



## RONALD ROSS- MOSQUITO, MALARIA AND MUCH MORE

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**Malaria has been, and still is, a major cause of not only human suffering and death and infant mortality, but also an economic burden on the society. According to the WHO Report of 2022, in 2021 alone 247 m people were affected by malaria. Apart from the use of antimalaria drugs, the importance of different preventive measures including the use of mosquito nets and insect repellents in managing malaria cannot be gainsaid. It should be underscored that the determined research efforts by medical personnel such as Ronald Ross, Patrick Manson, Charles Louis Alphonse Laveran, Giovanni Battista Grassi, and a few others, despite several hardships they faced in pinning the mosquito as the transmitter of malaria was epoch-making. Obviously, this finding has played a key role in reducing the global impact of malaria. In this communication, I outline the efforts of Ronald Ross and the travails he went through while pursuing it, as well as his attitude in denying his co-workers their due credit, and the extroversion rooted in him which eventually made him turn hostile to his collaborators and to his mentor, Patrick Manson.**

**Key words:** Patrick Manson, Giovanni Grassi, Kishore Mukhopadhyay, *Plasmodium*, *Anopheles*, *Culex*, India

### Short biography of Ronald Ross

Ronald Ross (1857–1932, Portrait 1) of Scottish descent was born in Almora (29°60' N, 79°66' E) Kumaon Hills, (presently Uttarakhand) in 1857. Three generations of his ancestors served the Indian Army. His father, Campbell Claye Grant Ross was a General in the Indian Army (<https://royal.societypublishing.org/doi/epdf/10.1098/rsbm.1933.0006>, accessed on 10 August 2023). Ross was the eldest of the 10 born to Campbell Ross and Matilda Elderton. At eight, Ross went to England for education. At 17, he wanted to be an artist, but his father pushed him to study medicine. Ross joined the St Bartholomew's Hospital Medical School, London. During his stay as an unqualified Assistant House Surgeon at Shrewsbury Infirmary (1877–1878), thus speaks Ross (Ross, 1923, p. 35), '... that the medical profession and all its associates and associations were little to my taste or inclination...'. He failed the Licence of the Society of Apothecaries examination and hence could not compete for the Indian Medical Service in 1879 and his father Campbell Ross declared that he would cut Ronald's allowance unless he continued studying medicine (Thornton, 1961). In 1880, Ross left England taking up the position of a ship surgeon and continued preparing for the British medical examinations during travels. In 1881, he obtained a Licence of the Society of Apothecaries in London, returned to India, and served in the III Anglo–Burmese War of November 1885. He was later admitted into the Indian Medical Service, served briefly as a doctor

with the Madras Infantry, and later posted as the Acting Garrison Surgeon in Bangalore. He returned to England in 1894 on a year-long furlough and obtained a Diploma in Public Health (DPH) issued by the Royal Colleges of Physicians and Surgeons of England. During his DPH training, Ross learnt bacteriology with Emanuel Edward Klein (1844–1925). In 1901, Ross was awarded the Fellowship of the Royal College of Surgeons (FRCS) of England. Ross was granted the Nobel Prize in Physiology or Medicine in 1902 with the following citation: 'for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it' (<https://www.nobelprize.org/prizes/medicine/1902/summary/>, accessed on 16 August 2023). The Royal Society admitted him as a Fellow in 1901. The Crown of UK honoured him with the following: Commander of the Order of the Bath in 1902, Knight Commander of the Bath in 1911, and Knight Commander of St. Michael & St. George in 1918. Ross married Rosa Bessie Bloxam in 1889. Ronald and Rosa had two daughters Dorothy (1891–1947) and Sylvia (1893–1925), and two sons Ronald Campbell (1895–1914) and Charles Claye (1901–1966). Despite winning the Nobel Prize, Ross lived in penury towards the end of his life and advertised in *Science Progress* to sell his research papers in 1928 for £2,000. They were bought by Lady Houston who presented them to the British Museum (Centre for Disease Control and Prevention, 2015, <https://www.cdc.gov/malaria/about/>

history/ ross.html/ accessed on 08 August 2023). Rosa Bessie, Ronald-Campbell, and Sylvia pre-deceased him. He died after a long illness in London aged 75 in 1932.

