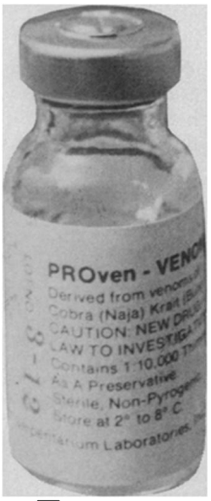


On Proving PROven

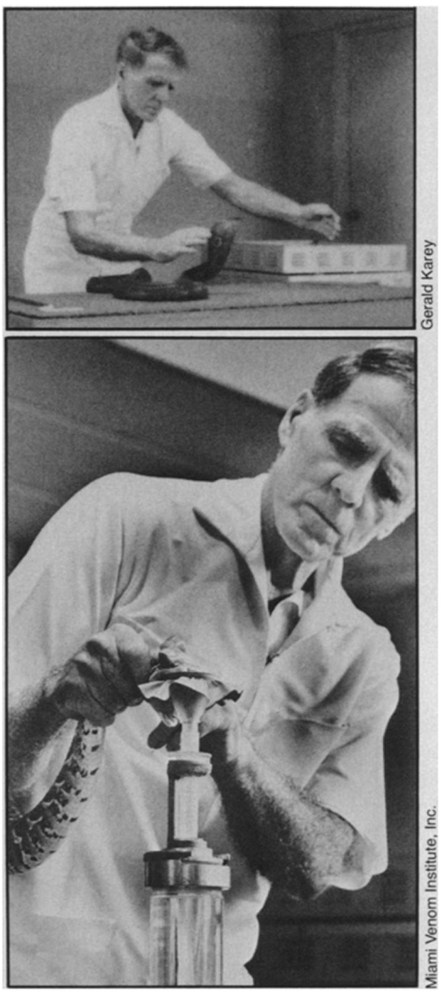
Some call it snake oil, others a wonder drug. Despite regulatory obstacles, scientific evidence to help determine its value may finally be on the way.

BY JANET RALOFF

The agile, white-suited showman doesn't say a word. In steely concentration he slides open the top of a metal box, reaches in and grabs the lizard. Its bite is lethal, intones an attractive assistant perched in safety on a chair toward the back corner of the outdoor stage. The lizard, two feet of squirming muscle, fights, but with trained precision the showman keeps it under control long enough to slide a round disk into its mouth. The lizard bites down on it, injecting venom. Before going back into its box, a tube is fed down the lizard's throat and a week's dinner injected. It's the mamba's turn next, to be followed by a viper, a krait and three cobras. In succession, each deadly snake is milked of its venom, which will be used for science and medicine, the assistant explains.

It's a risky way to earn a living. Several times daily the showman — who's now in his 70's — puts his life on the line as he attempts to distract a snake, hang its fangs over the side of a glass and milk its poison. But when it comes to snakes, he's generally regarded as the best. The U.S. Food and Drug Administration only wishes Bill Haast was handling the venom medicine he's manufactured for 25 years as well as he handles the asp.

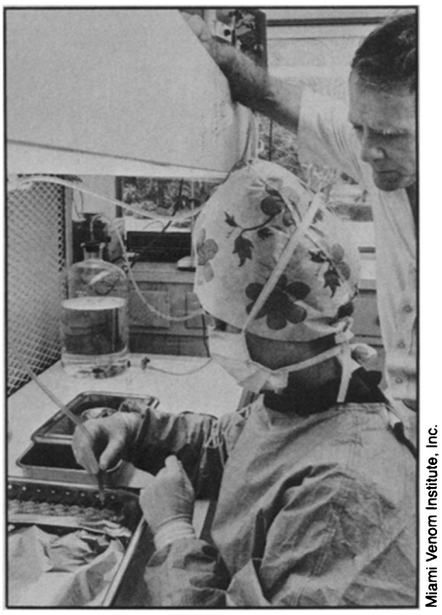
After numerous inspections, investigations and interviews over the past two years, the agency has drawn up a laundry list of federal laws it says Haast has violated in his production and distribution of PROven, the snake-venom solution being sold as medicine. In September 1980 FDA finally asked him to halt production of the drug. When he didn't, FDA got a court injunction, issued Jan. 16, 1981, ordering him to cease and desist operations immediately. When SCIENCE NEWS visited his laboratory last month, production of the controversial drug was still going strong at roughly 1,000 bottles per month.


