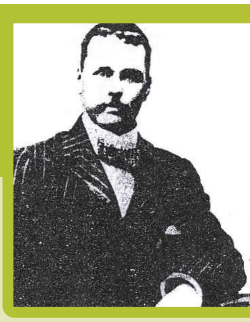
FIGHT AGAINST MALARIA AND RONALD ROSS



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Malaria has been one of the biggest killer diseases in the history of humanity. Not cholera or plague, nor to speak of AIDS. It is estimated that during the Second World War, more American soldiers in the far east died of malaria than that killed by the human enemy. It still remains the number one public health problem in many countries. More than one million people die in Africa. In India alone 20 to 30 million people suffer from malaria every year. In spite of continuous advances in malariology, and advances in public health services, it is still causing havoc taking heavy toll of life and inflicting severe damage to the health of the people. Malaria is one of the most important causes of economic misfortune, engendering poverty, diminishing the quality of food supply, lowering the physical and intellectual standard of the nation. It also harms economic progress in every way.

Human fight against malaria is a unique story. This is a long story spreading over two thousand years with many ups and downs. It is an example of how finding solutions to a long standing problem of such a magnitude requires combined efforts of every branch of science– medicine, biology and chemistry as well as organised health service, social action groups and above all strong political will. Whenever a favourable combination could be achieved, the control of the disease seemed at sight. And in fact, it had been eradicated from a large part of the globe. Slackness in any one respect or more has caused reversal of greater magnitude. In this article, however, we shall restrict ourselves mainly to the bioscientific aspects of the story depicting the nature of science and history of ideas. It might also illustrate how the knowledge of one period becomes a myth later in history and how science progresses gradually.

Till less than a century ago occurrence of malaria was spread over all continents. In the old world it has been a menace in the south and southeast Asia, Japan, northern Australia, southern Russia, Great Britain, continental Europe and almost all inhabitants areas of Africa. In the western hemisphere malaria was preponderant from central South America to the southern fringes of Canada. Today whole of North America, Europe and a large part of South America are almost free of malaria. All ancient civilisations namely that of China, Egypt, Greece, India, Iraq and Italy were plagued by malaria. It is said that Alexander the

Great of Macedonia died of the disease. Some believe that decline of Greek and Roman civilisations were partly caused by malaria.

Symptoms of Malaria

Usually malaria is characterised by a high fever with feelings of cold, headache, muscle-ache, dry mouth and rough skin. After a few hours the patient feels warm and has nausea, followed by sweating and remission of fever. If untreated this sequence recurs every 48 hour (72-96 hours in some cases) for several weeks. Thereafter the patient may be relieved for a few months or even a year. He often gets similar attacks repeatedly resulting in anaemia, enlargement of spleen, physical emaciation and lastly death. In one type of malaria, one or a few spells of high fever may lead to rapid deterioration and sudden death if suitable treatment is not given in time.

A Long Search for the Cause

As mentioned earlier, all the ancient civilizations were serious victims of malaria, Even two thousand years ago some of the physicians had preliminary ideas about the disease. They could recognise malaria by its symptoms and called it 'intermittent fever'. Some of them could even distinguish between different types of malaria also. It was widely noted that the disease preponderates in marshy areas, near swamps and was more frequent among people who slept outdoors. They thought that it was caused by breathing foul air poisoned by the stagnant water. The disease also acquired its name from the same belief (Italian: mal-bad, aria-air). It may seem to be silly today but even this belief helped to control the disease to some extent.

Since the disease was associated with stagnant water, the Romans tried to control the disease by flushing swamps and marshes. Roman officers posted in certain areas of the empire observed that the places having large population of buffaloes who frequently visited swamps were comparatively free from malaria. They imported buffaloes from Egypt to southern Italy where the disease was rampant. This measure also gave some respite. Can you imagine why?

After the decline of the Romans, the West entered the dark age. No significant progress in respect of malaria could be made in the next thousand years or more, till the late renaissance period. However, it has recently come to light that in the sixth century a Chinese philosopher accidentally discovered a 'warm wood' tree (Artemisia enua, Chinese name: Kunghow tsud) the bark of which was effective for the treatment and prevention of malaria.

After the advent of renaissance a new awakening swept through Europe. Old ideas and authorities were begun to be challenged. New ideas based on explorations, experiments and observation poured in. Ideas about land and oceans expanded. The new world (western hemisphere) was discovered. The Europeans started getting hitherto unknown samples of plants and animals as well as experiences and ideas extant in distant lands.