### A brief recap of malaria Research

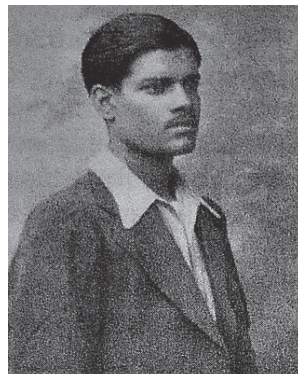
Malaria in humans is caused by five species of the parasitic *Plasmodium*: *falciparum*, *malariae*, *vivax*, *ovale*, and *knowlesi* (Apicomplexa: Haemospororida: Plasmodiidae) which are transmitted to humans by diverse species of female *Anopheles* (Diptera: Culicidae) mosquito. Presently we know that mated females are more efficient transmitters of the protozoan than virgin females, establishing an indirect role for the males in the spread of malaria (Dahalan et al., 2019); furthermore, it is known that one species of *Anopheles* can carry more than one species of *Plasmodium* concurrently (Mckenzie and Bossert, 1997). Infection by *P. falciparum* induces the malarial type- the ‘falciparum-malaria’- which is endemic to many nations in North Africa and causes the highest mortality. *Plasmodium vivax* induces benign-tertian malaria, an equally nasty societal problem resulting in staggering numbers of human deaths. These two species together account for millions of infections and *c.* 0.5 m deaths annually. Currently, this situation has become more alarming due the development of resistance to all known antimalarial drugs in these parasites (Ofir-Birin et al., 2021). Malaria possibly existed even during early Egyptian civilization; the presence of *P. falciparum* DNA in tissue of nearly 4,000-year-old Egyptian mummy has been reported (Nerlich et al., 2008).

Around 400 BCE, before the term ‘malaria’ was coined, the disease was called by various names such as marsh fever, tertian fever, quartan fever, and

intermittent fever. Hippocrates (400 BCE) believed that the disease was due to polluted air and the Italian term *mal'aria* (bad air) for the disease came in to use only after nearly 1,500 years (Hempelmann and Krafts, 2013). In the 1880s, the following medically relevant discoveries pertaining to microbes as causative agents of diseases were made which were of great heuristic value in solving the riddle regarding the causal organism and spread of malaria. Gerhard-Henrik Armauer Hansen (1841–1912) of Norway established that *Mycobacterium leprae* (Bacteria: Mycobacteriales) as the causal agent of leprosy (hence, *Hansen's disease*). Heinrich Hermann Robert Koch (1843-1910) discovered that *Mycobacterium tuberculosis* caused tuberculosis. Furthermore, the serendipitous discovery of a dye – a mixture of eosin and aged methylene blue – by the Russian physician Dimitri Leonidovitch Romanowsky (1861-1921) in 1891, later modified by Gustav Giemsa (1867-1948) a Polish-German chemist–bacteriologist, helped studying blood smears in a light microscope. Popularly known as the Romanowski-Giemsa stain, it dyed the malaria-parasite infected blood cells and their contents in determining the infection easy and dependably (Cox, 2010). Charles Louis Alphonse Laveran (1845-1922), a French army surgeon found on 8 November 1880 that malaria was caused by *Plasmodium* (a protozoan). Laveran using a microscope enabled with a 400x magnification established *Plasmodium* as the causal agent of malaria and reported his findings in the French Academy of Medical Sciences in December 1880 (Laveran, 1884). Since Laveran's contemporaries contended that malaria was caused by a bacterium, disagreements prevailed on Laveran's findings until the 1880s. T. Edmondston Charles, the editor of the English edition of the book of Ettore



Portrait 1. Ronald Ross  
(Courtesy: London School of Hygiene and Tropical Medicine)



Portrait 3. Kishori Mohan Bandyopadhyay (Courtesy: Vigyan Prasar, November 2021 / Vol. 24 / No. 11, p.16 file:///C:/Users/USER/Desktop/dream-nov-2021-eng.pdf)



(Source: Capanna, E. 2006)  
Portrait 2. Battista Grassi (1854-1925) (Drawing by Diego de Merich)