Gerald Karey
Miami Venom Institute, Inc.

Haast doesn't have to grab his snakes initially by hand (top) to milk them (bottom), but he thinks the venom is better when he does. Even so, being fragile, many like the krait can die of shock after one milking.

Some have compared the drug, which Haast is fighting to keep alive, with laetrile, although there are far more "walking testimonials" to this drug's effectiveness. Studies just beginning will be tackling issues such as safety and the drug's effectiveness. Perhaps the real story now is one of a maverick entrepreneur trying to understand the scientific regulatory environment as an outsider.

Quick to admit that he is no scientist, Haast's career has kept him on the edge of science all his life. But after years of amicable cooperation and appreciation from the scientific establishment, he suddenly finds himself at odds with it and on the road to becoming a pariah.

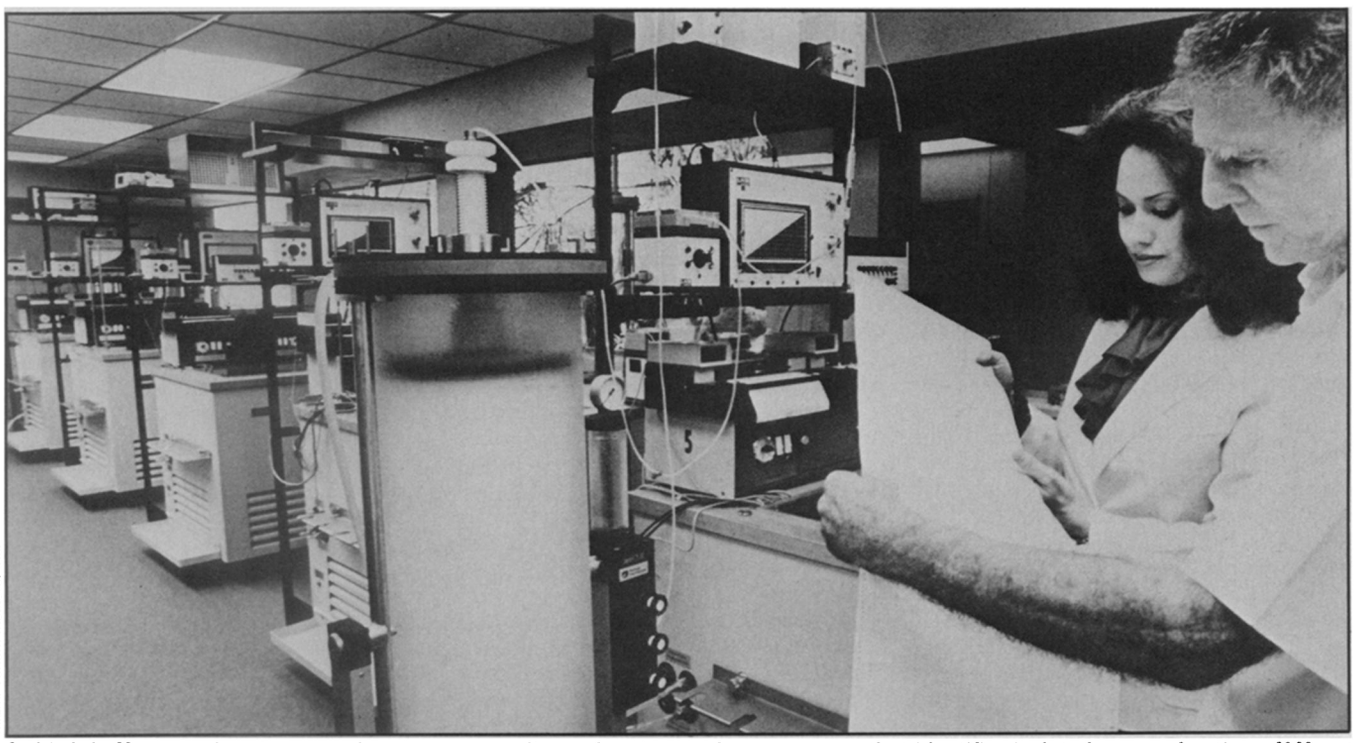

Miami Venom Institute, Inc.

