Tropical medicine: 100 years of progress

Herbert M Gilles* and Adetokunbo O Lucas†

*Liverpool School of Tropical Medicine, Liverpool, UK and †Harvard School of Public Health, Boston, Massachusetts, USA

Over the past century, tropical medicine has passed through several overlapping phases. Initially, the picture was of endemic and epidemic diseases that wreaked havoc on people living in warm climates and visitors to these areas. High morbidity and mortality associated with these diseases reflected the poor state of knowledge about their causes and epidemiology and the lack of effective technologies for their control. At this stage, tropical medicine was dominated by parasitic and infectious diseases that had affinity for warm climates and some specific nutritional disorders. The next phase involved the steady accumulation of knowledge about the aetiological agents and, in the case of parasitic and infectious diseases, identification of reservoirs and vectors. The development of new and improved technologies for the control of tropical diseases characterised the third phase. The new products included drugs, diagnostic tools, vector control measures and vaccines. In the fourth phase, the new technologies are being deployed in programmes aimed at achieving disease control and, where feasible, total elimination of the problem. In the course of these operations, many useful lessons have been learnt from both the successes and failures of major schemes. In particular, experience has shown the important role of research not only in providing new technologies but also in optimising their effectiveness when applied in control programmes. The role of social and behavioural factors in the epidemiology and control of tropical diseases has drawn attention to the value of a multidisciplinary approach in designing and implementing control programmes. There is a sense of cautious optimism that, if the lessons learnt over the past century are carefully applied, further gains can be made in controlling and eliminating the classical problems that characterised tropical medicine at the beginning of this century.

One century ago, a variety of acute and chronic diseases dominated the medical scene in many tropical countries. These diseases, collectively known as tropical diseases, occurred more frequently or were mainly restricted to warm climates. Many were caused by infectious agents that thrived in, or were transmitted by, vectors that required a warm climate. Climatic factors together with poverty and underdevelopment account for the higher incidence of these conditions in tropical and sub-tropical countries. Some non-infectious diseases turned out to be associated with
diet and nutrition that led to deficiency disorders and toxic manifestations. Health research has been highly successful in unravelling the complex patterns of health and disease in the tropics, identifying the causative agents, and developing effective technologies for their control. The deployment of these new technologies in national and regional control programmes has significantly altered the prevalence and distribution of tropical diseases. These changes have radically altered the profile of medicine in the tropics which is now increasingly dominated by chronic non-infectious diseases and accidents - cosmopolitan diseases that occur in warm and cold climates alike.

The history of tropical medicine in the past century can be conveniently examined in four overlapping phases in the fight against tropical diseases.

**Devastation**

At this stage, tropical diseases constituted a major cause of disease, disability and death. Tropical medicine provided limited relief for individual patients and it was relatively powerless to control the diseases in the endemic areas.

**Discovery**

In this phase, there was a steady accumulation of knowledge about the causative agents and their vectors, the life cycles of various parasites and their ecology. This phase also included the identification of nutritional disorders and toxic syndromes.

**Development**

The development of new tools and strategies for prevention, treatment and control of tropical diseases characterise the third phase.

**Deployment**

The deployment of new and effective technologies in the fourth phase has significantly reduced the incidence and prevalence of tropical diseases. At this stage, there is a new sense of optimism that we are steadily gaining the upper hand over tropical diseases and that an aggressive approach can control these diseases and where feasible, achieve global eradication.
Devastation

Take care and beware of the Bight of Benin,
For few come out, though many go in. [Sailor's ditty]

One hundred years ago, in many parts of the tropics, the endemic tropical diseases had a major impact on the life of communities as can be surmised from the following examples.

In the historic epidemics of cholera that occurred between 1817 and 1898, particularly in the Indian sub-continent, as many as 10% of the affected population died, which is in marked contrast to the recent epidemic in Peru (1992) where, out of 300 000 clinical cases, only 1% died.

For many centuries, plague occurred predominantly in Europe and the Middle East. The great Italian poet and novelist, Alessandro Manzoni gave an accurate description of the Plague of Milan of 1630 which reduced the population of the city from 250 000 to about 64 000. In the nineteenth century, plague moved down the trade routes to Canton where it caused 100 000 deaths and thence to other ports along the routes of the grain trade, including Bombay, Rangoon, Bangkok, Saigon and Manila.

