CHILD HOSPITALIZED with malaria is one of 200 million people a year who contract the parasite, most of them in Africa, where the current gold standard treatments are often prohibitively expensive.

MEDICINE

SEEDS OF A CURE

Desperate to develop new drugs for malaria and other ailments, researchers are running clinical trials with traditional herbal medicines—and generating promising leads

By Brendan Borrell

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THE TALL FULANI WOMAN CARRIED HERSELF INTO THE TRADITIONAL HEALER'S hut with the bearing of a princess. Like other members of this nomadic cow-herding tribe in southern Mali, she wore a long, flowing blue dress, painted her lips with indigo and henna, and adorned her earlobes with magnificent gold crescents. Once inside, however, the old healer watched her poise wither away. She was weak from recent childbirth, the palms of her hands were pale with anemia and her forehead was hot to the touch. The woman was so terribly exhausted that she nodded off just recounting her woes. "*Soumaya,*" the healer proclaimed. Malaria.

With that folk diagnosis in hand, the two Western doctors observing her visit—Bertrand Graz of the University of Lausanne in Switzerland and Merlin Willcox of the University of Oxford—got to work. The woman signed an informed-consent form, provided her medical history, and allowed the researchers to take a prick of her blood for parasite counts and other analyses. She would be taking part in a remarkable study to measure the cure rate of an herbal tea prepared with the leaves of a canary yellow poppy. By the time of her follow-up, three days later, she was well on her way to recovery.

Although many U.S. Food and Drug Administration–approved drugs have their origins in the natural world, running a clinical trial with a traditional herbal medicine falls outside mainstream practice. The conventional approach to natural drug discovery involves isolating pure compounds from plants, fungi and bacteria, screening and optimizing promising leads in the laboratory, evaluating their safety in animals and, only then, proceeding through clinical trials in humans. Yet few would quibble with the observation that the conventional approach is broken: 95 percent of experimental drugs fail in clinical trials. After too many failures, pharmaceutical companies have largely turned away from natural products. But the alternative—testing vast libraries of synthetic compounds in tiny vials—has not fared much better.

Against this backdrop, Graz and Willcox are attempting to turn the paradigm for natural products discovery upside down: starting with human studies and only isolating active compounds later. The scientists make careful observations of patients already using a variety of traditional herbal remedies to identify the most promising one, then conduct a clinical trial of that remedy. Finally, they identify the active compound, which becomes the starting point for drug development. Their approach, called reverse pharmacology, was inspired by the efforts of Indian scientists hunting for new drugs from ancient Ayurvedic medicine. The beauty of it is that even if a manufactured drug never emerges, the researchers can advise traditional healers and the communities they serve about which herbs work and which do not. And they can carry out this research with a budget suited to the developing world because the early stages require little more than a pen and paper. Their studies of a type of poppy in Mali are exhibit A for the potential success of this approach and have inspired some unexpected players in global health to take a second look at herbal medicines.

LEGACY OF FAILURE

A NUMBER OF HIGH-PROFILE DRUGS available today, including aspirin and codeine, grew out of the study of plants used by humans—ethnobotany, as it is known—yet such success stories have become vanishingly rare. The problem is that there has never been a clear path to gauge the potential of a plant before millions of dollars are invested in drug development. For its part, ethnobotany has always been more descriptive than analytic. Anthropologists might spend time with a shaman in the Amazon, documenting his or her plants and methods, but they have rarely remained in the field to evaluate the efficacy of these concoctions.

Nor has simply collecting and testing every species in sight panned out. An isolated chemical that shows promise in rats or petri dishes is not necessarily safe or effective in humans. The opposite is also true. Some plant compounds may have entirely unknown mechanisms of actions that standard lab tests might miss. One high-profile attempt at such bioprospecting came from Merck, which partnered with Costa Rica's National Biodiversity

IN BRIEF

Conventional methods of drug discovery, which involve testing compounds in vitro and then in animals before evaluating them in humans, have yielded few commercially available drugs in recent decades. **Some researchers** are thus taking a radically different approach in which they study patients who are already being treated with traditional herbal remedies and then analyze the most promising of these natural products in the laboratory.

PRECEDING PAGES: ANDREA BOLOGNESI (*boy*); MARY E. EATON *National Geographic* (*poppy*)

CHILD WITH MALARIA receives tea made from the Mexican prickly poppy during a trial of the herb in Mali (*left*), where traditional healers have long used the plant to treat the disease (*right*).

