The Multifactorial Epidemiology of Blackwater Fever

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Abstract. Blackwater fever is a massive hemolytic event usually occurring in the context of repeated falciparum malaria infections and intermittent quinine use. Its etiology is poorly understood, and it is rarely seen today. Historical epidemiological observations from the 20th century demonstrated variable patterns in prisoners in Andaman Islands, refugees in Macedonia, canal workers in Panama, expatriates in Rhodesia, and Second World War soldiers. Rates of blackwater fever per 1,000 malaria cases varied over two orders of magnitude. Islands, such as the Andaman Islands and New Guinea, had lower blackwater fever rates than continental areas. During the Second World War, blackwater fever rates in British soldiers in West Africa and Australian soldiers in New Guinea differed by a factor of 40 despite similar treatment regimens and falciparum malaria transmission risks. Blackwater fever is a complex interaction between host erythrocyte, falciparum malaria, and antimalarial drugs which remains poorly understood.

It has been said with truth that the putting forward of theories about the causation of blackwater fever is a function inversely proportional to the knowledge of the established facts, and the ordinary doctor may well become lost in a fog of surmise. BMJ 1951¹

Blackwater fever has generally been appreciated as consisting of massive intravascular hemolysis that usually occurs in the context of *Plasmodium falciparum* infections suppressed by chronic use of quinine. Based on Vietnamese studies, blackwater fever occurs more often in persons with genetic polymorphisms causing deficiency of glucose-6-phosphate dehydrogenase (G6PD).² In the early 20th century, blackwater fever was a leading cause of death in British soldiers and administrators in Africa and the subject of intense research and speculation.³ When synthetic antimalarial drugs such as quinacrine became available and chronic suppression with quinine was discontinued, blackwater fever largely disappeared.⁴ When chloroquine resistance led to a revival of quinine for malaria treatment, occasional cases of blackwater fever were observed in U.S. soldiers, African children, and expatriates.^{5–7}

Blackwater fever was never mechanistically understood and remains largely a mystery because of the rarity of modern cases.⁸ Stephens' exhaustive review of blackwater fever epidemiology leaves the reader confused, as nearly every association imaginable is described in some populations.⁹ The overwhelming impression is that the rate of blackwater fever was extraordinarily variable, being very high in tropical Africa and almost nonexistent in parts of Asia, such as the Philippines. Historical epidemiological series with sufficient documentation to calculate blackwater fever cases per thousand malaria cases were collected and analyzed with the aim of measuring the variability of blackwater fever in different populations.

Blackwater fever and malaria data were abstracted from a variety of historical records. Indian prisoners confined on the Andaman Islands had 70 years of detailed malaria epidemiology with blackwater fever which was only observed from 1908 to 1928.¹⁰ Although blackwater fever was common in

British soldiers during the Salonika campaign of the First World War, ethnic Greek refugees in Macedonia after the war produced better statistics.^{11,12} Because control of tropical diseases was crucial to the building of the Panama Canal, detailed records of malaria and blackwater fever were available from military and company records.^{13,14} A longitudinal study of blackwater fever in a relatively small population of white expatriate farmers in Rhodesia (now Zimbabwe) was conducted from 1913.¹⁵ After the Second World War, Findlay published detailed accounts of blackwater fever in British soldiers in West Africa as did Hamilton Fairley on Australian soldiers in New Guinea. Australian records were supplemented by unpublished data from the Basser Library in Canberra.^{4,16}

Although the precise definition of blackwater fever, the quality of malaria incidence data, and the time period covered varied, it was possible to construct epidemiological graphs for the four groups which are shown in Figure 1. Despite having decades of preceding malaria information, blackwater fever was not reported from the Andaman Islands Penal Colony until 1908. (Figure 1A) It subsequently disappeared by 1928, likely due to the overall decrease in malaria from environmental control of brackish-water breeding *Anopheles*. Blackwater fever in Greek refugees in Macedonia after their expulsion from Turkey circa 1920 was documented from 1923. (Figure 1B) Blackwater fever was most common during the construction period of the Panama Canal when thousands of workers from varied genetic backgrounds were given thousands of pounds of suppressive quinine. (Figure 1C) Once the Panama Canal was completed in 1914, the number of workers fell dramatically as did the number of malaria cases. Blackwater fever was a very infrequent observation in Panama during the 1920–1930s.¹³ Rhodesia was the archetypical example of blackwater fever in expatriates in Africa with high falciparum malaria infection rates coupled with irregular use of quinine for parasite suppression. (Figure 1D) Blackwater fever was a major cause of death in Rhodesian farmers, causing > 2% of all-cause mortality in the expatriate population.¹⁵

Figure 2 shows the number of cases of blackwater fever in British soldiers in West Africa and Australian soldiers in New Guinea during the Second World War.^{4,16} Although in very different geographic areas, both military groups were from the same genetic background, under great falciparum malaria infection pressure and used very similar treatment and prophylaxis drug protocols. Daily quinine was abruptly discontinued in West Africa in March 1943, whereas the transition

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FIGURE 1. The number of blackwater fever (columns) and malaria (lines) cases seen in four different geographic areas in the early 20th century. (A) Andaman Islands; (B) Macedonia; (C) Panama Canal; (D) Rhodesia. Units are years (A and B) and months (C and D). Denominator populations are uncertain but are in the order of magnitude of (A) 10,000s; (B) 1,000s; (C) 10,000s; and (D) 100s.^{10,12,14,15} This figure appears in color at www.ajtmh.org.