Yellow fever was first recognized as a separate disease in tropical America where it had a profound effect on military activities in the region, killing whole armies of susceptible European troops. An epidemic in Senegal in 1778 killed 59 of a community of 92 immigrants, while sailors of the period were only too aware that after voyages to West Africa and South America they could be killed by ‘Yellow Jack’. The first garrison of Cape Coast Castle in Ghana in 1923 was ravaged, there was only one survivor a year later, while of a garrison of 535 troops in Ghana in 1926, 115 died of yellow fever within two months.

A trypanosomiasis epidemic in Uganda killed 250 000 people, 80% of the population at risk; while in 1921, 3% of the population of Sokoto town in Nigeria died during an epidemic of meningococcal meningitis.

Malaria has been recognised for over 4000 years. The ravages of malaria especially those experienced in wars have been repeatedly documented.

During this period of devastation, tropical diseases left an indelible mark on the political map of Africa; the pattern of European settlement being largely determined by the prevalence of the major tropical infections. Thus, falciparum malaria and yellow fever gave rise to West Africa being labelled ‘the white man’s grave’ while the highlands of Kenya were favoured and South Africa was ideal.

In summary, this was a phase when tropical diseases wreaked havoc among populations; the syndromes and epidemics were described yet we were powerless either to prevent or control them, since effective
remedies were not available, except for quinine. The aetiology of the diseases that were decimating communities in the tropics as well as immigrants was largely unknown.

### Discovery

This was the period when a steady accumulation of knowledge about the aetiology of many of the important tropical diseases occurred. Parasites and other microbial agents were identified; their relationship to vectors was established, the ecological settings that favoured their transmission were analysed. Moreover, the importance of nutritional disorders was recognised and the effect of food toxins described. Table 1 shows some of the key discoveries that were made during this period.

Historical facts, controversies and anecdotes concerning some of the discoveries listed in Table 1 contribute to the fascination of tropical medicine and will be briefly referred to below.
While working in Lassance, in the interior of Minas Gerais, Brazil, Carlos Chagas examined the gut of a ‘barbiero’, as the reduvid bug is called in Brazil, and confirmed the presence of numerous flagellates. His first patient was Berenice who was 2-years-old when first seen and presented with intermittent fever, oedema, lymphadenopathy and hepatosplenomegaly. Blood examination revealed the presence of *Trypanosoma cruzi*. Berenice died of unrelated heart disease in her 60s. Chagas also showed that armadillos could act as a reservoir host. He thus discovered the organism, described the clinical features and identified the reservoir host – a remarkable triad of discovery¹.

Yellow fever was at first believed to be contagious and the controversy was so furious that it led to a duel between two physicians that resulted in their killing each other. Finlay produced the first experimentally based evidence of the mosquito transmission of yellow fever². Walter Reed, who headed the American Commission on yellow fever to Cuba, is, however, credited with the discovery of the mosquito transmission of yellow fever. Using volunteers, one of whom died, he showed that:
(i) the infective agent would pass through a bacteria-tight filter, hence was probably a virus;
(ii) patients were infective during their first three days of fever; and
(iii) the extrinsic incubation period in *Aedes aegypti* was 12 days³. It was later discovered that, in addition to *A. aegypti*, forest dwelling mosquitoes, both in the Amazon and in Africa, were also vectors of yellow fever⁴.

The highly respected bacteriologist Noguchi, however, proclaimed that the aetiological agent of yellow fever was *Leptospira icteroides*, not a virus⁵. It took the death of Stokes in Lagos at the age of 40, to resolve the confusion between leptospirosis and yellow fever⁶ and Noguchi was forced to concede that *Leptospira* was not the organism responsible for yellow fever. Ironically, Noguchi himself died in Accra (Ghana) from yellow fever in 1928.

In Zululand, a wasting disease of cattle which was locally named nagana, was decimating the herds on which the livelihood of many of the people depended. Bruce established the causal relationship between a trypanosome, later named *Trypanosoma brucei*, and nagana⁷.

