Profile of Janet Hemingway

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As the wheels of a biplane approach a desolate airfield in the Solomon Islands, a man wearing only a loincloth breaks through the brush, brandishing a spear and a flail. From behind the plane's windows four biologists watch with wary eyes and silently map an escape route. "You're thinking, 'What am I supposed to do here?'" recalls Janet Hemingway, Director of the Liverpool School of Tropical Medicine, International Director of the Joint Centre for Infectious Disease Research, and a recently elected member of the National Academy of Sciences. "And then you realize this is a welcoming committee."

Throughout her career, Hemingway has tackled the problem of malaria transmission from many perspectives: She has worked shoulder-to-shoulder with villagers in tropical countries, performed basic research in molecular biology and biochemistry, uncovered countless mechanisms of insecticide

resistance, and helped develop life-saving quinolone antimalarial drugs (1). In her Inaugural Article (2), Hemingway explores the increasing challenge of insecticide resistance in *Anopheles gambiae* and *Anopheles funestus* mosquitoes, malaria vectors prevalent in the southern African country of Malawi. The findings reveal that pyrethroids, the most effective antimalarial insecticides known to date, are under siege by resistant variants of *Anopheles*, and increased monitoring in the impoverished country is desperately needed to track the underlying mechanisms of resistance before malaria regains a stronghold.

A Rebel with Just Cause

Hemingway was born in 1957 to a working-class family in the small coal-mining town of West Yorkshire, United Kingdom. Her parents owned a corner shop and her

grandfather worked in the mines. At around age five, Hemingway's grandfather presented her with a pair of retired "pit" ponies that had pulled coal trucks in the mine but had never been ridden. "I was kind of plopped on top of one, and off we went," she recalls. Much of the next few years was spent outdoors "running riot" with ponies Captain and Blaze, a Labrador-sheep dog cross named Rinty, and a growing menagerie of birds, frogs, and animals that family and neighbors left in her care. "It was every girl's dream, I suppose, trying to sort out these two little ponies and everything related to animals and the outdoors."

Soon, Hemingway's family moved and she transferred from a large comprehensive school to a small, all-girl grammar school. Although Hemingway passed the requisite examinations, the new headmistress disliked her previous placement and objected to her admission. Despite her obvious bent toward biology and genetics, all of the science classes were full by the time she enrolled, and so she studied the arts. Hemingway plodded through her coursework, determined to do just well enough to get by.

Around the age of 16, Hemingway contemplated becoming a veterinarian, although no one in her family had attended college. "When I went to the headmistress and told her I wanted to stay in school, she laughed because she didn't think I was going to get through my exams," Hemingway recalls. "She hadn't worked out that I was actually bright." Against resistance from the headmistress, who objected to girls pursuing science, Hemingway switched her studies to gain the advanced-level courses required for college admission. "I picked biology—which felt a bit like falling off a bus, it was so easy—and chemistry, which I had never done before." Options for the third required subject were limited, though, and Hemingway settled for the unusual combination of biology, chemistry, and religious studies. Ultimately, the coursework did not satisfy the requirements for veterinary school and was not deemed rigorous enough for most universities in the United Kingdom, but it afforded

Janet Hemingway. Photo courtesy of McCoy Wynne Photography.

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at least one option: admission to an undergraduate program in zoology and genetics at the University of Sheffield (South Yorkshire, England).

During her second year at the university, days after selecting a thesis project on fruit fly genetics from a list of approved topics, Hemingway attended a guest lecture on malaria control by Graham White from the British Museum of Natural History. "Once a rebel, always a rebel," Hemingway recalls. "I thought, why bother doing something on *Drosophila* when I can go and work on these mosquitoes?" Hemingway broke the news to her zoology and genetics advisors, who studied octopus behavior and *Drosophila* genetics, that she wanted to switch to a topic of her own making: one that ventured into new territory for the university.