Marchiafava, and Amico Bignami (1894) translated by an American physician James Harry Thompson (1824-1904) remarks, 'On the 6th of November 1880, Laveran saw a flagellate organism free in the blood of a patient suffering from malaria, and at a single bound arrived at the conclusion that it was the parasite of malaria (page ix), Edmundston Charles also remarks in page xvi: 'All must be most unwilling to explain the position by assuming any want of skill on the part of Laveran, as we marvel at his acuteness in having with imperfect means arrived at the discoveries, he announced in 1880'. In 1884, Charles Laveran could convince Louis Pasteur (1822-1895), Charles Edouard Chamberland (1858-1908), and Pierre Paul Émile Roux (1853-1933) of his discovery that the malaria-inducing agent was indeed a species of *Plasmodium* (Laveran, 1884). In 1897, Ronald Ross in India discovered that culicine mosquitoes transmitted the avian malarial parasite *P. relictum* and suggested that human malaria parasites might also be transmitted by mosquitoes (Ross, 1898; Manson, 1898). In 1898, Italian pathologists Giovanni Battista Grassi (Portrait 2, 1854-1925), Amico Bignami (1862-1929), and Giuseppe Bastianelli (1862-1959) communicated the results of their research as a note to the *Accademia Nazionale Reale dei Lincei* (The Royal National Lincei Academy) on 28 November 1898 stating that human malaria was transmitted by *Anopheles claviger* (Bastianelli et al., 1898). Their second communication to the Academy on 22 December 1899 described the life cycle of *Plasmodium* within the mosquito (Grassi et al., 1899).

Initially, how malaria was transmitted from person to person remained unclarified. When Ross came to England in 1894, he met Patrick Manson (1844-1922) who, working in China, had proved that the casual organism of filaria was a nematode (later named as *Wuchereria bancrofti*, Nematoda: Rhabditida: Onchocercidae by the British biologist Thomas Spencer Cobbold in 1877) transmitted to humans by *Culex fatigans* (= *C. quinquefasciatus*, Diptera: Culicidae) (Manson, 1878). Based on this observation, Manson proposed that the causative agent of malaria in humans could also be transmitted by mosquitoes (Manson, 1894). Manson showed Ross dyed blood smears having malarial parasites and convinced him that malaria was caused by a blood parasite and not by intestinal infection as Ross had thought. Manson also taught him the procedure of staining parasitic Protozoa (Nuttall, 1933) and motivated Ross to study the role of mosquito in the spread of malaria (Raman, 2013). Manson himself could not proceed to work on his hypothesis partly due

to declining health although, in 1900, he proved that mosquito was the vector. He did this by showing that a volunteer (his son Patrick Thurburn Manson) got the disease when bitten by *Anopheles* mosquito (imported from Rome) which had been previously fed on a patient suffering from malaria (Manson, 1900).

On return to India, in 1893, Ross was posted as the General-Duty Medical Officer with the Madras Infantry, Secunderabad. Strongly influenced by Manson, Ross commenced his experiments to establish the role of mosquitoes in transmitting the malarial parasite. Ross was guided by Manson through sustained correspondence which are archived as more than 200 letters and telegrams (Bynum and Overy 1998). Manson even went to the extent of influencing the Indian Government to transfer Ross back to a post which would enable him to work on malaria, when Ross was transferred to a malaria-free Rajputana (now Rajasthan and parts of Madhya Pradesh and Gujarat). Ross resented that the then Government of India did not support his research on malaria (<https://www.nobelprize.org/uploads/2018/06/ross-lecture.pdf>, accessed 05/08/23):

'When, however, I asked the Director General for the services of one or more junior medical officers, I was told that none could be spared at the time. As a matter of fact there are always many medical officers in military employment in India, who can be spared if they are urgently called for; and the truth is that the necessary trouble was not taken. I then wrote to Manson begging him by all means in his power to obtain assistance for me from England; and thought that the Royal Society, which is subsidised to a small amount by Government, might afford to give it. The matter was considered; and it was finally agreed to appoint, with the help of the Colonial Office, a commission of three gentlemen to investigate malaria. Two of these were sent in the autumn to study the subject - in Italy; and, after much difficulty, the third was allowed to come to me. He arrived at Christmas with orders to stay for two months - not to help me but to verify my statements!'