Although Castellani, of Castellani’s paint fame, was the first to find trypanosomes both in the blood and in centrifuged deposits of cerebrospinal fluid in his patients with sleeping sickness, he refused to consider them the causative agents of the disease and persisted in the belief that a streptococcus was responsible⁸. He, however, continued his studies under Bruce’s direction, and eventually showed that the trypanosome was the cause of African sleeping sickness. An unfortunate and distasteful controversy arose when it was implied that Castellani had not considered the possible role of the trypanosome until Bruce suggested it to him⁹.
It was left to Stephens and Fantham to establish that this was a new species of human trypanosome for which they proposed the name *Trypanosoma rhodesiense*. Ten years earlier, Forde and Dutton had discovered *Trypanosoma gambiense* in the Master of the government steamer, plying the River Gambia. It was Warrington Yorke who demonstrated the transmission of *T. rhodesiense* by *Glossina morsitans* and established that game animals were the reservoirs of human infections. Dutton, Stephens and Warrington Yorke were all academic members of the Liverpool School of Tropical Medicine, when they made these discoveries.

The controversies that occurred over the discoveries of yellow fever and trypanosomiasis pale into insignificance when compared to those provoked by malaria, which, even today, arouses unusual passions and dogmatic opinions.

The discovery, in 1880, by Laveran of the malaria parasite in the blood of a soldier attracted little attention and was not widely accepted. The influential Italian scientist Marchiafava continued to favour the bacterium theory promulgated by Klebs and Thommarsi-Crudeli; yet, with Celli, he was stimulated by Laveran’s visit to Rome to examine blood films from malarious patients and published their results without reference to Laveran. Within a period of 6 years, four Italian malariologists between them – namely Marchiafava, Celli, Bignami and Golgi – discovered that malaria could be caused by three different species of parasite which they named *P. falciparum*, *P. vivax* and *P. malariae* with different clinical presentations and different morphological features.

The mode of transmission remained to be elucidated. It was left to Ronald Ross, working in Calcutta, to work out the life cycle of the bird malaria parasite in the mosquito. Grassi, Bastianelli and Bignami described the entire sporogenic cycle of the human malaria parasite in mosquitoes of the genus *Anopheles*, which resembled that described by Ross. Grassi claimed that he was the person who had discovered how malaria was transmitted since he had been completely unaware of Ross’s work. An acrimonious and protracted quarrel between Grassi and Ross took place which ended, however, with Ross (the first Professor of Tropical Medicine in Liverpool) being awarded the Nobel Prize in 1902.

The tissue stages of *P. falciparum*, *P. vivax* and *P. ovale* were demonstrated by Short, Garnham and a group of American scientists.

Various nutritional disorders, including vitamin deficiencies, were also discovered. The spectrum of marasmus at one end and kwashiorkor at the other was defined. Thus Cecily Williams in 1933 working in the Gold Coast concluded that protein deficiency was the cause of the skin lesions and oedema she was encountering in children. She gave it its distinctive Ga name – *kwashi* meaning first and *orkor* second – “the deprived child.” In 1968, Osuntokun found an association between tropical ataxic neuropathy and cassava consumption.
Development

During this phase, tropical medicine profited from the general advances in biomedical sciences which produced new drugs, vaccines and other immuno-prophylactic agents, improved diagnostic methods, and led to the development of pesticides\textsuperscript{21}.

Drugs

One century ago, the anti-malarial drug quinine, derived from the bark of the cinchona tree, was virtually the only anti-infective agent. Ehrlich’s work represented the new age of synthetic drugs producing Salvarsan, an organic arsenical for the treatment of syphilis. Some of the new products were specifically effective against tropical parasitic diseases, \textit{e.g.} antrypol (trypanosomiasis, onchocerciasis) and pamaquine, chloroquine, primaquine and pyrimethamine (malaria). New antibiotics and other anti-infective agents in general use, find useful applications in the treatment of tropical diseases, \textit{e.g.} penicillin for yaws and rifampicin for leprosy.

