Paradigm shifts in malaria study and control

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Abstract

The history of the study of malaria, its parasites and vectors, and aspects of public health and control has shown some irregularities. Mostly the research was a steady accumulation of knowledge, but there were also deadlocks, fundamental disagreements and sometimes a drastic reorientation. In this article we follow the major events, some of the investigators involved, and how they promoted their ways of the fight against this disease. Every episode or moment is calibrated with the theory of science, developed by Thomas Kuhn. His idea of paradigms in science and sudden shifts is helpful for the understanding of what steered the various levels of malaria research. It also may keep investigators on the alert of dead ends and breakthroughs in future.

1 Introduction

Studying the history of science in general, or one particular scientific subject, raises the question whether the progressing insight is a continuum or a process that goes in fits and restarts. Is the increase in understanding of, for example the disease malaria more or less predictable or erratic? What are the factors that play a role in the accumulation of knowledge and technical abilities? For answers to such questions we have to rely on (medical) historians and "practitioner historians" -in this case (retired) malariologists- who have written about the history of the disease and its control. Also the schemes of thought of science philosophers may offer helpful insights. Once we enter into such a discourse, we have to be aware that historiography is coloured by nationality and scientific background of the writers and the time in which they live(d).

We are now more than a century living with the modern idea of malaria, as a feverish disease, caused by some parasitic protozoa of the genus *Plasmodium* and transmitted by anopheline mosquitoes, a highly complex intercourse of three organisms belonging to different phyla in the animal kingdom. Thanks to modern science and changing habits in populations, the countries in the moderate climate zones are mostly free of malaria since about half a century; Sub-Sahara Africa, Southern Asia, the Southwest Pacific and tropical South America remain more or less highly endemic. Scientists at present active in research have a long way to go on the road towards mastering the disease, the parasite and its vectors. Some conjure up visions of great effects, with vaccines, drugs or sophisticated vector debilitation; others have decided doubts about the feasibility of getting rid of malaria. So many scientists, so many opinions. The majority of workers just do their everyday tinkering in the laboratory or in the field; only a few anticipate on the unpredictable future of malaria research and control. Mostly it is like sailing a calm tropical river, but unexpectedly, a cascade looms up, or even a dangerous fall. The course of research and its application is generally smooth, but there are periods of jerking along.

How do leading malariologists deal with consensus or divergence of opinions on how to tackle the problem and protect the suffering of people? Is it a matter of money, education, uplifting of socio-economic standards, biotechnology, or logistics? And what about our ethical, moral or religious points of view, do they matter in this endeavour? Not to speak of dealing with local and western politicians and the peoples they represent.

Thomas Kuhn, an American science historian (1922-1996) has given insight in the way science progresses, in his book "The Structure of Scientific Revolutions" and his following publications. His ideas found a ready reception in the scientific world. But the history of malaria has never been described in the Kuhnian way. The aim of this essay is to test how the successive episodes in the understanding of malaria and its control fit with his ideas. Kuhn's key word paradigm shift is now used for any new idea in science and by the public at large, whether it is relevant to Kuhn's own theory, or not. In the context of malaria, many examples can be found through the internet. We'll see if this casual use of the term is all correct.

After summarizing the theory of Kuhn we follow the

course of history of malaria with seven-league strides (depending on historiographers of past and present (see bibliography: history is an interpretative discipline!) and test how Kuhn's theory applies to scientific progress in the past. The main point of this exercise is to make future malariologists of various disciplines aware of differences in the approach to malaria, because research will lead to new insights and tools, and also to make them prepared for divergence of opinions. Some believe it will be possible to eliminate or even eradicate the disease; others remain skeptical and fear the retaliation of nature. Awareness of deeply felt differences to come (*e.g.* future vaccination effects) may help to avoid clashes and find common grounds.

2 Kuhn's theory

Knowledge about our environment begins with no fixed idea, no paradigm, but two or many ideas about how it works. There is interest in a phenomenon, but no consensus about facts or methods. There may be different schools of thought that compete. It is considered as *immature science*. Once a theory gets accepted by the scientific community a consensus emerges and *immature science* matures. One paradigm governs from then on the research in *normal science* that gets the character of *puzzle-solution*. It is a pragmatic activity that fits with time and ideas about the world in which the researchers live. The paradigm itself needs no proof; the cumulating facts match with the theory and with reality. Students and young researchers submit to the leading scientists, who tell them what to investigate and what not; this creates an atmosphere of conserving the paradigm. Young people are discouraged to use their intuition and to express originality. Dogma's and a conservative attitude are essential for the progress of *normal science*, which builds on previous achievements and may reach major progress, sometimes over a long period of time. As the American science writer Paul de Kruif put it in the nineteen fifties: "in our land you train investigators as you train seals before they get a penny of the all-important research grant money." The facts in *normal science* have significance within the prevailing *paradigm*. This social-epistemological relationship between the workers at various levels, who face nature in its approachable aspects, is typical in Kuhn's theory.

