Alphonse Laveran's discovery 100 years ago and today's global fight against malaria[1]

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On 6 November 1980, the world of medicine and science celebrated the 100th anniversary of a discovery that is a milestone in medical history. This date pinpointed the revelation of the cause of an ancient disease which is still defying us today.

This febrile disease, often showing a characteristic periodicity of paroxysms and an enlargement of the spleen, was well known to Hippocrates and to other Greek and Roman physicians. The association of this disease with marshes was confirmed by the experience of centuries and was reflected in the name of 'marsh-fever', although the terms 'intermittent fever' or 'ague' have commonly been used. The introduction into Europe in 1632 of 'Peruvian bark', and later its main alkaloid – quinine – allowed the distinction between true 'marsh-fever', cured by the new drug, and other fevers. The name mal'aria – referring to bad or spoiled air – came from Italy in 1740 and indicates the general belief, at that time, that some noxious vapour or miasma was responsible for the disease.

Already in the middle of the 19th century many morbid anatomists including, among the first, Meckel in 1847, noted the presence of brown pigment in the organs of persons who died of pernicious fever. Meckel also pointed out that the dark colour of the spleen, liver, brain or kidneys on autopsy of these cases was often associated with the accumulation of pigment in the blood. This was confirmed by Virchow and Frerichs in Germany. It is this pigment that formed the starting point of the work of Alphonse Laveran.

Alphonse Laveran was born in 1845 in Paris, the son of a distinguished French army doctor. At the age of 18 he entered l'École du Service de Santé Militaire at Strasbourg from which he graduated in 1867. With the outbreak of the Franco–Prussian War, he saw active service with the army. In 1874 he was appointed Professor Agregé des Maladies et Epidemies des Armées in Paris, a position occupied previously by his father. In 1878 the 33-year-old 'Médecin-major de 1re Classe' was posted to Algeria, to the military hospital at Bone. There he had the opportunity of conducting post-mortem examinations on cases of pernicious malaria and, like others before him, noted the pigmentation of internal organs. On examining under the microscope a drop of blood taken from the spleen, he found that besides free pigment there were also leukocytes containing ingested particles and also pigmented, spherical, hyaline corpuscles and crescent-shaped bodies. On 6 November 1880, in examining the blood of a young soldier, he saw at the edge of one of the spherical corpuscles several actively moving filaments.

He assumed at once that the pigment-containing clear cysts or cells were living organisms and not products of degeneration of red blood cells. The actively mobile filaments that occasionally emerged from these bodies and disturbed other blood corpuscles were like flagella and these, together with the small cysts, must be the cause of the disease. (We know today that Laveran was looking at the phenomenon of exflagellation of male gametocytes, fully described by MacCallum in 1897.) Laveran described his discovery in a short paper presented on 23 November 1880 at the meeting of the Académie de Médecine in Paris (*see* Figure 1).

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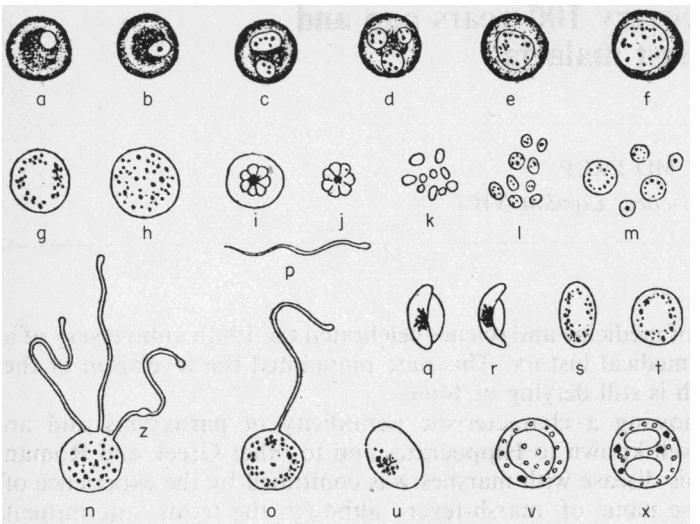

Figure 1. Malaria parasites (*Haemamoeba malariae*) observed and drawn by Alphonse Laveran; published in *Comptes Rendus de l'Academie des Sciences*, 24 October 1881. (From Sergent & Sergent 1929)

One must not forget that Laveran saw the new bodies in a fresh, unstained blood-film, on a slide under a coverslip, using a microscope with a dry lens (1/6″) giving a magnification of about 400 diameters. One can only admire his eyesight and his powers of observation! The differential staining, introduced by Romanowsky in Russia, was still unknown at that time.

