Science Withou

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RICK FRIEDMAN

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Dyann Wirth is a geneticist at the Harvard School of Public Health. Wirth works with researchers throughout the world to study malaria.

By Alison Davis

In the time it takes you to read this page, three African children will have died of malaria.

The devastation caused by this mosquito-transmitted disease in many areas of the developing world is almost too huge to imagine, stealing a child's life every 30 seconds.

"Among infectious diseases, malaria is one of the top three killers worldwide," says Dyann Wirth. "It's a huge public health problem."

Wirth, a geneticist at the Harvard School of Public Health in Boston, Massachusetts, studies malaria and how it spreads. Because of the global scope of the problem, Wirth teams up with scientists in countries faced with the harsh reality of the disease.

Ultimately, she wants to transfer what she learns through basic research into practical strategies for managing malaria, wherever it strikes.

New Tricks for an Old Disease

Malaria is one of the oldest diseases known to humankind, with early descriptions of it etched into ancient Egyptian scrolls. As recently as the 1700s, people believed malaria rose from stinky swamps and passed through the air. They gave it the name *mal aria*, for "bad air."

Not until just before the turn of the 20th century did researchers identify the true source of malaria. The British physician and entomologist Sir Ronald Ross found evidence of malaria infection inside the egg cells of female mosquitoes carrying certain types of parasites.

With more study, scientists eventually confirmed that female *Anopheles* mosquitoes, which feed on blood to nourish their eggs, spread malaria. Infected mosquitoes pass on the disease as they bite people in search of their next blood meal.

Malaria can be tricky to diagnose because its early symptoms resemble those of many other conditions. These include fever, chills, sweating, headaches, muscle pain, nausea, and vomiting—all symptoms that can appear with common viral infections that usually go away by themselves.

CDC/ JAMES GATHANY

During a blood meal taken from a person infected with malaria, *Anopheles* mosquitoes pick up parasites and spread them to the next person they bite.

Left untreated, though, malaria can quickly progress as the parasitic invasion travels to the liver and all over the body, leading to organ damage; severe swelling of the abdomen, eyes, feet, and hands; coma; and death.

If malaria is caught early, doctors can treat it with medication. One of the most widely used treatments is a drug called chloroquine, which destroys malaria-causing parasites in the bloodstream. Chloroquine is a synthetic derivative of quinine, a natural chemical isolated in the early 1800s from bark of the cinchona tree (early civilizations called it the "fever tree").

When researchers learned how to make chloroquine around the time of World War II, they heralded this discovery as a major victory for public health.

Today, though, public health officials face a substantially gloomier outlook. Parasites quickly develop ways to outwit drugs, allowing the disease to spread.

"When it comes to malaria, the single most important problem is the [lack of] effectiveness of drugs in the Third World," says Wirth.

Although malaria strikes mostly in developing countries, it is not just someone else's problem.

World travelers can play an unsuspecting role in spreading infectious diseases. If you take a trip overseas and come into contact with an infected mosquito, you're at risk for getting, and spreading, malaria.

The relative ease of global travel makes our world an ever smaller place, and mosquitoes don't care who they bite.

Seeds of Science

Wirth, 54, isn't a medical doctor. She is a basic researcher who earned her Ph.D. in cell biology and virology. She loves pursuing the fundamental mysteries of biology by asking questions and testing things.

She grew up in the midwestern town of Racine, Wisconsin. Neither of Wirth's parents were scientists, yet she remembers an early fascination with the natural world. The first toy Wirth ever specifically asked for was a microscope, when she was about 8 years old.

"It's true!" she admits.

Even though Wirth attended a relatively small grade school that didn't have a lot of resources or high-tech scientific gadgets, she clearly recalls a feeling of excitement about science. Every few months, shipments of new supplies for science class showed up, and she couldn't wait for her teacher to unpack them.

"My very favorite elementary school memories were investigating the contents of those huge steamer trunks, which had tons of goodies for learning about biology, astronomy, geology, you name it," says Wirth.

Exploring the trunk contents gave her great satisfaction, nurturing what became a lifelong interest in many different areas of science. Later, Wirth was lucky to find summer research programs for high school and college students. She enjoyed the experiences so much, she knew science would be a permanent part of her life.

"I can't imagine not thinking about science," she says.

Wirth's inquisitive nature has not faded with time. But as she grew into adulthood, she felt a pressing need to connect science with society. The mindset stuck.

"I feel very strongly that scientists have an obligation to help get their discoveries translated into treatments," she says.

On her own time, Wirth works with international groups such as the World Health Organization and Doctors Without Borders. Through these alliances, Wirth hopes to advance the development of treatments for tropical diseases, in spite of the modest financial incentive they offer to drug companies.

Parasite Secrets

Moved by this compelling blend of scientific curiosity and social conscience, Wirth has dedicated nearly all her professional life to investigating the basic workings of *Plasmodia*, the parasites that cause malaria. These organisms' bizarre ability to infect creatures as different as humans and mosquitoes continues to amaze her.

As Wirth explains, *Plasmodia* and other parasitic protozoans (the word means single-celled animal) do something else very unusual: They live within other cells.