At certain points in time, the sturdy house of research may shake because the paradigm is questioned. Scientific discoveries unveil *anomalies* (or *vice versa* the awareness of anomaly leads to discovery). The insecurity about the prevailing paradigm and about the puzzle solving of *normal science* may come about through technical failures or through a (sometimes serendipitous) discovery, or a unique combination with new technology developed in other realms of science. If the insecurity is strong and diverse enough, it will lead to a *crisis*, thus ending the period of *normal science*. In any community of scientists, there are some who are bolder than most, who seek alternatives to existing paradigms or because they perceive a path forward or have a breakthrough in research. Others will resist the alternative, which will be subject to scorn and scrutiny. The crisis will precipitate *revolutionary science*, usually during a short period, and temporarily, there is no paradigm.

Successive transition from one paradigm to another via a *scientific revolution* is the usual developmental pattern of *mature science*. Such a shift is a change in a fundamental model of events or methods and leads to innovation. In time, as the challenging paradigm is supported by additional evidence, it will replace the old paradigm, and a *paradigm shift* will have occurred. The new way of thinking has become *incommensurable* with the old. There is no way of mutual understanding (unless with the help of historians who have learned to master both languages). Questions, terminology and methodology are essentially different. Kuhn makes his point by using clear examples. In reality there are grey areas of transition and he admits that. As we shall see, when fitting his ideas to the history of malaria, it sometimes wriggles.

3 Kuhnian theory applied to malaria

3.1 From miasma to protozoa

Fevers have always been considered as a phenomenon caused by external sources. For many patients and their families it was simply the Almighty who sent the scourge. But for doctors and students of nature, the main factor causing fever has been bad air that emanated from foul marsh water, hence the Italian term mal'aria, literally 'bad air'. This was coherent with the prevailing miasma theory. Also the term paludismo, used in the Romanesque language group, indicated the marshes as the place of origin of the fevers. But there was growing discontent with the miasmatic nature of malaria. Scientists began to investigate microbes as causes of the fevers. In 1879 Tommasi-Crudeli and Klebs indicated that water originating from marshes contained microbes that would convey malarial disease. The point was never proven, but as malaria at that time was a container term for many types of fever (intermittent, remittent, bilious, including typhoid and other feverish diseases) it would have been difficult to confirm the theory anyway. Historians are faced with changes in the meaning of terms: malaria in 1850 was the *agent* of "malarious disease" (*i.e.* a disease caused by bad air), whilst it is now used for the *disease itself* ("plasmodiosis"). That shift gradually dawned. Several doctors had already seen "pigment" in blood and organs of individuals who died of (intermittent) fever. But the

first to realise that malaria was caused by a protozoon inside red blood cells was the French army doctor, Alphonse Laveran. After this discovery in a Constantine hospital, Algeria (1880), he concluded that patients with fever but without these parasites in the blood had no malaria.

In this first change in the thinking of the cause of malaria, the miasma theory was dismissed by the discovery of the agent *Plasmodium* that causes the fever, and often leads to complications that may become lethal. The *immature science* (if one can speak of science at all) matured into *normal science*, even though it took another decade before the impact of the understanding and the diagnosis of the disease was widely appreciated in the international medical and scientific communities. It is clear that with the new paradigm of a protozoan microbe causing the disease, the idea of miasmas as contagious agents had become obsolete. No scientist could go back and plea for bad air as the cause of malaria any more. The two ideas had resulted in a different way of looking at reality (malarial disease *versus* plasmodiosis) and became *incommensurable* (incomparable), so typical in Kuhn's concept of a *paradigm shift*.

At this level of a coccidian protozoon as cause of the disease we call malaria (or paludisme), the Lavaranian discovery has been universally accepted. But his descriptions of the highly diverse morphology and of threads escaping from some forms in extravasated blood (signifying life or degeneration?) brought many new questions. Thus, leaving the recognition of this new paradigm in the understanding of malaria in its unique and eternal right, we have to step down one level in the understanding of the parasite-host interaction, and follow the scientific developments in their course.