FIGURE 2. Blackwater fever cases in British soldiers in West Africa and Australian soldiers in New Guinea during the Second World War. In West Africa, the soldiers switched as a group from prophylactic quinine to quinacrine in March 1943, whereas the same switch in medications in New Guinea which occurred in mid-1943 was not as abrupt because of supply problems.⁴ Note that the Australian cases are quarterly while the West African cases are shown by month. It is possible that a few Australian cases of blackwater fever existed before the reporting system which started in late 1942.¹⁶

to quinacrine occurred more gradually in Australian soldiers during 1943 because of logistical issues.⁴ Malaria control measures became more effective toward the end of the war and both military groups continued to use quinine for the treatment of acute malaria. The US Army reported 25 cases of blackwater fever from the Southwest Pacific during the Second World War. As 15 cases occurred in black soldiers on a single island, it seems likely that G6PD deficiency may have been involved.¹⁷

Table 1 compares the rates of blackwater fever per thousand malaria cases across the populations studied. There are several limitations to these data because of varying diagnostic definitions and reporting procedures. Note that the figures parse into pairs of those areas with low (New Guinea, Andaman Islands), high (Panama, West Africa), and very high (Macedonia, Rhodesia) rates of blackwater fever. The rates vary over two orders of magnitude which indicate that even if the precise rates are inexact, it is likely that the broad range of values across the six populations forms a valid picture of blackwater fever in the 20th century.

The variable epidemiology of blackwater fever makes it likely that it is associated with a variety of host, parasite, and drug factors regardless of the mechanism leading to massive hemolysis. Dissecting out these different factors in historical datasets is difficult, but some points can be drawn from the data presented.

One of the most likely host factors involved in blackwater fever is G6PD deficiency. As shown in studies from the 1990s in Vietnam, G6PD deficiency along with falciparum malaria and quinine were the primary risk factors noted.² The high (Panama) and very high (Macedonia) rates of blackwater fever reported suggest that G6PD deficiency was an important factor in these populations. Late in the construction phase of the Panama Canal, 80–90% of the blackwater fever cases occurred in European (largely Spanish and Portuguese) workers even though they were outnumbered by their Caribbean and USA counterparts. Because of the dynamic number of various worker groups, it is difficult to calculate an actual risk value, but in 1909, the relative risk of developing blackwater fever in European workers was 24 times that in

TABLE 1
Blackwater fever rates and ranges as estimated per 1,000 malaria cases in the different groups described in the text

Geographic area	Blackwater fever cases/1,000 malaria cases	Range low point	Range high point	Reference
New Guinea	0.2	0 (June 1944)	0.8 (September 1943)	16
Andaman Islands	0.5	0 (1927)	6.5 (1922)	10
Panama Canal	6.4	0 (September 1912)	31.3 (April 1911)	14
West Africa	8.3	0 (1945)	11.6 (1942)	4
Macedonia	36.8	4.7 (1923)	85.9 (1936)	12
Rhodesia	74.6	0 (September 1918)	286 (August 1915)	15

workers from the USA and 45 times than that in workers from the Caribbean.¹⁴ There were no groups to compare with the Greek refugees in Macedonia but the high rates of G6PD deficiency in modern Greece suggest G6PD played some role. The “intemperate habits” of Rhodesian expatriates was blamed for the record number of blackwater fever cases.¹⁵ It seems likely that alcoholic binges and sleeping in substandard housing could have exposed many of the Rhodesian expatriates to higher falciparum malaria infection rates in this area of seasonal transmission.

Medical researchers of the early 20th century were convinced that the variable rates of blackwater fever were caused by certain strains of falciparum malaria parasites that specifically caused blackwater fever. They conducted never-to-be-repeated experiments where men were intentionally given falciparum malaria infections to test the strain-specificity of blackwater fever.^{18,19} Although nearly all blood transfers resulted in symptomatic falciparum malaria infection, none produced blackwater fever. Whether this was a valid test of strain-specificity or not, certain hyperendemic areas were known for blackwater fever (West Africa, Rhodesia, and Macedonia), whereas it was almost never reported from the Philippines or Ceylon. One possible factor is the difference between island and continental environments. Relatively few *P. falciparum* strains exist on isolated islands whereas parasites spread more freely on continents. The lack of blackwater fever cases on the Andaman Islands during the 19th century in a population under intense observation by medical officers who were fully aware of the diagnosis suggests that its appearance early in the 20th century was the result of the introduction of new parasites. This may also explain part of the differences between rates of blackwater fever in British and Australian soldiers during the Second World War as the New Guinea island environment has been shown to produce much less malaria mortality despite similar infection rates to Africa.²⁰

Quinine was widely understood as the “trigger” for blackwater fever based on most cases having taken quinine in the recent past before developing hemolysis.²¹ Neither quinine nor falciparum malaria individually usually cause massive hemolytic episodes. The most convincing evidence of the role of antimalarial drugs in the genesis of blackwater fever occurred during the Second World War.⁴ Blackwater fever markedly decreased in British soldiers in West Africa after switching to quinacrine and the less marked changes in Australian soldiers may have been because of their heavier reliance on quinacrine from the beginning of the war. (Figure 2)

Blackwater fever may seem like an antique disease with little modern relevance, but it seems to have returned recently in epidemic form in Ugandan children.²² If one could understand the complex interaction between human erythrocytes, falciparum malaria, and antimalarial drugs, it seems likely that such

insights could aid in better understanding the evolving epidemiology of malaria. Such understanding might at least partially dispel the remaining fog of surmise surrounding blackwater fever and place this marker of severe malaria in its proper context.

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