In the seventeenth century a large variety of substances derived from plants, animals and minerals were tried to cure different diseases including malaria. Most of them were of no value; some of them were even harmful. Among those some were products sent from abroad. One of these products was the bark of a Peruvian tree (native name: quina quina) which the local people used a s a medicine for fever. This was thought to be a good benign cure of malaria in Europe and became very popular. The demand for the bark of the tree rose so high that soon it became difficult to arrange for its transport. The supply source also tended to become exhausted. Some dishonest merchant began to substitute it by a similar looking bark of another tree. Strangely, this attempt of gross adulteration became an unexpected benefit. It was found out that quina quina was not as effective as the new adulterant was. The new tree yielding the effective medicine of malaria was named Cinchona after the name of the wife of the then Portuguese governor. Later the active fraction extracted from Cinchona bark called quinine remained the only potent cure till mid-twentieth century. Is it not strange that a drug that served humankind for three centuries was discovered accidentally that too from an adulterant?

The Parasite Discovered

After a satisfactory treatment was found, physicians tried to verify the cause of malaria. Some of them volunteered to drink water of the swamps that were said to be the cause of fouled air. Some deliberately breathed the air around the marshes. No one got malaria. The age old ideas began to change. Several speculations were floated. Some scientists dissected and examined the body parts of the dead patients; others examined the blood of suffering patients. A few held the newly discovered bacteria as the causative agent. But no satisfactory solution could be found for a long time.

Malarial parasites were apparently first seen by Meckel in 1847. Several others also reported some stages in the blood of human being. Significance of their discovery was not recognised until Laveran's somewhat explicit studies were published in 1880 who was able to see them in the blood corpuscles of malarial patients. Subsequently the scientists reported different stages of the parasite in and out of the RBC. By then it was known that malaria is also common in many birds and apes. In 1885 Marchiava and Celli produced cases of malaria by inoculating human volunteers with blood containing the parasites. Gradually it was accepted that malaria is caused by a protozoan parasite belonging to the genus *Plasmodium*. It was also found that there are four species of the genus namely, (i) *P. vivax*, (ii) *P. falciparum*, (ii) *P. Malariae* and (iv) *P. ovale* which are responsible for different kinds of malaria.

P. vivax causes benign, tertian (fever every alternate day) malaria, resulting in slow degeneration of the patient engendered by destruction of the RBC. The benign nature of this type of malaria often tempts patients to neglect its treatment. This altitude has aggravated its effect on the population. *P. falciparum* is responsible for malignant, tertian malaria (also called cerebral malaria). It is the most dangerous form of malaria. It affects the brain leading to fast deterioration of the patient and sudden death if proper treatment is not given in time. *P. malariae* causes benign, quadrant (fever every 72-96 hours) malaria which is not so much dangerous. *P. ovale* is responsible for tertian malaria which is even milder.

The relative incidence of these parasites and hence the occurrence of different malarias varies in different parts of world. Some differences are also observed in the same area from year to year. *P. vivax* is of widest distribution (about 65%-69%) : *P. faliciparum*, the killer malaria comes second (25%-30%) : *P. malariae* has a restricted distribution (1%-3%) and *P. ovale* is a rare parasite in man.

Carrier Identified

Once it was known that malarial parasites are causative agent of the disease and a person gets malaria if he receives blood of another person containing the parasite, scientists wondered who injects the parasites in the normal cases. Since malaria is associated with stagnant water which was the home of many insects including mosquitoes, the latter became the main suspects. As early as in 1717, Lancisi stated that marshes cause malaria though the transformation of minute worms into mosquitoes which infused a poisoned liquid into the wounds they inflict. What did he observe in the marshes? Must be mosquito larvae, what else? In 1883 Kreig and King produced circumstantial evidence to pinpoint the mosquito as an agent of transmission of malaria. Laveran, Manson, Pfeiffer and many others were of the same opinion. But experimental proof was eluding them. It was Ronald Ross who first took up experimental investigation into the role of mosquitoes.

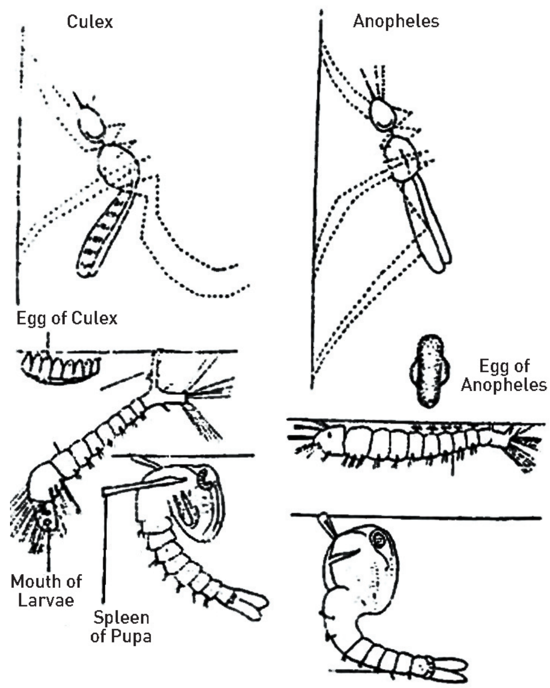

Fig. 1. Life history of the mosquito (Anophles and Culex). Note the differences in the sitting postures of their adults; shape of egg and position of larva.

