Guinea worm: from Robert Leiper to eradication

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SUMMARY

Guinea worm disease, dracunculiasis or dracontiasis, is an ancient disease with records going back over 4500 years, but until the beginning of the 20th century, little was known about its life cycle, particularly how humans became infected. In 1905, Robert Thomas Leiper was sent by the British colonial authorities to West Africa to investigate the spread of Guinea worm disease and to recommend measures to prevent it. While carrying out his investigations, he made important contributions to the aetiology, epidemiology and public health aspects of Guinea worm disease and provided definitive answers to many outstanding questions. First, he tested the validity of previous theories; second, he confirmed the role of water fleas, which he identified as *Cyclops*, as the intermediate hosts in the life cycle; third, he investigated the development of the parasite in its intermediate host; and fourth, he recommended measures to prevent the disease.

[The crustacean Order Cyclopoida in the Family Cyclopidae contains 25 genera, including *Cyclops* which itself contains over 400 species and may not even be a valid taxon. It is not known how many of these species (or indeed species belonging to related genera) can act as intermediate hosts of *Dracunculus medinensis* nor do we know which species Fedchenko, Leiper and other workers used in their experiments. It is, therefore, best to use the terms copepod, or copopoid crustacean rather than *Cyclops* in scientific texts. In this paper, these crustaceans are referred to as copepods except when referring to an original text.]

Leiper described the remarkable changes that took place when an infected copepod was placed in a dilute solution of hydrochloric acid; the copepod was immediately killed, but the *Dracunculus* larvae survived and were released into the surrounding water. From this, he concluded that if a person swallowed an infected copepod, their gastric juice would produce similar results. He next infected monkeys by feeding them copepods infected with Guinea worm larvae, and thus conclusively demonstrated that humans became infected by accidentally ingesting infected crustaceans. Based on these conclusions, he advocated a number of control policies, including avoidance of contaminated drinking water or filtering it, and these preventive measures paved the way for further research. The challenge to eradicate Guinea worm disease was not taken up until about seven decades later since when, with the support of a number of governmental and non-governmental organizations, the number of cases has been reduced from an estimated 3·5 million in 1986 to 25 in 2016 with the expectation that this will eventually lead to the eradication of the disease.

Key words: Robert Leiper, *Dracunculus medinensis*, dracunculiasis, Guinea worm disease, *Cyclops*, copepod, disease control, safe drinking water.

INTRODUCTION

Guinea worm disease, dracunculiasis, is one of the oldest known human parasitic diseases and has been described in the Papyrus Ebers from about 1500 BC, the Bible from about 1250 BC and in various subsequent Arabic, Persian, Greek, Roman, Egyptian and other texts (see Grove, 1990 and Tayeh, 1996*a*). The nature of the infectious agent, however, remained elusive and was believed to be a vein by Persian physicians who called it by a variety of names including Medina vein. The scientific name, *Dracunculus medinensis*, incorporating the word for dragon with Medina, is attributed to Bastian in 1863 (who conclusively demonstrated that it was a worm) and the common name, Guinea worm, to Sir John Tennent in 1868 (see Grove, 1990 for a detailed discussion of the controversy surrounding the nomenclature).

An association between Guinea worm disease and water had been recognized since the earliest times, and after the discovery of its cause, controversy ranged as to how the worm got from water to the human host whether by ingestion or through the skin. In 1869, while looking for worms in contaminated water, the Russian helminthologist, Aleksej Fedchenko, noticed that the water contained cyclopoid crustaceans, which he identified as *Cyclops* sp. and, when he dissected them, found that they harboured larval worms that he suspected might be the intermediate stages of the Guinea worm and postulated that humans became infected by accidentally ingesting the crustacean in drinking water (Fedchenko, 1870). Other eminent scientists began to investigate this possible mode of transmission and the German helminthologist Rudolf Leuckart, probably the leading helminthologist at