Ross pursued his work while he was with the 19th Madras Infantry in Secunderabad. In February 1898 he was transferred to Calcutta (Kolkata) where he used the facilities in Surgeon-Lieutenant Colonel David Douglas Cunningham's (1843-1914) laboratory to investigate transmission of malaria in birds (Manson, 1898, Ross, 1923 page 259). According to Ross,



although the Government of India was ‘good enough’ to post him in Calcutta to continue his research, he could not work on human malaria due to anti-plague riots and hence studied malaria of birds (Ross, 1910); the plague epidemic which broke out during this time was a humongous challenge and the Government tried different measures to control it, which, sometimes, interfered with the normal life of the local people leading to massive riots (Chandavarkar, 1992). In 1908, while studying bird malaria, Ross observed sporozoites of the malarial parasite within *Culex fatigans* fed on birds infected with the parasite (Ross, 1910). Based on these observations, he stated (Ross, 1910, page 25),

‘Owing to the great similarity of the avian and human parasites, there was no doubt that the latter had the same history’.

In the meantime, in 1898, Giovanni Battista Grassi, Amico Bignami, and Giuseppe Bastianelli from Italy not only established that malaria in humans is transmitted by *Anopheles claviger*, a Culicidae endemic to the Palaearctic realm including parts of Europe, North Africa, and Asia, and segments of northern Arabian Peninsula, but also described the complete life cycle of *Plasmodium* within *A. claviger*. They have published these findings in the Proceedings of the Lincei Academy, Rome (Grassi et al., 1899). Grassi, although a physician, was more interested in zoology and studied zoology at the University of Heidelberg and became a Professor of Zoology at University of Catania (Sicily) (Capanna, 2006). Hence, he could determine the vector as a female *Anopheles claviger* (Grassi et al., 1899). However, with Ross claiming priority for his work began the battle between Ross and Grassi.

In 1900, Grassi states (Manson-Bahr, 1961, page 16):

‘He (Ross) says that from his experiments came evidence that the mosquitoes with spotted wings were *Anopheles*. No, dear Mr Ross, the great word -*Anopheles* - which signified a new era in the study of human malaria, was first pronounced by me. We must say from the zoological point of view that the description and many drawings of Ross were so badly done that they cannot be trusted. I remain your humble servant, Mr Ross, in continuing this useless polemic, which amuses me’.

Ross (1910) vehemently opposed the idea that the human-malaria problem was solved by the Italians. He firmly believed that their work was a mere importation of his work on bird malaria. He was convinced that until

his research was published, the Italian scientists did not believe the mosquito hypothesis and that his work held priority over theirs. Ross mentions that they (the Italians) showed human malarial agent was carried by mosquito (Ross, 1910, page 27):

‘... fifteen months after my original success with the same parasite in Secunderabad’.

Ross was adamant with this claim of his; he adds (Ross, 1910, footnote, page 27):

‘For a long time some writers attributed to them (Italians) the discovery of the mosquito-cycle of the important human parasites, and to me only the study of the humble Proteosoma of birds. But according to zoological rules, priority in the discovery of the life-history of any group of organisms belongs to that investigation which first discloses the new life-history in any member of the group – which is only just, since there is usually little difficulty in repeating the same observations for other members of the group’. He wrote sarcastically in *The Times* (5 February 1908, London), ‘Sir, After a man has spent years over the solution of a difficult problem, it is always gratifying to find credit given, not to him, but to those who have performed the easy task of repeating and confirming his work. ‘Your correspondent makes out that I performed only the humble feat of cultivating the parasites of birds in mosquitoes, that I failed in cultivating the human parasites and that the Italians did all the important parts of the work...’.

### The less-known side of Ross

Ross was a multifaceted personality with a greater passion for arts than medicine. He even designed a compact portable compound microscope to observe blood smears and entered into a contract with a company in London to make it for him. He insisted and received a royalty of £2.87 from the company in 1909 for selling 23 of the microscopes designed by him (Nye and Gibson, 1997). According to the British poet John Edward Masefield (1878–1967) (Obituary notices, *The Times*, of August 22, 1933):

‘Ross was an extraordinary man, for he made himself famous as a poet, and was an eminent mathematician, a clever painter, and a skilled musician’ (Masefield, 1933, page 113, ‘Sir Ronald Ross’–1857-1932’.