Institute in the 1990s to take stock of every palm or weevil they could find in the country's national parks and evaluate its pharmaceutical potential. The project was abandoned six years ago without a single blockbuster success. In essence, big pharma's chemists decided they preferred working with compounds they could synthesize on their own, and their lawyers, no doubt, found it easier to lay claim to them with patents. Today these companies evaluate millions of these compounds for hints of biological activity through an automated process called high-throughput screening.

Of course, identifying a biologically active compound is only the first step. In the U.S., the journey from drug discovery to regulatory approval takes 12 years and costs up to $800 million. High-profile flops, such as Sanofi-Aventis's weight-loss drug Acomplia or Pfizer's cholesterol drug Torcetrapib, both of which failed only in the final stages of costly clinical trials, have demonstrated that this model is failing for the developed world. It has had even worse consequences when it comes to neglected diseases in the developing world, where most of the population cannot afford medications that are, by and large, manufactured abroad.

The lack of effective new drugs and the prohibitive cost of existing drugs are particularly troubling where malaria is concerned. Every year this mosquito-borne parasite infects 200 million people in tropical countries, killing half a million. Malaria has evolved resistance to just about everything researchers have thrown at it. In Africa, where 85 percent of the world's malaria cases occur, the current gold standard treatments, artemisinin-combination therapies (ACTs), are subsidized and theoretically available at government clinics and village shops. Yet poor roads and the availability of other, substandard medications make the drug combination's efficacy look a lot better on paper than on the ground. In one recent survey in Mali, 87 percent of children who came down with malaria were initially treated at home, and one quarter received traditional medicines alone. Taking those factors into consideration, some researchers think traditional practices deserve a closer look. But time is running out. Traditional medicine in Africa and other regions is threatened by both modernization and intense competition from Chinese herbal manufacturers, which have outposts in far-flung villages. "If we don't study it now," Graz says, "it may well vanish in large parts of the world within a single generation."

FLOWER POWER

THE IDEA FOR REVERSE PHARMACOLOGY evolved gradually, by trial and error, as Graz and Willcox homed in on and began testing the magical poppy from Mali. Graz is a committed defender of observational studies, in which investigators make inferences about the effect of a treatment based on observation. This type of study contrasts with randomized clinical trials, which randomly assign patients to a treatment group and a control group. Graz recognizes that a randomized controlled trial is the only way to truly tell if a drug works. Yet such trials are often conducted under unrealistic conditions and with only a subset of the patient population, he notes. Although observational studies are not experiments, by documenting and analyzing patient outcomes at clinics, they give researchers a better idea of what works in the real world.

Such a counterintuitive take is what brought Graz to Mali in December 2002. He planned to a run a type of observational trial he invented called the Retrospective Treatment Outcome study, or RTO, with the help of Drissa Diallo, director of the department of traditional medicine at Mali's National Institute of Research in

COURTESY OF MERLIN WILCOX

Public Health. Over many months, their team visited households in which a family member had recently been sick with malaria. Graz tallied 66 plants that families said they used alone or in combination to treat the illness. "The failure rate was high," Graz notes. But there was a bright spot in the data. Of the 952 patients they tracked, 30 used tea made from the leaves of *Argemone mexicana,* a poppy native to Mexico that came to Africa in the 1800s. Everyone who took it reported complete recovery. The study was like high-throughput screening but with humans, which made a promising lead all the more significant.

Graz contacted Willcox with the news. Willcox had run several clinical trials on antimalarial herbs, with mixed results. The two had previously agreed that if Graz were to identify a plant that seemed to work in the RTO, Willcox would come down to run a cohort study, which follows a group of patients over time, and, they hoped, later a clinical trial. When Graz arrived at an Internet café in the city of Sikasso in southeastern Mali to begin his background research on the poppy, however, he made a disturbing discovery. He found a paper entitled "*Argemone mexicana* Poisoning: Autopsy Findings in Two Cases." In 1998 more than 3,000 people fell ill in Delhi, India, and more than 65 died as their bodies swelled from a buildup of lymph. They had all eaten mustard seed oil adulterated with *A. mexicana,* which contains the poison sanguinarine.

Graz and Willcox were spooked. Could their promising natural remedy for malaria kill patients instead of curing them? Many effective drugs can be deadly at the wrong dosages, yet that did not seem to be happening in Mali. The researchers tried to determine the lethal dose of the *Argemone* tea by subjecting mice to increasing amounts of it, but the mice suffered no ill effects. Eventually they determined that sanguinarine occurs only in the poppy's seeds, not the leaves that go into the healer's tea.