3.2 From one parasite to several

In those days microscopes had less distinguishing power and resolution, and there were few stains to contrast the parasites from their host cells. Some Italian medical researchers (Marchiafava, Celli and Golgi) started to unravel the complex array of parasite morphology in the human blood and apart from the development into dividing schizonts, they distinguished three species, all with slightly different morphology and causing different clinical courses (*P. vivax*, *P. falciparum* and *P. malariae*). Laveran himself was very slow to accept different parasite species (in that he was a typical representative of *normal science*).

Another early medical man to enter the field was Professor Robert Koch from Berlin. He was used to use the microscope (with the sophisticated Abbe condenser system) and certain stains to facilitate the visibility of microbes (Romanovski/Giemsa stain). He had started studying malaria in Italy and left on a malaria expedition to the Dutch Indies and German New Guinea. When in Batavia (present day Jakarta) he was greeted with enthusiasm and respect by the circle of Dutch physicians (1899). But it soon turned out that there was no basis for discussions: Koch stated that he was unable to collaborate with colleagues who did not use a microscope to diagnose malaria.

The first remarkable point in the historical development of modern malaria research is that it took so long before medical men realised that clinical diagnosis needs microscopical confirmation. Though they may have embraced the parasite theory of Laveran, doctors came to admit only gradually that their clinical diagnosis of malaria often failed, as some patients did not respond to quinine; malaria in the restricted form of plasmodiosis required the microscopical proof of the presence of the parasite in the blood. Koch was one of the first to practice that (by the way, diagnosis is still a major problem in Africa, where personnel of health centres often adhere to the equation: fever = malaria $\rightarrow$ treatment).

The morphological discoveries and their usefulness for the diagnosis were all in line with normal science: they fitted to Kuhn's description of *puzzle-solving* and did not require a change of paradigm. Technical innovations, like the Abbe condenser and new staining methods, were not made specifically for malaria research, but facilitated the puzzle solving process. However, with the paradigm of parasites, an *anomaly* started to cause concern: where does the parasite come from, if not from bad air?

3.3 Biting bugs

Just before Koch took off to the Indian Archipelago, the British military doctor Ronald Ross had published his discovery in 1898 that malaria parasites (of birds) were transmitted by mosquitoes. During the past five years Ross had been coached by Professor Patrick Manson in London, who had discovered that filarial worms were transmitted by mosquitoes. Moreover, there was a similar discovery by Theobald Smith in the United States that Texas fever was caused by a protozoon (*Babesia*) and was transmitted by ticks (1889-1893). The time was ripe for a whole new idea of the origin of (some) infectious diseases: insects and other arthropods could transmit pathogens. The problem was that most doctors lacked basic biological knowledge. Manson thought that a female mosquito would die after egg laying and suggested to Ross to try drinking water with mosquito eggs and dead mosquitoes: Ross' good servant took the cup and got malaria! This experiment never worked again, and Ross had to dismiss the idea, until he found that he could infect mosquitoes on malarious birds, and make other birds malarious when he let these mosquitoes take blood, after they had developed the parasite inside.

In Italy a zoologist, Giovanni Battista Grassi, proved in the same year that only members of the mosquito genus Anopheles transmit human malaria. The subsequent fight

between Ross and Grassi about the priority of discovery precipitated a crisis over national pride, and till this very day British and Italian practitioner historians tend to describe the event with respective couleurs locales (see bibliography). Contemporary conservative doctors claimed that malaria occurred in places without anopheline mosquitoes (*crisis*!), but soon the mosquito-theory ceased to be a theory and the role of anopheline mosquitoes as vectors was no longer contested. We can again speak of a *paradigm shift*.

A new period of *normal science* started with consensus about one prevailing paradigm, that of the triad mosquito-parasite-man. And a second paradigm as a corollary of the first one was the idea that this life cycle can be interrupted at several places. The (ethical) idea to prevent people from getting malaria or to cure them if they had got the disease has since been upheld, through periods of hope, deception, determination and even outright certainty about complete elimination of the disease. Within this dogma we may consider research in each of the transitions of the life cycle as *normal science* in which *puzzle-solving* goes on, but the problem of a parasitic disease had now broadened into other domains of science. Clinicians had to share the malaria field with biologists, entomologists, epidemiologists and public health workers, and besides a parasite-killing drug, other methods of control emerged. We will see how these lines related to each other, and whether *anomalies*, *crises* and *revolutionary discoveries* disrupted *normal science* and gave way to new *paradigms*.

