

# Commentary on “Forms of fever in the West African expeditionary force”

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## Original article

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*During 1914 and 1915 a considerable number of naval ratings and marines were landed in the West African Expeditionary Force in the Cameroons, and many of them contracted fever, which manifested itself during their shore service or after re-embarking. It was very noticeable in the cases we had the opportunity of observing that marked debility and cachexia was produced. This was doubtless due in part to the excessive heat and general unfavourable climatic conditions and also to the difficulties in obtaining sufficient and suitable food.*

*One of the main causes of fever was malaria, and the infection was generally of the tertian malignant type, but in some blood films quartan parasites were also found. There can be no doubt, however, that the Laverania malarie parasite gave rise to the most frequent, important, and intractable infections that occurred amongst our men. We have to thank Staff Surgeon Verry for many films sent for examination from cases invalided to the Cape (Royal Naval Hospital, Simonstown).*

*In a number of cases, which are more difficult to explain, no malarial parasites have been found and the pyrexia is not controlled by quinine. It has also been noticed that some of the pyrexial cases, with or without malarial infection, are peculiar in having a very marked eosinophilia for which no cause could be found. The stools have been examined for ova and parasites, and it is chiefly on this account that we should like to draw special attention to the following case.*

*The patient, a private, Royal Marine Light Infantry (RMLI), was landed for ten months, at first on the banks of the Niang River and later on the Campo River. A history commonly*

*given was that the men lived in thatched huts near the banks, that mosquitoes and flies were very abundant (especially on the Campo River), that the latter were rather like house flies or larger, and that they bit both by day and night, followed people about, and when killed often contained blood. Although none of these have been brought home for examination, they were undoubtedly tsetse flies. The patient had an attack of fever soon after landing, but suffered most severely while near the Campo River. Before leaving the coast (December 17, 1915), trypanosomes were found in his blood and he received one injection of salvarsan. On his way home he was treated with quinine and after a short period at Plymouth Hospital he was sent to the Seamen’s Hospital, Greenwich, for treatment.*

*On admission in March, 1916, he was debilitated, anaemic, and depressed mentally, had lost much weight and suffered from irregular attacks of pyrexia. There was no adenitis, no hyperaesthesia, no tremors and no rash. The reflexes were normal. At every attack of fever he had cough, but there was no expectoration and no abnormal physical signs. His blood pressure was low, the pulse was wanting in tone and showed a marked dicrotic wave. A slight cardiac bruit was present but the spleen and liver were neither tender nor palpable. The urine was free from albumin and the faeces contained no ova or cysts.*

*The most striking feature of his blood picture was the high eosinophilia, which has continued constantly with or without evidence of trypanosomes, which are found from time to time in the peripheral blood.*

*He has been under continuous treatment here for six months and now appears to be in good health and spirits, but he has not quite regained his usual weight and the blood picture is still abnormal. At first, when the attacks of pyrexia were very frequent he felt ill, the headaches were severe, with general muscular pains, cough, and nausea*

followed by profuse sweats. The last attacks have been very much less severe.

The course while under treatment may be divided into three periods:

First, March 4 to April 10. Very irregular, frequently repeated attacks of fairly high fever with heavy outbreaks of trypanosome infections, culminating on April 10 with one trypanosome to every two white cells (at least 3,000 to every mm<sup>3</sup> of blood). These attacks caused much depression and the man was not improving. The treatment had been atoxyl 5g intramuscularly every third day, and also four subcutaneous injections of oxide of antimony (Martindale).

The second period extends from April 10 to June 6. During the great outbreak of trypanosomes on April 10 we gave him the antimony intravenously, followed by increasing doses subcutaneously and atoxyl on alternate weeks. The result was still very unsatisfactory. The gradual rise in the successive trypanosome outbreaks was very marked up to June 4, when they reached to 58 per 1,000 white cells. The organism appeared to be entirely atoxyl-resistant, though the patient was gradually improving in condition.

