



Snakevine Leads Scientists on Sinuous Drug Trail

M. J. Friedrich

MANYALLALUK, AUSTRALIA—Ever since penicillin was derived from mold in the early part of the 20th century, researchers have scoured the earth in search of microorganisms that produce new and different antibiotics that may prove useful in fighting human infections. Microbes that live in the soil have been the most abundant source of these agents. But a recent finding suggests that when looking for new antibiotic-producing microbes, scientists might do well to brush the dirt from under their microscopes and replace it with woody plants.

Researchers have discovered a previously unknown microorganism, living within the tissues of an Australian plant, that produces a novel class of antibiotics (*Microbiology*. 2002;148:2675-2685). In cell culture, these new compounds have demonstrated activity against a variety of human pathogenic bacteria and fungi. Further work is required to determine whether they would be safe and effective for human use.

The new microorganism is a species of *Streptomyces*, a genus that has supplied the world with more than 50 licensed antibiotics. Tentatively designated *Streptomyces munumbi*, the microbe seems to exist in a symbiotic relationship with its plant of residence,

the snakevine (*Kennedia nigricans*), a plant that certain Aboriginal groups in Australia use for wound healing.

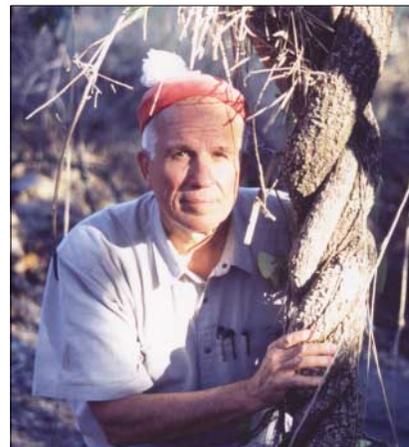
Streptomyces munumbi is a type of endophyte—a microorganism that resides in plant tissue rather than the soil, where most antibiotic-producing *Streptomyces* species have been found. Gary Strobel, PhD, professor of plant sciences at Montana State University, Bozeman, who along with postdoctoral fellow Uvi Castillo, PhD, also of Montana State University, discovered the new microorganism, said in an interview that endophytic microorganisms may represent an untapped source of compounds that could be useful in medicine as well as in agriculture.

GIFTS FROM DOWN UNDER

Studying the interactions of microorganisms and higher plants to look for useful compounds has taken Strobel to nearly every continent. His latest find was made in a remote spot in the Northern Territory of Australia, in a community called Manyallaluk, where Aboriginals from a variety of tribes live.

Strobel often consults with local people to identify plants they have traditionally used for medicinal purposes. In the Manyallaluk area, he worked with tribal leader Reggie Munumbi Miller and his assistants to identify plants of ethnobotanical interest. One of the plants that Munumbi Miller gave Strobel was the snakevine, the stems of which Aboriginal groups have used to make a mash that they apply to wounds to promote healing. The plant is “rather unremarkable” in appearance, said Strobel in a recent interview, and one that he might have overlooked had it not been brought to his attention.

Returning to the laboratory with snakevine samples, Strobel and his colleagues cultured the plant tissue and discovered the new streptomycete—



Suzan Strobel

Out in the Australian bush, Gary Strobel with a mature snakevine coiled tightly around a tree.

the first member of this genus to be found growing in a woody plant. He and his colleagues isolated four compounds, dubbed munumbicins, that were then tested against various pathogens. He named the new organism and the chemicals it produces for Munumbi Miller, who died not long after Strobel visited.

FROM FIELD TO BENCH

In the laboratory, the four compounds, designated munumbicin A, B, C, and D, demonstrated strong antibacterial and antifungal activity against a number of infectious agents, including *Bacillus anthracis* (anthrax) and multidrug-resistant strains of *Mycobacterium tuberculosis* (tuberculosis) and *Staphylococcus aureus*. It also was active against *Plasmodium falciparum* (malaria). In addition, the compounds demonstrated some activity against various cancer cell lines.

James Jensen, PhD, professor of microbiology at Brigham Young University, Provo, Utah, tested the compounds for antimalarial properties and found them to be “very potent.” The munumbicins, he said, appear to have



Kathleen Donald

A tender young snakevine (*Kennedia nigricans*) with heart-shaped leaves.



W. M. Hess, Brigham Young University



Scanning electron micrograph of *Streptomyces* NRRL 30562 growing on the natural host, snakevine (*Kennedia nigricans*), showing numerous mycelia bearing chains of spores $\times 4400$.

broad-spectrum antimicrobial activity that has “proven efficacy at least in the lab against some of the great bugaboos of human disease.”