Ross became popular and received the Nobel Prize for ‘Physiology or Medicine’ in 1902, ‘for his work

on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it.’

(The Nobel prize in physiology or medicine, 1902). This work of Ross was done mainly in India between 1895 and 1899 and was based on his initial studies on the malaria of birds and he suggested that mosquitos transmitted the human-malarial parasite as well. Considering the significant work of Giovanni Grassi, who actually demonstrated the developmental stages of malarial parasite in the Anophelinae and identified the specific vector of the malarial parasite as *Anopheles* and also demonstrated the transmission into a healthy human volunteer, the Nobel Committee felt that the prize should be shared between Ross and Grassi (Chttopadhyay, 2015). However, Ross was intent on getting the sole recognition and began a defamatory campaign against Grassi. Robert Koch (1843-1910, German physician and microbiologist) who was appointed by the Nobel Committee to resolve the conflict, decided in favour of Ross. An interesting point here is that earlier, Grassi had criticised the work of Koch strongly in his book entitled *Studi di uno Zoologo sulla Malaria (Studies on Malaria by a Zoologist - Grassi, 1901)* and this criticism served as the trigger for Koch to turn against Grassi. Thanks to the review by Verhave (2022) based on the notes of Koch (in German), we now explicitly know of the hostile relationship between Koch and Grassi. The wrath of Koch against Grassi could be felt in the following letter he wrote to Ross on 10 the February 1901 (Verhave, 2022, page 20):

‘...although I consider Grassi to be a rogue and a robber in scientific domains, I should not pass over his scientific merits where they ought to be mentioned. But it is my conviction that he has no such merits. What he claims as his, is either stolen or fabricated... His statements regarding the development of the malaria parasites in the body of the mosquito, if he really has seen them as he states (which, by the way, I do not believe) are only a confirmation of your discoveries. His illustrations are nothing more than copies of yours. The first infection experiments which were made in Rome by Grassi and his collaborators, and so very loudly advertised to the entire world, I consider to be inventions; for they were made in a season during which there are no fresh infections in Italy...’.

It is clear that Koch influenced the Nobel Committee

to decide in favour of Ross from another letter he had written to Ross which reads as follows (Verhave, 2022, page 21):

‘...the situation in your battle for priority against Grassi, in which you must not under any circumstance stay behind... I recently had to explain to a member of the Jury of the Nobel Prize that the important discovery of the courses of development of the parasite in the mosquito is exclusively thanks to you and ... that the Italian researchers are as little involved in it as Manson. I can only inform you about this most confidentially.’

Ross was a self-centred person. He was in constant fight with his colleagues (McCallum, 2008). Despite the encouragement and guidance he received from Manson, Ross failed to acknowledge him as his mentor in his Nobel prize acceptance speech and mentioned Laveran instead (Ross, 1902). The correspondence between Ross and Manson during the later stage of their acquaintance reveals the break in their friendship was mainly because of Ross’s personal pride (Bynum and Overy, 1998). Similarly, he did not acknowledge the commendable help he received for from his co-worker Kishori Mohan Bandyopadhyay (Portrait 3, 1883–1929) in any of his publications (Chttopadhyay, 2015). Beisel and Boëte (2013) state:

‘The importance of his Indian research assistant Kishori Mohan Bandyopadhyay is acknowledged by many. The fact that he was not a co-recipient of the prize, but merely received a gold medal, is read by many as an effect of colonial relations.’

Bandyopadhyay was a science graduate from the Presidency College, Calcutta and was an enthusiastic colleague deeply interested in malaria research. He did all the field work for Ross by identifying and bringing several malaria patients from nearby villages to the laboratory as volunteers from whom Ross collected blood samples. Many high-profile Indians of Bengal of that time, including Upendranath Brahmachari, Jagadis Chandra Bose, Brajendra Nath Seal, Sivanath Sastri, Surendranath Banerjee, and Prafulla Chandra Ray solicited George Nathaniel Curzon (the Viceroy of India, 1898–1905) to recognize Bandyopadhyay appropriately (Chttopadhyay, 2015). Heeding this representation, Bandyopadhyay was awarded the King Edward VII Gold Medal in 1903. Ross’s interest to decipher the mystery of malaria on the one hand and his selfishness on the other projects him more as a Janus-faced person.

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