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that time, suggested that Fedchenko should investigate the development of the worm in copepod crustaceans based on the similarity of the first stage larvae to those of *Cucullanus elegans*, the life cycle of which he, Leuckart, had already determined. Fedchenko, however, failed to demonstrate the complete life cycle as cats and dogs fed infected copepods did not become infected. Other scientists doubted his theory and also failed to complete the life cycle, so Fedchenko's theory was largely abandoned. It is against this background that Leiper began his ground-breaking research into dracunculiasis

LEIPER'S MISSION TO WEST AFRICA

Early in the 20th century, Guinea worm disease had become recognized as a serious problem in terms of incidence and severity in the main towns of the Gold Coast (now Ghana) and Nigeria particularly as it affected British troops and the health of the labour force with consequences for political stability and the economy of these colonies. The British colonial administration required action in order to determine the mode of transmission of the disease and measures to control it. Thus, the Committee of the London School of Tropical Medicine asked Robert Thomas Leiper, in 1905, to go to Accra in the Gold Coast (now Ghana) West Africa charged with finding ways to control the disease.

Leiper had been appointed by Patrick Manson as helminthologist at the London School of Tropical Medicine in 1905 at the age of 24 (Cox, 2017). He had only recently graduated in medicine with no tropical experience and little or no training in scientific methodology and only one publication on a turbellarian worm from a sea urchin (Leiper, 1904). Nevertheless, in 1905 with Manson's support, Leiper departed to West Africa to undertake this assignment.

At that time, little was known about the behaviour of *D. medinensis* and how it might be controlled. Leiper was aware that Fedchenko had shown that copepods were the intermediate hosts of *D. medinensis*, and had correctly surmised how humans become infected with the parasite, but that he and other scientists had failed to complete the life cycle. Leiper took up this task with enthusiasm and vigour. Leiper's experiments and observations were to become classics and set standards that persist to the present time.

Dismissing existing theories and confirming others

Leiper began by reviewing all the prevalent conflicting hypotheses: (1) that the development of the embryos can be completed without the intervention of an intermediate or second host or (2) that development in the intermediate host is essential for the larva to be able to re-infect man. Under each of these hypotheses, Leiper listed several theories that had been promoted at that time. He dismissed the first category and provided experimental evidence that the embryos cannot infect humans directly via the skin or mouth until after they had undergone further development in the copepod intermediate host (Leiper, 1907).

In order to demonstrate that infection was due to the ingestion of infected crustaceans, he fed a monkey on bananas containing copepods that had been infected for 5 weeks and which contained apparently mature larvae. Six months later, a careful post-mortem examination of the monkey revealed the presence in the connective tissues of five worms that possessed the anatomical characteristics of *D. medinensis* (Leiper, 1906*a*, 1907). In order to demonstrate the absence of a second intermediary host, Leiper referred to his work in Nigeria in which he found that the only organism in the ponds that could cause infection were infected copepods (Leiper, 1907).

The behaviour of embryos in water

Leiper then observed that *Dracunculus* embryos can survive in water for 3 days and some for 6 days. He did not specify the temperature of the water but noticed that the larvae stayed alive a day or two longer in mud, probably by saving energy while dormant. *Dracunculus* embryos are unable to obtain food in water, although they have a mouth and a digestive tract and must find a suitable crustacean within a few days and must be able to enter the body cavity of the crustacean host. Leiper observed that the embryos are frail and can die quickly if dried by evaporation but cannot be revived by adding water (Leiper, 1907).

Behaviour and metamorphosis of the embryo in copepod crustaceans

Leiper observed that the mode of entry of the embryo is through the intestine of the copepod and not through the integument as previously believed and that the larvae showed no tendency to leave the crustacean host and become free-swimming. As time went on, the larvae became inactive, and when the crustaceans died, the larvae also died. Two days after emergence, the larvae lost their very delicate enveloping pellicle and thereafter development ceased. Further changes were only in the differentiation of internal structures and the larvae finally became mature on the fifth day and that the striate cuticle was cast on the eighth day (Leiper, 1907).