David Teplow, PhD, associate professor of neurology at Harvard Medical School, has analyzed the structural characteristics of the munumbicins. The chemical and structural properties of these compounds provide clues to finding the active sites, and understanding the mechanisms of action, of these agents.

Teplow said in an interview that in the ongoing search for newer and more potent antibiotics, natural products such as the munumbicins can provide the building blocks for scientists to work with in the laboratory. If, for example, the compounds prove too toxic

to humans—preliminary studies of the effects of the munumbicins on human cells show some toxicity at higher concentrations—or not toxic enough to infectious agents, investigators may be able to design safer and more effective drug analogs based on the molecular structures of the original compounds.

Should the munumbicins or their derivatives prove safe and effective as anti-infectious agents, Jensen said, the compounds must also be inexpensive to produce to be of any use in combating malaria, tuberculosis, and other infectious diseases in developing countries. “We don’t know at this point how much it costs to produce this stuff. The future of this drug as an antimalarial agent would depend on its cost-effectiveness.”

BACK TO NATURE

A little to the north of Manyallaluk in the Kakadu region of the Northern Territory, Strobel identified another endophytic streptomycete from the fern-leaved grevillea (*Grevillea pteridifolia*), a plant whose flowers produce nectar eaten by local Aboriginals. The microorganism produces antibiotic compounds—kakamycins—that are currently being analyzed.

Finding a second antibiotic-producing streptomyceteous endophyte that makes its home in plant tissue provides even greater impetus for



Gary Strobel

The endophyte *Streptomyces munumbi* is shown here growing on a nutrient agar plate.

exploring the plant realm for additional microbes, he said.

However, microbial biochemist Arnold Demain, PhD, of Drew University, Madison, NJ, said that the search for natural products is currently not an approach to drug discovery that the larger pharmaceutical companies are pursuing with vigor. By ignoring nature’s bounty, these companies may be missing out, said Demain. He suggested that rather than beginning from scratch and searching for active compounds in the laboratory, pharmaceutical firms might do well to return to nature to discover new starting compounds that can be further refined in the laboratory. “Nature is much more able than chemists to make interesting chemical compounds,” he said. □

Addiction Treatment Strives for Legitimacy

Brian Vastag

NEW YORK—Some drugs are made in laboratories. Others, like penicillin, are discovered by accident. And then there’s ibogaine, a sacramental substance from West Africa that some say interrupts heroin, cocaine, and other addictions. Over the past 40 years, the tale of ibogaine’s flirtation with legitimacy boasts more twists than the roots of *Tabernanthe iboga*, the shrublike source of ibogaine.

After riding the backpacks of Westerners to the radical 1960s New York City underground, ibogaine rose from a counterculture star to a serious project funded by the National Institutes of Health (NIH). In 1995, after spending several million dollars on laboratory and animal studies, the NIH decided not to pursue ibogaine development. Since then, patent disputes have divided the drug’s champions; a growing network of informal clinics has sprung up; and pharmacologists have discovered that

ibogaine works on the brain in a manner unlike that of any other known drug (see sidebar 1).

After all this, ibogaine and two of its derivatives appear closer to legitimacy now than ever before. In 1998, a University of Miami Medical Center researcher opened an ibogaine clinic on the Caribbean island of St Kitt’s. Although the US Food and Drug Administration (FDA) had approved human trials with ibogaine, Deborah Mash, PhD, associate professor of



neurology and pharmacology at Miami, could not secure funding for a stateside study. Instead, she solicited private investment and won favor from the government of St Kitt's, where a team of physician counselors and addiction specialists now collect data that Mash hopes will cement support for US trials of ibogaine or its metabolite, noribogaine.

Meanwhile, another pharmacologist, Stanley Glick, MD, PhD, director of the Center for Neuropharmacology and Neuroscience at Albany Medical Center, has painstakingly moved a derivative of ibogaine toward its own clinical trial. After 12 years of basic research on scores of molecular variations on the ibogaine theme, Glick recently forged an agreement that represents his best chance for a clinical trial. Signed in November 2002, the contract obligates investors to raise \$5 million within 2 years to fund the first human studies of 18-methoxycoronaridine (18-MC).

But even as ibogaine's supporters sniff success, they worry that the drug's origins will continue to stunt its development. "It's been a continuous battle for respect," said Glick. "Ibogaine has really become notorious because it didn't originate in a lab, but in the counter-culture."

