Wednesday April 25th is World Malaria Day and every day we are reminded of the significance of this disease by posters informing us that ‘every forty-five seconds a child dies from malaria’. Malaria, according to the World Health Organisation (WHO), is the fifth leading cause of death in low income countries below respiratory infections, diarrhoea, HIV/AIDS and heart disease and above stroke and tuberculosis. Globally, HIV/AIDS kills 1.8 million people every year; tuberculosis kills 1.7 million and malaria kills 660,000 but this figure, as we shall see later, is probably too low and might be nearer 1.25 million. Whatever the correct figure is there is no doubt that malaria is a major killer and in this lecture I am going to try to explain what can be done about it. Malaria is a disease of the warmest and wettest parts of the world between the summer isotherms of 70°F North and South, an area that embraces much of Africa, Asia and the Middle East. One third of the world’s population lives in these areas under potential threat from malaria which, according to the most recent WHO statistics, affects some 216 million individuals mainly infants in sub-Saharan Africa. A disease that affects so many people is an enormous twenty-first century threat not only in terms of human mortality and morbidity but also because of the massive sums of money required to manage the disease, money that might be better spent on other health initiatives and economic improvement in low- and middle-income countries. The most serious problem is that most experts now believe that malaria is a disease that cannot be eradicated.

So what went wrong? It is not very often that a complex question like this can be answered in one word but this word is EVERYTHING.

In order to understand what went wrong it is necessary to go back a long way. Malaria is an ancient disease and morphological, epidemiological and molecular evidence tells us that during our human evolutionary history we acquired our malaria parasites from our primate ancestors in Africa probably before our species, *Homo sapiens*, emerged 100,000-195,000 years ago. Malaria must, therefore, have accompanied human migrations out of Africa and by 50-60,000 years ago, when humans had spread throughout much of Africa and Eurasia, malaria must have been endemic everywhere where populations were large enough to sustain the infection except in the coldest extremes.

How our early ancestors viewed this disease we will never know and our knowledge of the earliest history of malaria must remain speculative until written records began. The most relevant early records are those that refer to fevers. Although fevers are commonplace, and would have attracted little attention, malaria fevers must have been regarded unusual. Most fevers increase slowly, reach a crisis and then subside. Malaria fevers, on the other hand, occur in periodic waves every 24 or 72 hours and, in addition, are usually associated with seasons and with living in marshy conditions. This unusual combination of features attracted the attention of early scribes and leaves us in no doubt that what they were describing must have been malaria. The earliest records are from Chinese documents from about 2700 BC, clay tablets from Mesopotamia from 2000 BC, Egyptian papyri from 1570 BC and Hindu texts as far back as the sixth century BC. The Chinese documents are particularly interesting because they describe the use of wormwood to treat malaria fevers and Egyptian writings refer to the use of fabric screens to protect against biting insects. Over the next centuries records become more frequent and less ambiguous. The early Greeks, including Hippocrates in about 400 BC, wrote about the characteristic malarial fevers seen in people, particularly those living in marshy places and physicians and it was generally believed that malaria was caused by the inhalation of miasmas, unpleasant vapours rising from the marshes.

For over 2500 years the belief that malaria fevers were caused by miasmas persisted but it was not until the incrimination of microorganisms as causes of infectious diseases and the development of the germ theory of infection by Louis Pasteur and Robert Koch in 1878-1879 that the search for the real cause of malaria intensified and precipitated an unsuccessful search for a bacterial cause. In 1879-80, Charles Louis Alphonse Laveran, a French army officer working in Algeria, when examining fresh unstained blood of malaria patients realised that he had found not a bacterium but a single-celled organism, a protozoan. This signalled the end of the miasma theory and Laveran was awarded the Nobel Prize for Medicine in 1907. By the end of the nineteenth century, it had also become clear that the fevers characteristic of malaria coincided with the bursting of infected red blood cells and the release of the products of multiplication every 48 or 72 hours.

There was, however, one outstanding question about the disease, how did the parasite get from one human to another? Gradually circumstantial evidence had accumulated that suggested that mosquitoes might somehow be connected with the transmission of malaria but how this could happen remained elusive.
The next important figure in this story is Sir Patrick Manson, ‘the father of tropical medicine’, who, having made major discoveries in the field of helminth worms, turned his attention to the possibility of mosquito transmission of malaria. He was, however, unable to go to malarious countries himself and needed someone to carry out the necessary investigations and experiments for him. His colleague-to-be was Ronald Ross, an army surgeon working in India where malaria was endemic. Manson directed operations at a distance and Ross, after a series of carefully executed experiments, discovered that avian malaria parasites were transmitted by mosquitoes. He postulated that this might also be true for human malaria parasites and later, when working in Sierra Leone, he demonstrated that this was indeed the case. In the meantime, however, Italian scientists working in Rome and Sicily (where malaria had been endemic for centuries) produced the final proof when they fed local mosquitoes on infected patients and subsequently transmitted the infection to uninfected individuals via the bite of these mosquitoes and also showed that it was only female Anopheles mosquitoes that could transmit malaria.

