



The making of modern malariology: from miasma to mosquito-malaria theory

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ABSTRACT

The history of medicine teaches us that understanding the principle and natural origin of diseases is key to their effective management. Ancient Greek and Roman physicians abandoned supernatural interventions, as previously believed to be the sources of diseases, and instead expounded a theory of natural cause called *miasma*. Malaria (the very word meaning 'bad air') is the archetype, and is the most vicious of them all, then and thereafter, in the entire history of humankind. The search for its origin and transmission was as old as the miasma theory itself. Some rays of light dawned during the Italian Renaissance from Girolamo Fracastoro in the form of contagion theory, but its true nature was as enigmatic as ever. The Pandora's box of dilemmas was closed only on the closing of the 19th century CE. Yielding no medical enlightenment after a good two millennia, the miasma theory was confronted by the fledgling germ theory, and finally subjugated by the mosquito-malaria theory. The epoch-making discoveries came from two army physicians, Alphonse Laveran in Africa, who discovered the malarial parasite, and Ronald Ross in India, who discovered the mode of transmission. The saga is classic in the annals of science where theories are tested and falsified, and the one with the most credible and durable evidence survives, in spite of the odds and authoritative hostilities.

Key words: Contagion; disease; germ theory; malaria; miasma; mosquito-malaria theory.

This day designing God
 Hath put into my hand
 A wondrous thing. And God
 Be praised. At His command,
 I have found thy secret deeds
 Oh million-murdering Death.

I know that this little thing
 A million men will save –
 Oh death where is thy sting?
 Thy victory oh grave?

Malarial parasite, is the answer. (In stark contrast to that of the same question 1 Corinthians 15:55 poses.) These lines were penned down by Ronald Ross in the evening of 21 Au-

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gust 1897 in a jubilant mood of confirming his discovery of the parasite (that which we call *Plasmodium* by other name, was ‘peculiar pigmented cells’ to Ross) inside a mosquito just the day before, thereby deciphering the perpetual conundrum of what transmit malaria.¹ Malaria is an unrivaled cause of extermination of humans since time immemorial, and still is, upon which the Führer Hitler would blush in defeat. According the latest report of World Health Organization in December 2013, there were 207 million cases of malaria in 2012 alone, and death toll was 627,000 (with an uncertainty range of 473,000 to 789,000). An African child dies every minute as of now. Paradoxically it is glad tidings that mortality rates have declined by 42% since 2000.^{2,3}

Now every schoolchild knows malaria is caused by *Plasmodium* through the bite of female anopheline mosquito. But the fact was less evident in the last quarter half of 19th century CE, and was embroiled in a murky past before then.

IN THE BEGINNING WAS CREDULITY

Humans in days of old stereotypically held the notion that diseases were a deliberate curse inflicted by malevolent gods or malicious ghosts. But Ancient Greek philosophers began to realize the elusiveness in such baseless trepidations. Hippocratic School began to reject such supernatural agents. Some Greek and Roman philosophers thought that diseases might be caused by tiny animals dwelling in swampy places or by contact with the sick and with contaminated articles. They believed that disease-causing animals living in swampy places, so small as to be visible, might enter the body through the mouth and nose, and cause grave illnesses. Alternatively, epidemic diseases such as malaria and cholera might be caused by comets, eclipses, floods, earthquakes, or major astrological disturbances that charged the air with poisonous vapours known as *miasma* (Ancient Greek μίασμα for ‘pollution’ or ‘defilement’).⁴

As the very etymology of the word would give away, malaria (a contraction of Italian

words *mala* for ‘bad’, and *aria* for ‘air’) is a typical miasma. The earliest record of the disease was perhaps in the Egyptian document called Ebers papyrus (c. 1,550 BCE) discovered at Thebes, Egypt, which mentions fever accompanied with splenomegaly (enlargement of spleen).⁵ During the 5th century BCE, Greek scholars had numerous records of medical cases, which could be loosely related to malaria. Sanctified now with an epithet ‘father of medicine’, Hippocrates studied in Egypt and clearly described symptoms of some diseases in his treatises *Epidemics* and *On Airs, Waters, and Places* in 400 BCE. He defined the fatal nature of malaria (of course the name was not yet in the picture, so it was variously called ‘marsh fevers’, ‘agues’, ‘tertian fevers’, ‘quartan fevers’, or ‘intermittent fevers’) and their associated splenomegaly.^{6,7} The Romans knew better than to live in plains and valleys where mysterious fevers and mosquitos were rampant.⁸ It was those Romans who gave the name malaria, and ironically, one of the factors attributed to the downfall of the Roman Empire.⁹⁻¹¹

A 1st-century BCE Roman writer Marcus Terentius Varro was astonishingly close to giving the modern concept of malaria. He theorised that malaria was certainly caused by ‘tiny animals’, which he called *animaletti*. These tiny animals, invisible to the eye, bred in marshes, spread in the air, entered people through mouth and nose, and gave them grave maladies.^{12,13} From the atrocious Medieval Crusades, we come to learn that the miasma killed more warriors than did warfare, and still is.¹⁴ The belief that malaria was inherently connected to miasmatic swamps and marshes thrived well until the end of 19th century CE.¹⁵

One of the earliest proper uses of the name malaria was in the mid-18th century CE by Italian historian and chancellor of Florence, Leonardo Bruni in his *Historia Florentina* (1,444 CE) in which he described soldiers suffering from ‘*mala aria*’. The new terminology was introduced into English by Horace Walpole in his letter 5 July 1740: ‘There is a horrid thing called the *malaria*, that comes to Rome every summer,

and kills one.’ John MacCulloch adopted the word into the English scientific literature in 1827.¹⁶

