PORTRAITS OF SCIENCE

Mosquitoes Bite More Than Once

W. F. Bynum

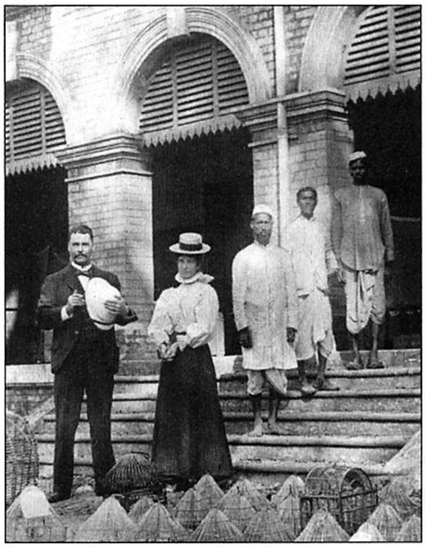
1400
1500
1600
1700
1800
1900
2000

Learning how to dissect mosquitoes and working out which parasite was the malaria pathogen in human disease won Ronald Ross a Nobel Prize.

Malaria (mal aria: bad air) and influenza (influence) are among those diseases whose current names embody older etiological explanations. Under a variety of guises, including ague, intermittent fever, marsh fever, or sometimes simply The Fever, malaria has been recognized since Hippocratic times and has an even longer association with human beings. A lot was known about its distribution and clinical course, and since the 17th century, there has been an effective therapy, quinine. That the disease was most commonly found in swamps and badly drained areas suggested to most observers that it was literally caused by dank, foul air, the product of decaying organic matter (*1*). Only in the late 19th century were its biological cause and mode of spread elucidated, the latter above all by Ronald Ross.

Ronald Ross became a great medical scientist almost by accident. A child of Empire, he was born in British India, son of a general, and tended largely by Indian servants until sent to England when he was 8 years old. His schooling was unremarkable, although he developed a taste for art and literature. His father determined that he should become a doctor, and he did just enough to pass his exams at St. Bartholomew's Hospital Medical School in London. Having failed the examination of the Society of Apothecaries, however, he was ineligible to join the Indian Medical Service, so he spent a year as a ship's surgeon, during which time he began his first novel. Passing the Society of Apothecaries exam at the second attempt, his performance on the Indian Medical Service examinations was such that he received a commission only for the Madras service, the least prestigious of the three Indian Presidencies (Bengal and Bombay were the more desirable appointments) (*2*).

Ross's first tour of duty lasted from 1881 to 1888, during which time he was a pretty ordinary British medical officer in India, hunting, fishing, playing golf, and only disinterestedly performing his medical duties. He had finished his first novel, as well as writing some poems and short plays, and was developing a long-standing interest in mathematics. His first furlough back to England was well spent, for he acquired some further training in public health, bacteriology, and microscopy and returned to India with both a bride and a microscope. He spent a lot of time looking for what was sometimes called "Laveran's germ," the "*plasmodium*" that a French army medical officer had described in 1880 in the blood of victims of malaria (*3*). Ross was unsuccessful, and his first published medical paper attributed malaria to a gastrointestinal disorder. Nevertheless, when he obtained a second furlough, in 1894, he did the most important thing in his professional life: on 9 April 1894, he called on Patrick Manson (1844–1922), the foremost London authority on tropical diseases. Manson was not at home, but the London post then being rather like e-mail (with five or six deliveries a day), they got together the following day, when it took Manson "a few minutes" to show Ross how to find the *plasmodium* in blood smears. It is difficult to see what you have not been taught to look for.



Ronald Ross

(1857–1932)

Surgeon-Major Ross, Mrs. Ross, Mahomed Bux, and laboratory assistants in the laboratory at Calcutta in 1898.