3.4 Two schools of control

With the new knowledge having been established, scientists figured that malaria could now be controlled. Koch had gone in 1900 to German New Guinea (now Papua NG) and set up experiments to protect individuals and groups or whole villages against malaria by giving curative doses of quinine, followed by lower prophylactic doses for a long time. This Koch regimen was widely accepted for years. Koch considered it unfeasible to control mosquitoes. Ross and allies, however, did think they could suppress the rate of exposure to biting anophelines by reducing larval proliferation: oiling the surface of water and/or to fill ponds and drain soils. Mosquito netting and house screening became additional tools to prevent contact between man and mosquitoes. Settling at a distance from the indigenous villages, and keeping cattle between settlements and breeding waters were practiced by European colonials. The two schools of thought, each with its own paradigm (quinine cure and prophylaxis *versus* no mosquito contact) became rivals and remained this way until far into the 20^{th} century. One might say that despite increasing knowledge, malaria science had fallen back to a state of immaturity, because scientists were constantly disagreeing about the best way to control the disease.

One British army doctor, Sidney P. James, got engaged in major anti-mosquito works in British India and when this campaign failed, he converted to the idea of socio-economic upheaval and education of a population, combined with quinine for the patients, and he kept an antipathy for the purely entomological approach. The other, Nicolaas H. Swellengrebel, was a Dutch biologist inspired by Malcolm Watson, who developed the idea of "species sanitation" in the Netherlands Indies: find out which mosquito species is the vector, study its behaviour and, based on that, design a way of control, ignoring all other mosquito species (1919). After World War I the two met as members of the Malaria Commission of the League of Nations. In Italy they saw how "bonifications" reduced malaria through improvement of the living conditions of the rural populations and through drainage of wetlands. Angelo Celli claimed that malaria was a social disease and education was a tool to make people understand how to avoid biting mosquitoes. James and Swellengrebel were impressed and agreed, though the latter was more sceptical. He thought that malaria reduction was a welcome byproduct of expensive agricultural betterment.

On behalf of the League of Nations' Malaria Commission James and Swellengrebel were sent to the USA in 1927 to study why malaria there was on the retreat. They concluded that this was a process already in motion before anti-mosquito measures were installed. The retreat was a "natural" phenomenon, most likely due to improved living conditions. However, Swellengrebel got second thoughts and reported separately that the American vector was quite different from the European one. In Europe, the malaria situation was complicated, as vast areas with the zoophilic *Anopheles maculipennis* had no malaria. This enigmatic phenomenon of "anophelism without malaria" did not occur in the US, where the anthropophilic *An. quadrimaculatus* went hand in hand with malaria.

The joint report had already raised concern among several American malariologists and the dissident report added to the diverging views of the Americans and Europeans. Moreover, the American public health expert Lewis Hackett of the Rockefeller Foundation had started in Italy to work with a new insecticide, Paris green, with rapid effect, contrary to the slow working bonifications. He quickly obtained impressive results with this anti-larval method (in 1925 and successive years). The crisis culminated and the Health Board of the League of Nations arranged in 1928 for a Geneva meeting of American and European experts. Socio-economic reformers and mosquito exterminators were not reconciled.

One species of *Anopheles*, the African *An. gambiae* became a special target. This highly effective vector of *P. falciparum* had accidentally spread in Brazil and later in Egypt. When it had caused enormous epidemics, massive

control campaigns were launched, using Paris green, to exterminate the species (1938 and 1943). After the early campaigns in the Panama Canal Zone (1904), it was again proof that the anti-mosquito approach worked. Opposing voices however, pointed to the fact that this species was an intruder and thus not so deeply rooted as it was (and is) in Sub-Sahara Africa. Modern investigators point out that it was not *An. gambiae*, but its sibling *An. arabiensis*, which explains why it was such a competent vector in Brazil.

This long period of a two-party policy with different peer groups and their scientific domains had run into a Kuhnian crisis, because each party saw the *anomalies* of the other, and not those of their own. Only a *revolutionary discovery* could bring parties back under one new *paradigm*, but would that materialise?

3.5 Not one but two ideas

Two findings ignited a new idea: In the Netherlands, the biologist Pieter van Thiel had found that *An. maculipennis* in malarious and non-malarious areas differ slightly in morphology and behaviour (1927). Falleroni, a retired public health man in Italy, whose hobby was the study of mosquito breeding, published that the eggs of *An. maculipennis* from different areas were visibly different. Swellengrebel and Hackett took these findings further and the solution of the enigmatic "anophelism without malaria" appeared (1931). *An. maculipennis* was only superficially uniform; it consisted of sibling species with different behaviour, of which only some were transmitting malaria. All of a sudden, it was no longer necessary to take anti-larval measures against all *An. maculipennis* in Europe, but only against the real vector species. And Swellengrebel could finally propagate his "species sanitation" method internationally and in his homeland. After ten years of uncertainty and a major schism among experts, the quarrels had come to the head, but did not improve the malaria situation in Europe, not yet.