The researchers could now proceed with their studies with a clear conscience. And in September 2004 Willcox arrived in the Malian village of Missidougou. Chief Tiemoko Bengaly, a traditional healer whose grandfather had taught him to use *A. mexicana,* was happy to take part in a study of the plant's effectiveness. In contrast with Graz's retrospective study, which looked back in time, Willcox's prospective study would follow patients forward, allowing for more exacting observations and lab tests.

On one of the healer's mud-brick, straw-roofed buildings, Willcox installed a gleaming solar panel and a car battery to run microscopes, centrifuges and an electrocardiography machine. He cautioned Bengaly to shake out the poppy seeds before preparing the tea but otherwise allowed the healer to follow his own time-tested recipe: boiling the leaves for three hours in a black cauldron, over a wood fire. It was the height of the rainy season, and nearly 100 patients were clamoring to be examined on the first day.

Early on, Bengaly prescribed a single dose of tea for three days, but Willcox noticed that patients were not recovering. When he asked if that was normal, Bengaly said that he thought that dose was more "scientific." Puzzled and concerned, Willcox asked what the usual dose was. Bengaly did not have one. He usually gave patients dried plants and told them to drink as much as possible for about a week. Implementing this higher dose, Willcox now saw results. Parasite counts dropped from around 30,000 per microliter of blood to less than 2,000. After two weeks, 89 percent of adult patients had no fever. The poppy seemed to be working.

To prove that the plant was effective against malaria, Graz and Willcox needed to bring this unorthodox drug-discovery process full circle with a randomized controlled trial. Back in Missidougou, the researchers enrolled 301 patients with malaria in the trial. They randomly assigned patients to be treated with a standardized dose of *A. mexicana* tea or with artemisinin-combination therapy and followed them for 28 days. The study, published in 2010, found that 89 percent of patients taking the poppy recovered, compared with 95 percent of patients taking ACT. The full cost of the *A. mexicana* trial, which was paid for by the Swiss Agency for Development and Cooperation, came to $500,000. Willcox and Graz estimate that using the herbal medicine instead of ACT could yield a cost savings of 75 percent.

QUININE OBTAINED **from the bark of the cinchona tree has been used to treat malaria for hundreds of years.**

The evidence from this relatively early stage study is so compelling that Graz and Willcox argue that *A. mexicana* tea should be recommended in Mali and other remote regions where it can be cultivated for adults with malaria that is not life-threatening. This approach could help prevent malaria from developing resistance to modern drugs and reserve scarce medicines for the most serious cases, which can lead to brain damage or death.

Reverse pharmacology dovetails with conventional drug discovery in the next phase of the process, as scientists isolate active compounds from *A. mexicana,* improve their chemical characteristics, and test these pharmaceuticals in rodents and humans in more recognizable clinical trials. Yet in contrast with the conventional model of discovery, in which chemical leads are so plentiful that they are abandoned at the first signs of trouble, reverse pharmacology has the potential to bring leads to the table that have proved to be highly effective and safe. In fact, under the conventional model, *Argemone* would have already been shelved. That is because the poppy compound that shows the greatest antimalarial activity in vitro, berberine, failed to fight the parasite in mice and humans. Why the whole plant is so effective remains a mystery, one that Graz and Willcox hope to crack with further study.

GETTY IMAGES

SCIENTIFIC AMERICAN ONLINE View a slide show of Borrell's photographs from his reporting trip to Uganda at ScientificAmerican.com/jun2014/reverse-pharmacology

PROMISE AND PERIL

THE REVERSE PHARMACOLOGY approach is particularly well suited to finding new drugs for acute diseases such as malaria that can be easily monitored, but it is hardly restricted to such remedies. About a decade ago in India, a consortium of universities, research institutes and pharmaceutical companies began using a reverse pharmacology approach to identify potential drugs for arthritis, diabetes and hepatitis from traditional Ayurvedic medicine. Following nationwide surveys of Ayurvedic physicians, Arvind Chopra of the Center for Rheumatic Diseases in Pune, India, and his colleagues came up with a short list of promising herbs for arthritis and began observational studies in clinics alongside animal pharmacology studies. In August 2013 they published the results of their double-blind randomized controlled trial of 440 patients in *Rheumatology,* showing that a combination of four herbal extracts performed as well as celecoxib (Pfizer's Celebrex) in reducing knee pain and improving knee function.

