The Ross Centenary Conference

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In this, O Nature, yield I pray to me.
I take the fever'd hands... We seek the laws.
O God reveal thro' all this thing obscure
The unseen, small, but million-murdering cause.[1]

The Indian Society for parasitology hosted an international meeting in the historic central Indian city of Secunderabad, from August 18-22, 1997. Hundreds of Indian and international delegates attended the conference, delivering almost 350 symposium, oral and poster presentations in addition to the keynote addresses. These covered many aspects of the parasitology, history, epidemiology, treatment, control and prevention of malaria as well as of nematodes and trematodes. The key purpose of the conference, however, was to celebrate the life and discoveries of Sir Ronald Ross, best remembered for his discovery of the means of transmission of the malarial parasite by *Anopheles* mosquitoes, in Secunderabad on August 20, 1897.

Global Importance of Malaria

Malaria remains one of the world's major public health problems. WHO estimates that malaria causes up to 500 million clinical episodes and 2.7 million deaths per annum,[2] with 80% of the mortality occurring in sub-Saharan Africa. Other estimates of mortality are even higher.[3] Indirectly, malaria probably contributes to more deaths; in areas where good treatment is implemented, the fall in death rates cannot be attributed to reduction of malaria alone.

Evidence-based health policy is a still evolving concept.[4,5] Using Disability-Adjusted Life Years (DALYs), calculated as the sum of years of life lost and years of life lived with disability to quantitate disease, the Global Burden of Disease Study ranked malaria as the eleventh most important cause of DALYs in 1990, responsible for 2.3% of the total.[4] These workers derived this estimate from a total global malaria mortality in 1990 of 856,000[6] a far more conservative estimate than was made by the WHO.

The Future of Malaria

The Global Burden of Disease study predicts that, by the year 2020, malaria will have fallen to the twenty fourth rank of DALYs.[4] This optimism is warranted only if some of the current problems facing malaria control programmes can be solved. Previous hopes of substantial reductions in, or even the elimination of malaria is now considered premature.[7,8]

Problems facing malaria control programmes include the long recognised resistance of *Anopheles* mosquitoes to insecticides and *Plasmodium falciparum* to anti-malarial drugs.[9] Hopes for a malaria vaccine have been repeatedly disappointed.[8,10] The cost effectiveness and clinical benefit of using insecticide impregnated bednets has also been questioned, at least in areas of holoendemic transmission.[11,12] A proposal to "seed" wild mosquito populations with genetically modified mosquitoes incapable of transmitting malaria, first made in the 1960s, remains an intriguing idea rather than reality.[13]

The area of malaria distribution is again enlarging, after a long period of shrinking, particularly as a consequence of failing public health measures, insecticide resistance and environmental change including to the climate,[14,15] urbanisation and possibly expanded irrigation.[16] Good public health measures are, however, likely to minimise the risk of malaria re-establishment in rich countries, including Australia.[15,17]

Malaria research funding

As with many diseases mainly affecting populations of developing countries, the funding for malaria research is proportionally much lower than for diseases primarily affecting those in wealthier countries. The total global expenditure in 1993 was US$84 million ($42 per death assuming 2 million global deaths), compared to $789 per asthma death and $3,274 per death from HIV/AIDS.[18]

Recognition of the difficulty in reducing the burden of malaria is embodied in the WHO-World Bank proposal for a multi-agency thirty year control programme[19,20] and its appearance on the agenda of the summit of the Organisation of African Unity.[8]

The Ross centenary conference therefore provided a chance to celebrate the achievement and insights of the past in the hope of inspiring the future battle against malaria.

From miasma to vector-borne infection

The first observation of micro-organisms in 1683 had not led to the end of the miasmatic era. A belief that micro-organisms may be the result rather than the cause of putrefaction was plausible in an era when spontaneous generation of organisms far more complex than bacteria was accepted. Malaria, along with cholera was, until well into the 19th century, considered to epitomise a miasmatic disease. "Mal-aria" was also known as "paludism", from the Latin "palus," meaning "swamp". Believing malaria to arise by poisoning from foul emanations arising from tainted soil, public health officials sometimes devoted considerable energy to documenting and correlating water table depths and fever deaths, an example of the "sanitary statistic" era of modern epidemiology.[21]

The work of Fracastorius, Henle, Snow and others gradually established the foundation for the infectious disease stage of modern epidemiology, with its paradigm of the germ theory.[21] But even after Pasteur disproved spontaneous generation in the 1860s, the cause of malaria remained unknown and its aetiology was still considered miasmatic. Then, in 1879, parasites in the blood of patients infected with malaria were described by the French researcher Alphonse Laveran, working in Algeria. Laveran was eventually awarded the Nobel Prize for this work.