With their approval, Hemingway asked White for help in establishing the university's first mosquito insectary. Not everyone was pleased, however. The building's janitor was accustomed to mopping the floors around the innocuous *Drosophila* cages in other laboratories, but Hemingway's mosquitoes were another story. The mosquito larvae were kept in plastic bowls and transitioned to netted cages when they matured, "but the odd one is bound to get out," Hemingway says. "I was forever apologizing because usually the mosquitoes like biting early morning and early evening, and the only living thing around at that time was the cleaner." The janitor's patience ran out when Hemingway decided to study predatory *Toxorhynchites* mosquitoes, which were about five-times larger than the other species and did not bite humans but fed exclusively on the larvae of their prey. "The first morning after they arrived, the cleaner walked in and just kind of stood there, staring at the new mosquitoes," Hemingway recalls. "And then he said, 'That's it! Those things will take a pint of blood if they bite me!'" Despite Hemingway's reassurance, the janitor quit on the spot and Hemingway was forced to clean the laboratory for the rest of the year.

By this time Hemingway was seen as a rising star in academic circles. Her work in establishing the insectary had spurred close relationships with many prominent entomologists in the United Kingdom, and they eagerly awaited her graduation. "About half an hour after I heard that I was to receive a first-class honors degree, the phone rang and it was George Davidson from the London School [of Hygiene and Tropical Medicine]. He said, 'I hear you just got a first. Think you'll come and do a PhD with us?'" After a brief chat, Hemingway accepted his

offer. "About an hour after he'd rung, all the rest of them rang, but by that point I'd already said yes to George."

To the Tropics

At the London School, Hemingway studied the biochemistry and genetics of insecticide resistance in *Anopheles* mosquitoes, the primary transmitters of the *Plasmodium falciparum* protozoan, which causes malaria. Her project characterized the genetics of resistance to pyrethroids and other insecticides in various species of mosquitoes (3). She completed her doctorate in less than two years and was soon en route across the Atlantic in pursuit of a postdoctoral program. Hemingway joined the laboratory of George Georgiou at the University of California at Riverside, and continued her studies on the biochemical mechanisms used by insects to evade organophosphate and carbamate insecticides, as well as the use of supplementary chemicals to combat the growing problem of resistance (4, 5).

In 1984, Hemingway was awarded a Medical Research Fellowship and returned to London. Hemingway also received a prestigious 10-year Royal Society Junior Research Fellowship. The award unveiled a new horizon for Hemingway, allowing her to develop an independent research base in London while traveling extensively and establishing research collaborations between the ministries of health and various universities in malaria-endemic regions of the world. "It was just this great adventure, really, that I had set off on—and someone else was going to pay me to do it! It sounded like a great career to me."

Over the next decade, Hemingway lived for nearly half a year in each rural village, returning to her research base in London for six months before moving on to the next country. With time, she became adept at performing biochemical and genetic assays in the field to explore the enzymes responsible for insecticide resistance in local mosquito populations (6). Throughout Hemingway's travels, she never ceased to be surprised at the villagers' eagerness and curiosity about her work.

Over the years, Hemingway has traveled to Sri Lanka, Sudan, Thailand, India, and Tanzania. Extended stays in each country afforded Hemingway a deep understanding of the complex cultural, economical, political, and environmental issues affecting malaria transmission. By the end of her fellowship, Hemingway had blazed an international trail of productive, often decades-long, research partnerships between clinicians and entomologists. She continues to oversee research centers in Malawi, Tanzania, and Ecuador, as

well as projects in Cambodia, Mozambique, Mexico, South Africa, Sri Lanka, Thailand, Equatorial Guinea, and the United States. In recent years, data from these ongoing collaborations allowed Hemingway to collaborate with others to create a comprehensive world map of the major mosquito vectors of malaria, overlaid with climate data to reveal the geographic boundaries for each species (7). Hemingway hopes the map will serve as a community resource for regions where malaria is endemic.