The third period is from June 5 to the present time, when intravenous treatment only has been used, at first 0.35 galyl every week and later alternating with intravenous injections of antimony oxide (Martindale's) in large doses (0.15g). The galyl had a very marked effect on the temperature and the trypanosome count, but there was a paroxysm on the twenty-first day and again about three weeks later. On that occasion the drug was given in a concentrated form, when the trypanosome count was rising and when sterilization of the blood should have been complete, but over the following two days the trypanosome count rapidly rose. On the third day therefore, when there were a large number of trypanosomes in the peripheral blood, a fresh, well-diluted dose was given with entirely satisfactory results.

The alternate use of intravenous injections of the galyl and antimony has caused a steady and marked improvement in temperature, trypanosome count, and the patient's condition, and a successful result is not impossible if the treatment can be continued. The patient is well under the influence of the arsenic at the present time, as shown by the fact that 2g of hair gave a good arsenic mirror with Marsh's test.

The absence of benefit from the concentrated dose of galyl is most interesting and points to the rapid elimination of the drug by the kidney before it had given rise to any sterilizing effects in remote parts. This is more likely to occur when given for syphilis, as the treponema is more inaccessible than the trypanosome. The early failure of the initial dose given in Africa and the absence of the usual efficaciousness

of atoxyl are noteworthy features.

Cyclical outbreaks of the trypanosomes are very marked. These appeared to occur about every fifth day, the alternate ones being frequently less intense. Each is attended by a definite rise in temperature and signs of some toxic absorption (trypanolysin). Even when the temperature is abnormal, these periodic rises can be traced, though less marked during the later periods of the treatment. The blood counts are very interesting. The polymorphonuclear cells showed frequent and large excursions, generally rising with the trypanosome curve and inversely to the eosinophil count (Figure 1). The eosinophils were very high during the first three months. The fall at, or about, the time of the trypanosome rise is almost always very marked. The slow falling curves in June and July with the rapid rise after the outbreak of trypanosomes is very suggestive of some toxin being released by the trypanosome, which stimulates the production of these cells. It is noticeable that the lowest eosinophil count was at the time of the highest trypanosome count. In 1911, Dr. Newham, in a paper on the "Leucocyte Variation in Trypanosomiasis," noticed much the same condition in a case at the Albert Dock Hospital, the eosinophils increasing to 26%, and Kerr reported a case with 6-12%, in which no intestinal parasites were present.

No auto-agglutination of the red cells has been observed in this case, but when the patient's serum was mixed in equal parts and one in ten with the blood of rats and guinea pigs infected with a Rhodesian strain of trypanosome, there was a very marked agglutination of the red cells, but no apparent effect on the trypanosomes.

Morphology of the Trypanosomes. These are dimorphic in character and not to be distinguished from *T. gambiense*, but the mild symptoms, difficulty in obtaining animal infections, and number of small forms, are rather suggestive of the possible new species of *T. nigeriense* described by Macfie. The length averages 16µm with extremes of 12-24µm. Short forms are rare and the slender forms common (Figure 2). The posterior end is pointed, and the micronucleus is about 1µm from the end. The nucleus is oval and generally about 8-10µm from this. Posterior nuclear forms were never seen. Few chromatic granules were noticed in the protoplasm and the undulating membrane is well marked and broad in the more robust forms. In studying the parasites from day to day, they were found to vary in accordance with the period of incidence. At first, in the early part of this rise, they were often very slender. On the second day near the apex of the increase they were larger and more robust, and dividing forms were present showing, either double micronuclei and nuclei, or almost complete longitudinal fission (Figure 2). On the third day, with the falling curve, the slender form again predominated, indicating a definite multiplication in the peripheral blood.