The transmission paradigm had gradually got more and more complicated (from mosquito to *Anopheles*, to *Anopheles* species, to *Anopheles* subspecies or type, to several, genetically differing *Anopheles* sibling species) and is typical of *puzzle solving* of *normal science*, no matter how important the solution to the problem of anophelism without malaria was. About half a century later, when similar sibling species were discovered among the African *An. gambiae*, control efforts could be focused in that hotspot of malaria.

The other emerging idea came from James. He proposed to destroy malaria mosquitoes inside houses and leave the many more that sheltered in stables, untouched. The idea, based on the European vector, was successfully run into the ground at the first international malaria congress in Rome (1925), and was hardly mentioned in the second one in Algiers (1930).

Malaria control was still equal to extermination of mosquito larvae and socio-economic improvement would only work on the long run (if at all). But Swellengrebel took up the idea and experimented on spraying "malaria houses" with pyrethrum during the transmission season in the Netherlands (1935). He got impressive results and the technique was taken over by Paul Russell in British India and G. Park Ross in South Africa, indicating that many vector species take their blood meals inside human dwellings and rest on the walls to digest the blood. Spraying killed mosquitoes that contained parasites and thus prevented transmission. The new principle was finally recognised at the third malaria congress in Amsterdam (1938), but it was not very practical as pyrethrum had only a knock-down effect and spraying had to be repeated during the transmission season. The method of house spraying was another important piece in the puzzle, which, as demonstrated below, would later become part of a *paradigm shift*.

Meanwhile, scientists had stopped fighting; a new generation of experts had emerged and accepted that various tools were available and had to be tested in the field, not only in Europe, but also in the tropics. And gradually it dawned that there may be parasite-alone magic bullets or circumstances (*e.g.* islands) where drug treatment alone may do the job, but it is more likely that a combination is needed. During the thirties, the economic crisis did not allow for bickering about theories and principles. To make things worse, World War II broke out. With it, quinine and pyrethrum became scarce and malaria increased. European malaria research got into a heavy crisis and virtually came to a halt. But as always, military activity in (sub-)tropical areas enhanced malaria research by the belligerent parties.

3.6 DDT and global eradication

In 1939 the Swiss investigator, Paul Müller, working at the Geigy company in Basle revealed the potent and long-lasting insecticidal properties of DDT (first synthesised by an Austrian chemist, Zeidler in 1874), a discovery for which Müller was awarded the Nobel Prize in 1948. In 1942 DDT turned out to be very effective for the delousing and typhus control in the Allied Forces and the civilian population of Naples, and it appeared also a useful tool for malaria control. It replaced pyrethrum that had to be applied every one or two weeks (virtually impossible in poor rural communities, unless backed by a strong organisation). DDT was a scientific revolution, because its effect was long-lasting, cheap, and required applications only once or twice a year. Applied to the walls of houses, the residual insecticide would remain active, killing infected mosquitoes *before they could transmit the malaria parasite*. At the end of the War also the cheap and easily used drug chloroquine

(discovered in 1934) became available as an anti-malarial chemical, with which mass drug campaigns could be organised. Consensus spread rapidly and united malaria experts in their now promising fight against malaria. And after a few years some of them even saw a possibility to eradicate malaria. George Macdonald underpinned this approach with a mathematical formula, in which the life expectancy of exposed mosquitoes appeared crucial to lower the basic reproductive rate (because of its exponential relation in the formula). It led to a major and world-wide change in malaria control and eventually evolved into the WHO idea of global eradication. Therefore, I consider the *combination* of the properties of DDT with the house spraying, along with chloroquine as a true *paradigm shift* in malaria control.

However, the use of DDT and other persistent insecticides came with a price at various fronts. The revolutionary use of DDT to limit the transmission of malaria made research on the specific local ecology and of biology and behaviour of the malaria mosquitoes seemingly obsolete. Swellengrebel was one of those who saw it happening and looked on it sadly. He observed the campaign in Sardinia, where DDT was lavishly sprayed, not only in houses! Its leader, Fred Soper went for eradication of the local vector (*An. labranchiae*, one of the siblings of *An. maculipennis*). Swellengrebel did not believe that this approach would succeed; he was for integration of several techniques. Curiously, malaria eradication was achieved on the island, but the primary aim, eradication of the vector mosquito, failed. Another major difference of opinion emerged during a WHO conference in Kampala, 1950. Some experts (Bagster Wilson, Swellengrebel and P.C.C. Garnham) posed the point that interference with transmission through DDT-house spraying would severely impair the herd immunity against malaria among adult Africans living under highly endemic conditions. But a majority reposted that the price for adult immunity was widespread child mortality and that it was immoral to withhold DDT from the continent. Furious debates followed, but this crisis was dampened by some diplomatic concessions. The eradication missionaries had their way: malaria should be controlled without knowing in advance what consequences to adult immunity would result.