Mash is concerned that burgeoning unsanctioned use will compromise years of laboratory and clinical work. "We've got this explosion of underground clinics, and I'm scared that everything I work for is going to go right down the toilet," Mash said in a recent telephone interview. As an endowed, tenured professor, Mash has all the right credentials: a 29-page curriculum vitae listing 155 publications; a history of millions of dollars in federal grants; a spot at the table of several National Institute on Drug Abuse (NIDA) review committees; and a reputation as a brilliant brain scientist.

And yet, Mash feels that ibogaine's tumultuous history (see sidebar 2) has isolated her. "I'm the only one [doing clinical research]," she said. "I figured, somebody ought to test the

An Odd Drug

Other hallucinations passed before my eyes—burning skulls and faces, the figures of women in black dresses stretching out long white arms toward me from the edges of my vision—but when I tried to speak of them, they disappeared. Meanwhile, the iboga was making me sick. I fought back waves of nausea. I wanted to reach the deeper visionary state, but I was also afraid of the drug.—Journalist Daniel Pinchbeck, in *Breaking Open the Head: A Psychedelic Journey Into the Heart of Contemporary Shamanism*. New York, NY: Broadway Books; 2002.

At low doses, ibogaine is a mild stimulant. At high doses, users report deeply emotional visions, sometimes pleasant, sometimes harrowing. Patrick Kroupa, who credits ibogaine with 3 years of sobriety after 15 years of addiction, said, "It was like dying and going to hell 1000 times."

Whatever the subjective experience, pharmacologists have spent decades puzzling out the brain effects of ibogaine. Their conclusion: it's unlike any other known drug. Kenneth Alper, PhD, assistant professor of psychiatry at New York University School of Medicine, said that the drug appears to work on "every neurotransmitter system we know about." It binds to *N*-methyl-D-aspartate receptors and μ - and κ -opioid receptors; all three play prominent roles in current theories of addiction.

Ibogaine also acts as an antidepressant by binding to serotonin transporters, thereby increasing serotonin levels in the nucleus accumbens. Evidence of impact on the dopamine and acetylcholine systems is less compelling, but deserves consideration, said Alper (*Alkaloids Chem Biol*. 2001;56:2-33).

Most recently, Stanley Glick, MD, PhD, published support for his theory that ibogaine reduces drug-seeking behavior in rodents by blocking $\alpha 3\beta 4$ nicotinic receptors (*Eur J Pharmacol*. 2002;438:99-105).

Meanwhile, Deborah Mash, PhD, a neuroscientist at University of Miami Medical Center, is convinced that ibogaine is nothing but a short-acting prodrug. It quickly metabolizes into noribogaine, she said, which boasts a half-life so long that she has been unable to measure it. This property, she believes, explains ibogaine's purported ability to block drug cravings for weeks or months (*Alkaloids Chem Biol*. 2001;56:79-113).—B.V.

damn thing. You know, either it works or it doesn't."

SCIENTISTS LOOK INTO USE

In 1999, Kenneth Alper, MD, PhD, assistant professor of psychiatry at New York University School of Medicine, hosted the first serious scientific conference devoted to ibogaine. He and Glick compiled the proceedings into a thick volume (*Alkaloids Chem Biol*. 2001;56:1-330). In the preface, Geoffrey Cordell, PhD, a pharmacology researcher at the University of Illinois at Chicago, writes that while ibogaine probably "won't save the world from addiction," it deserves a "prominent position in the list of anti-addictive strategies" under study.

Animal data support Cordell's conclusion. Dozens of articles referenced in the conference proceedings report reductions in self-administration of morphine, heroin, cocaine, alcohol, and nicotine in rodents given ibogaine. The effects

last from 1 to 5 days, depending on dosage and other variables. Noribogaine and 18-MC produced similar results.

That means the central hurdle for ibogaine's supporters is amassing compelling human data. While unknowable scores of addicts continue ingesting ibogaine hydrochloride—a purified powder—or iboga—a whole-plant extract containing a dozen or more active alkaloids—few trained researchers witness the events.

"There's basically one big uncontrolled experiment going on out there," said Frank Vocci, PhD, head of anti-addiction drug development at NIDA.

Consequently, supporters have had to rely on anecdotal accounts. At a pivotal 1995 NIDA meeting, Howard Lotsof, credited with discovering ibogaine's purported antiaddictive potential, presented a collection of case reports. He reported that 10 (19%) of 52 treatments led to cessation of heroin or cocaine use for a year or longer; 15 (29%)



treatments led to 2 months or less of sobriety. The remaining treatments were followed by sober periods between 2 months and 1 year. Despite Lotsof's report, the NIDA peer review panel voted nine to four to reject a clinical grant application from Mash.