During his year of furlough, Ross and Manson became friends, and Manson told Ross of his belief that malaria is transmitted by the mosquito. Manson had a particular affection for the mosquito, his own early scientific career being founded by his demonstration, in China, that the filaria parasite completes its developmental life cycle in that insect (*4*). (He then believed that human beings acquired filariasis by drinking mosquito-contaminated water.) Manson was not the first to suggest that mosquitoes spread malaria, but Ross returned to India determined to prove what he called Manson's "grand induction." The 173 letters that the two men exchanged between 1895 and 1899 constitute one of the great scientific correspondences (*5*). The 100 or so letters that they wrote to each other in the two decades afterward poignantly document the gradual cooling of a creative friendship and the difficulty of a teacher-pupil relationship evolving naturally into one of equals.

The Indian letters (until Ross's return to England in 1899) offer a wonderful insight into the research that led Ross to his Nobel Prize. The two men were separated by thousands of miles and a 3-week transit time for a letter or a slide to reach the other; nevertheless, their intimacy grew apace. The avuncular Manson acted as Ross's London agent and sounding board, offering advice, both good and bad, on the best way to nail down the mosquito hypothesis. Above all, he tried to cheer his young protégé in his frequent periods of discouragement and despair. He lost his temper only once, when Ross threatened to throw up his medical career, take early retirement from the Indian Medical Service, and devote himself to literature. (Anyone who has read Ross's literary output will sympathize with Manson.)

For Ross's part, the problems were numerous and real. His medical superiors were unsympathetic to his increasingly shrill requests for research leave, being more concerned with frontier wars, public health, and medical care. It took him a long time to unlearn some of the things that Manson had taught him, such as that mosquitoes bite only once and that the probable mode of disease transmission was through egg-contaminated water. There was virtually no literature on the taxonomy of Indian mosquitoes, and

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he encountered what in retrospect were the crucial anopheline species only 2 years into his work. Moreover, mosquitoes have many other parasites besides plasmodia, but neither Ross nor anyone else knew much about how to classify them or assess their significance for human disease.

Despite these and other difficulties, Ross persisted and was rewarded on 20 August 1897 with the first sight of a *plasmodium* in the stomach wall of a mosquito he had dissected (he was an expert in mosquito dissection by then). He knew he was on the right track, and the occasion, which he ever after celebrated as "Mosquito Day," inspired him to write the most memorably poetic words of his life (*6*):

This day relenting God
Hath placed within my hand
A wondrous thing; and God
Be praised. At his command,

Seeking his secret deeds
With tears and toiling breath,
I find thy cunning seeds,
O million-murdering Death.

I know this little thing
A myriad men will save,
O Death, where is thy sting?
Thy victory, O Grave?

The 18 months between Mosquito Day and Ross's departure from India won him the Nobel Prize, but it would not have happened without the 2 years' slog before. Knowing what he was looking for, and in which mosquitoes, he was able to follow the development of the malaria parasite into the mosquito's salivary glands, which further suggested that malaria is a disease of injection. Ironically, his long-sought research leave was spent in Calcutta, where human malaria is rare, so his final experimental demonstration was with bird malaria. He was also leaned on by the Indian Government to spend 2 months of that 6-month leave in Assam, investigating kala-azar (visceral leishmaniasis), to which he contributed little.

Ross was 40 years old when he first witnessed the *plasmodium* in a mosquito; he received his Nobel Prize 5 years later (the Nobel committees were never very loyal to Alfred Nobel's request that the prize be awarded to the best scientific work done in the preceding year). The honors that were showered on him after his return to England—election to the Royal Society, the Nobel Prize, a post in the newly founded Liverpool School of Tropical Medicine, and a knighthood—brought him little contentment (*7*). For one thing, he longed to be in London, not Liverpool, although by the time he settled there in 1912, even London offered him no real peace. He resented the fact that his medical practice (and income) had never thrived (like Manson's), and that his life as a researcher seemed undervalued and underpaid. He spent much energy in a bitter and belittling priority dispute with the Italian parasitologist G. B. Grassi, who believed that the Nobel spoils should have been his, because he and his group had demonstrated the malaria cycle in human beings (*6*).