Tropical doctors now have at their disposal a wide range of effective anti-infective drugs, but many gaps remain to be filled. There are no drugs for the treatment of life-threatening viral infections, like Ebola disease; no effective agent for eradicating chronic infection with Chagas’ disease; and only a limited range of drugs for dealing with visceral Leishmaniasis. Although ivermectin has revolutionised the treatment of onchocerciasis, there is still a need for a safe macrofilaricide. The emergence and spread of drug resistant malarial parasites remains a major challenge for the development of new therapeutic agents\textsuperscript{22}.

The rational development of anti-parasitic drugs, based on comparative biochemistry, remains an elusive goal. Although biochemists have identified metabolic pathways in parasites that differ significantly from the pathways in humans, it is still proving difficult to translate this knowledge into useful therapeutic products\textsuperscript{23}.

Vector control

During the past century, scientists have developed technologies for the control of arthropod vectors and molluscan intermediate hosts of tropical parasitic and infectious diseases. At first, the available tools were mainly physical measures that were designed on the basis of knowledge of the ecology of the invertebrate vectors and intermediate hosts. Later, the development of a variety of chemical pesticides made it possible to achieve more effective vector control.
Physical measures Detailed knowledge of the breeding, biting and other behavioural features of vectors facilitated the design of physical measures to control their populations and reduce their ability to transmit infections. Environmental interventions that eliminated breeding sites of insect vectors were among the most successful control measures for some arthropod borne diseases. Such measures are more effective when the breeding sites of the vector are restricted to clearly demarcated areas that can be eliminated, for example by the drainage of swamps, periodic drying of irrigation canals or the sanitary disposal of refuse which would otherwise favour the breeding of flies. More difficult are situations where the target sites are more extensive as, for example, the almost ubiquitous breeding of \textit{Anopheles gambiae} in small collections of water including upturned leaves and the hoof marks of animals in the tropical rainforest. The use of mineral oils on open stretches of water control mosquito larvae through physical effect of blocking their respiration. Guinea worm is being effectively controlled by protecting sources of drinking water and by filtration of water from contaminated sources.

Mechanical measures for the control of adult insects are much less successful and mainly rely on establishing mechanical barriers between the vector and the susceptible host in the form of protective nets on doors, windows and beds. Adult reduvid bugs that transmit \textit{T. cruzi}, the causative agent of Chagas’ disease, live in the cracks of the mud walls; this ecological niche can be eliminated by improved construction of houses. The display of flies caught on strips of sticky paper is visually impressive but does not necessarily have a significant effect on the populations of the target flies. Bush clearing along river courses can deprive tsetse flies of their resting place in the shade. Much more effective are the traps for capturing tsetse flies that were designed and optimised on the basis of detailed study of the behaviour of the various species of the fly.

Chemical pesticides The development of chemical pesticides, both larvicides and adulticides, increased the effectiveness of vector control measures. First isolated in Germany in 1874, it was not until 1939 that Muller recognised the residual insecticidal properties of DDT (dichlorodiphenyl-trichloroethane). This was a major breakthrough that greatly facilitated the logistics of vector control especially for indoor resting species of mosquitos. The application of this and other residual insecticides contributed to the elimination of malaria from many parts of the sub-tropics. Short acting, ‘knock-down’ insecticides, mainly pyrethroids, have also been applied for immediate effect for spraying indoors or in fogging machines outdoors. They have also been effectively applied by
impregnating bed nets for malaria control and tsetse fly traps for the control of African sleeping sickness.  

**Vaccines**

Much research effort has been applied in attempts to develop vaccines for use in tropical diseases. Although effective vaccines have been developed against many viral and bacterial diseases, anti-parasitic vaccines have remained elusive. Using the powerful research tools of modern biology – immunology, molecular biology and genetic engineering – some progress has been made towards the goal of developing effective vaccines against malaria. The initial clinical trials of malaria vaccines have given promising results, but the products have not achieved sufficient levels of protection to be of practical use.

**Diagnostic tools**

Major advances have occurred in the sensitivity and specificity of diagnostic tools in tropical medicine. Simple microscopy was available a century ago. Since then, a wide variety of diagnostic tools have emerged. For identifying parasitic and other infections in humans, for differentiating species and sub-species of vectors, and for assessing the nature and severity of pathological damage to the infected host. The detection of specific antigens or nucleic acid sequences, using monoclonal antibodies and DNA probes, is replacing older tests based on antibody detection. The newer tests are more specific and give a better indication of current or recent infection than antibody detection. Although direct microscopy remains the most specific diagnostic test of malaria infection, new simple dip-stick tests are providing accurate diagnosis without requiring laboratory resources or a high level of skill.