She regrouped and eventually opened the Healing Visions clinic in St Kitt's. In 2000, Mash and colleagues published the data from 27 cocaine- or heroin-addicted patients treated at the center (*Ann N Y Acad Sci.* 2000;914; 394-401). The researchers conclude that "self-reported depressive symptoms and craving were significantly decreased" at 1 month after stopping treatment with ibogaine. They also note that ibogaine treatment "decreased participants' desire and intention to use heroin." Mash is now analyzing safety and efficacy data for 257 patients.

SAFETY CONCERNS

At Healing Visions, patients receive what Mash calls "state-of-the-art care," with round-the-clock monitoring and access to the latest emergency equipment. But individuals who seek out ibogaine in other settings receive no such supervision. "It's caveat emptor," said NIDA's Vocci.

Vocci also said that safety was "not the main concern" at the pivotal 1995 NIDA meeting, which he chaired. However, that review panel did cite safety issues. One reviewer wrote that the drug's toxicology profile was "less than ideal," with bradycardia leading the list of worrisome adverse effects.

In fact, between 1989 and 2000, three reports of patients dying after taking ibogaine surfaced, sparking a swirl of questions about the drug's safety. The first death, of a 40-year-old woman in France, apparently stemmed from pre-existing heart disease. A lack of medical information hindered investigations into the other two deaths and led to conflicting conclusions about whether ibogaine was to blame.

In a 1996 radio interview with WBAI in New York City, Mash said that, in the French case, the patient "was very sick, she had a very sick heart and she



Tabernanthe iboga, the West African source of ibogaine, used by some to treat addiction.

shouldn't have been given ibogaine under any circumstances. . . ." And in the second death, "we don't completely know the mechanism of lethality, but it did appear to be respiratory collapse in this case. The bottom line is that you need to be under medical supervision. . . . Ibogaine is an important drug but it is not to be used outside the medical establishment, not ever, ever, ever."

Despite Mash's warnings, unsanctioned ibogaine use appears to be soaring. A sophisticated "underground railroad" of sorts has sprung up in New York, spearheaded by Dana Beal, a long-time marijuana legalization advocate. When heroin- or cocaine-addicted individuals develop an interest in ibogaine, they often call Beal, who acts as intake counselor.

During an interview in his home, the one-time headquarters of the radical 1960s *Yipster Times* newspaper, Beal said that if he thinks someone is a good candidate for ibogaine, he helps arrange a visit to an informal clinic.

The best known operation, according to Beal, is in the Netherlands at the Amsterdam home of Sara Glatt, who practices various types of alternative medicine. Glatt has treated some 85

people during the last 3 years. When an addicted individual arrives, Glatt asks for a history of heart problems or bad experiences with psychedelic drugs. Judging from that information and the individual's weight, Glatt provides between 2 g and 6 g of powdered iboga, the whole-plant extract that contains at least a dozen active ingredients in addition to ibogaine.

Whereas Glatt charges upward of \$1000 for her services, the newest clinic, in Vancouver, British Columbia, offers free ibogaine. The clinic's founder, Marc Emery, won 2000 of 140 000 votes in the 2002 Vancouver mayoral election running on a platform of open access to ibogaine. He recently solicited an ibogaine e-mail list for feedback on a proposed treatment regimen.

Lotsof, on the other hand, has already published a rigorous protocol (Lotsof H, Wachtel B. *Manual for Ibogaine Therapy: Screening, Safety, Monitoring, and Aftercare*, First Revision. Published online. Available at <http://www.ibogaine.org/manual.html>. Accessed November 26, 2002). In the preface to the first revision, Lotsof and co-author Boaz Wachtel write that the manual is "intended for lay-healers who have little or no medical experience, but who are nevertheless concerned with patient safety and the outcome of ibogaine treatments." The manual suggests inclusion and exclusion criteria, ibogaine regimens and doses, and considerations for posttreatment care. A naive physician would likely accept it as a standard medical protocol.

Back in the realm of sanctioned drug development, Glick and Mash are now focused on bringing their respective ibogaine derivatives into clinical trials. "That's certainly the way to go now," said Vocci. Alper voiced a similar opinion, saying that he views ibogaine as proof of concept that the best hope for a therapeutic drug lies with ibogaine derivatives. Glick, too, is certain that the FDA will never approve ibogaine. In addition to safety concerns and the drug's social history, the hallucinogenic effects of ibogaine (see sidebar 1) could be problematic.



A Brief History of Ibogaine

1885: First published description of religious use of *Tabernanthe iboga* in Gabon appears in France; it reports that initiates of the Bwiti religion eat rootbark to induce visions and “meet their ancestors.”