THE CONTAGION THEORY

The kinds of evidence used to support the concept of pathogenic miasma and the alternative concept that diseases were transmitted by contagion were analysed by the Italian Renaissance physician and poet Girolamo Fracastoro. In 1530 he published a classic study of the venereal disease known to Italians as the ‘French disease’ in a form of medical poem *Syphilidis sive morbus gallicus* (*Syphilis or the French Disease*), thereby coining its modern name. Having observed the epidemics of syphilis, plague, and typhus that had ravaged Italy in the 16th century, he compared the implications of the miasmatic theory of disease with those of contagion theory. He distinguished three different modes of contagious diseases. The first kind infected by direct contact only. The second kind infected by contact and also by means of *fomites*, inanimate articles such as clothing, linens, and utensils that had been in contact with an infected person. In the third category he placed contagion transmit-

ted not only by contact and fomites, but also capable of being transmitted at a distance – tuberculosis, certain eye diseases, and smallpox seemed to fall into this category.¹⁷ He formalised his contagion theory in a 1546 treatise, *De contagione et contagiosis morbis* (*On Contagion and Contagious Diseases*), and he therefore may be properly resurrected as the founder of germ theory of diseases.¹⁸⁻²¹

In general, the notion of contagion existing in tiny germs or seeds did not appeal to medical practice. Attempts to suppress epidemics by quarantines, isolation and disinfection often proved to be futile. While such measures might have mitigated the spread of bubonic plague to a limited extent, they were ineffective against typhus fever, typhoid fever, and cholera. The case of malaria was particularly up against a brick wall. As duly expressed by the American physician Alfred T. Magill in his elaborate 1834 lecture: ‘Physicians of all countries have tortured their brains, and exhausted all known resources of the Chemical art, in attempting to discover the properties of the invisible agent of disease and death... None of all the many “ills which flesh is heir to,” has probably been so prolific of destruction and misery to the race of mankind, as miasmatic exhalation.’ The miasmatic foundation was so durable that scientists tried to identify the principal gas such as carbonic acid and hydrogen as the cause of malaria. And the *modus operandi* of malaria control was regular turning of soil.²²

In 1840 a German physiologist Jacob Henle revived the contagion theory and published his examination of the relationships among contagious, miasmatic, and miasmatic-contagious diseases. His essay *Von den Miasmen und Conatigien und von den miasmatisch-contagiosen Krankheiten* (English version published as a book *On Miasmata and Contagia*) in his book *Pathologische Untersuchungen* hardly caught the eyes of his contemporaries; but after the establishment of the germ theory of disease, it was retrospectively recognised as a milestone. Based on his description, malaria could be classified as a purely miasmatic disease, while smallpox, mea-



Figure 1. Girolamo Fracastoro lectures the shepherd Syphilus and the hunter Ilceus the danger of yielding to illicit temptation that leads to syphilis. Credit: Wellcome Library, London. <http://wellcomeimages.org>

sles, scarlet fever, typhus, influenza, dysentery, cholera, plague, and puerperal fever were miasmatic-contagious. Whereas syphilis, foot-and-mouth disease, and rabies were strictly contagion in nature.²³⁻²⁵

AN UNHEEDED GOSPEL

A remarkable proposition was promulgated by an American physician Charles Earl Johnson in 1851 in his elaborate address to the Medical Society of North Carolina, in which he expressly refuted the miasmatic view of malaria. He forcefully criticised the flaws in the gaseous origin of the disease, stating that no chemical analysis or microscopic investigation had ever been able to identify the miasma. He inferred his arguments from available medical reports of the time, some interesting points of which are:

- The delta of the Mississippi was a recorded healthy place although it has a nearby river, ponds, marshes and lots of stagnant water.
- Labourers of North Carolina were the healthiest people of working classes in spite of their constant exposure to swamps, and drinking swamp water.
- South American countries such as British Guiana and Brazil which were literally flooded with tropical swamps were free from malaria epidemics.
- Java Island in Southeast Asia, a region known for epidemics, had luxuriant vegetation and agricultural fields, supplemented with hot and wet tropical climate, ideal for miasmatic disease, was but the healthiest part of Asia.
- A highly polluted Thames was a good source of drinking water.
- On the other hand, the driest regions such as Guinea in Africa, Spain, Malta, Gibraltar, and several states of America, were frequented with malarial fevers.

He concluded with self-esteem that he 'furnish sufficient evidence to convince us that

there is no truth in the doctrine of the miasmatic origin of disease.'²⁶ Sadly it was a miasmatic insight everyone turned a blind eye to.