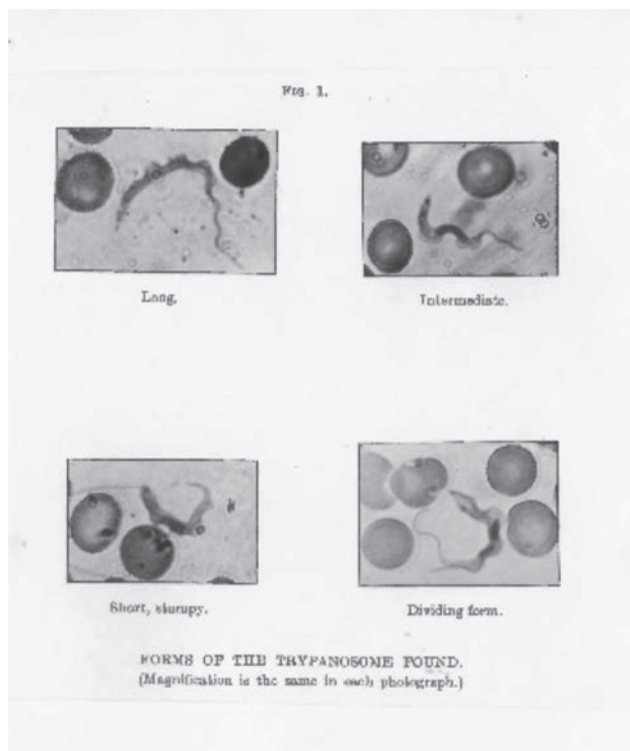


Figure 1. Forms and morphological characteristics of the trypanosomes.

Two other cases are now under treatment, both from the Campo River, and giving a similar history. They were admitted for malaria with malignant and benign parasites being seen in the blood, but both have the same extraordinary eosinophilia without any trypanosomes or filaria in the peripheral blood and no evidence of intestinal infection. Macfie states that the parasites could not be found in the peripheral blood from cases of Nigerian infection. One patient, however, shows irregular oedema and the other has a palpable cervical gland, but neither now shows any pyrexia, tremors, hyperaesthesia or enlargement of spleen. It is probable that both are latent cases of trypanosomiasis and are being treated accordingly. Their further course will be anxiously watched.

In conclusion, we would recommend that all cases with a marked eosinophilia for which no cause can be determined coming from the Cameroon region be looked upon as possible cases of trypanosomiasis and a very guarded prognosis be given.

### Commentary

The paper by Bassett-Smith and Mangham briefly describes the causes of febrile illness among Royal Navy (RN) personnel and Royal Marines (RM) deployed as part of the West African Expeditionary Force to Cameroon between 1914 and 1915 (1). The paper subsequently reports a case of trypanosomiasis in a RM private. It illustrates several

aspects related to infectious disease in the tropics, which are as relevant today to military populations as they were 100 years ago.

Throughout the history of conflict, infectious diseases have been an important cause of morbidity and mortality among military personnel and have influenced the course of military operations and the outcome of campaigns (2, 3). Whilst diarrhoea, respiratory and cutaneous infections predominate and typically result in mild, self-limiting disease, tropical febrile illnesses acquired on deployments can occur and result in significant disease (4). These issues are not merely of historic or theoretical concern. A very recent retrospective analysis of aeromedical evacuations related to infectious disease among French troops deployed mainly to Africa showed that malaria, pyrexia of unknown origin, cerebro-meningeal infections (of likely viral aetiology), invasive amoebiasis and primary HIV infection accounted for 58% of diagnoses and resulted in admission to intensive care in 10% of cases (5).

Bassett-Smith alludes to the significant burden of malaria as a cause of fever among personnel in Cameroon, which is both important and interesting. Firstly, it highlights the severe disease that may result from this protozoal infection, which remains a perennial problem for the military. As recently as 2000, a malaria outbreak occurred among British Forces deployed to Sierra Leone and resulted in almost 100 cases (6). While bite-prevention measures and malaria prophylaxis are important in reducing the risk of acquisition, even with strict adherence a diagnosis of malaria must be considered in anyone who has returned from an endemic area in the previous year, and for individuals returning from the tropics with a fever. The diagnosis should be considered to be malaria until proven otherwise. Clinical features and physical signs are not reliable in diagnosing malaria and therefore blood films and rapid antigen-based diagnostic testing should be used at the earliest opportunity and repeated in accordance with current guidelines (7). Secondly, the use of certain historic terms is a valuable reminder of the evolution of medical language. The terms 'tertian' and 'quartan' malaria refer to fevers associated with the cyclic lysis of red blood cells that occurs as the parasites complete their development in erythrocytes every two or three days respectively. However, this cyclic pattern is not pathognomonic for particular species of *Plasmodium* (the genus of protozoa responsible for human malaria) and is actually a rather rare phenomenon; therefore such terms are no longer used in clinical practice. Likewise, 'benign' (*P. vivax* and *P. ovale*) and 'malignant' (*P. falciparum*) malaria were used to describe the clinical course of infection which, again, is rather misleading because while the most significant morbidity and mortality is caused by infection with *P. falciparum*, there is certainly nothing benign about infections resulting from other species; in particular *P.*

*vivax* may cause severe and complicated disease.