During her travels, Hemingway recognized the need for stronger action on the public health front. In the 1980s, she worked with the Industrial Insecticide Resistance Action Committee, the National Malaria Control Program, and a local research center in Chiapas, Mexico to establish the world's first large-scale resistance management program to test the long-term public health effects of insecticide application models. Since 1985, Hemingway has been a standing member of the World Health Organization's Expert Committee on Insecticides and Insecticide Resistance. To urge the development of additional insecticides and antimalarial drugs, she aggressively pursued relationships with industrial firms. Her first partnerships were forged with Sumitomo Chemical Company and Wellcome Industries, Ltd, and she soon targeted larger firms, such as Syngenta (formerly Imperial Chemical Industries), Novartis, and Bayer. In 1990, Hemingway became the sole academic member of the Joint Industries Pesticide Resistance Action Committee, where she served until 2004. The following year, she joined vector biologists Barry Beatty, Tom Scott, and Brian Sharp in founding the Innovative Vector Control Consortium, funded by the Bill and Melinda Gates Foundation. Over the past eight years Hemingway has served as CEO of the consortium and helped stimulate international industries and academic researchers, as well as the African and Latin American Ministries of Health, to develop new pesticides for malaria and dengue control, as well as products for monitoring insecticide resistance in disadvantaged areas.

Higher Calling

As her fellowship drew to an end in the mid-1990s, Hemingway accepted a position as the director of biosciences research at the University of Wales, Cardiff. In accepting the position, Hemingway became the United Kingdom's youngest female professor at the time. The new role was both a culture shock and a welcome opportunity, as she was tasked with supervising a large department

of several hundred biology and preclinical researchers. “I learned a huge amount managerially,” she says of the experience, which prepared her for her next and most recent career move, one that she made with the utmost reluctance.

In 2000, eight years into her term at the University of Wales, Hemingway was recruited to the world’s oldest tropical medicine institution, the Liverpool School of Tropical Medicine. The school was in need of restructuring when Hemingway arrived in 2001, but she quickly rose to the challenge. “I set the benchmark higher, I think, because I came in and said, ‘I’m expecting this of you, but I’m also expecting to do this myself. If I can do it and run the institute, then I’m not asking too much of you.’” Hemingway gave the middle tier of researchers more administrative involvement and, over the course of her tenure, raised more than £35 million of capital funding, tripled the faculty, and doubled the size of the campus without taking on any debt. Meanwhile, she has raised £33 million in grant funding to support her own research. “It’s seen as a huge success story in the UK,” she says. “We’re still growing, despite the global recession.”

Hemingway has long favored a multi-pronged approach to vector control, using tools from basic science to fieldwork, a strategy that she calls “bench to bush.” In a 2005 article in PNAS, Hemingway and others developed a microarray chip representing

230 genes from *A. gambiae* to identify the genes up-regulated in insecticide-resistant and -susceptible mosquitoes (8). Recently, Hemingway helped develop quinolone-based antimalarial drugs that fight malaria by inhibiting two key enzymes—NADH:ubiquinone oxidoreductase and cytochrome *bc*₁—in the respiratory pathway of the *P. falciparum* protozoan (2). She previously contributed to the *A. gambiae* and *Aedes aegypti* mosquito genome sequences and recently helped map the genome of *Culex quinquefasciatus* (9). Hemingway’s current projects include the biochemistry of xenobiotic resistance enzymes and various models of mosquito control in large-scale operational programs based in Mexico and Mozambique.

Passing the Torch

In the years before Hemingway retires she hopes to increase the number of researchers studying vector biology, a field that was

largely discouraged when the failed malaria eradication efforts of the 1960s steered attention from mosquito control to drug development. “There was a whole generation of scientists that didn’t get trained up at that point,” says Hemingway, who herself entered the field with a just small cohort of vector biologists. “Now that trend has reversed and vector control is back on the agenda, but there are too few of us who can actually service that requirement.”

Under her guidance and enthusiasm, the new recruits will head to some of the most treacherous regions of the Earth to confront the problem of insect-borne disease. “You can’t look at malaria eradication if you don’t go into some of these dangerous places,” Hemingway says. “Somebody has to do it; somebody has to take these agendas forward, because some of these places you just can’t ignore.”

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- 2 Wondji CS, et al. (2012) Impact of pyrethroid resistance on operational malaria control in Malawi. *Proc Natl Acad Sci USA* 109(47):19063–19070.
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- 8 David JP, et al. (2005) The *Anopheles gambiae* detoxification chip: A highly specific microarray to study metabolic-based insecticide resistance in malaria vectors. *Proc Natl Acad Sci USA* 102(11):4080–4084.
- 9 Arensburg P, et al. (2010) Sequencing of *Culex quinquefasciatus* establishes a platform for mosquito comparative genomics. *Science* 330(6000):86–88.