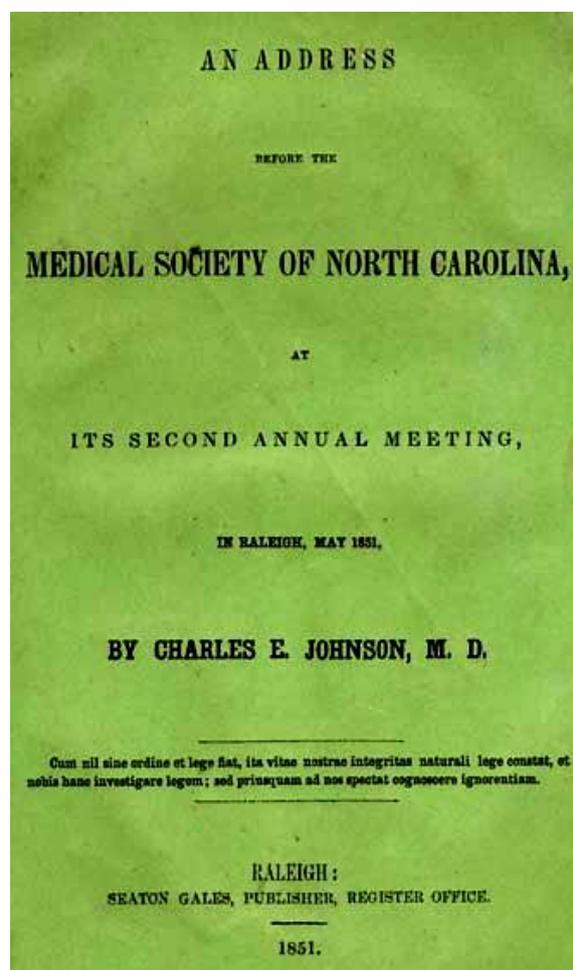


Figure 2. The forgotten gospel of malaria.

THE GERM THEORY OF DISEASES

Medical microbiology owes in large measure to Louis Pasteur, professor of chemistry at the University of Strasbourg, France. He discovered that fermentation is caused by microorganisms. He showed that it was the growth of microbes that caused spoiling of beverages, such as beer, wine and milk – the fact that was the last nail in the coffin of a two-millennium-old idea of spon-



Figure 3. Father of modern microbiology, Koch.

taneous generation. In 1862 he established that when milk is adequately heated to kill most microbes already present within them, it can be preserved from souring; the so-called technique of 'pasteurization', the very principle of germ-killing, and which is still in application in an industrial scale.^{27,28}

On 6 July 1885 a nine-year-old Joseph Meister was brought by his despondent mother to Pasteur after severe attack by a rabid dog. The dog left him with deep wounds on his hands, legs, and thighs. There was no balm in Gilead, or anywhere, for rabies. Death was writing on the wall. Advised by physicians that the case was hopeless, and in spite of legal issues he could potentially face being not a certified doctor, Pasteur began a series of inoculations with his new vaccine.^{29,30} Meister cheated death. The daring clinical trial was one giant leap in the entire history mankind, and within a year more than 2000 people had received the rabies vaccine. The saviour Pasteur was instantly raised to an international reputation.^{31,32}

In Germany, a physician Robert Koch had

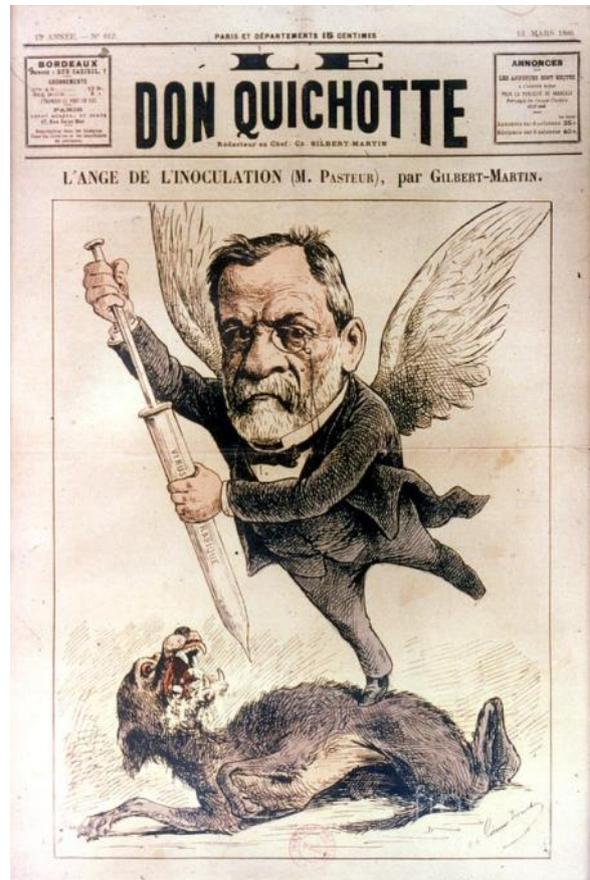


Figure 4. Caricature of Pasteur, the germ killer.

witnessed an outbreak of anthrax in 1870s. In 1876 he isolated the pathogen and identified it to be a bacterium, *Bacillus anthracis*, established its life cycle, and explained the natural history of the disease. An understanding of the complete and complex life cycle of *B. anthracis* immediately explained the mystery of the persistence of anthrax in pastures that farmers came to think of as cursed by the disease. Because spores could survive under harsh conditions, one contaminated carcass dumped in a shallow pit could serve as a reservoir of spores for many years.^{33,34}

But it was again Pasteur who developed a preventive vaccine for anthrax. But then his arch-rival Jean Joseph Henri Toussaint had published a successful result with an attenuated vaccine against anthrax in dogs and sheep, and on

July 12 1880, by demonstrating before the French Academy of Sciences. To overpower Toussaint, Pasteur, with the cooperation of the Agricultural Society of Melun, organised which is arguably the most dramatic demonstration of scientific discovery of all time. He vaccinated flocks of sheep before the eyes of all and sundry at Pouilly-le-Fort on 5 May 1881. His vaccination was by a clear mile a shattering success against Toussaint's, and his fame boosted with much fortune.^{35,36} By his last breath in 1894, millions of sheep and cattle had been vaccinated against anthrax.³⁷

Nicknamed the 'Pied Piper of microbiology', Koch continued juggernaut discoveries of bacterial germs such as *Staphylococcus* that cause wound infection, and *Vibrio cholerae* that cause cholera.³⁸ In 1882 he also isolated what he named *Tubercle bacillus* (now *Mycobacterium tuberculosis*), the causative bacterium of tuberculosis. His findings were sternly disputed as not all scientists were willing to accept the idea that a single pathogen could be responsible for a disease as complex as tuberculosis. But that did not deter him to receive the 1905 Nobel Prize in Physiology or Medicine, as he was successively proven right.³⁹⁻⁴¹

The theme of these stories: diseases, if not all, are definitely caused by germs – the central tenet of germ theory. This was a complete turn of understanding diseases purely on natural basis.