These same Italian scientists dominated malaria research at the end of the nineteenth century, by which time they had recognised two forms of tertian malaria (48 hour periodicity) caused by *Plasmodium falciparum* (malignant tertian) and *P. vivax* (benign tertian) and one, *P. malariae* (72 hour periodicity) that caused quartan malaria. Of these *P. falciparum* was, and is, the most dangerous form and accounts for nearly all deaths from malaria. (A fourth species, *P. ovale*, a tertian form was identified in 1922 and a fifth, *P. knowlesi*, a quotid form first identified in 1932 was only recognised as a serious infection in humans in 2004).

The life cycle in humans, however, remained incompletely understood and nobody knew where the parasites developed during the first 10 days or so after infection during which they could not be seen in the blood. This question was resolved in 1947 when Henry Shortt and Cyril Garnham, working with experimentally infected primates in London, showed that there was a phase of division in the liver before parasites appeared in the blood and called this the exoerythrocytic phase. Shortly afterwards Shortt, Garnham and their co-workers found exoerythrocytic forms in all the four species of malaria parasites in humans.

By the early 1950s, therefore, the whole life cycle of the malaria parasite as we understand it today had been elucidated. It was by then known that the infection begins when the infective stages (sporozoites) are injected by a mosquito and invade liver cells where they undergo asexual multiplication resulting in the production of many uninucleate merozoites. These merozoites flood out into the blood and invade red blood cells where they initiate a second phase of asexual multiplication resulting in the production of about 8-16 merozoites which in their turn invade new red blood cells. This process is repeated almost indefinitely. As the infection progresses, some young merozoites develop into sexual stages, male and female gametocytes, that circulate in the peripheral blood until they are taken up by a female anopheline mosquito when it feeds. Within the mosquito the gametocytes mature into male and female gametes, fertilisation occurs and a motile zygote is formed within the lumen of the mosquito gut, a process known as sporogony. The motile zygote penetrates the gut wall and becomes a conspicuous oocyst within which another phase of multiplication occurs resulting in the formation of infective stages that migrate to the salivary glands and are injected when the mosquito feeds on a new host.

From earliest recorded times, people have been aware of diseases and have devised ways, often unsuccessful, to avoid or prevent them. The Greeks and Romans, for example, situated their houses away from marshy places. The discovery of the role of mosquitoes in the transmission of malaria provided malarialogists with new control strategies and from about 1900 onwards the prevention of mosquito biting by avoidance, screening and mosquito proofing dwellings and anti-larval measures such as the use of oils and larvivorous fish and draining their habitats had become commonplace as had the use of the insecticide pyrethrum and its synthetic derivatives, pyrethroids.

By 1950 malarialogists began to think seriously about eradicating malaria. There were by then two possible targets for chemotherapy both for the prevention and cure of malaria, the liver stages and blood stages, for which the drugs proguanil and chloroquine were cheap and effective. For the control of the mosquito, pyrethroid insecticides were being replaced by a cheaper and more effective insecticide, DDT.

It was against this background that in 1955, the WHO was presented with a document stating, *inter alia*, that it was ‘...not unreasonable to begin planning for world-wide eradication of malaria’. This suggestion was taken up enthusiastically by the WHO, other health organisations and governments, especially those in the newly-independent countries in Africa, and adopted by the World Health Assembly in 1956 and implemented as the Global Eradication Programme in 1957 at which time it was estimated that 250 million people were infected with malaria and one million, mainly children, died every year. The policy was very simple and was based on spraying houses with residual insecticides such as DDT and treatment of infected individuals with anti-malarial drugs. After initial successes in India and Sri Lanka the global eradication programme became unsustainable and was abandoned in 1969 when the numbers infected and dying were more or less the same as at the beginning of the programme. The WHO then quietly changed the name of the Malaria Eradication Division to the Division of Malaria and Other Parasitic Diseases. The word ‘eradication’ gradually drifted into abeyance.

To return to the question, what went wrong? The reasons can be summarised as follows: (1) Resistance to anti-malarial drugs, (2) Resistance to DDT and other insecticides, (3) Other priorities, for example family planning and smallpox. (4) Relaxation of malaria control measures, (5) Wars and conflicts, (6) Social and political upheaval, (7) Population movements, (8) Lack of sustainable funding and (9) Inflexibility.