Think about it, says Wirth. That's an entire, eukaryotic (nucleus-containing) cell living *inside* another eukaryotic cell that's not a whole lot bigger than itself.

Despite this sizing challenge, parasitic protozoans can deftly maneuver inside different cell types and infect different parts of the body. As a class of organisms, parasitic protozoans harm humans and other forms of life in many ways.

For example, one such parasite, *Giardia lamblia*, can settle into the cells of your small intestine if you drink unfiltered stream water. Even crystal-clear, icy-cold water can be contaminated with small amounts of fecal matter that contains

CDC

This microscopic photo shows the malaria parasite *Plasmodium falciparum* (ring-shaped objects) growing inside human red blood cells (larger, reddish circles).

Giardia-infected intestinal cells. A *Giardia* infection can give you diarrhea and vomiting that lasts for days.

Toxoplasma gondii is another example of a single-celled parasite that can be harmful to people. This organism finds its way into the intestines of cats, which can pass on the disease to people through cat feces containing cells with *Toxoplasma* living inside. Many people who are infected have no symptoms or may feel like they have the flu. Unborn babies and people with weak immune systems, however, can develop serious eye or brain damage.

Of the four species of the *Plasmodium* parasite that cause malaria in humans, a variety called *Plasmodium falciparum* is the most widespread and dangerous, accounting for 80 percent of all human malarial infections and 90 percent of deaths.

Yet despite the impact of these tiny organisms on public health, scientists still don't know most of the details about how *Plasmodia* and other parasitic protozoans damage the body.

What happens to a *Plasmodium* parasite once it gets into a red blood cell, then the liver? What does it do inside the gut of a mosquito?

What about the mosquito? Is it changed by a parasitic interaction? Do red blood cells hold secrets of past encounters with *Plasmodia* or other parasites? Exactly how does the human immune system react to the parasite?

These and many other mysteries of parasite biology remain unsolved. But, according to Wirth, knowing the answers is absolutely critical for understanding and treating malaria and other diseases caused by parasites.

DNA Shows the Way

The trouble with parasites, Wirth explains, is that they are especially agile when it comes to developing counterattacks to the drugs we use to kill them. With their strange characteristics and uncanny talent for evading medical attack, *Plasmodia* are by all measures biological survivors.

The biological survival process works like this. When a constraint of any kind is put on an ecosystem, all species within the system feel pressure to find a way around it in order to survive. The ones that are best at adapting "win," and live. The others, unable to change, die off. This is evolution at work.

In the case of antimalarial drugs, only those parasites that have the molecular tools to fight off our medicines can survive and make more of themselves. Through evolutionary change, the molecular features that give a survival advantage are passed on to offspring. Over time, these features show up as DNA signatures: particular, recognizable genetic sequences.

Wirth's main focus is on DNA. As a geneticist, she studies inheritance, the process of transmitting genetic information from one generation to the next.

DNA carries genetic information in creatures as varied as earthworms, sunflowers, people—and of course, in parasites like *Plasmodium*. You might think of it this way: Each organism's genome, or its entire set of genes, is like a molecular scrapbook that chronicles events happening over time.

Millions of these events occur. A parasite's interactions with the human immune system…its encounters with the body chemistry of a mosquito…run-ins with antimalarial medicines…and so on. All these interactions leave traces in DNA. Evolution leaves its marks within genes, through slight changes, additions, and subtractions of DNA building blocks, or nucleotides.

But the tricky part is that the scrapbook comes without captions. There's nothing indicating what's what. No tags saying, "DNA changed by chloroquine, September 10, 2005," or, "*Anopheles*, Argentina, summer 2001."

Rather, scientists like Wirth compare DNA sequences of the resistant parasites with those that still respond to drugs. They focus on regions of sequences thought to be involved in drug resistance, as suggested by earlier lab work.

"We look across populations of parasite genomes and ask a very simple question: Where are the differences?" Wirth explains.

In genetic-speak, researchers call those differences polymorphisms. When a genetic change affects a single DNA nucleotide, the change is known as a single-nucleotide polymorphism (SNP, pronounced "snip").

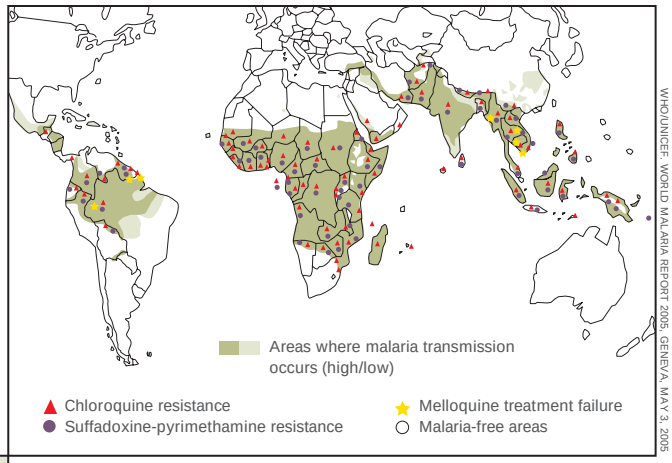
DYANN WIRTH

Wirth collaborates with Senegalese researchers working at a malaria clinic in Pikine, Senegal (top), and at a hospital lab in Dakar (bottom). The scientists also spend time gaining expertise in Wirth's Boston lab.

