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1 Guinea worm: from Robert Leiper to eradication

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13

14 Running title: Robert Leiper and Guinea worm eradication.

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19 SUMMARY

20 Guinea worm disease, dracunculiasis or dracontiasis, is an ancient disease with
21 records going back over 4,500 years but until the beginning of the twentieth century
22 little was known about its life cycle particularly how humans became infected. In
23 1905 Robert Thomas Leiper was sent by the British colonial authorities to West
24 Africa to investigate the spread of Guinea worm disease and to recommend measures
25 to prevent it. While carrying out his investigations he made important contributions
26 to the aetiology, epidemiology and public health aspects of Guinea worm disease and
27 provided definitive answers to many outstanding questions. First, he tested the
28 validity of previous theories, second, he confirmed the role of water fleas, which he
29 identified as *Cyclops*, as the intermediate hosts in the life cycle, third, he investigated
30 the development of the parasite in its intermediate host and, fourth, he recommended
31 measures to prevent the disease.

32

33 [FOOTNOTE NEAR HERE]

34

35 Leiper described the remarkable changes that took place when an infected
36 copepod was placed in a dilute solution of hydrochloric acid; the copepod was
37 immediately killed but the *Dracunculus* larvae survived and were released into the
38 surrounding water. From this he concluded that if a person swallowed an infected
39 copepod their gastric juice would produce similar results. He next infected monkeys
40 by feeding them copepods infected with Guinea worm larvae and thus conclusively
41 demonstrated that humans became infected by accidentally ingesting infected
42 crustaceans. Based on these conclusions he advocated a number of control policies

43 including avoidance of contaminated drinking water or filtering it and these
44 preventive measures paved the way for further research. The challenge to eradicate
45 Guinea worm disease was not taken up until about seven decades later since when,
46 with the support of a number of governmental and non-governmental organizations,
47 the number of cases has been reduced from an estimated 3.5 million in 1986 to 25 in
48 2016 with the expectation that this will eventually lead to the eradication of the
49 disease.

50

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

53

54

55 INTRODUCTION

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

66 An association between Guinea worm disease and water had been recognised
67 since the earliest times and after the discovery of its cause controversy ranged as to
68 how the worm got from water to the human host whether by ingestion or through the
69 skin. In 1869, while looking for worms in contaminated water, the Russian
70 helminthologist, Aleksej Fedchenko, noticed that the water contained cyclopid
71 crustaceans which he identified as *Cyclops* sp. and, when he dissected them, found
72 that they harboured larval worms that he suspected might be the intermediate stages
73 of the Guinea worm and postulated that humans became infected by accidentally
74 ingesting the crustacean in drinking water (Fedchenko, 1870). Other eminent
75 scientists began to investigate this possible mode of transmission and the German
76 helminthologist Rudolf Leuckart, probably the leading helminthologist at that time,
77 suggested that Fedchenko should investigate the development of the worm in
78 copepod crustaceans based on the similarity of the first stage larvae to those of

79 *Cucullanus elegans*, the life cycle of which he, Leuckart, had already determined.
80 Fedchenko, however, failed to demonstrate the complete life cycle as cats and dogs
81 fed infected copepods did not become infected. Other scientists doubted his theory
82 and also failed to complete the life cycle so Fedchenko's theory was largely
83 abandoned. It is against this background that Leiper began his ground-breaking
84 research into dracunculiasis

85

86 LEIPER'S MISSION TO WEST AFRICA

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

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

102

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

110

111 *Dismissing existing theories and confirming others*

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

120 In order to demonstrate that infection was due to the ingestion of infected
121 crustaceans he fed a monkey on bananas containing copepods that had been infected
122 for five weeks and which contained apparently mature larvae. Six months later, a
123 careful post-mortem examination of the monkey revealed the presence in the
124 connective tissues of five worms that possessed the anatomical characteristics of
125 *Dracunculus medinensis* (Leiper, 1906a; 1907). In order to demonstrate the absence
126 of a second intermediary host, Leiper referred to his work in Nigeria in which he

127 found that the only organism in the ponds that could cause infection were infected
128 copepods (Leiper, 1907).

129

130 *The behaviour of embryos in water*

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

139

140 *Behaviour and metamorphosis of the embryo in copepod crustaceans*

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

149

150 *Behaviour of Dracunculus larvae and copepods in hydrochloric acid solution*

151 Leiper's next investigation was to mimic the conditions in the human stomach. He
152 observed and described in detail how the copepods containing the *Dracunculus*
153 larvae behave when placed in a drop of water together with 0.2 per cent hydrochloric
154 acid, representing the acidity of the gastric juice in the stomach (Leiper, 1906b).
155 Although the copepods died the larvae regained their former activity, at first slowly,
156 but gradually with increasing strength and speed, and burst into the body cavity of the
157 dead crustacean. Eventually, the young worms reached the water and there swam
158 with great speed. In a control experiment, copepods containing embryos of the same
159 date of infection and in all respects similar to those used in the experiment but to
160 which no acid had been added remained alive for a further period of two weeks but
161 the larvae they contained did not exhibit any changes. Some copepods died, but the
162 larvae did not try to escape and died as well.