**Deployment**

The accumulation of knowledge about the biology of the parasites, the ecology of their vectors and the patterns of host-parasite relationships has prompted an aggressive approach to the control and elimination of tropical parasitic and infectious diseases. New technologies are being deployed to tackle the most vulnerable points in the life cycle of the parasites. The main strategies include control of non-human vertebrate
reservoirs, diagnosis and treatment of infected humans who serve as reservoirs. It has been possible in some diseases to interrupt transmission by vector control. For some infections, e.g. yellow fever, the main strategy has been the protection of the susceptible host by vaccination. Chemotherapy and chemoprophylaxis have been widely used for individual protection as well as in mass campaigns. Selectively targeted chemotherapy has been successfully used in the control of chronic infections, like schistosomiasis, onchocerciasis and lymphatic filariasis.

The current picture of tropical diseases is a mixture of outstanding successes and some significant failures. The incidence and prevalence of some tropical diseases, e.g. onchocerciasis, leprosy, Chagas’ disease and lymphatic filariasis, have declined in recent years; there is now the prospect of global eradication of guinea worm infection. On the other hand, there have been some disappointing setbacks. For example, not only did the attempted global eradication of malaria fail but the epidemiological situation has worsened in areas where, previously, the disease had been well controlled. Many lessons have been learnt from the experiences accumulated in the course of managing programmes for the control of tropical diseases.

The value of research

There is abundant evidence of the value of knowledge-based and science-based strategies. The value of research that is aimed at the development of new and improved tools like drugs, vaccines, diagnostic tests and vector control measures is well recognised. There is less appreciation of the need for local-specific research to provide accurate situation analysis of the prevalence, distribution and determinants of infection and disease. Effective strategies aimed at making optimal use of available technologies should be based on sound knowledge of local epidemiology of the disease as well as a thorough understanding of the role of social and behavioural factors.

The value of broad non-specific interventions

Without underestimating the role of specific technologies, like drugs and insecticides in the control of tropical parasitic and infectious diseases, the value of broad, non-specific interventions must not be overlooked. The provision of adequate amounts of safe water, sanitary disposal of garbage and human wastes and good personal hygiene make major contributions to the improvement of health in the tropics.
Public education

General education of the public, especially female education, is strongly associated with improved health for individuals and their families. In endemic areas, the educated members of the community apply health education messages more effectively than their illiterate neighbours.

Integrated management

The combination of several control measures can be synergistic. For example, experience has shown the value of integrated pest control instead of relying solely on the application of pesticides as a single tool for vector control. Multi-strategic approaches have proved very valuable in the elimination of guinea worm.

International collaboration

Since parasites and their vectors do not respect national boundaries, national control measures may be undermined by the situation in neighbouring states. Regional and sub-regional programmes such as, for example, the Onchocerciasis Control Programme in West Africa have demonstrated the value of inter-country collaboration.

Prospects

The past hundred years have taught many lessons about how to approach tropical diseases. The successful ventures give rise to cautious optimism that many of the residual problems can be eliminated by a vigorous application of existing technologies. Improved housing, safe and adequate water supplies and environmental sanitation will facilitate the control of many of the persistent problems and there is the promise of new and improved tools from biomedical research.

References

1 Chagas C. Nova entidade morbida do homen. Rezumo geral de estudos etiologicos e clinicos. Memorias do Instituto Oswaldo Cruz 1911; 33: 276–94
2 Finlay GJ. El mosquito hipoteticamente considerado como agente de transmission de la fiebre amarilla. Annales de al Academic de Cienas Medico, Fisicos y Naturales de la Habana. 1881; 18: 147–69
7 Bruce R. Croonian lectures. BMJ 1915; I: 1073–8
11 Dutton JE. Preliminary note upon a trypanosome occurring in the blood of man. Thompson Yates Lab Rep 1902; 4: 453–68
15 Ross R. On some peculiar pigmented cells found in two mosquitoes fed on malarial blood. BMJ 1897; ii: 1786–8