It should have been no surprise that resistance should have developed to anti-malarial drugs, as it was already
known that penicillin and other antibiotics were losing their efficacy as bacteria developed resistance to them. Similarly there was already evidence that insects had begun to tolerate higher and higher levels of DDT, a cheap and effective insecticide widely used by farmers to protect their crops against insects. Unfortunately, the runoff from crops contaminated rivers where mosquito larvae first became tolerant of and later became resistant to DDT. DDT is a cumulative poison and the massive amounts of DDT being used began to accumulate higher and higher up in the food chain until it was suspected that it was responsible for the deaths of carnivorous mammals and bird of prey and a possible threat to humans. This perceived problem attracted the attention of the public and authorities after the publication of Rachel Carson’s seminal book, *Silent Spring*, which had an unfortunate consequence; the banning of the production and use of DDT. This was a disaster for malaria control that had relied on the spraying of DDT on the walls of houses and the tragedy is that is that this usage in no way contributed the ecological damage attributed to DDT.

As if these problems were not enough, insufficient attention had been paid to anything other than the scientific and clinical aspects of the malaria eradication programme and it was not foreseen that, as more and more African countries became independent, wars, conflicts and population movements would disrupt or terminate the programme. In addition African leaders were led to believe that malaria would be eradicated so diverted funds to what they perceived to be more pressing needs. The WHO failed to respond to changing circumstances and the cost of the scheme proved to be unrealistic.

Thus by 1969, the WHO had little to show for its campaign, and the numbers of individuals infected remained at 250 million and those dying at one million. The situation then continued to deteriorate and it has been estimated that from 1972-1976 the global toll from malaria increased by 2-3% and by 1980 it had been reluctantly accepted that malaria could not be eradicated. The WHO subsequently advocated more modest aims: early diagnosis and treatment, selective and sustainable preventive measures (bednets), strengthening of local capacity and early detection of epidemics. The next important WHO campaign, Roll Back Malaria, initiated in 1998 reiterated these aims but also included an intention to reduce the burden of malaria by half by 2010, mainly based on early diagnosis and treatment and the provision of bednets. This campaign also failed as is also likely to be the case with the Millennium Development Goal of halving malaria by 2015.

Where are we now? All is not doom and gloom but there is an urgent need to be realistic and to distinguish between what is feasible and what is not. In order to do so we need to assess what has been achieved and how these achievements can be implemented.

The first question to ask is how much malaria is there? The starting point in 1955 was 250 million infected and 1 million deaths each year and these figures have persisted until relatively recently. Nowhere could I find any real justification for the figure of 250 million people infected and the nearest I could come to was by taking the highest estimate, 320 million and the lowest, 170 million, averaging them and coming up with 245 million which isn’t all that far from 250 million but this is not the best way to come up with an accurate global figure. Malaria is notoriously difficult to diagnose and my guess is that we just don’t know how many individuals are actually infected. The number of deaths should be easier to calculate and the WHO figure of 655,000 (very close to ‘a child dies ever 45 seconds’) is widely accepted. This figure has recently been reassessed by Christopher Murray and colleagues who calculated that that the real figure is nearer 1.24 million. The discrepancy is probably due to the fact that the Murray report found that there were more children between 5-10 infected with malaria than had previously been thought. In some ways this is good news, given that according to these new figures, malaria mortality has actually declined from a high of 1.82 million in 2004 and is steadily declining. This is particularly progressive given the increase in the population in sub-Saharan Africa.

If we accept these figures the challenge is how to sustain this progress. We do, in fact, have a number of tools including new diagnostic techniques, anti-malarial drugs, insecticide treated bednets and the promise of a vaccine. Let us consider the advantages and limitations of each of these.

New diagnostic techniques. In the past the only way to diagnose malaria with any certainty was to examine a stained blood smear. This is time-consuming, requires skilled personnel and expensive microscopy. Newer diagnostic techniques are based on the identification of parasite enzymes an almost immediate readout similar to tests used for pregnancy. These tests are cheap and easy to perform but require improvements in sensitivity, specificity, ease of use and reliability. Newer and better diagnostic tests are being developed so that they can be used by relatively unskilled personnel.