1939: Sold in France as a stimulant until 1970.

1962: Howard Lotsof, a 19-year-old from Staten Island, receives ibogaine from an LSD chemist and gives it to 19 other people. He later reports that five of seven heroin and cocaine addicts in this group, including himself, stop illicit drug use for up to 18 months and experience little or no acute withdrawal.

1970: The US Food and Drug Administration (FDA) classifies ibogaine as a Schedule I drug, making it illegal. Belgium also outlaws ibogaine, but today it remains legal in the rest of the world.

1985: Lotsof receives a US patent for use of ibogaine in opioid withdrawal. Additional patents describing ibogaine treatment for cocaine and other addictions follow.

1989: Ibogaine addiction treatment begins in informal clinics in the Netherlands. By 2002, informal clinics have opened in the United Kingdom, Canada, Slovenia, and Mexico.

1991: After intense pressure from activists, the National Institute on Drug Abuse (NIDA) begins funding preclinical toxicology and other laboratory research on ibogaine.

1993: The FDA approves a US clinical trial of ibogaine sponsored by University of Miami neuroscientist Deborah Mash, PhD.

1995: NIDA review committee rejects funding for Mash’s clinical trial.

1999: Mash opens ibogaine clinic on Caribbean island of St Kitt’s. By late 2002, she has collected safety and efficacy data on 257 addicted patients.

2002: Long-running legal dispute between Lotsof and Mash ends with the University of Miami winning patents for noribogaine, a metabolite of ibogaine. Stanley Glick, MD, PhD, director of the Center for Neuropharmacology and Neuroscience at Albany Medical Center, signs contract to bring ibogaine derivative 18-MC into clinical trials.
—B.V.

After NIDA rejected ibogaine clinical trials, both Mash and Glick struck out with the pharmaceutical industry, which has been traditionally cool to antiaddiction drugs. The Pharmaceutical Research and Manufacturers of America (PhRMA) reports that in 1999, for example, its roster of drug giants had 10 antiaddiction agents in clinical trials. The same companies had more than 400 cancer drugs in clinical development. When asked to explain the disparity, Jeff Trehwitt, spokesman for PhRMA, said, “We certainly don’t know a reason, unfortunately.”

But ibogaine researchers and others, including a spokeswoman for the Substance Abuse and Mental Health Services Administration (SAMHSA), say that addiction stigma and low profit potential are keeping companies away.

Whatever the case, the dearth of pharmaceutical and other treatments means that the societal costs of addiction will continue to climb. SAMHSA reports that in 2000, illicit drug addiction cost the United States \$160 billion in medical care, lost productivity, and crime and incarceration, up from \$117 billion in 1997. Illicit drug addiction is here to stay.

So too, it appears, is ibogaine. □

MISCELLANEA MEDICA

• **Norman Gant, MD**, professor of obstetrics and gynecology at the University of Texas Southwestern Medical Center at Dallas, has received the Baden-Gibbs Award from the Texas Association of Obstetrics and Gynecology. Gant is also executive director of the American Board of Obstetrics and Gynecology.

• **Donna J. Dean, PhD**, has been named first deputy director of the National Institute of Biomedical Imaging and Bioengineering, the newest component of the National Institutes of Health in Bethesda, Md. She was acting director when the institute was established. **Roderic I. Pettigrew, MD, PhD**, heads the institute.

• **George A. Alexander, MD**, a brigadier general in the US Army National Guard, has been assigned as deputy surgeon general for the Army National Guard.

• **Rodney Landreneau, MD**, has joined the University of Pittsburgh Medical Center Cancer Centers (UPMC), Pittsburgh, Pa, as director of the Comprehensive Lung Center at UPMC Shady-side. He was previously director of the Center for Lung and Thoracic Diseases at Allegheny General Hospital.

• **Ruth Kirchstein, MD**, who served as acting director of the National Institutes of Health, Bethesda, Md, for nearly 2 years, until the appointment of **Elias Zerhouni, MD, PhD**, as director, will stay

on at the NIH as senior advisor to the director.

• **Robert Darling, MD**, a captain in the United States Navy, has been appointed senior medical advisor to the Navy Medicine Office of Homeland Security. He will also serve as the Navy Medical Corps specialty advisor for Homeland Security. Darling was previously medical director of the aeromedical isolation team at the US Army Medical Research Institute of Infectious Diseases at Ft Detrick, Md.

Editor’s Note: Miscellanea Medica appears in the Medical News & Perspectives section occasionally. Items submitted for consideration should be directed to the attention of Marsha F. Goldsmith, Editor, *JAMA Medical News & Perspectives*.