Meanwhile Willcox and Graz have been spreading the word about reverse pharmacology, training African scientists in several countries who would like to study herbs that boost lactation in women or improve symptoms associated with HIV infection. Last December, Graz traveled to the Pacific island group of Palau, ranked as the seventh most obese nation in the world, to identify traditional medicines that are effective against diabetes and hypertension. His RTO of 30 plants revealed that *Morinda citrifolia,* a tree in the coffee family, was associated with weight loss and that *Phaleria nisidai* was associated with lower blood glucose levels. A clinical trial of *P. nisidai* is now in the works. Success against diabetes, which afflicts tens of millions of people in the developed world, could reinvigorate the hunt for natural products by pharmaceutical companies.

Not everyone is convinced this new strategy for developing drugs is appropriate. Take, for example, Nicholas White, now at Oxford, who knows firsthand about the importance of traditional medicines. In 1979 he found an obscure article in a Chinese journal about an herb called *quinghao—Artemisia annua*—which had been used for more than 2,200 years to treat malaria. Working in the lab, he identified the active compound as artemisinin and ran it through the standard gauntlet of safety trials before progressing to successful human clinical trials in the 1990s. It was, in other words, a success under the conventional model of drug discovery, which is why he is so skeptical of reverse pharmacology. "It seems a bit naive," he observes. Making basic observations of healers is one thing, but running a clinical trial is potentially unethical. "Malaria is a life-threatening infection: Is it right to give a person a bark or a toad?" he says.

Willcox and Graz are used to hearing such challenges. During a presentation Willcox gave at a meeting of the Royal Society of Tropical Medicine and Hygiene in Liverpool, an audience member pointed out that their clinical trial would not pass muster under the guidelines followed by British ethical review boards, which require Western doctors to provide a Western standard of care. Others have suggested that all the money and effort spent on the research should have gone toward administering conventional drugs. "That money would have lasted two years, and after that, what?" Willcox demands. One reason why Diallo initiated the collaboration is because Mali already has a system of approving "improved herbal medicines" and sought to expand the list and beef up the evidence for it. A Malian ethical review board approved the study, and the National Institute of Research in Public Health is now honing a standardized *A. mexicana* syrup that can be manufactured and distributed locally.

Willcox and Graz have also found an unlikely ally in the Geneva-based Medicines for Malaria Venture. "It's been an interesting journey," admits chief science officer Timothy Wells. The only organization focused on research into malaria treatments (as opposed to vaccines), it is staffed by veterans of the pharmaceutical industry, and it funds projects that follow the conventional model of drug discovery. Several years ago it paid Novartis, GlaxoSmithKline and other drugmakers to test more than six million proprietary compounds in their libraries for antimalarial activity. They came back with 25,000 hits. The study raised the bar as to how potent a compound should be to warrant further investigation, but it has not necessarily brought researchers that much closer to a novel antimalarial agent.

When Wells saw the clinical trial data for *A. mexicana,* he was floored. "It's not as a good as ACT," he says, "but the point is that it has not been optimized." Derivatives of artemisinin, for instance, have been designed to be more soluble, and quinine drugs used today have gone through several iterations to enhance their efficacy. To move things in that direction, Medicines for Malaria Venture is now funding the next phase of the research on *A. mexicana* to identify the active compounds in the drugs and measure their metabolism in the body. The organization funded a search for active compounds in another antimalarial herb, which showed promise in a clinical trial in the Democratic Republic of Congo.

CROSSING BORDERS

IN JANUARY 2013 WILLCOX traveled to Missidougou to pay his respects to the family of the healer Tiemoko Bengaly, who had died the previous year. It was the week that the French military began air strikes against Islamist militants in the north, and the turmoil underscored just how important it is for Africans to have local sources of medicine. In 2010 the Global Fund to Fight AIDS, Tuberculosis and Malaria terminated $18 million in malaria grants over charges of corruption, and in 2012 the fund announced it was shuttering the Affordable Medicines Facility, which has provided subsidies to importers to help get reliable drugs into village shops.

Willcox and Graz had plans to measure the public health impact of their *A. mexicana* recommendations, but the tenuous political situation put them on hold. Willcox dared to stay in the country only for a week. One morning he looked out of the car he was riding in and saw those yellow flowers rustling in a fallow field. "It's a stopgap insurance policy," Willcox says, "something to fall back on when you haven't got anything else." SA

MORE TO EXPLORE

***Argemone mexicana* Decoction versus Artesunate-Amodiaquine for the Management of Malaria in Mali: Policy and Public-Health Implications.** Bertrand Graz et al. in *Transactions of the Royal Society of Tropical Medicine and Hygiene,* Vol. 104, No. 1, pages 33–41; January 2010.

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