Behaviour of Dracunculus larvae and copepods in hydrochloric acid solution

Leiper's next investigation was to mimic the conditions in the human stomach. He observed and

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described in detail how the copepods containing the *Dracunculus* larvae behave when placed in a drop of water together with 0·2% hydrochloric acid, representing the acidity of the gastric juice in the stomach (Leiper, 1906*b*). Although the copepods died, the larvae regained their former activity, at first slowly, but gradually with increasing strength and speed, and burst into the body cavity of the dead crustacean. Eventually, the young worms reached the water and there swam with great speed. In a control experiment, copepods containing embryos of the same date of infection and in all respects similar to those used in the experiment but to which no acid had been added remained alive for a further period of 2 weeks but the larvae they contained did not exhibit any changes. Some copepods died, but the larvae did not try to escape and died as well.

From all these experiments and observations, Leiper concluded that 'The young (larvae) must be discharged directly into fresh water soon after the parent worm has succeeded in creating a break in the overlying skin and before the wound has become markedly septic. The embryos must find a *Cyclops* within a few days. They must, moreover, succeed in entering its body cavity. Five weeks later they will have developed into mature larvae. They must, therefore, be taken into a human stomach, and having been set free from their host by the gastric juice, reach the connective tissues by penetrating the gut wall' (Leiper, 1907).

Leiper made another important discovery when he found two males each 22 mm long in an experimentally infected monkey and commented on the importance of the discovery of the male and immature female forms in the connective tissues, thus showing that the life cycle of Guinea worm was in accord with what was known of the after-development of other filarial parasites (Leiper, 1906*a*). Thus, in a very short period of time, Leiper had completed our knowledge of the life cycle of *D. medinensis*. He also made several recommendations for future research. These included: to explore the conditions under which the intermediate host (*Cyclops*) lives and multiplies in tropical settings; to ascertain the natural enemies and the food supply of the *Cyclops*; to observe whether *Cyclops* can survive the summer drought; to experiment and explore whether by adding chemicals, *Cyclops* could be destroyed in suspected water without risking human health. In the same paper, Leiper also set out very clearly his prognosis for Guinea worm disease.

'It is evident that dracontiasis will disappear from the Gold Coast towns with the provision of properly controlled water supply obtained either from artesian wells or through pipes from rapidly flowing streams' (Leiper, 1907).

Later, Leiper (1936) stressed the need for regional surveys of crustaceans as important intermediate hosts in the spread of human disease.

Seasonality of infection

Leiper believed that knowing the season of infection was very important for the success of preventive measures in that area. As far as we know, Leiper was the first scientist to compare the seasonal incidence of Guinea worm with the monthly rainfall (Leiper, 1911*a*). He was fortunate that there were rainfall data from 1891 to 1894 in the Gold Coast as well as Guinea worm incidence data during the same period that enabled him to draw such tables. The life cycle of *D. medinensis* is 1 year and, although he did not compare the rainfall in a year (risk factor) and new cases in the following year (infection), as is done nowadays (Cairncross *et al.* 2002), he did show that rainfall in the years 1891–1894 was consistent in its seasonality. The highest peak occurred between April and May with a smaller peak in October to November. Later, scientists developed this method by plotting worm emergence (the infection) in a year with the rainfall 1 year earlier since the incubation period is approximately 1 year.

Leiper observed that in the Gold Coast there are different periods for wet and dry seasons: (1) a long dry season, November to March; (2) a long wet season, April to June; (3) a short dry season, July to September; and (4) a short wet season, October and November. He recommended the use of artesian wells or pipes from rapidly flowing streams for provision of drinking water during the dry seasons, which is the season of infection in Ghana, and also the filling in of surface water and shallow wells.