Haast oversees assistant filling PROven bottles. FDA *questions manufacturing practices, which Haast is still changing.*

Haast and the FDA each complain about the other's unreasonable attitude and inability to cooperate fully. And while there is ample evidence that each has at least tried to cooperate in the past, the standoff is likely to become more resolute with the opening this week of a new half-million-dollar clinic in Miami that will be devoted solely to treating patients with PROven. Frederick Sessler, who serves as both clinic president and board chairman, has a vested interest in seeing that Haast's production of PROven is not halted by FDA; he's been granted worldwide distribution rights for the controversial drug.

Haast is a legend. He founded the Miami Serpentarium in 1948, and over the years has supplied venom to more than 90 research institutions throughout the world, including hospitals, universities, the National Institutes of Health and pharmaceutical manufacturers. But he has paid for his status as the world's leading venom producer. He got his first bite, from a timber rattler, at age 11 while hiking at scout camp. Since then he has received about 140 more and been at death's door at least 15 times.

To improve his chances of surviving what has become a more or less routine occupational hazard, Haast has injected himself weekly for decades with minute quantities of snake venom. The prophylactic mixture now contains the poisons of 28 different species to maintain antibody levels that permit his body to fight off what might otherwise be fatal bites. He is the only person alive known to have spontaneously survived a krait bite. Venom of the krait *(Bungarus multicinctus)* is believed to be seven or eight times more toxic than that of the cobra *(Naja naja siamensis)*. A single drop contains enough



Miami Venom Institute, Inc.

In his lab, Haast and assistant study computer readings of an ion-exchange process that identifies isolated venom fractions. If Haast doesn't eventually win FDA *approval to use PROven in this country, Sessler of the Miami Venom Institute threatens to move Haast and his PROven-manufacturing facilities to Jamaica. If PROven is approved, Sessler plans to franchise PROven clinics throughout the U.S.*

poison to kill 16 persons and is ordinarily considered 100 percent fatal if untreated, 95 percent fatal when it is treated. Haast's conditional immunity to the toxins appears to have helped others, too; his blood, given to snake-bite victims via transfusions, has served as an antidote.

While no one questions the value of Haast's own weekly venom injections, it is a variant drug illegally prescribed to others as an "experimental" medicine that has authorities up in arms. Haast describes the drug as an improved version of Venogen, used 25 years ago for multiple sclerosis treatment. Manufactured exclusively at the Serpentarium as PROven, the biologic (a statutory definition for drugs that are, among other things, derived from viruses, toxins or pathogenic organisms) has been prescribed for patients with arthritis, multiple sclerosis, lupus, herpes zoster, herpes simplex, muscular dystrophy, Parkinson's disease, myasthenia gravis and amyotrophic lateral sclerosis (also known as Lou Gehrig's disease). There's even talk of its possible use in treating cancer.

During most of its recent evolutionary period PROven was distributed locally in Florida, primarily through Haast's family physician, the late Ben Sheppard. Sheppard became the drug's staunchest convert, using it on his own patients and claiming remarkable results.

Word got out — largely, Haast claims, through a 1978 article by Bernie Ward in Delta Airlines' SKY magazine. Ward quoted Sheppard as saying, "With arthritis, we have a good batting average. Not 100 percent by any means, but if we get the patients early enough we can relieve the pain and swelling. With chronic cases, I can't promise as much, but even then I can promise relief of pain .... I took the darn stuff myself and it worked for me. I have free use of my hands now and no pain. I've been treating myself with the cobra venom for about four years, the longest anyone has been getting it, and to my knowledge nothing else works as well." Ward quotes Sheppard as adding that "while we do know less about multiple sclerosis, I can promise those patients one thing: They will get good results on bladder control. This is one of the tragedies of multiple sclerosis, the loss of bladder control."

In response to Ward's optimistic article came a deluge of patients — a large share of them with chronic M.S. — and physicians who could no longer offer them hope of getting any better. They came from as far away as Alaska, Israel and Argentina. Treatment required the trek to Florida, Sheppard and Haast claimed, because the pair had not yet obtained FDA approval for interstate commerce in PROven.