During the following year Laveran examined nearly 200 patients and was able to demonstrate his parasite in 148 of them. A full account of his studies was reported to the Académie des Sciences on 24 October 1881. Laveran now recognized four different forms of the parasite: an element curved like a crescent, transparent spherical bodies about the size of a red blood cell to which actively moving flagella were sometimes attached, another spherical element, motionless and containing pigment, and spherical elements containing pigment, sometimes motile but of much smaller diameter (Figure 1). He named his parasite *Oscillaria malariae*. E Richard, a colleague of Laveran, stationed at Philippeville, Algeria, soon confirmed Laveran's observations.

In 1882 Laveran went to Rome where many cases of malaria could be found, coming from the notorious and pestilential Pontine Marshes of the Roman Campagna. At the famous Santo Spirito Hospital, using a microscope with an oil immersion, he was able to demonstrate his findings, but his Italian colleagues could not be convinced and interpreted Laveran's bodies as degenerated red blood cells.

At that time Klebs and Tomasi-Crudeli described their *Bacillus malariae* as a cause of the disease: they found it in swamp ooze, in water, and in the urine of patients. Culture of this organism caused fever when injected into rabbits. This view, supported by a number of German bacteriologists, was held obstinately until 1884, even by such Italian luminaries as Marchiafava and Celli.

However, a year later Marchiafava and Celli recognized their error and in 1885 Camillo Golgi described two species of malaria parasites morphologically quite different: one, quartan, which completed its life-cycle in man in three days and the other, tertian, which completed its life-cycle in two days. Golgi also showed that the paroxysms of fever were related to the multiplication of parasites in the blood stream.

On his return to Paris in 1884, Laveran published the first edition of his book, 'Traité des fièvres palustres', and was appointed professor of military hygiene at Val-de-Grâce Hospital, a position which he held for 10 years until his retirement from the Army. He then entered the

Pasteur Institute and took up the study of pathogenic protozoa of man and animals, and especially of trypanosomiasis, leishmaniasis and piroplasmosis.

In 1894 Marchiafava and Bignami found that in addition to the two species of malaria parasites, the tertian and quartan, described by Golgi, there is also another one, particularly frequent in summer and autumn and causing severe disease. Their monograph on the cause of aestivo-autumnal fevers (today's *P. falciparum*) did not convince Laveran. For nearly 20 years after his discovery he believed that there is only one species of malaria parasite which he then re-named *Haemamoeba malariae*[1].

Laveran also intensely disliked the name malaria, which he considered unscientific and vulgar, based on superstition. Not being able to agree to various alternative names such as 'fièvres des marais, fièvres maremmatiques or limnémiques, paludose or impaludisme', Laveran eventually settled on the name 'paludisme' and adopted it for the second edition of his book published in 1898.

Laveran's connection with malaria parasites of monkeys is also of interest. In 1897 Robert Koch collected some monkeys in East Africa and found parasites in their blood resembling those of man. Two years later Laveran saw in the blood of grivet monkeys (*Cercopithecus aethiops*) parasites which he described in detail and gave them the name of *Haemamoeba kochi*. These parasites, in a different form, were seen later in the liver of other monkeys by French scientists, but it was Garnham who in 1947–48 recognized their true nature, gave them the new generic name of *Hepatocystis* and concluded that they represent the tissue stage of a plasmodia-like parasite. This was the opening act for the major discovery in 1950 by Shortt and Garnham of liver stages of all malaria parasites of man.

Undoubtedly stimulated by Ross, Laveran founded in 1902 a society for antimalaria work in Corsica. In 1904, in collaboration with Mesnil, he published a monumental monograph on trypanosomes and trypanosomiasis.

In 1908 he founded the French Societé de Pathologie Exotique and served as its president for 12 years. Laveran received many honours both at home and abroad and in 1907 he was given the Nobel prize (Figure 2). He was a foreign member of the Royal Societies of London and Edinburgh. He died after a short illness, in 1922, leaving no children of his marriage.

Laveran's list of publications comprises nearly 600 titles. His biographer, Marie Phisalix, described him as a man of simple and modest character, but others found him self-righteous or intolerant and his relations with some of his colleagues were often strained.

In Laveran's obituary notice of 1923, Ronald Ross says: 'His writings are a model of clarity and completeness: every sentence is precise and unambiguous. His manner was like his writing – to the point, exact and decisive. He was regarded with affection and admiration by all who came into contact with him'.

