along with local health workers, out of curiosity. "It was fun for people. It was a very isolated region. Just to participate in it was an interesting thing," he said.

A Federal Investigation

In March 1999, Harvard sent a six-person team to Anhui to make sure the research was ethically and scientifically sound.

James H. Ware, the academic dean at the School of Public Health and a member of the site committee, said it was unusual to send overseers to such a remote location, but the scale and "sensitivity" of the genetic research warranted it.

The team included representatives of the School of Public Health, the Medical School and Brigham and Women's Hospital. Among the six designees were Xu himself, Weiss and one of their research collaborators.

They spent just two days in Anqing at Xu's research headquarters.

Ware said the Chinese they met were clean and well dressed. The notion of an oppressed, malnourished or illiterate population was at odds with what he saw, he said. "I came away extremely impressed." The program passed.

Five months later, regulators from the Department of Health and Human Services launched an investigation of Harvard's genetic research in China, based on the complaint of Gwendolyn Zahner, a former School of Public Health faculty member. She alleged violations of U.S. human subject protection regulations.

Zahner, now at the Research Triangle Institute in North Carolina, said she grew concerned about the project while on a Harvard committee assigned to review a proposal by Xu and his colleagues to conduct thousands of colonoscopies in Anhui. The study never received funding. But Zahner said she was surprised at Harvard's seeming lack of concern over patient protection.

She investigated further and concluded that reviews of other studies hadn't adequately weighed the risks of the Chinese government misusing sensitive genetic information. Some of Xu's research appeared to have started ahead of any ethics review, she said.

Zahner visited Anhui four times to gather information for her complaint, and was twice questioned by police.

"During my questioning, they knew every place I'd been and individual Chinese citizens to whom I'd spoken," Zahner said in an interview. "No one could conduct meaningful independent oversight of this research under those conditions."

Harvard officials said they took cultural differences into consideration and built protective measures into the studies to prevent the Chinese government from obtaining participants' genetic information.

And while grant documents and studies refer to at least four Harvard-Anhui Medical University studies that began prior to ethics committee approval, officials said those were "unofficial collaborations" in which Xu was helping the Chinese as a private consultant.

"As the AMU-Harvard collaboration evolved and Dr. Xu became a principal investigator, studies then fell under the purview of our institutional review processes," said Harvard spokeswoman Herman.

However, records show thousands of vials of DNA were being shipped from Anhui to Harvard for analysis and storage under some of those informal arrangements. U.S. rules say ethics committee approval is needed before such analysis can proceed. Herman said Harvard officials now realize approval was needed, after reviewing regulations and a recent NIH advisory that clarified the rules.

In China, Xu's critics have attempted to stop or at least slow his expanding genetic research empire, but have had little success.

"It is bad research, pure and simple," said Yang, of the Genome Project. "They cheated the patients. They came in for health checkups, they didn't know what their blood was being used for, and then they never gave them the results of the tests."

Yang sits on the national board appointed to review international collaborations. He said the board last year rejected two of Xu's most recent research applications and held up a third out of concern that he was overextended and couldn't meet China's newly enacted patient protection standards. Yang said Xu appealed to Chinese leaders and forced a compromise that would allow him to proceed with the projects if they received approval from the U.S. government.

Qiu Renzong, one of China's leading medical ethicists and a senior government adviser, called for a joint U.S.-Chinese review of Xu and the Harvard experiments.

"There are so many questions about them," Qiu said. "As principal investigator, he is responsible for everything that happened."

The U.S. Embassy's November advisory about medical research in China concluded that while "good practices are widely understood by Chinese researchers, the lack of accountability and poor supervision can mean that good practices are not followed on the front lines of research projects."

As a result, "Research should be conducted primarily in the more prosperous parts of China, unless there is strong justification for doing otherwise," the advisory said. Beijing officials have a hard time overseeing research in remote areas, and local officials tend to cover up problems, it said. People lack freedom, making reliable informed consent a challenge.

"Local officials can sometimes have such great arbitrary power that a farmer may not want to say 'no' to them," the advisory said.

The advisory said "good connections should not be a reason for choosing a research site in a "backward" area.

But Frank E. Speizer, co-director of Brigham and Women's Channing Laboratory, which oversaw the asthma research, challenged the notion that residents from Anhui needed special protection.

"I find it hard to call China a developing country," he said. "It's a very sophisticated country."

Officials at the School of Public Health say they have provided adequate oversight and that the Anhui project meets the university's high standards for human research. Ware said he has tightened oversight in the past few months by requiring Xu to report all his research activities to the school, even the unofficial collaborations and consultant work that had not been reported previously.

At Millennium, chief business officer Steven H. Holtzman, a presidential appointee to the National Bioethics Advisory Commission, said he had no reason to believe that Harvard broke any rules in carrying out company-sponsored research in China. But he said Millennium is "more sensitized" now to the need to keep a closer watch on such research, as is the research community as a whole.

Holtzman said the embassy's concerns didn't apply to Millennium's research, because it was a well-run, low-risk operation "that could potentially shed light on the biological basis of a disease."

Millennium pulled out of Anhui last year, without a significant medical or business discovery to show for its \$3.5 million investment. The DNA is still in the databank, and the company has hopes it will yield clues to disease in the future. Millennium has moved into a field of genetics that seeks to customize medical treatments for individual patients. The company has grown into a successful, billion-dollar enterprise that has made millions for top executives.

In March, Worth Magazine profiled Millennium Chairman and CEO Mark Levin after the company's stock more than doubled in three months. In April, he made the news again for paying a Rhode Island state-record \$10.8 million for a 33-room vacation mansion with resident llama.

Holtzman acknowledged Anhui's early supporting role in Millennium's success. "We're here now," he said. "But you don't get from there to here unless you do what's important at the time."

Xu continues on in Anhui. With grants from NIH, he is launching a \$3.5 million study of hypertension in 700 adults and teens and a \$3.3 million nicotine study that will look for clues to cigarette addiction in the blood of 3,400 people.

Back in Toutuo, little has changed for Wang Guangpu, the barber.

He said he still has the health cards his family received three years ago. He keeps them in a safe spot, just in case.

"We Chinese are simple people," he said. "All we want is a little off the price of medical care. It would be better, say, if the price is 100, maybe we'd pay 60 or 70. We didn't even get that."

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