The case report itself is very interesting and illustrates the many difficulties associated with Human African Trypanosomiasis (HAT) including its chronic nature and the requirement to use highly toxic agents for treatment (e.g. antimony oxide and the arsenicals atoxyl and galyol). Today, while there have been advances in diagnostics and improvements in the treatment of HAT, with several new drugs in various stages of development, problems with toxicity and efficacy persist (8). HAT, also known as sleeping sickness, is a parasitic disease caused by protozoa belonging to the genus *Trypanosoma* and transmitted to humans following a bite from an infected tsetse fly (acquired from human beings or from animals harbouring the human pathogenic parasites). Two forms of HAT exist. *T. brucei gambiense* occurs predominantly in west and central Africa, accounting for 97% of reported cases of sleeping sickness and causes a chronic infection often only manifesting several months or years after acquisition, when patients present with advanced neurological disease (8). In contrast, *T. brucei rhodesiense* is restricted to eastern and southern Africa and results in less than 3% of reported cases, causing in an acute illness, which rapidly progresses over the weeks and months after infection. HAT is invariably fatal if untreated or treated inadequately (8). A case of HAT was reported in a British soldier as recently as 2006 (9).

In addition to the tropical pathogens already mentioned, military personnel deployed to Africa are also at risk of acquiring other illnesses such as rickettsial infections (e.g. African tick typhus), enteric fever, schistosomiasis, visceral leishmaniasis, yellow fever, dengue and viral haemorrhagic fever (including Lassa fever, Ebola and Crimean-Congo haemorrhagic fever). Lassa fever has previously been reported among British troops and indeed, at the time of writing, there is an outbreak of Ebola virus in Sierra Leone and Guinea, which has resulted in significant mortality (10).

Finally, it would be remiss not to mention, even briefly, the work of Sir Percy W. Bassett-Smith, one the authors of the original article. Bassett-Smith qualified in medicine

from the Middlesex Hospital in 1882 and joined the Royal Naval Medical Service in 1883. For the next two years he served in the Sudan campaign as surgeon on board HMS RAMBLER. During this and subsequent deployments, Bassett-Smith made extensive biological, geological and surveying observations for which he was awarded the Gilbert Blane medal in 1899. He became a lecturer in tropical medicine and demonstrator of bacteriology at Haslar Hospital in 1900; over the next decade he combined clinical instruction in tropical diseases with pathology teaching and research. He was appointed professor of clinical pathology at the Royal Naval Hospital, Greenwich in 1912, a position he held until his retirement from the Navy in 1920, at the rank of Surgeon Rear Admiral. After leaving the Navy, Bassett-Smith practiced as a consultant physician in London. He was elected President of the Royal Society of Tropical Medicine and Hygiene in 1923 and throughout his career authored numerous medical and academic papers on many subjects in tropical medicine and infectious diseases. His significant contributions to both the Navy and his medical specialty were recognised when he was created CB in 1911 at the coronation of King George V, and KCB in 1921 following his retirement from the Service (11).

In conclusion, as the British military return to contingency operations, of which expeditionary operations are a key element, the paper by Bassett-Smith and Mangham in this WW1 special supplement is a timely reminder that British Armed Forces have deployed, and will continue to do so, to regions of the world where tropical infections are endemic and of significant risk to personnel. Therefore, while the size and technological shape of the Royal Navy has changed considerably over the past 100 years (we can only wistfully imagine serving at the Royal Naval Hospital in Simonstown today), many of the threats posed by infectious diseases on tropical deployments have not. Pre-deployment risk assessment, vaccination strategies, the use of appropriate preventative measures and chemoprophylaxis whilst deployed, and early diagnosis and treatment of individuals presenting with illness, are all crucial to ensure the health of our personnel and to maintain operational effectiveness.

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