Ward's article also attracted the attention of a number of people at FDA, notes Harry Meyer, director of the agency's Bureau of Biologics. FDA representatives immediately contacted Haast and Sheppard and eventually convened a public workshop on the use of cobra and krait venom to treat human disease. Besides Sheppard and others associated with PROven, Meyer brought in chemists who specialized in the biological and pharmacological activity of snake venoms and clinical researchers specializing in the study of arthritis and multiple sclerosis. Meyer also headed a team of experts that toured Haast's facility. But overall, what they saw and heard left them far from sanguine about Haast's production and Sheppard's use of PROven, Meyer told SCIENCE NEWS.

Haast "is totally unscientific," Meyer says. "I went down [to the Miami Serpentarium] to look at his production methods and recognized this enormous variation." According to Meyer, "One of the things that sort of jarred us," is that prior to FDA's investigation, Haast's "product had continually changed in composition. I mean you're dealing with, biologically, very active toxins, you're not talking about table salt." This surprised Meyer, particularly since Haast had stated repeatedly at the earlier FDA workshop that the PROven formulation had been standardized for years regarding both the respective species and concentrations used. "If you study a highly potent compound and during that same study you ... switch the composition, there's no way to draw any sort of objective data," despite testimonials from satisfied patients, Meyer says.

"Then you have the other element," he says, "misrepresentation." Throughout the FDA workshop, Haast and associates were questioned about production techniques, procedures, quality-control tests and specific venom constituents. Haast maintained that PROven contained selected venom fractions from two snakes and two snakes only, the cobra and krait. Yet independent toxicological studies on

PROven samples by researchers at FDA and at the Venom Research Laboratory of the Veterans Administration Medical Center in Salt Lake City made that explanation appear suspect.

"If you inject a mouse intraperitoneally [with PROven], of course you kill the mouse with a very small dose. But the first thing you notice is a massive hemorrhage in the peritoneum of the mouse," Meyer says. "If you inject a tenth of a [cubic centimeter] of it intradermally into a guinea pig, looking for local skin effects, the first thing you see is the skin turns black for about a half-inch all around the lesion, which means you have a massive local hemorrhagic effect. Well, that's not what you'd expect to see with the krait and the cobra."

Meyer confronted Haast with the data, and "he conceded that he did have something else in it. It was water moccasin venom," Meyer says. Haast explained that it was a secret ingredient; by guarding it he hoped to keep others from stealing his medicinal formula. FDA in turn explained that Haast wasn't allowed to keep secrets. Manufacturers of prescription drugs are required by law to inform the government of the exact formulation of their drug.

"It was also subsequent to that that we finally saw the correct records for production. They showed not only that PROven had water moccasin in it," Meyer recalls, "but it showed that [Haast] had used a variety of different kraits and cobras."

That wasn't all. When FDA first made contact with Haast in 1979, "he did absolutely no sterility tests," Meyer says. "Well, I mean there's nothing more basic than sterility tests for any injectible product." Similarly, Haast's manufacturing plant was "largely lacking" in other quality-control procedures required by FDA, including the monitoring of each batch for variations in toxicity, variations in potency (does its shelf-life vary) and monitoring of "a whole host of in-step [chemical fractionation] processes" to assure that one batch was the same as the next, Meyer says. Such procedures fall under FDA's good-manufacturing practice guidelines.

FDA inspections also documented that PROven manufacturing involved three components shipped from outside Florida. That constitutes interstate commerce whether or not PROven itself leaves the state, and means the drug must meet FDA's drug and biologics requirements.

It didn't. The label was legally "misbranded" because it didn't bear adequate instructions for use and was "false" since it failed to list the proper name and quantity of each ingredient. Haast also lacked a biologics-manufacturing license from FDA. What's more, PROven was considered "adulterated," a statutory term indicating it was not produced under good-manufacturing practices.

But none of these legal charges even deals with whether PROven is safe or effective. Establishing both are generally considered the toughest stumbling blocks to a new drug's introduction. However, there have been no full-scale safety or efficacy tests ever conducted on PROven, and even the preliminary animal-toxicology tests were conducted outside Haast's laboratory. Haast claims that stacks of glowing testimonials and unsolicited PROven patients attest to both the drug's safety and efficacy. FDA disagrees.