163

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

173

174

175 Leiper made another important discovery when he found two males each 22 mm long
176 in an experimentally infected monkey and commented on the importance of the

177 discovery of the male and immature female forms in the connective tissues, thus
178 showing that the life cycle of Guinea worm was in accord with what was known of
179 the after-development of other filarial parasites (Leiper, 1906a). Thus, in a very short
180 period of time, Leiper had completed our knowledge of the life cycle of *Dracunculus*
181 *medinensis*. He also made several recommendations for future research. These
182 included: to explore the conditions under which the intermediate host (*Cyclops*) lives
183 and multiplies in tropical settings; to ascertain the natural enemies and the food
184 supply of the *Cyclops*; to observe whether *Cyclops* can survive the summer drought;
185 to experiment and explore whether by adding chemicals, *Cyclops* could be destroyed
186 in suspected water without risking human health. In the same paper Leiper also set
187 out very clearly his prognosis for Guinea worm disease.

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

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

193

194 *Seasonality of infection*

195 Leiper believed that knowing the season of infection was very important for the
196 success of preventive measures in that area. As far as we know, Leiper was the first
197 scientist to compare the seasonal incidence of Guinea worm with the monthly rainfall
198 (Leiper, 1911a). He was fortunate that there were rainfall data from 1891 to 1894 in
199 the Gold Coast as well as Guinea worm incidence data during the same period that
200 enabled him to draw such tables. The life cycle of *D. medinensis* is one year and,
201 although he did not compare the rainfall in one year (risk factor) and new cases in the

202 following year (infection), as is done nowadays (Cairncross *et.al.* 2002), he did show
203 that rainfall in the years 1891 to 1894 was consistent in its seasonality. The highest
204 peak occurred between April and May with a smaller peak in October–November.
205 Later, scientists developed this method by plotting worm emergence (the infection) in
206 one year with the rainfall one year earlier since the incubation period is
207 approximately one year.

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

215

216 *Leiper's discoveries in summary*

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

225

226 *Leiper's recommendations for the control of Guinea worm disease*

227 The main objective of Leiper's trip to West Africa in 1905 was to study the aetiology
228 of Guinea worm disease with a view to recommending ways to control it. He
229 suggested that infective individuals should be prevented from coming into contact
230 with infected and uninfected copepods and that this should be the aim of any
231 organized effort to control the disease. Thus for West Africa he recommended the
232 avoidance of contaminated water and the provision of safe drinking water during the
233 season of infection. Leiper subsequently visited India and recommended replacing
234 step wells, where people descend down a series of steps to collect water directly from
235 the source, with draw wells where people collect water in buckets and therefore do
236 not come in direct contact with any water. He also recommended building high
237 parapets around the mouths of wells to prevent people from wading into the water
238 and to prevent the return of spilled water. To kill the adult copepods in well water, he
239 suggested raising the temperature of the water in the well, suddenly, by passing steam
240 through it from a mobile boiler (Leiper, 1911b). He was aware that this method might
241 not prove practical, but taking into consideration that the disease was seasonal, it
242 would only have to be done during the transmission season. Most importantly, Leiper
243 was careful to indicate that any preventive measures should be simple and
244 inexpensive and should take into account the climate, people's behaviour and
245 different drinking water sources. Leiper made one more important suggestion for the
246 possible control of Guinea worm disease when he revisited West Africa in 1912 and
247 observed that the disease was absent in places where there were fish living in the
248 water sources and suggested that this might be a method of controlling the disease
249 (Leiper, 1913). Apart from this one paper and a review in 1936 (Leiper, 1936) Leiper
250 never returned to the study of Guinea worm disease and by 1908 he had turned his

251 attention to hookworms and later schistosomiasis, the work for which he is best
252 known (see Stothard *et al.*, 2017).

253

254 FOLLOW UP STUDIES BY OTHER SCIENTISTS

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

273

274 CONTROL AND ERADICATION OF GUINEA WORM DISEASE

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

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

296 Apart from these sporadic initiatives, Guinea worm disease remained
297 virtually neglected until 1980 when a number of counties, mainly in Africa, realised
298 that it was a serious health problem and that a coordinated international campaign to
299 eradicate the disease was necessary and urgent action was required. The challenge of