But what about the way that the parasites, described by Laveran and the Italians, were transmitted to man? This remained a mystery for 17 years after the first discovery. The most likely mode of transmission was by water, although the possible role of mosquitoes was contemplated by several physicians including King in the USA and Manson in England. Laveran himself wrote in 1884 'Les Moustiques jouent-ils un rôle dans la pathogénie du paludisme? La chose n'est pas impossible. . .', but he did not pursue this hypothesis. The elucidation of the mystery of the life-cycle of the parasite in an Anopheles mosquito and its transmission by bite did not come until 20 August 1897 and was due to another Army medical officer working in India with an admirable patience and insight. His name was Ronald Ross.

The story of Ronald Ross's discovery has been told many times before. It deserves a mention now, since it became the basis for malaria control by attack on the vector, through the destruction of larvae of mosquitoes or prevention of their breeding.

[1]The terminology of the four species of human malaria parasites was very confused for many years. Varying generic names such as Haemamoeba, Haematozoon, Haemosporidium, Laverania and Plasmodium were used, not to mention some 20 different specific names of malaria parasites of primates. It was not until 1954 that the International Commission for Zoological Nomenclature put some order into the generic and specific names of human plasmodia, allowing the sub-generic name Laverania, as an alternative for *Plasmodium falciparum*.

Figure 2. Alphonse Laveran's fight against malaria. Cartoon by B Moloch, published in *Chanteclair* (1908)

In the modern history of malaria control, four periods are generally recognized. The first, from 1898 to 1922, is that of larvicidal methods by oiling or dispersion of Paris green dust on water surfaces which breed larvae of Anopheles; other methods, such as the use of larvivorous fish, shading, or various types of drainage, were widely used during that period. They were successful in limited zones but could not be introduced in rural areas of the tropics.

The second period, that from 1922 to 1945, saw little progress of anti-mosquito measures but an upsurge of chemotherapeutic discoveries. These gave us most of the currently available antimalarial drugs, in addition to the 'good old quinine', and when used on a large scale lowered the incidence of malaria very greatly.

The third period was that of 1945 to 1970, when DDT and other insecticides were introduced into malaria control and stimulated the WHO to proclaim the possibility of malaria eradication. The advent of these 'residual' compounds presented the world with a new method of interrupting the transmission of infection, by attacking the mosquito vector during its most important stage epidemiologically, when it feeds on man in his dwellings.

It soon became obvious that the eradication of malaria did not require the total elimination of all the Anopheles, and several examples of the first successful campaigns (Italy, Cyprus, Greece, Guyana, Puerto Rico, and Venezuela) were most impressive. It appeared that the widespread use of DDT and other insecticides for indoor spraying of houses was the most reliable, feasible, and economical method for the interruption of transmission (the attack phase), especially in rural areas. In the next phase of the eradication programme (the consolidation phase), the remaining foci of infection could be detected by proper surveillance and eliminated by distribution of antimalarial drugs.

This simplified description of the principle of malaria eradication gives no idea of the operational complexity of a large-scale programme. Few other public health endeavours need such careful planning, efficient administration, adequate financing, and detailed evaluation.

The worldwide programme of malaria eradication was formally endorsed by the World

Health Assembly and in 1957 the WHO took over the coordinating activities and the provision of technical assistance. The initial successes were remarkable. By 1965 malaria had been eliminated from the whole of Europe, most of the Asian part of the USSR, several countries of the Near East, most of North America including the whole of the USA, most of the Caribbean, large areas of the northern and southern portions of South America, Australia, Japan, Singapore, Korea, and Taiwan. However, very little progress has been made in tropical Africa, because of the high intensity of the infection and for a number of technical, administrative and other reasons. It has been estimated on a global scale that 30 years ago the annual incidence of the disease was of the order of 250 million cases, with 2.5 million people dying of malaria every year. By 1965 the annual number of reported cases was about 100 million and during the 1960s about 15 million lives were saved.

The fourth period is that from 1970 to the present time; it represents a reassessment of the previous optimistic achievements and expectations because of a resurgence of malaria during 1972–76 in many countries where the previous results were good, at times too good to be true. While the success of malaria eradication on the continent of Europe, in most of North America, in Australia and a few countries of northern Asia was maintained, there has been a marked increase of the incidence in most of the countries of South-East Asia. In that large part of the world the number of reported cases increased from less than 2 million in 1972 to over 7 million in 1976. Recently the figures started to decrease but not below some 5 million in 1978. Moreover, the rising incidence of malaria imported into Europe, the USA, and many other countries causes much concern.