Also, the agency considers Sheppard's clinical practice too sloppy to serve as even a rough gauge of the drug's potential effectiveness or safety. In a Sept. 18, 1980, letter to Haast, FDA associate director for regulatory affairs, Joseph Hile, wrote: "Our investigation of [Sheppard's] practices documents the unwarranted risk to patients which results from your continued unlawful promotion and distribution of PROven. Despite Dr. Sheppard's oral and written comments to the contrary, adverse reactions appear to have been common... recordkeeping and patient monitoring were dangerously inadequate. Even when reactions were reported to Dr. Sheppard or his clinic, such information was rarely entered into patients' records. Furthermore, no attempt was made to document the nature or frequency of adverse effects. For example, the FDA is aware of one instance in which a young woman, treated in Florida...died after returning to her home in Texas while continuing to use PROven supplied by Dr. Sheppard. Yet, when the patient's family reported her death to Dr. Sheppard, he made no attempt to obtain follow-up information, made no entry in the patient's medical records maintained in his clinic, and did not notify the FDA. Our FDA investigation initiated as the result of the report by another physician identified massive cerebral hemorrhage as the cause of death." FDA noted that since some snake venoms promote bleeding as a sign of acute toxicity, and since "FDA testing has shown that PROven, given in lethal doses, induces hemorrhages in experimental animals," then "it is at least possible the PROven caused or potentiated the event."

Because it is essential to document both the negative and positive effects of the drug, Meyer and others at FDA repeatedly asked Haast and Sheppard to develop well-controlled clinical studies. Though Haast has not objected to them on principle, he claims he can't afford them. However, he does object to cutting off current PROven users — allegedly several thousand — until completion of clinical trials.

FDA's Meyer said the Multiple Sclerosis Society had even considered conducting clinical trials with funds from his agency. But they've backed off. It would be difficult getting good clinical investigators interested, Meyer says, as long as FDA claims Haast isn't manufacturing the drug well enough to be sure it can be used safely and reliably in humans.

But there are also a number of recent events that could spell changes in PROven's status. For instance, Lloyd Feanny, executive medical director at the new Miami Venom Institute, claims he will begin detailed clinical PROven studies immediately, pending state approval of the principal investigators — something he expects to see in a few weeks. His studies won't be "controlled," however, because he considers it "most unfair" to deny patients the treatment many have so desperately come to seek. Anyway, he says, it's hard to do "blind" or "double-blind" studies since PROven causes what looks "almost like an allergic reaction" at the injection site; both investigator and patient would immediately know which patient had received the drug.

Haast himself claims to be expectantly awaiting FDA's next inspection of his plant. PROven production procedures, revised and standardized in April 1980, have been followed explicitly. And nearly $100,000 in new equipment — expected to arrive any day now — should easily assure compliance with FDA's good manufacturing practices, Haast brags. Based on FDA guidance, Haast and his biochemist already feel their sterility and quality-control tests exceed FDA requirements. Meyer concedes that since the last full inspection of the serpentarium facility occurred a year ago, Haast's claims might be accurate.

Finally, and potentially most promising, is a series of preliminary tests begun by Richard Straight and colleagues six months ago at the VA Medical Center's Venom Research Laboratory to test for efficacy. "What we have done has been to make sure we have selected the appropriate animal models to test [PROven] in and to line up the support from the veterinary community to supply us with animals, especially the dogs with autoimmune disease and with rheumatoid arthritis," Straight says. He will also look at testing PROven for safety in healthy animals.

"I would anticipate that if we had any reasonable results that it would serve as a basis for human studies," he says, adding that the studies themselves, however, will not really apply to humans.

He notes that several drug companies are already interested. Right now it is still too early to tell how any of the tests will come out. "I would say we're at least another six months away from even being able to decide whether we were ready to continue on and seek funding for detailed studies, and another two or three years" away from any potential answers.

Of course there's nothing to prove at this point that PROven even works, Straight says, "but I don't think you can reject it out of hand." There are enough data in the literature to suggest that these toxins have effects on cell membranes and the immune system. "So I think we would have to ignore a lot of data" —on venoms, their activities and their pharmacological effects — "to reject [PROven] out of hand." □