Fourty years ago, a folk healer in rural China discovered that arsenic could help fight leukemia. Today doctors around the world are treating patients with his poison.

BY ELISABETH ROSENTHAL

At the height of China’s tumultuous Cultural Revolution, when Mao closed universities and banished intellectuals to the countryside for a “real” education, Dr. Zhang Tingdong found himself dispatched from the city of Harbin to a remote agricultural commune in the far reaches of frigid Heilongjiang Province in the northeast of China. His mission was to seek out an uneducated doctor said to possess a miraculous curative elixir.

“Chairman Mao had called on Western-trained doctors to learn from traditional doctors, to change their focus to Chinese medicine,” says Zhang, who is now — as he was then — a blood specialist at Harbin Medical University. “So I went.”

Just getting to the clinic required a full-day train ride, followed by a second day on a cranky rural bus and a third day overland on a horse-drawn cart. It was only November, but the rivers had been frozen for more than a month.

When the team of urban doctors finally arrived at the clinic of the Democracy Commune on that day in 1972, they were dismayed by what they saw: an aged medicine man, “with wrinkles covering his face,” Zhang recalls, dispensing potions out of a primitive mud home dug into the earth to keep out the winter’s cold.

“The room was so dark it was hard to see, and dirty because they were burning crude oil inside to stay warm,” says Zhang, now 68. “And it was poor — so poor. He had no equipment at all.” What the doctor did have, though, was a powdery home-brewed concoction he’d learned from his father, made from two types of ground rock and the venom of a local toad. Some patients drank it; others rubbed it on their skin. Sometimes the doctor wrapped it in newspapers and shoved it into infected wounds. To the visitors’ surprise, it soon became clear that some of the patients — even some with cancer — got better, and some even seemed cured.

Today, Zhang cannot remember the name of old medic, who died a few years lat-

Dr. Liu Lianxin ministers to a cancer patient in Harbin, China.
The outlook for A.P.L. patients improved with the use of a new chemotherapy drug, all-transretinoic acid, in the 1990's. And now the use of arsenic has further improved the prognosis for these patients. But they are still among the sickest people to enter hospital doors.

Zhai Wentong is a patient on the 14th floor of the First Hospital of the Harbin Medical University, a spartan place (with that universal hospital smell) that has become a mecca for A.P.L. patients from all over northern China.

When Zhai's relatives took him to Harbin from a hospital near his home in Hebei Province, he was semiconscious, running a high fever and blind because his eyes had filled with blood, making them appear bright red.

He had been sick for six weeks. "Since Chinese New Year, I had been feeling worse and worse — so weak and sweaty," he says, lying in his hospital pajamas, raising his head with some effort. "I don't even remember when they brought me here." His sister adds. "At one point he asked for a mirror, but we didn't dare give him one, he looked so frightened." But after three weeks of arsenic he is smiling, though his eyes still have a yellow tinge from blood that hasn't fully resorbed. He says he feels "much, much better," and his blood counts are improving, though tests show that signs of leukemia are still there.

As with many traditional Chinese medicines, treatment with arsenic takes longer and recovery is slower than with Western medicine. In Harbin, patients get intravenous arsenic once a day for 30 days, and then, if they still show signs of leukemia one week later, they start a second course.

Arsenic is remarkably easy on the patient compared with conventional chemotherapy, which often brings with it side effects like nausea, anemia and hair loss. Arsenic takes about an hour each day to administer by IV, and the patients here say they generally feel fine, although some say they experienced a feeling of abdominal fullness.

The specific disease that arsenic trioxide handles so superbly is a relatively rare but formerly devastating form of leukemia called acute promyelocytic leukemia, or A.P.L., in which the bone marrow churns out a certain type of immature and aberrant white blood cell. The most severe result is a bleeding disorder called disseminated intravascular coagulopathy. Patients can die within minutes from massive bleeds inside the skull.

I have a particular interest in this disease. When I was a resident at Memorial Sloan-Kettering Cancer Center in the late 1980's, my colleagues and I unanimously voted A.P.L. the disease we'd least like to get — in a hospital where there were plenty of candidates for such an award. As young doctors, we would quake to get a patient with the diagnosis, basking ourselves for what was often a complicated and painful death.

The scientific route that brought arsenic trioxide to the bedside is a very old-fashioned one. Doctors started with the observation that something worked — and moved steadily backward for more than 25 years in an effort, still unfinished, to understand why and how. Contrast this with the 21st-century approach to drug development: first understand the molecular or biochemical defect that produces a disease or debilitating condition and then create a drug that corrects it.

In many ways the starting point of the process of discovery for arsenic as a cancer cure was the decidedly unscientific tenet of traditional Chinese medicine: "Give poison to cure poison." Zhang returned to Harbin carrying samples of the rocks and toad venom the old medic had used to make the poison — as well as the recipe. He retreated to his lab to analyze what on earth he had.

"They had made this medicine for decades, but they had no idea what the ingredients were," he says. Most traditional medicines are a mix of a small number of active compounds and huge number of other molecules that essentially tag along in the plants, rocks and animal parts used to make them. Teasing apart these complex chemical soups can sometimes take years, scientists say. And that has created a high barrier to winning approval for traditional medicines in the U.S., since the Food and Drug Administration insists on knowing each medicine's active components.

In his lab, Zhang discovered that one rock was principally mercury. The toad venom proved too biologically complex to analyze. And the powder from the second type of rock contained high levels of arsenic trioxide.