Manson and mosquitoes

In 1876, while working in China, the British researcher Patrick Manson had shown that mosquitoes had a role in the life cycle of filariasis. However, he thought transmission to humans occurred from drinking water contaminated by infected mosquitoes. The role of mosquitoes in the transmission of malaria remained unclear, but both Laveran and Manson speculated they might be involved.[22] There is tantalising evidence that this link may have been made earlier, both from the Indian vedas and East Africa.[22] In 1881 Finlay made similar speculations concerning yellow fever and mosquitoes,[23] but even in the 1890s the majority of the learned medical profession still considered vector borne transmission of malaria very unlikely.

By 1894, Manson, aged 50, living in London and intensely occupied by the promotion of tropical medicine as a separate discipline, was interested in further investigation of the malaria-mosquito hypothesis. Believing conditions to do this were unfavourable in England, where malaria had already become a rare disease, he unsuccessfully tried to raise funds to enable travel to a more malarious area in order to conduct his research. At this time Manson first met Ross, who was on leave from his post in malaria infested India.

The early life of Ronald Ross

The son of an army general, in a family with connections to British India extending for several generations, Ronald Ross (figure 1) was born in 1857 in the Himalayas, near the Nepali border. He remained in India, learning to speak Hindi, until 1865, when he went to Britain for his education.[24] By his own admission more interested in art and not keen to study medicine, he enrolled at St Bartholomew's Hospital medical school in 1874. While a student he treated his first malarious patient, "a tall fierce woman" from the English fens. Failing his medical finals in 1879 but passing his surgical exam, Ross first obtained work as a ship's surgeon, until passing his medical exam in 1881.

Military doctor

Ross returned to India, as his father had hoped. He served as a military doctor in many regions, including Burma and the Andaman Islands. His medical duties were not onerous and allowed plenty of time for pursuits including hunting, writing and the study of mathematics.

In 1888, Ross returned briefly to Britain, where he acquired diplomas in both public health and bacteriology as well as his wife, Rosa. On return, Ross's interest in malaria is evidenced by both his poetry and repeated attempts to find the malarial haematozoon seen by Laveran in the blood of malarious patients. His failure to do this was so frustrating that in 1893 he published several articles casting doubt on their existence.

Ross the malariologist

In 1894 Ross visited London, fortuitously meeting Manson, who convinced Ross of Laveran's finding by demonstrating plasmodium in the blood of malaria-infected patients. In his memoirs Ross recalled: "my doubts were now removed; and in a few days Manson demonstrated the other forms of the organisms to me in a patient lying at Charing Cross Hospital..."

Fired with enthusiasm from his meetings with Manson, at which the possible role of mosquitoes in malaria transmission must have been discussed, Ross returned to India in 1895, taking with him a portable microscope. A long distance collaboration by correspondence followed. Manson helped sustain Ross's spirits, appealed to Ross's army superiors to allow him time and suitable postings to pursue his malaria studies and used his influence with the *British Medical Journal* to hasten and support Ross's publications.

Ross in Secunderabad

Ross was posted to Secunderabad, close to Hyderabad, royal city of the Nizams, now in the state of Andhra Pradesh. There his work developed. He practised mosquito dissection and again tried to find Laveran's particles in Indian red blood cells. He started to cultivate mosquito larvae to have on hand a supply of insects to feed on malarial patients and then later dissect. These tasks were initially frustrating, and it took some time to realise that only certain mosquito species fed on human blood. Nevertheless, by May 1895, Ross had some success. He observed the early development of imbibed parasites in the mosquito stomach, though as he was not yet using anopheles mosquitoes further development was impossible.

This work was interrupted by transfer to Bangalore, in part to deal with a cholera epidemic. While there, he continued experiments giving volunteers water to drink in which "malariated" mosquitoes had died, seeking evidence to support an hypothesis analogous to Manson's filarial transmission mechanism. Unsurprisingly, he had no success.

Ross hoped to continue his malarial investigations in Bangalore, even though its elevation (800 metres above sea level) made malaria cases relatively rare. However, in March, 1897, he was again transferred, expressing his frustration to Manson in London. This transfer, however, offered new opportunities.