Anti-malarial drugs. There is no shortage of anti-malarial drugs but all have some side effects, resistance is always a possibility and most of them are very old. The most promising new drugs are those based on the Chinese herb, Artemisia Annua (wormwood) and its derivative Artesunates. These drugs are so important that they are only used in combination with other drugs, Artemesinin Combination Therapy (ATC), that can be varied in order to minimise the chances of resistance developing. Sadly, resistance has already been seen in Cambodia and the Thai-Burmese border where resistance to other anti-malarial drugs merged in the past. The problems inherent in developing a new anti-malarial drug are immense. Malaria parasites are single celled organisms, protozoa, whose nucleic acids and metabolic pathways are similar to ours so it is very difficult to find a drug that can target the parasite’s particular metabolic pathways without damaging our own. The cost of developing a new drug is also immense. According to Forbes Magazine the average is £810,000 but could be as much as £6.9 bn. Given that the development of drug resistance is inevitable and the return is likely to be negligible few
Insecticide-treated bednets. Insecticide-treated bednets (ITN) have proved to be the most effectible means of reducing malaria especially the development of Long Lasting Insecticidal Nets (LLIN). These nets are relatively cheap, £5–7, and available in a range of shapes and colours. The challenge is to increase their usage, particularly in sub-Saharan Africa, from less than 50% (8% in Chad to 82% in Mali).

Vaccine. The only way to achieve anything like a comprehensive elimination of malaria would be the development of a vaccine. In 1991, a book, Waiting for the Vaccine, was published and we are still waiting. There have been numerous abortive attempts to develop a vaccine and all have been total or partial failures. The most recent one, RTSS, reduced the risk of clinical malaria by 53% in a major clinical trial and this was hailed as a breakthrough in the press. What was not made clear was that this vaccine has been some 25 years in its development, required 3-4 inoculations and that any immunity was relatively short-lived. We do not know the real cost or the logistics of delivering so many injections. Given that we have not been able to complete the polioyltis vaccination programme, which involves no more than a single drop on the tongue for lifetime immunity, the challenge for a malaria vaccine is immense. In addition, some of the children in the trial unexpectedly developed meningitis. Had this trial involved a viral disease, the results would have been regarded as a failure. I have no doubt that eventually a vaccine against malaria will be developed but that it will be too expensive and too difficult to deliver to use in any malaria elimination scheme but might be useful for short term visitors to malarias areas such as tourists and the military.

Given that the only realistic tools we have are insecticide-treated bednets and drugs, what is the way forward? The answer is to be realistic. To quote from William Jobin’s book ‘A realistic strategy for fighting malaria in Africa’:

“Fantasies about eradication should not be allowed to derail realistic approaches to this problem. Available resources should be focused where transmission can be permanently reduced within African resources in those countries which have stable and democratic governments. Appropriate local strategies should be developed in ecological zones across the continent which match transmission patterns. Malaria transmission can be reduced to levels that are tolerable and sustainable.”

The realistic solution is that we should abandon the concept of eradication and replace it with campaigns to eliminate malaria as a health hazard wherever possible and to control malaria as best as possible where elimination is not economically or otherwise feasible. Starting from this standpoint, it is essential to make the best use of the drugs available and to involve the local populations. One intervention that has proved to be very easy to implement and has been very successful is intermittent drug treatment. This involves treating whole sub-populations with long half life combinations of drugs at fixed intervals regardless of whether or not individuals are infected. This has been very successful when applied to infants (IPTi) and pregnant women (UTPp). The actual combinations of drugs have to be carefully matched with the malaria status of the population as a whole. It would be no use to drugs to which the local strains of malaria are resistant. This method has been shown to be very successful in reducing malaria by up to 80% in large trials in The Gambia, Ghana, Mali and Senegal and also to a slightly lesser extent in Papua New Guinea.

These successes have been due to a large extent to the involvement of local people which leads to another simple scheme that has proved to be very successful, home-based management of malaria (MMM). This scheme involves training community health workers in diagnosis, use of drugs and education (particularly mothers). These community health workers provide 24 access within walking distance to affordable and appropriate treatment.

There is every reason to be optimistic and the Murray report suggests that malaria deaths could be reduced to 100,000 by 2020. This is still a large number but less than 10% of the numbers dying today and there is no reason to assume that this decline will not continue.

Malaria is not an intractable problem for a number of reasons: Malaria, cannot pass directly from person to person, is not a disease of poverty, is not associated with unsanitary conditions, is easy to prevent, is easy to diagnose and is easy and inexpensive to treat. In these ways, malaria is not as great a 21st Century threat as HIV/AIDS or tuberculosis. However, all three diseases are likely to suffer as a result of the decision of the Global Fund to Fight AIDS, Tuberculosis and Malaria to freeze its funds until 2014 because of the global downturn in the fortunes of the major donor countries. Although not as obvious as for AIDS and tuberculosis, malaria is our problem and this takes me back to back to the theme of my 1992 Gresham Professorial lectures, Tropical Diseases, their Problem or Ours?

Selected References


http://malarianomore.org.uk

http://christianaid.org.uk/

http://jshph.edu/about_malaria/

http://www.who.int/mediacentre/factsheets

Also look at World Malaria Day on the internet.