THE DEVIL IN THE DETAILS

The scientifically credible contagion theory itself did not provide a shred of clue to the etiology of malaria, which had to wait almost another half a millennium; nor the germ theory implied that malaria is due to germs. In 1847 a German physician Johann Heinrich Meckel observed black pigment granules from the blood and spleen of a patient who died of malaria. He further noted the occurrence of protoplasmic masses inside the granules. Without actually knowing the nature and significance, he might have been the first to see malarial parasite. A

German pathologist Rudolf Virchow, preserved for posterity in cell theory, was the first to relate the presence of pigments in blood cells to malaria in 1849.^{42,43} In 1879 Ettore Afanasiev, later founder of Italian school of malariology, postulated that it was those granules that cause the disease. These observations indicated that it could be possible to identify the causative agent and sparked the zeal for decoding the secret of the disease.⁸ So much so they even led to false trails and fruitless research.

A young French Army physician (of course he was professor of military diseases and epidemics at the School of Military Medicine of Val-de-Grâce in Paris) Charles Louis Alphonse Laveran working in Algeria, North Africa, detected mysterious pigments not only in blood plasma but also on and within erythrocytes. At the hospital in Bône, he noticed spherical bodies from a patient's blood, free or adherent to erythrocytes. Some of these bodies were glassy ('hyaline') and difficult to see; some had pigmented granules exhibiting amoeboid movements, and some pigmented bodies were crescent shaped. He knew then he was on hot trail of the parasitic nature of malaria. But that was not conclusive yet. It was on early morning of 6 November 1880 that he witnessed from a patient at the military hospital in Constantine what turned out to be a pivotal landmark in malariology, needless to say, a groundbreaking discovery in modern medicine. Laveran saw, in his own words 'a pigmented spherical body, filiform elements which move with great vivacity, displacing the neighboring red blood cells,' and also the actual formation of microgametocytes (male gametes) by the process of exflagellation. He meticulously examined the blood of 200 patients, and observed the peculiar bodies in all 148 cases of malaria but never in those without malaria. He also noted that after treatment with quinine the bodies disappeared. He correctly concluded thus that:

Parasitic elements are found in the blood of patients who are still ill with malaria. Up to now, these elements were thought incorrectly to be pigmented leukocytes. The presence of these

parasites in the blood probably is the cause of malaria.

He named the parasite *Oscillaria malariae*.^{44,45} He reported his finding to the French Academy of Medicine in Paris on 23 November and 28 December, but was received with general scepticism by Italian scientists, and Pasteur and his disciples, who favoured the bacteria germ theory for malaria.⁴⁶ He published his discoveries in 1881 in a monograph titled: *Nature parasitaire des accidents de l'impaludisme; description d'un nouveau parasite trouvé dans le sang des malades atteints de fièvre palustre*, and on 12 November 1881 issue of *The Lancet*.⁴⁷ The Academy was reluctant to overthrow the bacteria theory of Theodor Albrecht Edwin Klebs and Corrado Tommasi-Crudeli, the two giants of microbiology at the time, in favour of a protozoan reported by a young and hitherto unknown army physician. They went so far as to explain away that the purported protozoan was nothing but a degenerate erythrocyte, probably caused by a bacillus.⁴⁸

Klebs and Tommasi-Crudeli had discovered that diseases such as typhoid and diphtheria were caused by bacteria, and further fortified the germ theory. They claimed that they isolated a bacterium, which they christened *Bacillus malariae*, from the waters of the Pontine Marshes, where malaria was prevalent, which when isolated in culture and injected into rabbits caused febrile infections accompanied by enlarged spleens, characteristics of malaria.⁴⁹ It was based on this theory that Laveran worked on malaria, and completely disproved it as bacteria had nothing to do with malaria. He recollected in his *Nobel Lecture* (the 1907 Nobel Prize in Physiology or Medicine was for discovering the protozoan parasites as the causes of diseases) that the unanimous rejection of his discovery was that it was so new to the prevailing concept of diseases that 'many observers not knowing how to classify it found it simpler to doubt its existence'.⁵⁰

Fortunately the turn of 1880s was a time of great improvement in clinical microscopy, and soon, Laveran's position was gaining an unprecedented favour. With new staining tech-



Figure 5. Laveran fighting in antimalarial crusade.