"A wondrous thing"

While in Bangalore, Ross was using "brown" and "brindled" mosquitos, (*Culex* and *Aedes*) neither of which, though unknown at the time, are capable of malaria transmission. On return to Secunderabad in May 1897, he narrowly escaped death from cholera. Recovering, his attention shifted to a less common but distinctive "dapple-winged" mosquito, of the *Anopheles* genus. On August 16, ten newly hatched *Anopheles* mosquitos were fed on a malarious patient. Four days later Ross saw something new. Not only were the parasites visible in the mosquito stomach, as with earlier dissections, but numerous, distinctive and previously unobserved cells were found in the stomach wall. Ross was observing the next stage in the life-cycle of the plasmodium, an oocyst derived from the fertilised female cell of the parasite. Although he did not fully understand this he realised the finding was significant:

> This day relenting God
> Hath placed within my hand
> A wondrous thing...
>
> I find thy cunning seeds,
> O million murdering Death.[1]

Ross went on, despite further military obstacles and continuing scepticism from his superiors, to work in Calcutta, using the more convenient bird malaria as an animal model (see figure 2). In 1898 he was able to demonstrate that cells from the mosquito stomach not only moved on to the salivary gland but infected mosquitos were also able to infect healthy birds. This was a significant and original advance on the malaria-mosquito hypothesis as proposed by Manson.

Resignation and recognition

Ross then felt sidetracked by orders from his superiors, to investigate another parasitic disease, kala azar. Finally, fed up with his perceived mistreatment, Ross resigned from the Indian Medical Service in 1899 and returned to Britain.

Recognition in Europe came quickly. He was appointed to the newly established Liverpool School of Tropical Medicine and in 1902 was awarded the Nobel Prize. He travelled and consulted widely, including in West Africa, Mauritius and Greece.

Anti-vector campaigns

Ross thought that his great discovery could lead to the reduction or even elimination of malaria by reducing the vector population, even though the means available to do so were crude, such as using kerosene as a larvicide. An intensive attempt to reduce malaria at Mian Mir, near Lahore in the Punjab, by the use of labour intensive mosquito brigades proved unsuccessful, though Ross felt his theories were betrayed by half-hearted efforts.[25] In other locations, including Egypt, spectacular success vindicated Ross. William Gorgas credited the successful completion of the Panama Canal, until then prevented by mosquito transmitted yellow fever, to the application of Ross's discovery.[22] Ross also suggested the introduction of larva-eating fish to malarious areas.[22] His fanaticism in trying to eradicate malaria led to the appellation "Mosquito Ross";[25] he also recognised the role of antimalarial drugs, including quinine, in malaria control.

Ross the epidemiologist

Ross's forceful personality often caused antagonism. For example he sued his erstwhile mentor Manson for libel.[22] His strong personality may have detracted from full recognition of the value of other contributions, including to epidemiology and biostatistics. Ross claimed, justifiably,[26,27] to be the first to rigorously apply mathematical ideas in relation to epidemiology, particularly in his "theory of happenings".[28] In this he attempted to quantitate the probability of a malaria infection, given explanatory variables including the infective proportion of the population, the density of the mosquito population per person, the proportion of infective mosquitoes that feed and the probability of mosquito survival through the extrinsic cycle. Using his equations, he estimated the critical mosquito density below which malaria transmission cannot be maintained to be about 40 per person per month, in India.

Ross the polymath

Ross had other talents. A friend of poet laureate John Masefield, he wrote and published three novels, as well as plays and poetry. He composed music. His mathematical work was recognised as original and fundamental, if not quite polished.[29] His emphasis on reduction of the vector below critical thresholds to eliminate malaria was almost borne out by the great insecticide campaigns of the 1950s.

Commemoration

The building in which Ross made his discovery is the first in Hyderabad to be preserved and restored (figure 3). During the meeting it was dedicated as a memorial and inspiration for the future. A stamp was struck, and a hospital building named after him. Ross may be dismayed that, 100 years after his discovery, so much work remains to be done to reduce the burden of death and ill health from malaria in the twenty-first century.

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Figures

Figure 1.

Ronald Ross was born in 1857 in the Himalayas. By the time of this photo (1913) he was world famous. Photo courtesy London School of Hygiene & Tropical Medicine.

Figure 2.

In Calcutta, Ross used the more convenient bird malaria as an animal model. Bird cages are at the foot of the steps beneath Ross, his wife Rosa and a number of assistants. Photo courtesy of the London School of Hygiene & Tropical Medicine.

Figure 3.

A bust of Ross adorns this historic building in Secunderabad, where in 1897 Ross discovered the transmission of malaria by mosquitoes. Photo courtesy of the London School of Hygiene & Tropical Medicine.

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