The nature of technical problems was recognized at least ten years ago, in the shape of outdoor sheltering of some species of Anopheles, and the extension of resistance of several major vectors of malaria first to DDT, then to other insecticides, including some new ones such as organophosphates and carbamates. At the same time the finding that, in the northern part of South America and in large areas of South-East Asia, malaria parasites (especially *P. falciparum*) do not respond fully to treatment with some of our best antimalarials (such as chloroquine) undermined much of our confidence.

A number of other factors related to human ecology interfered with antimalaria activities: the inaccessibility of some localities, the custom of indoor replastering on the occasion of religious feasts or family events of houses already sprayed, the reluctance of some communities to have their houses sprayed, movements of nomadic populations, etc., were of growing importance. Urban malaria at the periphery of rapidly extending cities became a new phenomenon, especially in India and Pakistan. Among other obstacles, those of an administrative and operational nature were prominent. They ranged from shortages of trained manpower, to inadequate Government support, premature integration of malaria eradication activities into general health services, various logistic difficulties of procurement, and increasing costs of insecticides, drugs and transport.

The present resurgence of malaria indicates how far we are from the conquest of this disease. It also emphasizes the role of malaria as one of the many factors at the core of the great issue of socioeconomic development of tropical countries. It has become obvious that, in spite of the great achievements of the eradication programme, a large reservoir of endemic malaria remains over most of the tropics.

The World Health Assembly of 1978 emphasized that wherever malaria eradication has been achieved, it should be maintained through an alert vigilance system able to protect the relevant country or area from an introduction of the transmission.

On the other hand, in countries where only a degree of control is feasible, this must be adapted to existing epidemiological and economic realities, making wide use of antimalarial drugs, the time-honoured method of source reduction and residual insecticides. As mentioned before, the use of the last is now limited because of resistance of vectors and increased cost, Traditional methods, such as filling or alteration of potential breeding places of Anopheles larvae through various small and large scale drainage or reclamation schemes (ditching, filling, general sanitation, etc.), are today gaining ground.

Much attention has been given to three possible alternative methods of mosquito control: biological, genetic and environmental. In the first group of biological agents there is a whole range of methods from viruses, through bacteria, protozoa, fungi, waterplants, to bats and fish. Although the introduction of various predators of larvae was often claimed as beneficial, few of them were of real importance.

Genetic control of mosquitoes seemed to be promising a few years ago, because of two possibilities: the introduction into a local insect population of competitive sterile males of Anopheles, which by hybridizing with the local strain will cause sterility of female mosquitoes or distort the sex ratio. Practical difficulties of this and other methods when applied to mosquitoes with their high reproductive potential are so great that the hopes for their early application have now almost disappeared.

One need not be surprised by the fact that the past five years have seen an agonizing reappraisal, not only of the original concept of global malaria eradication but also of the possibilities of substantial control of malaria in some parts of the world.

A concentrated research effort may find new ways to attack the malaria parasite and its vector. Fields in which research is particularly important include the study of the behaviour of mosquito vectors, methods of environmental control, better and more acceptable insecticides, and the development of new antimalarial drugs, to meet the challenge of resistant parasites.

Much has been written about the possibility of a prospective malaria vaccine, but the present experimental results, however encouraging, indicate the practical difficulties ahead. Although research on a malaria vaccine is gaining momentum, it seems that in tropical areas synthetic antimalarial drugs will be our most reliable weapon for some time yet.

There is much hope that the present WHO programme of research and training in tropical diseases will provide some valuable replacements for the depleted and blunted magic bullets on which we relied in the past.

The difficulties that have reversed the advance of malaria eradication in many developing tropical countries are not only technical. We now recognize the importance of administrative, socioeconomic, financial, and political factors; they affect the improvement of health conditions in developing countries with low financial means, inadequate basic health services and shortages of trained manpower. Today's unsolved problems of malaria control, let alone those of eradication, are part of the dilemma of the developing world. The current economic upheavals, which are a result of the energy crisis, may aggravate the situation.

If the wealthier countries fully realize the future danger of a divided world and accept the obligation of providing adequate technical and financial assistance to bridge the present gulf, there is some hope that the situation may gradually improve; but the developing countries themselves must show the will to control the disease through community participation, appropriate social, political and economic decisions and expansion of basic health services in rural areas.

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