Leiper's discoveries in summary

By 1907, Leiper had established that Guinea worm disease is acquired by drinking water containing copepods infected with larval *D. medinensis*. When in the stomach of the mammalian host, the crustacean is killed by stomach acid, the larvae emerge and migrate to connective tissue where they mature and mate and, 1 year later, the mature female worm full of embryos emerges, usually from the leg. The larvae are ingested by the copepod, moult and develop to become infective and the life cycle is completed when a person drinks water containing the infective crustaceans (Muller, 1971).

Leiper's recommendations for the control of Guinea worm disease

The main objective of Leiper's trip to West Africa in 1905 was to study the aetiology of Guinea worm disease with a view to recommending ways to control it. He suggested that infective individuals should be prevented from coming into contact with infected and uninfected copepods, and that this should be the aim of any organized effort to control the disease. Thus, for West Africa, he recommended

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the avoidance of contaminated water and the provision of safe drinking water during the season of infection. Leiper subsequently visited India and recommended replacing step wells, where people descend down a series of steps to collect water directly from the source, with draw wells where people collect water in buckets, and therefore do not come in direct contact with any water. He also recommended building high parapets around the mouths of wells to prevent people from wading into the water and to prevent the return of spilled water. To kill the adult copepods in well water, he suggested raising the temperature of the water in the well, suddenly, by passing steam through it from a mobile boiler (Leiper, 1911*b*). He was aware that this method might not prove practical, but taking into consideration that the disease was seasonal, it would only have to be done during the transmission season. Most importantly, Leiper was careful to indicate that any preventive measures should be simple and inexpensive and should take into account the climate, people's behaviour and different drinking water sources. Leiper made one more important suggestion for the possible control of Guinea worm disease when he revisited West Africa in 1912 and observed that the disease was absent in places where there were fish living in the water sources and suggested that this might be a method of controlling the disease (Leiper, 1913). Apart from this one paper and a review in 1936 (Leiper, 1936), Leiper never returned to the study of Guinea worm disease and by 1908 he had turned his attention to hookworms and later schistosomiasis, the work for which he is best known (see Stothard *et al*. 2017).

FOLLOW-UP STUDIES BY OTHER SCIENTISTS

Leiper can be credited for his extensive work that revived scientific interest in Guinea worm disease and paved the way for further research by other scientists, while he continued his work on other diseases such as schistosomiasis. The most important work on the biology of Guinea worm disease conducted during subsequent decades has been reviewed by Muller (1971) and Cairncross *et al*. (2002). Scientists who continued Fedchenko and Leiper's work on the natural history of the disease include Roubaud (1918); Moorthy (1938); Onabamiro (1950) and others who have investigated the different stages of development of the larval worms. It was, however, some 50 years after Leiper's expedition to West Africa that several authors, including Muller (1968, 1971), repeated his work on the effect of gastric acid on infected copepods and the aetiology of the disease (Cairncross, *et al*. 2002). These later studies did not challenge Leiper's results but confirmed and added further details regarding the behaviour of the parasite and intermediate host under different conditions including temperature. Other researchers have continued the work of Leiper in evaluating different preventive measures to control and eventually to eradicate the disease. This possibility was first mooted by Leiper in 1907, although he could not have imagined that the incidence of Guinea worm disease would decline almost to vanishing point 110 years later.

CONTROL AND ERADICATION OF GUINEA WORM DISEASE

Despite Leiper's discoveries and recommendations, Guinea worm remained a neglected disease for over 70 years and authorities in endemic countries gave its control little priority probably because it mainly affected people living in rural and remote areas, far from urban centres. The first major intervention supported by a government to eradicate the disease was achieved in the former Soviet Union between 1923 and 1931 by the Tropical Institute in Bukhara with the aim of eliminating the disease from the city and eight other permanently inhabited areas nearby, the only remaining foci of infection in the USSR (Now Uzbekistan) at that time. Various measures of prevention were employed including protecting the water sources, draining ponds, cleaning water sources and treating them with chemicals. In addition, dogs suspected of infection with dracunculiasis were destroyed. The most crucial factor in eliminating the disease was the construction of a safe water supply system in Bukhara in 1929. The last indigenous case of human dracunculiasis in the country was reported in 1931 (Litvinov, 1991).

