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Drug Resistance in Malaria: A Peruvian Research Experience

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Drug Resistance in Malaria: A Peruvian Research Experience

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research article

Drug Resistance in Malaria: A Peruvian Research Experience

—Ryan Haley (Edited by Mandy Chesley–Park)

To begin, I'll start with the descent. As my Boeing 747 flew over the Peruvian rainforest, I looked out the window and stared down at strings of lights that appeared to be either convoys of boats or small cities along the Amazon River. Upon landing in Lima at 2 a.m., I quickly got my bags, spotted the taxi driver holding a sign with my name, and made my way through the screaming crowd. We raced through the city, the driver dodging potholes and calmly talking to me in Spanish while I tightly clutched my seat. At 4 a.m., after traveling for over twenty-four hours, I finally arrived at my apartment with two hours to sleep before I had to get ready for work. I opened my journal, noted the date and time, and wrote "70 days left." My arrival officially marked the first day of my summer 2007



The author at the US laboratory outpost in the Amazon.

research experience working for the United States Navy as a medical scientist studying malaria. Previously, I had known the disease only through textbooks and movies, but a summer in Peru would certainly change that.

An Introduction to the Problem

Malaria is caused by several different species of bacteria, but *Plasmodium falciparum* is the name of the single-celled parasite most widely known to cause this infectious disease (1). The parasite is transmitted by mosquitoes to humans, where it infects red blood cells and multiplies within them. These cells eventually rupture releasing more parasites that can restart the process in the human body or enter another mosquito and in turn spread infection. The parasite lodges itself in the host's liver, meaning that those who survive an initial infection may later be reinfected when the parasite becomes active again (2).

Malaria strikes over 500 million people annually, causing fatigue, high fever, severe chills, sweats, nausea, and vomiting, which can result in up to 2.7 million deaths each year, mostly in children (2). Several anti-malarial drugs, including quinine, have been developed in efforts to prevent reinfection by inhibiting the parasite's ability to draw sustenance from human blood cells (1,3). However, just as the overuse of anti-bacterial drugs has created drug resistant strains of bacteria, the overuse of anti-malarial drugs can create drug resistant strains of malaria. In parts of the world where overuse of a single drug is prevalent, such as the jungles of

Southeast Asia, central Africa, and northern South America, strains of bacteria resistant to this drug have been discovered (4,5). As a result, doctors are finding themselves unable to treat a disease that was once treatable.

My reason for traveling to Peru was to investigate this drug resistance at the genetic level. I went with the knowledge that the parasite's resistance to several anti-malarial drugs has been shown to correlate with the number of copies of the *pfmdr1* (*Plasmodium falciparum* multiple drug resistance 1) gene present (6). This gene is found within both resistant and non-resistant strains of the bacteria *Plasmodium falciparum*, but its mutation is what gives the parasite drug resistance (6). When the *pfmdr1* gene mutates, the protein the gene codes for also changes. The modified protein makes the organism resistant to a large number of anti-malarial drugs. Having more than one copy of this gene further enhances the parasite's drug resistance by increasing the rate of protein production. This is similar to having multiple workers help build a house: just as a house is built faster with more manpower, drug resistance of the malaria parasite builds with greater numbers of the mutated *pfmdr1* gene. The goal of my study was to learn if the malaria strains circulating in the Peruvian Amazon carried multiple copies of this gene, or if other factors were responsible for drug resistance in this region.

To answer my research question I spent the majority of my time at the main US military laboratory in Lima. Here I separated out DNA from infected patients' blood samples and performed real-time polymerase chain reaction (PCR), a process in which millions of copies of a small section of the *pfmdr1* gene are made from the parasite's DNA using two tiny strands of DNA called primers. This process was repeated, allowing the primers to attach to both the newly created DNA and the original parasite's DNA. I then compared the patients' samples to the lab-grown samples and determined how many copies of *pfmdr1* were present in the parasite infecting each patient.



The author with fellow researchers at the main US laboratory in Lima.

Fieldwork in the Peruvian Amazon

After six weeks of lab work in Lima, my mentor, Lt. Dr. Bacon, asked me to travel with him into the Amazon to get an overview of his malaria project. After spending the first day with Dr. Bacon and other research scientists, I would then be left to work alongside a physician for eleven days in the rainforest. I was excited to witness firsthand the importance of my laboratory work.

As we landed in Iquitos, a small city located on the Amazon River, an unbearable wave of heat washed over me, and I instantly started to sweat in my slacks and long-sleeved dress shirt. The airport consisted of a small building and a slab of pavement seemingly dropped in the middle of the rainforest. Our driver took us to the military base, zooming through narrow streets filled with open air markets; houses painted in vibrant whites, reds, blues, and yellows; and thousands of people wandering in loose-fitting clothes and flip-flops. I received a tour of the laboratory facilities and then spent the rest of the day traveling to one of the three malaria field sites from where my lab samples had come. We traveled up river on a long, slender single-engine boat to the village of Padre Cocha. On a hill stood a small cement health clinic occupied by a Peruvian infectious disease physician and a laboratory technician. The building's paint was chipping and both the door and windows were missing. There were no malaria patients that day; a slow day, but it was the dry season.



