Arsenic patent keeps drug for rare cancer out of reach of many

For thousands of years, arsenic has been known to have medicinal properties. It has been used at various times to treat syphilis and sleeping sickness, or occasionally to poison unsuspecting rats and husbands.

In the past few decades, some scientists have discovered arsenic's ability to cure acute promyelocytic leukemia (APL), a rare and fatal cancer that strikes relatively young people.

But despite its abundance and long history, arsenic treatment is inaccessible to all but the richest of people—because an American company holds the patent on a drug called Trisenox, a soluble form of arsenic trioxide.

Pharmaceutical companies point to the high cost of research and development as the reason for exorbitant drug prices. But in this case, critics charge, little research was necessary, and the patent that keeps the price high should never have been granted.

"When you have a miracle drug and it's not used, it's unacceptable," says Hugues de Thé, professor of molecular biology at the University of Paris, who has worked on arsenic therapy for more than 15 years. "I would never have even thought about patenting a drug that is 3,000 years old," de Thé says. "The idea that this drug is not used drives me crazy."

Arsenic's use to treat APL began in the 1970s, when researchers at Harbin Medical University in northeast China used a crude mix of arsenic trioxide and mercury to treat various cancers. But the work did not attract broader attention until the early 1990s, when it was published in a Chinese journal (*Chin. J. Intergr. Med.* **12**, 170–171; 1992). In their study, the researchers found that arsenic trioxide brought on complete remission for about two-thirds of those with APL.

In 1996, the researchers collaborated with another team at the Shanghai Second Medical University, led by the current Chinese Health Minister Zhu Chen, and presented the results to an international audience (*Blood* **89**, 3345–3353; 1997).

Raymond Warrell, chairman of the New Jersey–based company Genta Incorporated, recalls that when he reviewed the *Blood* article for publication, he recommended that it should be accepted "with extremely high priority."

But the Chinese group did not, as the reviewers had requested, describe how they had produced the arsenic they used, says Warrell, who was then a researcher at the Memorial Sloan-Kettering Cancer Center in New York.

The Chinese researchers had learned how to produce an inorganic, stable, soluble form of arsenic, which is generally insoluble. But because they did not describe the recipe in the literature, Warrell says, they left the door open for someone else to make a patentable formula.

It took no more than a couple of months for Warrell's group to make its own soluble arsenic trioxide. The results matched the success reported in China. In 1998, Warrell and his colleagues filed a patent for their formulation and launched a company dubbed PolaRx (*N. Engl. J. Med.* **339**, 1341–1348; 1998).

Because arsenic is toxic to animals, the researchers had trouble finding companies to develop the drug, but based partly on the Chinese results, they convinced the US Food and Drug Administration to allow a small clinical trial. "We agreed to give day-to-day feedback," Warrell says.

In 2000, Seattle-based Cell Therapeutics acquired PolaRx, including its arsenic trioxide patents, for $15 million in stock. "It was practically nothing—an embarrassing amount," says Warrell, who says he receives "a small amount" in royalties. In June 2005, Cell Therapeutics sold the drug to Pennsylvania-based Cephalon for $70 million.

Under international patent law, according to a Cephalon representative, the basis for the patent is the clinical use of arsenic trioxide and not the chemical itself. But de Thé notes that the clinical efficacy had already been shown by the Chinese. "The patent was taken after all the work was done," de Thé says, adding that making arsenic trioxide soluble "basically means they boiled it."

But Warrell defends the patent, saying that it at least helped generate companies' interest in bringing the drug to market. "Without the patent, it would have remained a curious Chinese drug, not available to anyone else," he says. "Most of the patients are young, and it gives them another 60 years of life. Relative to the benefit, it's cheap."

Still, at up to $50,000 for a full course, Trisenox is out of reach for most people in developing countries.

In Lebanon, for example, where the average income is $5,000 per year, it has been prescribed to just five people over the past two years. Four of them recovered from the cancer. The fifth died because his illness had progressed too far while he tried to raise money to buy the drug, according to Ali Bazarbachi, a medical professor at the American University of Beirut. The drug is also awaiting approval in Brazil, where its high price is likely to make it a last resort for those who fail treatment with other alternatives.

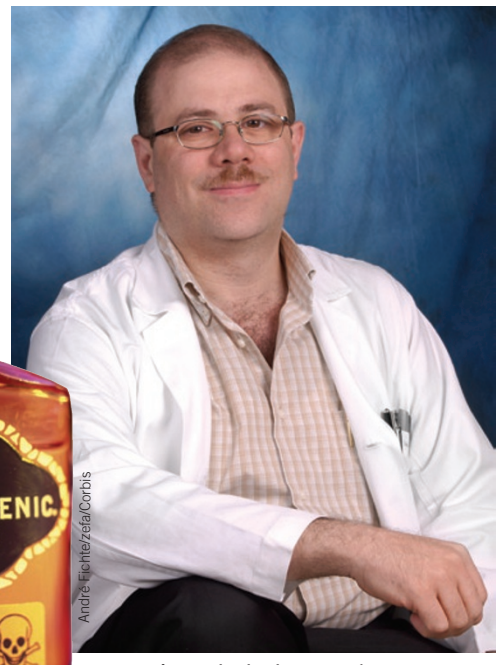
"Many hematologists around the world, including in Europe, think that both the patent and the price of arsenic are outrageous," says Bazarbachi.

Desperate for the drug, some countries are looking to scientists in Iran, where the patent is not valid, to produce the drug cheaply. Cephalon is also working with various countries to set up compassionate use programs. "It is not Cephalon's intent or practice to keep products away from patients in need," says Candace Steele, a spokeswoman for the company.

Because APL affects only two people in a million on average, and because there are other alternatives, such as retinoic acid, available—albeit with more side effects—arsenic is unlikely to become the focus of a large lobby group in any country.

In the meantime, arsenic is finding wider acceptance. At the annual meeting of the American Society of Clinical Oncology in June, Irani researchers presented data from the largest trial to date on arsenic trioxide alone, showing that of 141 individuals with APL treated with the compound, 85% had healed completely.

David Cyranoski, Tokyo



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Sweet poison: The high price of an arsenic-based cancer drug is "outrageous", says Lebanese scientist Ali Bazarbachi.