Moreover, widespread use of DDT and other remnant insecticides in agriculture induced the first signs of insecticide resistance in various insects and in malaria mosquitoes. It urged the policy makers at WHO to take rapid action. Thus, in 1955 the World Health Assembly launched the Global Malaria Eradication Program. Africa was left out, except for some regional efforts. The campaigns were organised in a military way and with enormous vertical organisations of sprayers, public health people and microscopists. DDT-house spraying proved to give impressive results in Europe, Venezuela and the Indian subcontinent.

However, after the euphoric period, soon *anomalies* began to appear. With the disappearing malaria, national malaria services diverted their attention, resources and personnel to other health problems. DDT-house spraying as a tool was not sustainable and re-emergence of malaria occurred all over. These developments were analysed by the Expert Committee of the WHO and regular reports were published, but nature's versatility was not beaten.

The *paradigm* of rapid eradication of malaria from large parts of the malarious world began to shake. Already in 1966 some delegations in the Expert Committee talked about a crisis in the eradication activities on several continents, initially to be downplayed. In 1969 the World Health Assembly announced the failure of the global programme and changed course towards the understanding of immunity. By that time, the world had begun to realise how DDT and other remnant insecticides persisted in the food chains. The Kuhnian *paradigm* of eradication, and all of the implications that came with it, had got into a severe *crisis*. Eventually, the production and use of DDT became internationally banned. Was it a point of no return and thus, a new *paradigm* ready to emerge?

3.7 Experiments *in vivo* and *in vitro*

At this point, I want to elaborate on two other lines of research and how they developed over time. The first is about the enigma that after the bite of an infected mosquito, it takes a week or more before clinical symptoms appear. And second, quinine appeared unable to prevent relapses after a primary attack of *P. vivax*. The Malaria Commission of the League of Nations went at length for many years to study alternatives for quinine. Meanwhile, the discovery of Julius Wagner von Jauregg that malaria fever helped neurosyphilitic patients to recover (Nobel Prize 1927), led to infection experiments with *P. vivax* on such patients and on healthy volunteers (James, Swellengrebel, Boyd in the early thirties). It was found that relapses only occurred after mosquito bites and not after sub-inoculation of blood from infected persons. Moreover, the mosquito-borne parasites disappeared for about a week from the circulating blood, whilst blood-stage parasites caused fever attacks within days. It led to the hypothesis that sporozoites hide or develop somewhere in organs or cells before they appear (again) in the blood. A new drug, plasmochin (pamaquine) was able to reduce the chance of relapses, which reinforced the idea that some parasites were in hiding. Then, the Italian G. Raffaele discovered that in bird malaria there were parasites not only in the blood but they also multiplied in the reticulo-endothelial system. Such massive multiplication was not observed in primate plasmodia, but finally, in 1948, Shortt and Garnham succeeded in revealing an exo-erythrocytic phase in liver parenchymal cells, after they had

inoculated a vast amount of sporozoites. This stage of the parasite appeared to multiply asexually as schizonts in the liver cells, and seed their merozoites into the blood, where they choose erythrocytes as new host cells. But not all of them do that immediately. Some remain dormant during and long after a primary attack, only to give rise to a relapse after months. Miles Markus, then a student of Garnham, named them hypnozoites in 1978.

Even though this course of research led to the completion of the life cycle of primate plasmodia, it is an example of *normal science*: successive generations of malariologists have tried to fit discoveries with nature, and to the paradigm of a pre-erythrocytic stage. I am sure that more details will be unveiled about *P. vivax* that is a main debilitator of mankind with the tertian fevers it causes. There is one handicap: it is extremely difficult to culture this parasite outside the human host.

That brings me to the other line of research: that of a vaccine. Already Koch was thinking of making a vaccine, as had been successful for other microbes around the previous turn of the century. He had been the first to realise that immunity exists among adult indigenous people (in Java, 1900): they hardly had parasites in their blood and this contrasted with the children of which many got sick or carried parasites. Schüffner and Swellengrebel brought the idea of group immunity further (1919) and combined it with the rate of spleen enlargement in adults and children. The Sergent brothers then proposed that immunity builds up and is maintained by repeated exposure to the parasite and/or its persisting presence (premunity).