300 eradicating Guinea worm disease was taken up by the American Centers for Disease
301 Control and Prevention, Atlanta, Georgia (CDC) (Hopkins and Foege, 1981). The
302 United Nations Development Programme (UNDP) subsequently added Guinea worm
303 to the United Nations International Drinking Water Supply and Sanitation Decade
304 1981-1990 (IDWSSD). Guinea worm disease featured in this initiative mainly
305 because the disease could only be transmitted through drinking contaminated water
306 and any success in reducing the incidence of or eliminating the disease could be used
307 as an indicator of success in providing safe drinking water. A major breakthrough
308 occurred in 1986, at which time Guinea worm disease was endemic in twenty
309 countries mainly in Africa, with an estimated 3.5 million cases. In 1986 The World
310 Health Organization, somewhat belatedly, formally supported a campaign for the
311 eradication of the disease. A key role in the campaign was played by the Carter
312 Center. The Center, established in 1982 with the twin aims of Resolving Political
313 Conflict and Combating Disease, had been the brainchild of the former United States
314 President, Jimmy Carter (President 1977-1981). Carter had a personal interest in
315 Guinea worm disease having witnessed its devastating effects during a trip to West
316 Africa with his wife in the early 1980s. His interest never waned and he made
317 several other trips to endemic areas during the 1980s. In 1986, this initiative became
318 the Guinea Worm Eradication Programme (GWEP) the ambitious aim of which was
319 the global eradication of Guinea worm disease. This was to involve the participation
320 of the health service in the endemic countries with financial support from various
321 organizations including the Department for International Development UK (DFID),
322 NGOs and hundreds of other donors including the Bill & Melinda Gates Foundation
323 largely channelled through The Carter Center. The approach was simple, the
324 provision of safe drinking water sources, community-based projects such as building

325 protective walls around wells and other water sources to prevent people coming in to
326 contact with contaminated water, the provision of fine-mesh cloth filters for
327 households without access to safe water, and the treatment of water sources with
328 chemical larvicides such as Temephos (Abate). At the personal level, individuals
329 were provided with cloth filters and, later, pipe filters, plastic tubes with a nylon filter
330 to remove the crustaceans and through which they could drink possibly contaminated
331 water safely. Despite a number of missed targets due to logistical difficulties and
332 lack of human, financial and technical resources (Cairncross *et al*, 2012) coupled
333 with local and international conflicts and population movements, progress towards
334 the eradication of Guinea worm disease was spectacular and by 1990 the number of
335 reported cases had fallen from an estimated 3.5 million in 20 countries to 892,055 in
336 16 countries. Thereafter there was steady progress and at the end of 2015 there were
337 only 22 cases in four countries, Chad, Ethiopia, Mali and South Sudan. (WHO, 2015)
338 (See Figure 1).

339

340 [FIGURE 1 NEAR HERE]

341

342 Since then, Mali has been declared free from Guinea worm disease and in
343 January 2017 there were 25 cases reported during 2016 in the remaining three
344 countries (GW Wrap Up, No. 242, 2016). The WHO has published a detailed time
345 line showing the progress of the eradication programme until 2013 (WHO, 2015).
346 Jimmy Carter has remained in the forefront of these campaigns and in 2015 stated
347 that he hoped to live long enough to witness the last case of Guinea worm disease
348 (Geggel, 2015). Currently, tremendous efforts and resources are being invested in
349 order to trace and stop the few remaining cases from transmitting the disease. One

350 problem here is that the infected individuals must have become infected a year earlier
351 and tracing backwards is labour intensive and expensive.

352

353 THE DOG THAT DIDN'T BARK

354 One of Leiper's lesser observations was that *Dracunculus medinensis* occurred in
355 wild and domesticated animals (Leiper, 1910). Since then it has been reported
356 sporadically in apes, cats, dogs, foxes, wolves, leopards, jackals, horses and cattle
357 (see Muller, 1971) but, somewhat surprisingly, this information has not been well
358 disseminated and does not appear in standard works on Zoonoses such as Palmer *et*
359 *al.*, 2011. Leiper must have been aware that dogs were susceptible to infection when
360 he tried to infect them with infected crustaceans but no one suspected that they might
361 act as reservoirs of human infection partly because it was thought that the species in
362 animals was different from that in humans or that dogs acquired their infections from
363 humans and not *vice versa*. In 2015, however, 459 dogs in 150 villages in Chad were
364 found to be infected with the human form of *D. medinensis* confirmed by genome
365 sequencing (Eberhard *et al.*, 2014). It is not known how this might threaten the
366 Guinea worm eradication programme but the authorities in Chad are taking no
367 chances. Sources of infection in dogs include fish that had ingested infected copepods
368 so villagers have been encouraged to bury or to otherwise destroy the remains of fish
369 and fish entrails. Villagers have also been encouraged to report infected dogs with a
370 reward of US\$20 to those that do so, tethering of infected dogs and treatment of
371 drinking water used by dogs with Abate. This illustrates the extreme measures that
372 authorities are taking to eradicate Guinea worm disease. In Uzbekistan in the 1920s ,
373 control measures included shooting and dissection of dogs but this may not be
374 acceptable or feasible under all circumstances. With continued efforts and goodwill it

375 is very likely that Guinea worm disease will be eradicated within the next year or two
376 and will join smallpox as the second human disease to be wiped from the face of the
377 earth. Robert Leiper died in 1969, well before anyone had seriously considered the
378 possibility of the global eradication of Guinea worm disease. When they did, the idea
379 was largely based on his pioneering work carried out over a century before.

380

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383 for-profit sectors.

384

385 DECLARATION OF INTERESTS.

386 No interests declared.

387

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474 FOOTNOTE.

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

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484 Figure 1. Annual number of cases of Guinea worm disease 1989-2015.

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