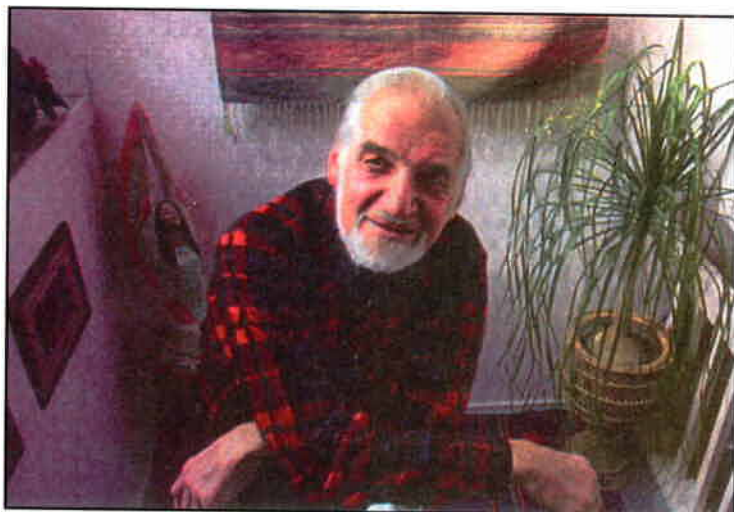


# The New York Times

© 2001 Rick Friedman. All Rights Reserved



James Estrin/The New York Times

Kenneth Aran, 78, says he joined an experimental study of a prostate cancer drug because he had nothing to lose and he wanted to help "somebody down the pike."



Rick Friedman for The New York Times

Maura Babbitt, a rare success story in the testing of unproven drugs, is free of her leukemia and is now back at work as speech pathologist in Attleboro, Mass.

## Finding Cancer Drugs in the Most Unlikely Places

By SANDEEP JAUHAR

On Dr. Steven Soignet's wooden desk at Memorial Sloan-Kettering Cancer Center in Manhattan is an old-fashioned medicine bottle. It is about six inches tall, the kind a country doctor might have used to dispense drugs years ago. Inside it is a silvery powder that has clumped into what looks like little nuggets of shiny gravel. The yellowed label identifies the contents: arsenic.

What is arsenic, the most famous of poisons, doing on a cancer doctor's desk? Serving as a reminder, perhaps, that cancer drugs are sometimes found in the most unlikely places.

In 1998, Dr. Soignet and colleagues in the department of developmental chemotherapy, following up on earlier work in China, found that low doses of arsenic induced remissions in patients with acute promyelocytic leukemia, or A.P.L., a blood cancer, that was resistant to standard chemotherapy. The drug had very few side effects, and remissions averaged five months.

Maura Babbitt was one of the earliest participants in Dr. Soignet's study. Told she had A.P.L. in 1997, at the age of 23, Ms. Babbitt came to Sloan-Kettering in May 1998 after relapsing on standard chemotherapy.

She was told by her doctors in Boston that she needed to be in remission to receive a bone marrow transplant.

"I was basically scared to death," Ms. Babbitt recalled. "When doctors mentioned arsenic to me, my first thought was, 'What? Rat poison?'" It reminded her of a book she had read as a teenager, in which a character poisoned people by putting arsenic — colorless, odorless, tasteless — on sugar cookies.

She got her arsenic intravenously every morning with a few other patients, mostly older men, in a place they called the arsenic room. She took it for 27 days straight, then again for 21. Besides fatigue, she suffered no side effects: no hair loss, no nausea, nothing. She went into remission and several months later got her transplant. Her doctors now say there is no evidence of cancer in her body.

"As far as I'm concerned, it's a miracle drug," Ms. Babbitt said.

Dr. Soignet's arsenic study is one of the recent successes of developmental chemotherapy, the field of cancer research dealing with human testing of unproven drugs. Developmental chemotherapy takes com-

pounds that have passed through a random screening and have shown promise in petri dish and animal studies, and tests them in human volunteers.

Because the National Institutes of Health randomly screens tens of thousands of compounds each year, drugs tested in early human trials often have the flavor of the accidental or bizarre. Paclitaxel, for example, one of the most successful new drugs in recent years, now widely used to treat breast cancer, was originally isolated from the bark of the Pacific yew tree.

Besides arsenic, other heavy metals are being studied for anticancer activity, including antimony and mercury. At Sloan-Kettering, trials are under way looking at high-dose Tylenol and green tea.

"Who would have thought platinum would be active against cancer?" asked Dr. Samuel Waxman, a cancer specialist at Mount Sinai Hospital in Manhattan, citing another metallic success. "It's really a fluke, a total, total fortuitous observation."

Developmental chemotherapy is driven by one simple fact: there is, as yet, no cure for cancer.

Patients want answers and, as the explosion of alternative medicine suggests, are increasingly willing to try unproven therapies. Pharmaceutical companies, in search of the next big drug, are increasingly sponsoring research in this area.

"Compared to 25 years ago, there's a hotbed of activity," said Dr. Waxman, whose foundation, the Samuel Waxman Cancer Research Foundation, also sponsors cancer drug development in the United States and abroad.

Even though cancer patients, many with



Don Hagan/Charles/The New York Times

Dr. David Spriggs in his lab at Memorial Sloan-Kettering.



Chester Higgins Jr./The New York Times

Dr. Steven Soignet showed that low doses of arsenic induced remissions in leukemia patients.

advanced or terminal disease, flock to these trials, many experts worry about the ethics of conducting studies — particularly the earliest human trials, called Phase 1, which investigate drug toxicity — on desperately ill patients.