Unfettered by current notions of informed consent, Zhang did a few animal studies with the potion and then started giving it by injection to his patients with leukemia, for whom there was no other treatment at the time.

"If I had told them what it was, they never would have agreed," he recalls with a chuckle. "But by that time, I'd seen it used in the villages and on animals and was confident it was safe."

Working with the mystery potion proved more complicated than he had expected, in part because he was giving it as an injection, a route that had not previously been tried. While some patients did begin to recover, others developed sudden blood-pressure surges after the shots, giving them terrible headaches. Still others developed kidney failure.

By a process of trial and error, in which he administered the potion's components separately and together, Zhang discovered that the toad venom was responsible for the blood-pressure problems and that the mercury-based rock was damaging patients' kidneys. In fact, it was the arsenic alone that proved capable of killing cancer cells in a test tube and of treating patients with disease.

Even then doctors had no idea of the proper dose — clearly, too large a dose would be toxic — or how long to continue the treatment. It was the first time the Chinese doctors had injected arsenic directly into patients' veins; the standard dose was one-fifth the dose considered most effective now.

For some time, the patients who died outnumbered those who left the hospital — in large part because researchers were using such a small dose. Dong Xiaoli was a 22-year-old factory worker when she became one of the first leukemia patients to receive arsenic, in 1974. "The first few months, I was mostly unconscious," she recalls. "I couldn't eat, really, couldn't even turn over in bed." Dong is now 49 and a aide at the hospital.

"I was in the hospital for nine months," she says. "There were three other beds in the room and the others kept dying. It was very scary. I didn't know how long I would live." Dong received arsenic therapy for five months before she realized she was getting "poison." She continued on the treatment for the better part of two years, until 1976.

Zhang recalls a sense of euphoria at the time. "Within six months I knew it was working, and I published a paper on it within a year — it just seemed that important," says Zhang, still youth-
ful and enthusiastic in his retirement, wearing an N.B.A. windbreaker over his shirt and tie.

But it took another 20 years for the rest of the medical world to concur. China was then still a poor, isolated country, more concerned with ideology than with medical cures. The collaborations with more sophisticated medical specialists — not only in the United States but also in China itself — that ultimately proved the curative power of arsenic took time.

It was not until the 1990’s, for example, that doctors in Harbin hooked up with researchers at a prominent institute in cosmopolitan Shanghai, where cancer specialists were working with all transretinoic acid, which had already shown great promise against A.P.L.

Retinoic acid was able initially to knock out detectable leukemia in a large majority of patients, vastly improving the prognosis of the disease. But despite all previously available treatment, the leukemia came back in 30 to 40 percent of the patients — and once it did, the disease was even more resistant to treatment.

The Shanghai specialists, scientists with research financing and international reputations, tried arsenic trioxide from Harbin with these patients, and they were awed. They began more technical studies on the drug than were possible in Harbin. And they spread the word abroad.

In 1997, doctors at Memorial Sloan-Kettering began their first small study with arsenic trioxide. “It was very, very impressive,” says Dr. Steven Soignet of the hospital’s department of developmental chemotherapy. “We had these patients who had all relapsed, and many were terribly sick in the intensive-care unit. Their blood pressure was low. They were needing constant transfusions. And we were there pushing arsenic through their IV’s. It was very dramatic.”

The results, too, were dramatic — so dramatic that American specialists are now rethinking the way they treat this disease.

Standard practice for treating A.P.L. at Memorial is to first give retinoic acid and other chemotherapy and later arsenic if the first drugs fail. That may be followed with a bone-marrow transplant to stamp out leukemia cells that the drugs missed. But bone-marrow transplants are painful, high-risk procedures that cost nearly $100,000.

In Harbin, where technical expertise is limited and most patients are poor, transplants were never an option — so doctors have always used arsenic, and arsenic alone, to treat A.P.L. They claim that 80 to 90 percent are cured. Though health insurance makes bone-marrow transplants affordable for most people in America, they are physically and emotionally traumatic. What if they were unnecessary to treat the disease?

It is ethically difficult for doctors to construct a study in which patients forgo an accepted therapy that works and has been proved, no matter how traumatic it is. But patients who took part in the first multihospital trial of arsenic in the United States, in 1998, ended up taking the lead of the 40 patients in the trial, 34 were disease-free after one round of arsenic treatment. Half of them did not have the follow-up transplant, some because they refused treatment and others because they did not qualify for the procedure.

“This has opened up a whole new paradigm,” says Soignet. “And we were seeing such amazing responses that we’ve decided to look at it for other cancers.” In China and in cancer-treatment centers all across the United States, arsenic trioxide is now showing promise in patient trials against a wide variety of tumors, including liver cancer, cervical cancer, multiple myeloma and cancer of the prostate.

At Harbin, intravenous arsenic therapy also “seems very effective against liver cancer,” says Dr. Liu Lianxin, who has been following 70 patients on arsenic for the past year. Liu has seen their tumors shrink and their pain vanish — although he adds that the treatment is so new for liver cancer that “you can’t talk about cures” or even know what the impact will be on survival.

Still, in the inherently cautious world of cancer specialists, there is unusual optimism about the powder that Dr. Zhang Tingdong rescued nearly 30 years ago from a mud hut on the Democracy Commune. In the United States, a form of it now goes by the brand name Trisenox.

“They’ve had some unbelievable discoveries in China,” says Soignet, adding, “If you get A.P.L now, you’ll probably be cured of the disease.”