Meanwhile, in several other endemic countries, the disease disappeared, not by deliberate eradication campaigns but by the provision of safe drinking water. By the early 1970s, for example, most areas of Saudi Arabia had piped water systems. In rural areas of Iran, *burkah* (traditional water storage cisterns) were treated with insecticides for malaria control, and although these measures failed to eradicate malaria, they had the incidental side effect of eliminating dracunculiasis (P. Ranque, personal communication, Tayeh, 1996*b*).

Apart from these sporadic initiatives, Guinea worm disease remained virtually neglected until 1980 when a number of counties, mainly in Africa, realized that it was a serious health problem and that a coordinated international campaign to eradicate the disease was necessary and urgent action was required. The challenge of eradicating Guinea worm disease was taken up by the American Centers for Disease Control and Prevention, Atlanta, Georgia (CDC) (Hopkins and Foege, 1981). The United Nations Development Programme (UNDP) subsequently added Guinea worm to the United Nations International Drinking Water Supply and

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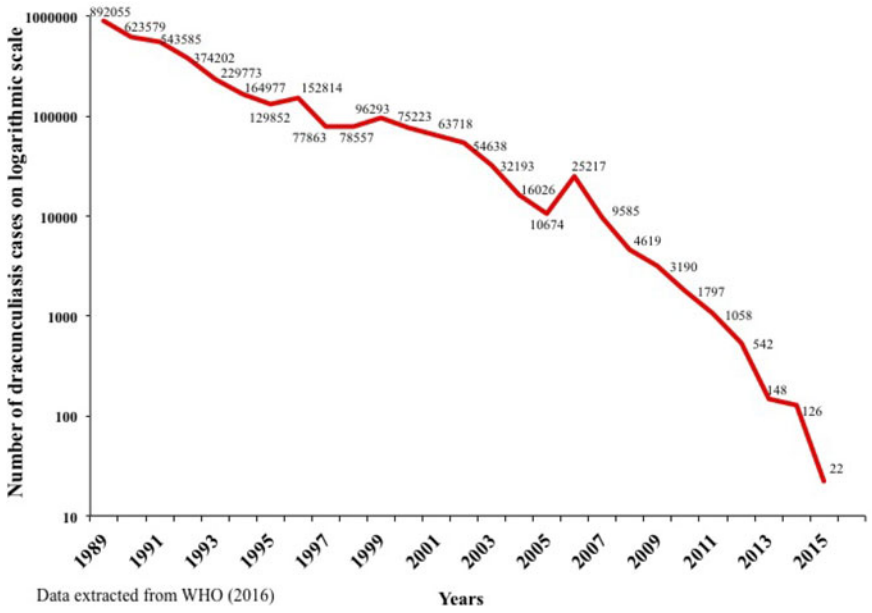

Fig. 1. Annual number of cases of Guinea worm disease 1989–2015.