The author and infectious disease physician Soloman Durant traveling by boat to a remote Amazon village.

The next day Dr. Bacon and the other scientists left Iquitos. I met with the Peruvian physician, a thin man named Soloman, and we traveled to a different site. This tiny village was made up of wooden homes with thatched roofs of palm leaves. The clinic was similar to the one in Padre Cocha, except that this day we had business. Several little boys sat on a wooden bench outside the clinic; one, wearing a pair of flip-flops, shorts, and a Mickey Mouse sweat shirt, was visibly shaking and sweating. He crossed his arms tightly, huddling to stay warm despite the intense heat of the jungle.

“That one looks like a malaria patient for the study,” Soloman told me. After examining the boy and taking a

blood sample, we looked under the microscope and quickly recognized infected blood cells. The boy would make a good patient for our study. This was just one of many malaria patients I saw in my short visit to Iquitos; returning to Lima, I knew that their blood samples wouldn't be far behind me.

The “Big Picture”

Back in Lima, I began to understand the larger picture and purpose of my work. I spent the remainder of my days in Peru analyzing hundreds of new samples from individuals infected with malaria. I tested each sample three times to ensure the number of pfmdr1 copies I was observing was correct. In all of these samples I did not find a single infected patient whose sample possessed two or more pfmdr1 genes. These results showed that increased anti-malarial drug resistance in Peru is not simply due to the presence of multiple copies of the pfmdr1 gene; rather, there is more to it.

Although this was not the answer I had anticipated, because of my research there is now one less possible reason for increased anti-malarial drug resistance in Peru, making it easier for scientists to identify the true reason. My data showed that this type of testing could be used in other countries whose populations are infected with malaria to develop more appropriate methods of treatment and slow down the spread of drug-resistant strains. While malaria may not be a large problem here in the United States, it is important to know that millions of people suffer from this disease. Learning how drug resistance develops will help scientists continue to effectively treat malaria and other diseases world wide



The author with Dr. Bacon and his research team at a malaria clinic in Padre Cocha.

On my last day, after saying my goodbyes and returning from work, I packed my belongings to leave the country I had come to call home. Although I would be returning to the United States, the important work I did in Peru would continue on in other researchers' hands. One last race through the city, a good conversation in Spanish with the taxi driver, and I arrived at the same airport where my summer research experience had begun.

Later, as I went through US customs in Georgia, a tall, thin woman in a red airport suit looked over my passport carefully. She raised her head, smiled, and in beautiful English said, “Good morning sir, you’ve been gone a long time. Welcome home.” I was *home*. So much had happened to me; I had done and seen things I never could have imagined. I learned the answer to my research question, and learned a lot about myself as well. My summer in Peru was the most difficult thing I have ever done in almost every way, but it was by far the most rewarding.

I would like to thank the Hamel Center for Undergraduate Research for their financial support of my study through a Summer Undergraduate Research Fellowship (SURF) Abroad. I would also like to thank Dr. Louis Tisa of the University of New Hampshire Department of Microbiology for his expert help in writing the grant proposal, the final report, and overall as my sponsor. Finally, I would like to thank Lt. Dr. David Bacon for hosting me both as a researcher and as a visiting scientist. His unique style of mentoring has, for me, been incredibly influential in my discovery of the scientific process.

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Author Bio

*Looking back on his Peruvian experience, **Ryan Haley** describes it as both a painful and rewarding experience. He quickly adds, “I would do it again in a heartbeat.” Ryan is finishing his last year as a biochemistry major and will be graduating in May 2008. Although he originally envisioned himself as a scientific researcher, following his experience in Peru, Ryan realized the demand there was for physicians not only in the United States but throughout the world. Now Ryan is feverishly applying to medical schools. He is glad he received “real world” experience during his SURF Abroad project; he also learned that travel and research demand flexibility. “You may not get what you want, but you get something.”*

Mentor Bio

*For Dr. **Louis S. Tisa**, mentoring is synonymous to teaching; “I try to help my students reach their full potential in any of their endeavors,” he explains. When Ryan approached Dr. Tisa with a SURF proposal to study malaria in Peru, Tisa was very supportive. Having worked with Ryan over the last year and half, Tisa knew that*

Ryan's work ethic would benefit both his experience and his on-site research. When asked if he too has benefited from Ryan's experience, he quickly responds, "What I gained from this experience was the satisfaction that I helped Ryan broaden his life's experience by living in another country that had a totally different culture." Furthermore, he reports that the molecular techniques Ryan learned in Peru have aided him in his classroom lab research. Tisa is an associate professor of microbiology and genetics at the University of New Hampshire. He takes pride in his students' progress and is proud of his work as a faculty mentor for the Research and Engineering Apprentice Program, in which he mentors socially disadvantaged high school students by encouraging them to pursue careers in math, science, and technology through hands-on experience.