As the first step Ross experimentally verified that it is the Anopheles mosquito and not the other species that suck in the material parasites from infected patients along with his blood. He also showed that these parasites multiply in the stomach wall of the mosquito establishing thereby that the Anopheles mosquito was the natural host of these parasites (1897). It was a very significant contribution. Then he went on to demonstrate that malarial parasites are injected into another victim during a mosquito bite. But without human volunteers he had to work with bird malaria (*Proteosoma sp*) in sparrows. He discovered *sporozoite* stage of malaria in the salivary glands of the mosquito (1898). So, the human mosquito-malaria enigma was solved.

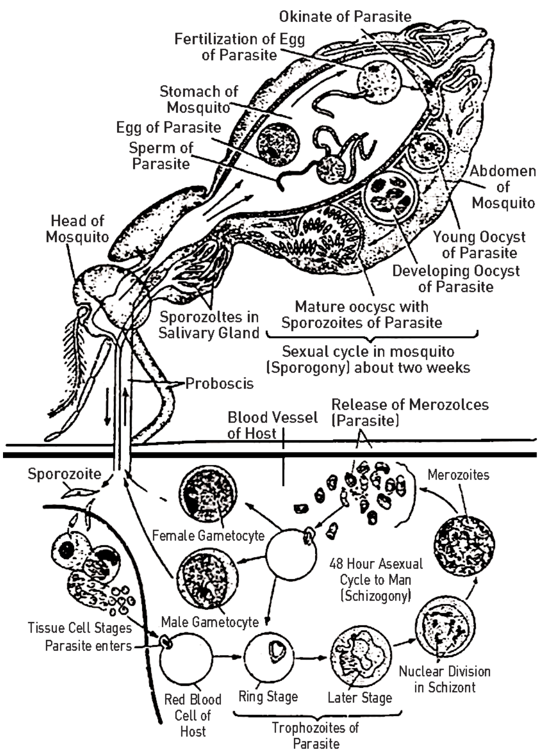

Fig. 2 Life history of malarial parasite *Plasmodium*, showing different stages in mosquito and human body.

Immediately after, Grassi (1898-99) found similar cycles in *P.falciparum*, *P. vivax* and *P. malariae*. He also unequivocally demonstrated that mosquitoes act as vectors and transfer malaria in man. Ross's work, therefore, cleared several mysteries of the past, opened the door for many future discoveries and paved the way for launching antimalarial campaigns on a global scale.

Ronald Ross

Sir Ronald Ross was awarded the Nobel Prize in 1902 'for his work on malaria by which he has shown how it enters the organism and thereby laid the foundation for successful research on this disease and how to combat it'. He was the second Nobel Laureate in medicine and physiology since its inception.

He was born at Almora in the Kumaon hills of Uttar Pradesh on 13 May, 1857. He came of a three generation Anglo-Indian family and was the eldest son of a general in the Indian Army. He had his medical education in England. After obtaining the MRCP Diploma in 1879, he worked as a surgeon of a ship for some time and then entered the Madras Medical Service. During his home leave in 1888, he studied bacteriology and got DPH Diploma. He also got some familiarity with mosquitoes. He returned to India in 1892 and began to take special interest in malarial parasites. He took the opportunity of observing and studying the parasites under the guidance of Patric Manson during his second leave in 1884. Coming back to India next year he devoted himself to experimental investigations of the mode of transmission of malaria. He remained in touch with Manson who always encouraged him. But his research was constantly being hampered by frequent transfers at it crucial stages. In spite of the impediments he continued resolutely and got the breakthrough in 1897 and 1898. Thereafter he was sent to Assam to investigate the large scale occurrence of black fever (kala azar). The same year he took retirement from the Indian Medial Service and migrated to England. He joined the Liverpool School as a lecture where he became a Professor in 1902. In 1912 he joined the King's College Hospital, London as a physician for tropical diseases. During the First World War (1914-18) he worked as consultant in various organizations to advice on antimalarial campaigns.

Apart from scientific papers and his Memoirs, he wrote several books on poems and romances. Ross was honoured with investiture of Knight Commander of the Order of the Bath in 1911 and in 1918 he became knight Commander of the order of Saint Michael and Saint George. Later, in 1926 the Ross Institute and Hospital for Tropical Diseases was established in his honour at Putney. He breathed his last at Putney in 1932.

Can you now understand why draining of marshes and introduction of buffaloes had helped Romans in reducing malarial cases locally. Obviously these steps caused disturbance to the breeding grounds of mosquitoes.