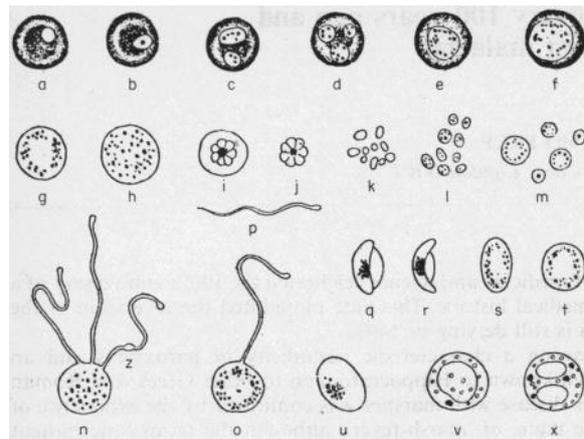


Figure 6. Laveran's drawing of *Oscillaria malariae* in 1881. Note the crucial crescents (q,r) and exflagellation (n,o), the features of *P. falciparum*.

niques such as methylene blue-eosin stain by Dimitri Leonidovitch Romanowsky in 1891, the parasites could be unambiguously identified. Unbeknown to Laveran, the Russian physiologist Vassily Danilewsky had discovered protozoans from the blood of birds and reptiles in the Ukraine. By 1885 he was able to classify them into three genera now known as *Plasmodium*, *Haemoproteus* and *Leucocytozoon*. In Italy Amico Bignami and Ettore Marchiafava, using a combination of Romanowsky's technique and an oil-immersion microscope objective newly developed by the Carl Zeiss Company, observed amoeboid movement of the organism invading erythrocytes.⁴⁹

Perhaps the decisive moment was from none other than Camillo Golgi (who eventually won the 1906 Nobel Prize in Physiology or Medicine for his work on nervous system, and whose name is immortalised with an eponymous cell organelle). In 1885 Golgi was able to identify the organismal character of the parasite. Not only that, he could distinguish between *Plasmodium* species and show the synchrony of the parasite in relation to paroxysm. He was able to differentiate between tertian (48 hour periodicity) and quartan (72 hour periodicity) malaria. It was thus established beyond doubt that Laveran had accurately described the gametocytes, the trophozoite, and the schizont stages. This implies that malaria was caused by a pathogen, and by nothing else. Hence, the germ nature of malaria became clear as day.⁵¹

Even then the bulwarks of germ theory Koch and Pasteur played doubting Thomas, and were only converted after they cast their own eyes before Laveran's preparation. Nevertheless, while the Europeans began to have a consensus on Laveran's discovery, the miasma theory was still in its heyday in America. For instance, R. C. Newton, a staunch supporter of Tommasi-Crudeli, reported his studies in 1895 and concluded that 'Aerial and aquatic transportation of malaria has been proved'.⁵² By 1890 it was universally accepted that malaria was caused by a protozoan parasite and, that there were three species with specific periodicities and other char-

acteristics responsible for benign tertian (*Haemamoeba vivax*), malignant tertian (*Laverania malariae*) and quartan (*Haemamoeba malariae*) malaria, now respectively known as *Plasmodium vivax*, *P. falciparum* and *P. malariae*. (*P. ovale* also causes tertian malaria, but its discovery was only in 1922,⁵³ and its subspecies as recent as in 2010.)⁵⁴

It may be added here that Laveran intensely despised the name 'malaria' because the term was unscientific and vulgar, and entirely a mis-attribute as the disease had nothing to do with bad air. He preferred the name 'paludisme' (Classical Latin *palus* for swamp/marsh) which is still used in France today.⁵⁵ If you happen to be in France, say as the French.

THE FINAL SOLUTION

The voice of one crying in the wilderness

A British-born American physician, Albert Freeman Africanus King, who witnessed and attended Abraham Lincoln being assassinated on 14 April 1865, had a rather queer name. 'Africanus' is a ridiculous proper noun for a human, but subtle in Linnaean nomenclature, and in his case it was for his father Edward King's support of colonisation of Africa. A brilliant academician, practising physician and scientific thinker, he first shared his idea of malaria transmitted by mosquitos with his two friends C.V. Riley and L.O. Howard in late 1881. To his friends such a brave new world of brainwave was casting pearl before swine. He nevertheless organised his hypothesis and was read before the Philosophical Society of Washington on 10 February 1882, under the title 'The Prevention of Malarial Disease Illustrating *inter alia* the Conservative Function of Ague'. The paper was never published and the only surviving record of the response was an undermining one by J.S. Billing, who scribbled 'that since ague did not invariably result from insect bites, the most that could be claimed was that they accomplished an accidental inoculation with malarial poison'.⁵⁶ King knew very well the fate of US Army Sur-

geon William Crawford Gorgas who had written an article 'Mosquito Origin of Malarial Disease' in *Baltimore Observer* in 1807. Gorgas' 'ludicrous' idea was wiped off from the face of the earth. Unfettered, King amassed more knowledge on insect biology, with the recent discovery of Patrick Manson that filariasis was transmitted by mosquitos as a stronghold theoretical ground. In 1883 he completed his theory and published as a 15-page article in September 1883 issue of *The Popular Science Monthly*, making an introduction as:⁵⁷

I now propose to present a series of facts... with regard to the so-called "malarial poison," and to show how they may be explicable by the supposition that the mosquito is the real source of the disease, rather than the inhalation or cutaneous of a marsh-vapor.

His facts were listed in a 19-point thesis.⁵⁸⁻⁶⁰ To paraphrase his lengthy arguments: Occurrence of malaria always coincided with conditions that are also ideal for mosquitos, such as in the time of day, geographical area, temperature, and climate. But the veritable loophole in his proposition was that he believed malaria was transmitted by mosquito through its eggs.⁵⁷

The Holy Grail

Discovery of the parasite was only as good as it gets. It had no direct implication to the more important aspects, namely control and treatment of the disease. The crux of the matter, how the germ of malaria was transmitted remained a confined mystery, and the miasmatic nature uncertain as ever. The germs could well be transmitted through bad air. As the discoverer Ronald Ross himself put it, "I call it here the Great Problem!"