Wirth and her international research team are currently scanning the DNA of several *Plasmodium* chromosomes in search of SNPs, or patterns of SNPs called haplotypes, that spell drug resistance in the genetic language of parasites.

For these experiments, Wirth and her coworkers first draw small amounts of blood from patients at malaria clinics in Africa, South America, and Asia. Everyone has already agreed to participate in these research studies. After retrieving parasite DNA from the blood samples, the scientists used standard chemical techniques for reading and comparing DNA sequences.

Since the scientists must compare millions of DNA nucleotides from hundreds of samples, they let a computer equipped with specialized software do the grunt work. Certain recurring SNPs that the computer identifies become promising targets for designing vaccines or creating new drugs.



WHO/UNICEF. WORLD MALARIA REPORT 2005. GENEVA. MAY 3, 2005

Resistance to antimalarial drugs such as chloroquine (red triangles) is widespread throughout much of Africa and other parts of the developing world where malaria transmission is high (dark green).

Team Science

For about 7 years, Wirth has been collaborating with researchers in Dakar, Senegal, to use genetic approaches like these to track and fight malaria. Part of the effort involves working closely with local scientists in this West African region, teaching them how to use and apply modern genetic technologies. This partnership helps to inform their decisionmaking about implementing public health measures.

One interesting observation that Wirth and her team have made is that human activity, such as commerce, can help spread mosquito populations and drug resistance. For example, standing water in irrigation ditches or old construction sites can create breeding sites for mosquito larvae.

In other words, the things people do can propagate malaria and the drug resistance that goes along with it. Through her studies, Wirth and her coworkers have been surprised and alarmed to observe the spread of resistance across extremely wide geographic areas.

An overarching goal of Wirth's research is to use genetic testing to develop an early warning system to detect when malaria drugs aren't working, allowing time to try different approaches. For example, a mixture of different drugs can minimize the development of resistance, says Wirth.

The global significance of Wirth's efforts may seem obvious. Yet she's quick to note that progress wouldn't have been possible without somebody digging around asking basic questions.

Among other things, her experiments have helped guide the search for genetic signatures of antimalarial drug resistance

among the 24 million nucleotides that make up the *Plasmodium* genome.

Without the fundamental groundwork, Wirth emphasizes, "We wouldn't even know where to look."

A Magical Time

While Wirth's research helps lead the effort to develop new methods for malaria surveillance and treatment, it also creates new understanding about genetics. This information helps build on knowledge of the role heredity plays in disease.

In a similar vein to the approach Wirth is pursuing, other scientists scan the genomes of people to find small differences that may foretell our health. The scientific methods Wirth and her coworkers use are the very same techniques used by researchers looking for hereditary links to breast cancer, heart disease, depression, and many other disorders.

This scientific pursuit helps us paint a picture of the past and plan for the future. Learning how an organism's biology and behavior change over time is even helping scientists create predictive models for responding to disease outbreaks (see sidebar below).

Now that researchers have access to the sequences of many parasite genomes, it is fairly easy for scientists like Wirth to look broadly at parasite DNA and compare it with that of other organisms. Vast scientific horizons, like the uncharted galaxies once facing early astronomers, lie ahead.

As with planet hunters, today's biologists explore genome space, searching for yet-undiscovered patterns—biological constellations, perhaps—hiding in an organism's genome. The information will most surely have ripple effects, extending our understanding of the larger universe of human health and disease.

Wirth predicts that as technology races forward, new tools will fuel rapid growth in fundamental knowledge. This, she says, is the raw material needed to stop infectious diseases in their tracks and improve global health.

"I think this is a magical time for discovery, for really making a difference," Wirth says. ■

The MIDAS Touch

RICK FRIEDMAN

Admit it, you need a computer to get through the day. Doing homework, instant-messaging your friends, buying stuff online, finding directions—computers make it easier for you to get these and many other things done.

Believe it or not, computers may also make your world a safer, healthier place.

Biology is changing into an information science, with computers taking on new roles in the discovery process and even playing the part of a community health investigator. For example, as part of a National Institutes of Health-funded experiment, scientists use computers to play out various scenarios and develop action plans to respond quickly to a sudden infectious disease outbreak or a deadly act of bioterrorism.

The project, named MIDAS, for Models of Infectious Disease Agent Study, hinges on an international network of scientists with a wide range of expertise: mathematicians, computer scientists, epidemiologists, geneticists, and public health experts.

As one of its first projects, the MIDAS team created mathematical models to simulate an outbreak of a particularly deadly strain of avian influenza virus, or "bird flu." The researchers created a hypothetical Southeast Asian community of people living close together in neighboring towns or cities.

By plugging in data related to the infectiousness of the virus, population density, and the locations of schools, hospitals, and other community structures, the scientists programmed the computer to figure out the consequences of vaccinating specific groups, giving antiviral drugs, limiting travel, and other interventions … all in preparation for the real thing, should it happen.—*A.D.*