Sanitation Decade 1981–1990 (IDWSSD). Guinea worm disease featured in this initiative mainly because the disease could only be transmitted through drinking contaminated water and any success in reducing the incidence of or eliminating the disease could be used as an indicator of success in providing safe drinking water. A major breakthrough occurred in 1986, at which time Guinea worm disease was endemic in 20 countries mainly in Africa, with an estimated 3·5 million cases. In 1986, the World Health Organization (WHO), somewhat belatedly, formally supported a campaign for the eradication of the disease. A key role in the campaign was played by the Carter Center. The Center, established in 1982 with the twin aims of Resolving Political Conflict and Combating Disease, had been the brainchild of the former United States President, Jimmy Carter (President 1977–1981). Carter had a personal interest in Guinea worm disease having witnessed its devastating effects during a trip to West Africa with his wife in the early 1980s. His interest never waned and he made several other trips to endemic areas during the 1980s. In 1986, this initiative became the Guinea Worm Eradication Programme (GWEP), the ambitious aim of which was the global eradication of Guinea worm disease. This was to involve the participation of the health service in the endemic countries with financial support from various organizations including the Department for International Development UK (DFID), NGOs and hundreds of other donors including the Bill & Melinda Gates Foundation largely channelled through the Carter Center. The approach was simple, the provision of safe drinking water sources, community-based projects such as building protective walls around wells and other water sources to prevent people coming in to contact with contaminated water, the provision of fine-mesh cloth filters for households without access to safe water, and the treatment of water sources with chemical larvicides such as Temephos (Abate). At the personal level, individuals were provided with cloth filters and, later, pipe filters, plastic tubes with a nylon filter to remove the crustaceans and through which they could drink possibly contaminated water safely. Despite a number of missed targets due to logistical difficulties and lack of human, financial and technical resources (Cairncross *et al.* 2012) coupled with local and international conflicts and population movements, progress towards the eradication of Guinea worm disease was spectacular and by 1990 the number of reported cases had fallen from an estimated 3·5 million in 20 countries to 892 055 in 16 countries. Thereafter, there was steady progress, and at the end of 2015, there were only 22 cases in four countries: Chad, Ethiopia, Mali and South Sudan (WHO, 2015) (see Fig. 1).

Since then, Mali has been declared free from Guinea worm disease, and in January 2017, there were 25 cases reported during 2016 in the remaining three countries (GW Wrap Up, 2016). The WHO has published a detailed time line showing the progress of the eradication programme until 2013 (WHO, 2015). Jimmy Carter has remained in the forefront of these campaigns and in 2015 stated that he hoped to live long enough to witness the last case of Guinea worm disease (Geggel, 2015). Currently, tremendous efforts and resources are being invested in order to trace and stop the few remaining cases from transmitting the disease. One problem here is that the infected individuals must have become infected a year earlier and tracing backwards is labour-intensive and expensive.

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THE DOG THAT DIDN'T BARK

One of Leiper's lesser observations was that *D. medinensis* occurred in wild and domesticated animals (Leiper, 1910). Since then, it has been reported sporadically in apes, cats, dogs, foxes, wolves, leopards, jackals, horses and cattle (see Muller, 1971), but somewhat surprisingly, this information has not been well disseminated and does not appear in standard works on Zoonoses such as Palmer *et al.* 2011. Leiper must have been aware that dogs were susceptible to infection when he tried to infect them with infected crustaceans but no one suspected that they might act as reservoirs of human infection partly because it was thought that the species in animals was different from that in humans or that dogs acquired their infections from humans and not *vice versa*. In 2015, however, 459 dogs in 150 villages in Chad were found to be infected with the human form of *D. medinensis* confirmed by genome sequencing (Eberhard *et al.* 2014). It is not known how this might threaten the Guinea worm eradication programme, but the authorities in Chad are taking no chances. Sources of infection in dogs include fish that had ingested infected copepods, so villagers have been encouraged to bury or to otherwise destroy the remains of fish and fish entrails. Villagers have also been encouraged to report infected dogs with a reward of US$20 to those that do so, tethering of infected dogs and treatment of drinking water used by dogs with Abate. This illustrates the extreme measures that authorities are taking to eradicate Guinea worm disease. In Uzbekistan in the 1920s, control measures included shooting and dissection of dogs, but this may not be acceptable or feasible under all circumstances. With continued efforts and goodwill, it is very likely that Guinea worm disease will be eradicated within the next year or two and will join smallpox as the second human disease to be wiped from the face of the earth. Robert Leiper died in 1969, well before anyone had seriously considered the possibility of the global eradication of Guinea worm disease. When they did, the idea was largely based on his pioneering work carried out over a century before.

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DECLARATION OF INTERESTS

None.

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