The credit of discovery was achieved through a lot of perseverance, encouragement, frustration and literally suffering from the disease.⁶¹⁻⁶⁴ Ross was a low-profile surgeon in the Indian Military Service in the 1880s, with an innate propensity to poetry and mathematics, and to

whose utter aggravation, failed to get permanent posting. A home leave to England in March 1893 was therefore a huge sigh of relief. To top that it was a moment that would eventually changed his career, profile and prominence, for he met his future mentor, Patrick Manson, who would catapult him to eternal fame and glory.

Patrick Manson was an expert in tropical disease particularly in Asia (for obvious reason, he is remembered with an appellation 'father of tropical medicine'), and was then a physician at Seamen's Hospital and lecturer at St George's Hospital in London. He had analytical lines of reasoning.^{65,66} Firstly, based on his earlier discovery in 1877 that mosquitos (*Culex fatigans*, now *Culex quinquefasciatus*) are vectors lymphatic filariasis, a parasitic disease caused by a roundworm *Filaria sanguinis hominis* (now *Wuchereria bancrofti*),^{42,67} he had a strong conviction that insects are vectors of most, if not all, parasitic diseases. (Manson's sympathetic persona might be reflected by his expression of the title '...on the mosquito considered as a nurse', the 'nurse' is to us vector.)⁶⁸ Hence, by intuition, malaria too could possibly be transmitted by mosquito.^{69,70} (It is most likely that Manson or his disciple knew nothing of King's theory.) This became the mosquito theory, or more appropriately malaria-mosquito theory. Secondly, he surmised that of all places India was the most suitable place for investigation, because of the weather and lifestyle of the people such that mosquitos were never a rarity. Thirdly, he was strongly of the conviction that malaria was caused by a protozoan parasite, supporting Laveran.⁴⁶ Of course the germ theory of malaria was in no way a scientific consensus at that time, and it is no surprise that Manson was ridiculed by his colleagues for having such unproven notion.

Manson had an added misfortune of affliction with the so-called 'rich man's disease', gout, which he acquired in China and permanently rendered him physically disabled to carry out field research to substantiate his theory. He had in fact devised an ingenious procedure for observing *Plasmodium* in a stage of exflagellation

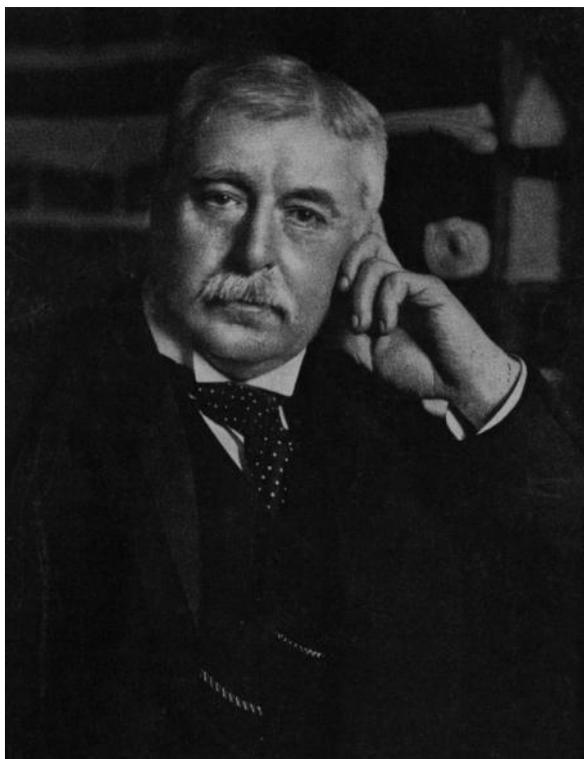


Figure 7. (Almost) made for each other. The guru Patrick Manson (left) and his disciple Ronald Ross (right).

from blood samples. He did not have further knowledge or opportunity to search for the implications thereof, and he badly needed an exceptional investigator, and for the purpose, his 'greatest discovery' came in the form of an army surgeon on vacation. He and Ross met on 10 April 1894, and which, as things turned out, proved to be a truly 'love at first sight' and the two as 'perfect couples' (all in a strictly platonic allusion). He demonstrated to Ross the *Plasmodium* from slides and explained his observations, and how India would be a good choice for investigating malaria.⁷¹ He took him to different hospitals. Once on their way in Oxford Street in November 1894, he placed his hands on Ross' shoulder and confided to him the gist of his theory, saying, 'Do you know, I have formed the theory that mosquitoes carry malaria just as they carry filaria.'

In his *Memoir* (p. 127), Ross recollected his contrition, stating, 'My doubts [of Laveran's

germ theory of malaria] were now removed.' He was authentically a born-again medical researcher, the fact compellingly evidenced by his overtly action on his arrival to India on 20 March 1895. Even before the luggage was cleared in the custom office, he dashed straight to Bombay Civil Hospital in search of malarial patients and started making blood films.

He would not have to discover the hard way by himself a straightforward fact that scientific milestones are not normally made in an impulse of enthusiasm, had he paid attention to Pasteur's abiding adage that 'in the fields of observation chance favoured only the prepared mind'.⁷² By the technological standard of his time (which basically consisted of a oil-immersion microscope with maximum objective lens of 100x), it took a bit more than scurrying off a train to a hospital to observe the details of something as minute as *Plasmodium*.