Eluding Control

Once the vicious cycle of man-mosquito-malaria was known it became clear the eradication of malaria can be attempted in two ways: (i) curing malaria patients by effective drugs thereby reducing the source of the parasite, and (ii) destroying the mosquitoes mainly by controlling their breeding and development so that the transmission of malaria was interrupted.

By mid-twentieth century preparation for malaria eradication was complete. Effective drugs (quinine, chloroquine, antibiotics) for cure of malaria became easily available. At the same time powerful insecticides (DDT, BHC etc.) and mosquito repellents for suppressing mosquito menace were also on the racks. Adoption of the two pronged attack went very well by early sixties of the twentieth century. The disease was totally suppressed in several countries and quite tamed in many others including India. The death per year came down from three million in 1946 to two million in 1961. The total number of incidence also sharply declined. It was hoped that the disease would totally be controlled within two decades. However, only those countries whether developed or developing, succeeded in their efforts which never loosened their grip on the eradication campaign. A sense of complacence crept in at this crucial junction of the campaign both at the global efforts as also at the country level campaigning. The attention was diverted to the wars in the Southeast Asia, flow of money tapered off and the operation plans had to be down sized. Medical attention both for research and training shifted to more challenging areas, malaria eradication programmes of the Public Health Services became tardy. This was followed by injudicious use of drugs often faulty treatment schedule as well as indiscriminate use of insecticides. The consequence was disastrous. New strains of drugs resistant parasites and insecticide resistant malarial mosquitoes emerged to make the task of cure and control more difficult. The worst was the development of drug resistance types of malignant of cerebral malaria (*P.falciparum*) and their rapid invasion in different parts of the world including India.

However, experts say that the war against malaria is not lost as yet. The man-malaria fight can still be tilted in favour of human if we renew the campaign with all the vigour and resources at our command correcting our past mistakes. Even with arsenal of existing drugs and the available insecticides the campaign can achieve success. In this centenary year of Ross's great discovery and fiftieth year of India's independence. We could make us proud by taking a sincere pledge to eradicate the curse of malaria from our country.

Description of the Prize Winning Work*

"Towards the middle of August (1897) I had exhaustively searched numerous grey mosquitoes and a few brindled mosquitoes. (Unable to obtain literature on mosquitoes, Ross made a working classification of his own and invented simple names. His grey mosquitoes belonged to the genus Culex, his brindled mosquitoes to the genus Stegomyia.) The results were absolutely negative; the insects contained nothing whatever....

" I had remembered the small dappled winged mosquitoes (genus Anopheles), but as I could not succeed either in finding their larvae or in inducing the adult insects to bite patients, I could make no experiments with them. On the 15th August, however, one of my assistants brought me a bottle of larvae, many of which hatched out next day. Among them I found several dappled-winged mosquitoes, evidently of the same genus as those found about the barracks, but much larger and stronger. Delighted with this capture I fed them (and they proved to be very veracious) on a case with crescents in the blood. Expecting to find more in the breeding bottle and wishing to watch the escape of the motile filaments in this new variety, I dissected four of them for this purpose immediately after feeding. This proved to be most unfortunate, as there were no more of these insects in the bottle, and the results as regards the motile filaments were negative. I had, however, four of the gorged dappled-winged mosquitoes left; but by bad luck two of the dissections were very imperfect and I found nothing. On the 20th August I had two remaining insects both living. Both had been fed on the 16th instant. I had much work to do with other mosquitoes, and was not able to attend to these until late in the afternoon when my sight had become very fatigues. The seventh dappled-winged mosquito was then successfully dissected. Every cell was searched, and to my intense disappointment nothing whatever was found, until I came to the insect's stomach. There, however, just as I was about to abandon the examination, I saw a very delicate circular cell apparently lying among the ordinary cells of the organ, and scarcely distinguishable from them. Almost instinctively I felt that there was something new. On looking further, another and another similar object presented itself, I now focused the lens carefully on one of these, and found that it contained a few minute granules of some black substance exactly like the pigment of the parasite of malaria. I counted altogether twelve of these cells in the insects, but so tired with work and had been so often disappointed before that I did not at the moment recognise the value of the observation. After mounting the preparation I went home and slept for nearly an hour. On waking, my first thought was that the problem was solved; and so it was.

"Next morning... the eighth and last dappled-winged mosquito... was killed and dissected with much anxiety. Similar bodies were present in it...The objects lay, not in the stomach cavity of the insects, but in the thickness of the stomach wall...

"These two observation solved the malaria problem. They did not complete the story, certainly; but they furnished the clue. At a stroke they gave both of the unknown quantities– the kind of mosquito implicated and the position and appearance of the parasites within it".

***From Ronald Ross. "Research on Malaria" has prix Nobel en 1902**

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