Immunity research in malaria lingered, only to be boosted when experts got Africa in focus. The above-mentioned clash between experts during the Kampala conference in 1950 had to do with immunity. It brought forward a new classification of degrees of endemicity, each with its own description of immunity, again based on spleen size measurement. Epidemics could occur in populations with low endemicity (*i.e.* bitten by one or a few infected mosquitoes per year); solid immunity built up after early years of more or less dangerous malaria (mostly *P. falciparum*) is conveyed by almost nightly or weekly exposure to infected mosquitoes.

These ideas were useful during the eradication campaigns (mostly outside Africa), but when the global eradication was ordered off, one alternative was to intensify the study of immune response against the various stages of the parasite. Immunology in the nineteen seventies and eighties was booming as a new discipline, and malaria research followed suit. Millions of rodents were used to test the potency of antibodies and cellular immune responses against *P. berghei* and related rodent plasmodia (the only easy and cheap laboratory model with a mammalian host, however mostly using the short-cut inoculation of infected blood).

Then in 1976, Jim Jensen and his mentor William Trager serendipitously discovered the way to grow and culture *P. falciparum* in human blood outside the body. It caused a *revolution*, as it was now possible to study this dangerous human parasite in detail, and to grow "buckets full" to make a vaccine. Many laboratories around the world turned away from rodents and started working *in vitro*: again a *shift of paradigm*. But the antigens of the parasite turned out to be manifold and a vaccine was far away. Only now, thirty-six years later, with old generations of researchers gradually replaced by younger ones, along with the emerging new tools in molecular biology and genetics, and, not unimportantly, with much more research money available, the hopes for a vaccine get stronger. Human trials with vaccine candidates are being carried out, both in western laboratories with volunteers, and in malarious countries on a population scale.

I am inclined to consider the course of events towards a vaccine as an example of *normal science*, in which every solved puzzle leads to a new one, and fact-gathering with increasing accuracy, but always within the paradigm. In the Kuhnian way, this is in no way a depreciation of the research done and the vision maintained. But the discovery of culturing *P. falciparum* was not anticipated, and caused such a massive turn in laboratory techniques that there is no way back. All new technologies of molecular biology and genetics were and are eagerly applied and opened the way to vaccine development. This true *paradigm shift* has indeed turned out to be productive.

Meanwhile, other developments absorbed the attention of field workers. The problem of antimalarial drug resistance was arising globally. During the seventies the situation in Africa and elsewhere worsened because *P. falciparum* developed resistance in parts of that continent to chloroquine; it spread quickly, and subsequently other antimalarials followed. It cost the lives of many. The Chinese discovery of artemisinin as a fast-acting drug was timely, and in combination with slower acting drugs it gives high hopes for successful management of malaria in large areas. Artimisinin-based combination therapies are highly efficient and reduce the likelihood of resistance developing. ACTs are now accepted in most malarious countries of Africa and Asia. Because of its originality and their impact ACTs may be considered a *paradigm shift*, away from the monotherapies.

During the years of the ban on DDT many people succumbed to malaria who might otherwise have lived. This ban now has been lifted but it is strictly to be used for malaria control (but how to maintain that rule in poor agricultural settings?). The *paradigm* of DDT-house spraying-eradication has survived a serious *crisis* and out of that *revolutionary* period no new *paradigm* emerged.

Another development, important for control, was the discovery of impregnating bed nets with pyrethroid insecti-

cides, and more recently with longer lasting derivatives. The repellent and killing effects on mosquitoes and the use of such bed nets on a population scale have a considerable protective value, taken up by several foundations and programmes. The integration of these methods has recently caused a decline in mortality and transmission intensity in parts of the heartland of malaria! An unexpected but promising development.

3.8 From malaria control to malaria elimination

Some scientific discoveries are far ahead of eventual application (despite loudly voiced hopes in the press). The genomes of man, parasite and mosquito are being unravelled, but ten years after publication their practical use for protection and control is still unclear. Meanwhile, field and laboratory experts, physicians and entomologists are developing new tools with which to try to protect larger populations. Today, the new term in control is "elimination" of malaria, with the aim to interrupt transmission in a geographical area to the end goal of zero incidence. And some experienced young scientists and field workers even have visions about eradication again, worldwide that is. Integration of all available tools (including health education) is necessary to block the parasite in man and mosquito. Who knows what revolutionary discoveries science has in store that may force us to bury our present paradigm of control.