It took Ross two months to see the crescent

stage (which we call gametocyte) of his own preparation for the first time. It was a significant discovery which he himself did not comprehend at the time. What he saw was the stages of exflagellation from rounded cells which he named 'spherules', meaning the early phase of sexual development of *P. falciparum*. To add to his confusion was the observation that not all spherules developed flagella. He had no way of knowing there are two gametocytes, namely microgametocytes that undergo exflagellation, and macrogametocytes, that do not. His only reference was Manson's customised chart prepared in 1894.⁷³ He nevertheless realized that this was a tremendous success and wrote to Manson that this was the first step towards supporting the mosquito-malaria theory, which would be later proved to be an absolute truth. Manson replied and christened the mission as 'a Holy Grail', and that Ross was the 'Sir Galahad' (the gallant knight in King Arthur's Round Table) who was definitely 'on the right track'.^{42,61,62}

But then Manson directed him to a false trail because his theory had an Achilles heel, which was the statement that mosquito did not directly transmit malaria to humans but through their contamination of water by their dead and decaying bodies.⁷⁴ His crucial mistake was that he failed to conjecture the precise mode of infection in his case of filaria, that is biting of the mosquito.⁴² The parasites would be released in the water, or would be swallowed as 'mosquito-dust' (which amazingly still rings of element of bad air notion). Ross conducted several human experiments by letting volunteers drink water in which he added mosquito infected with malarial parasite. It was a huge failure.

The fiasco was compounded by Ross' deployment in September 1895 to investigate cholera outbreak in Bangalore. One and a half years later in 1897 he transferred to Secunderabad. An irate surgeon was right to express that he was literally 'thrown out of employment', and threatened to resign if they did not put him on malaria investigation. His situation was exacerbated by his ignorance of zoology, as he began to discern that mosquito-infested Bangalore had hardly a

case of malaria, which directly implied that not all mosquitos were the vectors.

Before he moved to Secunderabad in April, he had a chance of short leave to visit a well-known malarious area near Ooty (by then more popularly as Ootacamund). He was down with severe malaria after three days of arrival, in spite of his prophylaxis with regular dose of quinine. His assistant managed to collect mosquitos upon which he made a chain of erroneous conclusions. Firstly he misidentified *Aedes* species as *Culex sylvestris*, as he called, and later believed it as *Stegomyia scutellaris*. Secondly he concluded that the species was the malaria vector. These assumptions were wrong as the species is not present in India, and does not carry *Plasmodium*. In July he performed several trials with what he called 'grey or barred-back' (probably *Culex fatigans*) and 'Brindled mosquito' (*Aedes aegypti*) with little success.⁷⁵

Malaria Day

But the dilemma would soon be over. On 16 August his assistant reported to him that adult mosquitos emerged from some pupae collected the day before, among which were 'dappled-winged mosquitoes' (which he often referred to as 'brown mosquito' type, but which a zoologist would call *Anopheles*). Due to their scarcity he had never tried with the species. With excitement he fed the mosquitos to a volunteer, Husein Khan, who was diagnosed with malaria as well as filariasis. Khan was enclosed in a bed net with the mosquito, and each bite would earn him one anna (approximate equivalent to modern 6 paisa). Twenty-five minutes later Khan came out of bed with 10 annas the richer.⁶²

The mosquitos were captured and reared. From the afternoon Ross started a daily dissection of the mosquitos, with nothing unusual for the first two days. He did find for a filaria in one, and he spoiled two specimens. On the third day he first noted 'peculiar vacuolated cells in stomach' from mosquito 35. Other mosquito types never showed anything unusual. And the fourth day, 20 August, was so momentous that

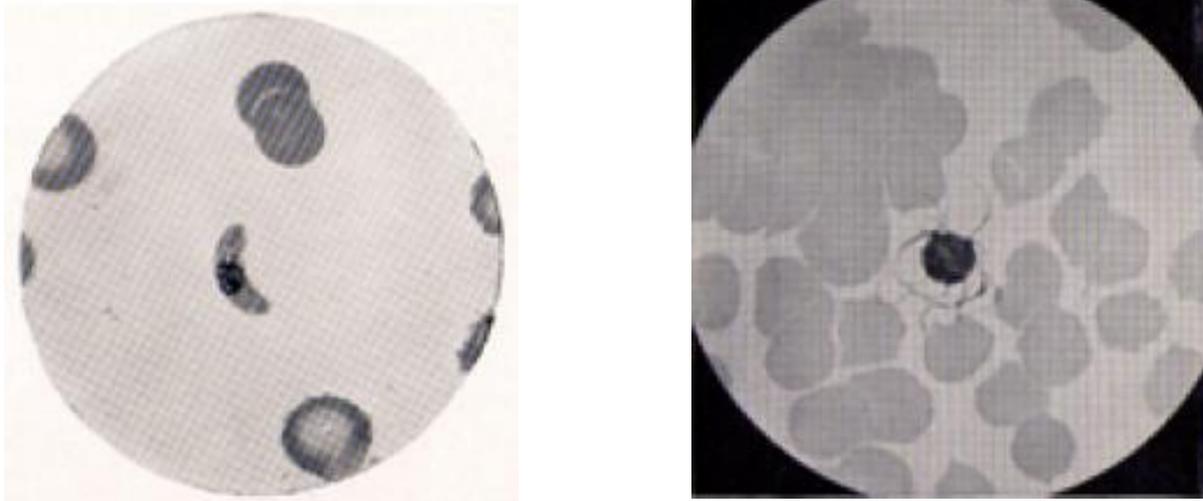


Figure 8. Slides of malarial parasite in crescent (left) and exflagellation (right) prepared by Patrick Manson in 1894.