Above all, Ross was aggrieved that the growing band of malariologists believed that the control and even eradication of malaria were not so simple as he had advocated. Ross passionately held that the key to malaria lay in the control of the offending vector, which initially seemed fragile and compelled to breed in puddles and urban water holes. These could be easily kept in check by "mosquito brigades," groups of workers whose job was to destroy the vector and its larvae. He later demonstrated mathematically how reducing the concentration of anopheline mosquitoes could have a real and potentially cumulative effect, but his mathematics went over the heads of his contemporaries. His pioneering contributions to malarial epidemiology were not appreciated until two decades after his death (*8*).

Ross's analysis of the economics of malaria control also went largely unheeded. By demonstrating how much malaria cost the governments of malarious countries, and how it was much more efficient to prevent it in the first place, Ross offered a sober reminder of the economics of prevention. At least since the 19th century, this lesson had been preached by far-sighted advocates of public health. The message is still relevant and is still too little-heeded by politicians and health planners.

Mosquito Ross, as he was sometimes later called, traveled widely, to Africa, the Mediterranean basin, and the Middle East, always preaching the gospel of war against the deadly anopheline mosquitoes. His position within malaria research gave him special kudos, even if his stridency and concentration on mosquito control at the expense of social betterment or the systematic use of quinine sometimes marginalized him from the malaria community. Ross remains a man easier to admire than to feel genuine affection for.

Like many prophets before and since, he said things that we forget at our peril. Three things stand out. First, Ross quantified the economic costs of malaria. Both the figures and the percentages will have changed over time, but Ross's approach should still command assent. He showed in hard figures that had the money spent in treating and burying soldiers and civilians been turned to prevention, the result would be a world with less malaria. His bitter contempt for penny-pinching governments who could respond only to the crisis at hand rather than legislate for the future earned him few friends.

Second, Ross was an eloquent spokesman for what later would be called the vertical program. Even during Ross's lifetime, malariologists were divided into those who believed that socioeconomic amelioration would in itself largely solve the malaria problem (as was happening in Europe) and those who held that holoendemic malaria was itself a block to economic improvement. Despite the fact that horizontal approaches are now in fashion, focused campaigns targeted at specific diseases can still pay off. Ross firmly believed that malaria was one disease ripe for deliberate control. King Edward VII, when he was still Prince of Wales, once famously said to doctors, "If preventable, why not prevented?" Ross came to see that anopheline mosquitoes were not so delicate as he had once thought, and malaria would require longer and more sustained effort. But the scientific understanding was in place, he argued, and all that was really lacking was the political will.

Finally, Ronald Ross passionately believed in the social value of biomedical research (*9*). Such research should be adequately rewarded, he insisted, and society should always hold its scientists in high regard. Of course, he included himself in the community of scientists whose worth he deemed socially undervalued. But he also worked tirelessly on behalf of the scientific community as a whole, campaigning for comrades who needed his help; and, through his long editorship of *Science Progress*, furthering the cause of what is now called the public understanding of science. His heart was almost certainly in the right place.

References

1. R. Russell, *Man's Mastery of Malaria* (Oxford Univ. Press, London, 1955).
2. E. R. Nye, M. Gibson, *Ronald Ross: Malariologist and Polymath. A Biography* (Macmillan, Basingstoke, UK,1997).
3. G. Harrison, *Mosquitoes, Malaria and Man: A History of the Hostilities Since 1880* (J. Murray, London, 1978).
4. D. Haynes, *Imperial Medicine: Patrick Manson and the Conquest of Tropical Disease* (Univ. of Pennsylvania Press, Philadelphia, PA, 2001).
5. W. F. Bynum, C. Overy, *The Beast in the Mosquito: The Correspondence of Ronald Ross and Patrick Manson* (Rodopi, Amsterdam and Atlanta, GA, 1998).
6. R. Ross, *Memoirs with a Full Account of the Great Malaria Problem and Its Solution* (John Murray, London, 1923); poem, p. 226.
7. H. Power, *Tropical Medicine in the Twentieth Century: A History of the Liverpool School of Tropical Medicine, 1898–1990* (Kegan Paul International, London, 1999).
8. R. Ross, *The Prevention of Malaria* (John Murray, London, 1911).
9. E. Chernin, *Med. Hist.* **32**, 119 (1988).