"It's important to stress the therapeutic intent of Phase 1 trials," said Dr. David Spriggs, director of developmental chemotherapy at Sloan-Kettering. "Otherwise the ethics of the whole process is suspect."

Meanwhile, experts in developmental chemotherapy continue to debate its basic premises: Are Phase 1 subjects too sick or vulnerable to give informed consent? Are they unfairly absorbing risk for future cancer patients, with little benefit to themselves? Are they serving as guinea pigs?

"Guinea pigs don't have a choice," Dr. Soignet responded. "Well, here patients do have a choice, but some people don't want to stop until they try everything."

Despite a few notable achievements, developmental chemotherapy has had only rare successes. Historically, fewer than 5 percent of drugs studied in Phase 1 trials have produced measurable tumor shrinkage. Even if a drug is ultimately shown to be effective, most patients in these trials receive doses too low to help them. A few receive doses that are too high and experience severe side effects.

In the standard Phase 1 format, an experimental drug is administered to a group of three patients, who are then monitored for toxicity to bone marrow, kidneys and so on. If they can tolerate the dose, another group gets the next highest dose, and the process continues in progression, often through 20 or more dose escalations, until a

dose-limiting toxicity is reached.

The Sloan-Kettering arsenic study was not a Phase 1 trial in the conventional sense of investigating an unknown drug. Arsenic has been around for centuries and has been used to treat a variety of ailments, including arthritis, syphilis, sexual dysfunction and African trypanosomiasis, or sleeping sickness.

In the 1980's arsenic was used successfully in Harbin, China, and in Shanghai to treat A.P.L., but this work was largely ignored in the West. "It can be very difficult to assess the quality of clinical data from a developing country," Dr. Spriggs of Sloan-Kettering explained.

Dr. Waxman of Mount Sinai agreed. His foundation was instrumental in bringing arsenic trioxide to this country for clinical trials.

"I'm all for getting these things here if they go through the proper trials," Dr. Waxman said in an interview. "The rules have to be the same here and there. There are no shortcuts."

Rules for cancer drug testing in the United States are rigorous. The process starts with laboratory studies on isolated cells and animals, looking into a drug's mechanism and potential targets. If these studies suggest that the drug may benefit humans, an application is made to the Food and Drug Administration for human testing. But experts say animal results are often a poor predictor of human response. Mouse tumors, for example, may grow much faster than human tumors, making them more sensitive to chemotherapy that targets rapidly dividing cells.

From Phase 1 trials, a drug moves on to Phase 2, where it is tested against a specific cancer, and finally Phase 3, where it is compared head-to-head with established treatment.

Informed consent is a problem in the best of circumstances, but in desperate patients entering complex studies, it may be even more illusory.

Researchers say that despite their best efforts, patients still often misunderstand the purpose of Phase 1 trials.

Many believe that a drug would not be in human trials if it were not promising. "Certainly the most common refrain, and you hear this all the time from patients, is 'if you have something promising, I'll be there,'" Dr. Spriggs said. "The thing is, by the time something has been shown to be

# Finding Drugs for Cancer in the Most Unlikely Places

*Continued From Page 7*

promising, it's no longer a Phase 1 study."

"We have to make consent not a form in the legal sense but a process," he added. "Oncologists must impart a sense of the limitations of these trials, that the opportunity for benefit is there, but also low."

Dr. Soignet says many patients enter these studies expecting a cure. "I tell families there's a low chance you will be cured, but you may very well be helping someone in the future," he said. "But families zone out. Sometimes a family member will all of a sudden say: 'What do you mean? This isn't curable?' I'll watch family members fall over when I say the study has no curative intent."

Kenneth Aran, 78, a retired high school teacher in Ossining, N.Y., had no such misconceptions.

After being told that he had prostate cancer in 1996, he underwent treatment with radioactive seed implants. Despite treatment, his prostate specific antigen level, a marker of the disease, continued to rise. His doctor told him about a Phase 1 trial at Sloan-Kettering for a prostate cancer vaccine, and Mr. Aran decided to enroll.

"My own sense going into this was I really had nothing to lose," Mr. Aran said. "I went into it largely with a good citizen attitude: if I can contribute something to somebody down the pike, then I wanted to do it."

He got six injections under the skin in his arm from October 1999 to April 2000. It is probably too early to judge how much the drug has helped, if at

all, though his P.S.A. level has stabilized. He continues to lead a physically active life, playing tennis, swimming and cross-country skiing.

Phase 1 methodology is being reformed, in part because of ethical concerns. In some studies, drug dosage is being adjusted in individual patients, not just groups of them, so that every participant has a chance to benefit, not just the random lucky few. In other studies, doctors are allowing patients to decide their own dose, based upon their own and other patients' experiences.

In one study at the University of Chicago, 76 percent of advanced cancer patients opted to choose their own dose of the drugs paclitaxel and vinorelbine, and 28 percent chose the highest available dose. More than half said in interviews that choosing their own doses made them feel in control and fully informed.

Though Phase 1 trials are imperfect, oncologists say they are essential for finding new cancer drugs. The successful new chemotherapies in recent years — paclitaxel, cisplatin — all started in Phase 1.

"I wish laboratory experiments could predict clinical success, but that is not the case," said Dr. Gary Schwartz, an oncologist at Sloan-Kettering. "If you went directly from the lab and bypassed these trials, you'd get into a total morass."

In the Phase 1 trials under way at Sloan-Kettering looking at high-dose vitamin D, Tylenol and green tea, there is no shortage of patients signing up.

"Why do people buy lottery tickets?" Dr. Spriggs explained. "When you talk to people who buy lottery tickets, ask them why. They can quote you the odds, they know they're low, but they still think they're going to win."