This brings me to a thought about the laboratory researchers involved. As from the time that immunity research in malaria boomed, most young researchers were more immunologists than malaria experts ("malaria is transferred by syringe"). Similarly, molecular biologists and geneticists dominate malaria research nowadays; they have generally no idea about mosquitoes or about malaria as a disease, or malaria in the field with its herd immunity (let alone about the history of malaria). This is not a disqualification of super-specialised research, in which programme-leaders and academic societies set the rules. It is rather the registration of the fact that in-depth research alone rarely leads to the transfer of laboratory products to the field.

Doctors, epidemiologists, entomologists and public health people are needed to do the ground work for vaccine trials and new anti-mosquito tools in the population, to carry them out and to evaluate the effects in areas of high and low endemicity. As for vaccines, let us be modest in our expectations: they may help locally, but will not solve the world's malaria problem. Just think of the minimal research spent on underestimated tertian malaria and *P. vivax*.

Without being too pessimistic, this route through malaria history makes me aware of the risk that entomologists and vaccinologists (again two different disciplines) will profoundly disagree about the best way to protect a population against malaria. Epidemiologists with their mathematical models may lack enough field data to show a safe route to follow. The problems for public health officials may become unmanageable. And in the end, it is the local population that remains with the sequels of 21^{st} century research.

Are western scientists prepared to let doctors deal with African children that have lost their temporary vaccine protection and get pernicious malaria at a later age? Or, even if a vaccine is developed that gives lifelong protection, is it ethical to let demography grow out of hand, only to cause famines, war or mass-migration? Wide-scale application of such a vaccine must go hand-in-hand with the acceptance of family planning in a population! The mathematical modellers may be the ones who can alert us that we can't allow ourselves to relax once malaria is "under control."

It is a good thing that present day malaria has been brought to the attention of the public at large through the media. It is no longer only the business of (bio-)medical science, and scientists have to face the social relations and claims from the non-scientific civil society and its politicians. As Kuhn has said, science is not an isolated activity; it involves paradigms with a world-vision, in which scientists have their responsibility also beyond their specialism. Let us work toward a paradigm of collaboration. That would be really revolutionary

4 Conclusions

Most on-going research in malaria and control is qualified as *normal science*. Even though some discoveries were very important for the understanding of parasite, mosquito and human biology and behaviour changed the methods of control, they mostly did not change the respective paradigms. And that is perfect if the community of scientists has a consensus about achieving the anticipated in new ways. However, *normal science* in malaria is generally not discussed in depth; research results are just presented at congresses and published, and despite peer reviews, only add to the cumulating bulk of knowledge. Science for science sake is not the way to control malaria. Too often grant applications begin with the obligatory statement of so many million deaths and suffering, only to propose the study of some minuscule part of the malaria machinery. It is the scientific sophistication that counts in the big money circus, not the science of applicable methods. And so, *natural science* grows passively, without much debate, or steering mechanism, ignoring dangerous rapids downstream. Such rapids may cause a shift of the prevailing paradigm. Real *paradigm shifts* in the Kuhnian sense are upheavals of perceptions of the disease, and consequently of the approach to control(-methods), so much so that post-shift scientists have difficulty imagining how they worked before the change.

We have considered the following ones as such: 1. the replacement of the miasma theory with the new reality of the malaria parasite; 2. the role of mosquitoes and particularly *Anopheles* in transmission; 3. global eradication through DDT and its use in house spraying; 4. the discovery of producing *P. falciparum in vitro*; 5. The use of ACTs. They changed the study of malaria and/or the concepts of malaria control dramatically, often painfully, but always irreversibly.

This choice is a personal one, and there is room for debate (for example, the grand scale of distribution of impregnated bednets with the subsequent emergence of resistance to modern synthetic pyrethroids mainly used singly!). But more important than just philosophising is the issue, how doctors, researchers and public health people face the problems to control/eliminate malaria, so different in severity, complexity and geographical location. This essay hopefully makes malariologists aware that they no longer work in splendid isolation of their own team or discipline. Today's society demands them to being called to account, and their inventions to be used for human protection.

Medical historians have a role to play in showing this co-evolution of social relations and facts. Analogies from history alone do not tell us much about how to collect and evaluate information in the present or the future. But a clear picture of the history of malaria translated by "bilingual" historians helps to avoid the escalation of internal disputes that so divided the experts in the past.

5 Acknowledgements

I acknowledge the teachings in medical history of Professor Eddy Houwaart (Free University, Amsterdam), who introduced me to the theories of Thomas Kuhn, and who gave his valuable comments on a draft of this article. I am indebted to Dr. Jochem Abbes for his bio-philosophical ideas. I praise Dr. Bart Knols for his inspiring drive to create an international discussion forum for solving practical problems in malaria control.

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