he named it ‘Malaria Day’, and is eventually adopted as the *World Mosquito Day*. (The finding was published in the *British Medical Journal* on 18 December 1897,⁷⁶ in spite of its mediocre scientific standard – no experimental controls, only 2 samples, no replicates, no taxonomic identification.)⁷⁷

On that historic day the Angel of Fate laid hands on Ross. After attending his patients in the morning, he dissected mosquito 36 and found nothing in it. He tried with other species mosquito 87 but to no avail. Around 1 o’clock in the afternoon he sacrificed mosquito 38, his last but one remaining specimen among the dappled-wing sort. He found twelve cells attached on the mosquito stomach, which were most definitely the parasites as he saw the cells were uniquely pigmented and some with the crescents.⁷⁸⁻⁸⁰ He laughed hysterically and shouted for the Hospital Assistant, who was quite taken aback as he was having a peaceful siesta, and exclaimed in perfect euphoria, ‘Dame Nature, you are a sorceress, but you don’t trick me so easily. The malarial pigment cannot get into the walls of the mosquito’s stomach; the flagella have no pigment; you are playing another trick upon me!’ He made schematic drawings of nine of the cells, sealed the specimen, went home for tea at about 3 p.m., and with satisfaction of a



Figure 9. The penultimate proof of malaria theory. Ross’ notebook on 20 August 1897, the ‘Malaria Day’.

job well done he had a solid siesta for an hour. It was after he awoken that the full significance of his observation dawned on him. He also construed that if the cells were genuinely parasites, they would be growing, which could be proven in his last brown specimen. He spent the night in agony of fear that his only brown mosquito would face a mishap or even a premature death.⁶¹

Quod erat domonstrandum

Ross' angel had not abandoned him. On the next day he found mosquito 39 alive and kicking, dissected it, and vindicating his assumption, he found the cells considerably larger.⁸¹ The final word was clear, malaria was transmitted through mosquito and only the brown type was – as Ross himself described – ‘the real culprit’. He lost no time in writing the malaria poem (as in the opening of this article) to his wife.⁶¹

But the complete puzzle was not solved such as how mosquito infects human. Manson's postulate was not yet proven nor disproven. Ross had to answer after a gruelling service in the army. In September 1897 he was called to Bombay for undisclosed duty, and upon arriving there, he learned that he was posted at Kherwara in Rajputana (modern Rajasthan). Kherwara he noticed was an undesirably (in his perspective) healthy place, totally without serious diseases, and found his destination hospital empty of patient. He aptly named his experience in *Memoirs* under the chapter ‘Punishment’. He felt that he glimpsed the Promised Land but was prohibited from entering, like Moses. He counted his days terribly depressed with insomnia and constant toothache. The native Bhil people were exceptionally superstitious, and flatly refused to aid his experiments, even when he found one patient with tertian malaria. He began to lose all hopes.^{61,62}

Manson who was then Medical Adviser to the British Colonial Office, came to the rescue as he persuaded the government to transfer Ross to Presidency General Hospital in Calcutta (now Kolkata). Ross was assigned ‘special duty’ to

investigate malaria and kala azar (visceral leishmaniasis) and he joined his post on 17 February 1898. He was further provided Surgeon-Lieutenant-General Cunningham's laboratory. An erudite Manson broke the news that an American medical student William George MacCallum had just reported the fertilisation process of bird malaria. MacCallum had described flagellated structures from the blood of crows and also recorded how the flagellated bodies fused with non-motile bodies to form a vermicule (which we now call ookinete). The parasite was called *Halteridium* (but now considered as *Haemoproteus columbae*) and he pondered what he saw was sexual reproduction of the protozoan. He even suggested that the flagellated forms were male gametes, the non-motile forms female gametes, and the vermicule the zygote; and asserted, ‘This is a process which we might have expected and which I am confident will be found to occur in the case of the human malaria parasites.’^{82,83} He was that close to cracking the code of the Great Problem, as Manson perceived it when confiding to Ross, ‘MacCallum's observation on *Halteridium*; if it is correct, it is of the greatest importance.’⁶²

Ross immediately picked on birds as they were a lot more convenient to work on because Calcutta was also in shortage of malarial patients, and even if one was positively diagnosed, medication would be immediately given. To make long story short, it was here that Ross achieved his legendary discovery of the precise mode of transmission of bird malaria *Proteosoma* (now known to be *Plasmodium relictum*). On 4 July he discovered that salivary glands were the storage sites of the parasites in the ‘grey mosquito’ (which was *Culex fatigans*, but now renamed *Culex quinquefasciatus*). On 9 July he made his killer move by demonstrating that feeding grey mosquitos on malaria-infected larks did transmit the parasite to healthy birds.^{1,84,85} He reported it on 21 May, but published only in November, with a conclusion that runs:

These observations prove the mosquito theory of malaria as expounded by Dr Patrick Manson, and in conclusion I should add that I have

constantly received the benefit of his advice during the enquiry. His brilliant induction so accurately indicated the true line of research that it has been my part merely to follow its direction.⁸⁶

No further prophesy was needed or, any bad air or water infestation notion, malaria was incontrovertibly transmitted by the bite of mosquitos. No articulation would suffice better than Ross' himself: 'The triumph of 20 August was now completed and crowned by that of 9 July 1898.' Without a shadow of doubt, the mosquito-malaria theory was – as Ross' mathematical intuition would love to conclude – hence, proved. But in a milder tone he put it to Manson on 9 July 1898.⁶⁰

Q.E.D. and [I] congratulate you on the mosquito theory indeed.

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