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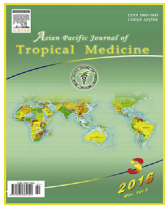

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Historic accounts of *Mansonella* parasitaemias in the South Pacific and their relevance to lymphatic filariasis elimination efforts today

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ABSTRACT

There are two species of filarial parasites with sheathless microfilariae known to commonly cause parasitaemias in humans: *Mansonella perstans* and *Mansonella ozzardi*. In most contemporary accounts of the distribution of these parasites, neither is usually considered to occur anywhere in the Eastern Hemisphere. However, Sir Patrick Manson, who first described both parasite species, recorded the existence of sheathless sharp-tailed *Mansonella ozzardi*-like parasites occurring in the blood of natives from New Guinea in each and every version of his manual for tropical disease that he wrote before his death in 1922. Manson's reports were based on his own identifications and were made from at least two independent blood sample collections that were taken from the island. Pacific region *Mansonella perstans* parasitaemias were also later (in 1923) reported to occur in New Guinea and once before this (in 1905) in Fiji. Although *Mansonella*-parasitaemias are generally regarded as benign, they are thought to be of public health importance because they can affect the epidemiological monitoring of other filarial diseases. In this article, we reviewed the historic literature concerning Pacific-origin *Mansonella*-parasitaemias in an attempt to explain how, despite repeated reports of Pacific-region *Mansonella*-parasitaemias, by as early as the 1970s, the WHO had arrived at the present-day view that *Wuchereria bancrofti* is the only cause of filarial parasitaemias in Papua New Guinea. We have also evaluated the evidence supporting the contemporary existence of Pacific-area parasitaemia-causing *Mansonella* parasites and assessed the relevance such parasites could have for present-day lymphatic filariasis elimination efforts in the region.

1. Present perspectives on the global distribution of human *Mansonella* parasitism

Bain *et al* recently reviewed the genus of *Mansonella* placing three species known to parasitize humans in the genus: *Mansonella perstans* (*M. perstans*), *Mansonella ozzardi* (*M. ozzardi*) and *Mansonella streptocerca* (*M. streptocerca*) [1]. Other species of *Mansonella* parasites, which principally infect animals, are also known to cause zoonosis in humans, however, such events are rare and have not yet been recorded to cause human parasitaemias, which would require an infecting female parasite to develop to maturity, mate, and then begin releasing microfilariae into an infected individual's blood [2,3]. *M. streptocerca* is also not usually regarded as causing human parasitaemias as *M. streptocerca* microfilariae, like those of *Onchocerca volvulus*, are usually found only in the skin and not in the blood [2]. Both *M. perstans* and *M. ozzardi*, however, are thought to commonly cause blood parasitaemias. *M. perstans*, for example, has been estimated to be infecting around 114 million Africans and is also thought to occur in South America [4–6]. *M. ozzardi* is thought to be widespread throughout Latin America and the Caribbean but is not usually recorded outside the New World [4–11]. Most contemporary accounts of the distribution of *Mansonella* parasites exclude the Pacific and, in fact, all of the Eastern Hemisphere [4–11].

2. Historic accounts of *Mansonella* parasitaemias from the Pacific region

In 1897, Sir Patrick Manson reported that he had found ‘a small sharp-tailed, sheathless filaria closely resembling, if not

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identical with, filaria Demarquayi' in the blood from a native living on the 'north-east coast' of New Guinea (NG) [12]. Shortly after this first report, which most likely came from material originating in what is present day Northern or Oro Provence of present day Papua New Guinea (PNG), Manson went on to describe further *Mansonella* parasites from blood slides sent to him by Seligmann and taken from a native residing in what is now the Kairuku-Hiri district of PNG. Manson reportedly described these parasites as 'identical in appearance to *Filaria demarquaii* (*F. demarquaii*)' [12,13]. Today, most contemporary identifications of filarial worms are done using microfilariae and 'Filaria Demarquayi' and '*F. demarquaii*' are both regarded as synonyms of *M. ozzardi* [1,14,15]. Using the modern WHO's 'Bench Aids for the Diagnosis of Filarial Infections', thus, the New Guinean parasitaemias that Manson reported as being caused by 'minute non-sheathed, sharp-tailed' microfilariae can be confidently classified as *M. ozzardi* parasites—exactly as Manson tentatively classified them more than 100 years ago [13–16]. Lynch reported finding *M. perstans* (under the synonym *Filaria perstans*) occurring in the blood of a native from the Fijian Provence of 'Lau' and Cilento reported *M. perstans* from the Dutch side of NG [17–19]. After Cilento's report, Manson's Tropical Disease began recording the parasite as probably occurring in NG and the parasite can be seen recorded on the Dutch side of the island up to and including the 18th edition of the book [20]. Sharp also described *M. perstans* as occurring in NG writing that its presence in the island was 'recorded by Manson himself' [21], which may have been a reference to Manson-Bahr's reporting of the parasite in Manson's Tropical Diseases. Given Manson's unquestionable interest in *M. perstans* and the fact that Lynch's report was published in the highly influential British journal the Lancet, it would be surprising if Manson was unaware of Lynch's report. Manson's son-in-law (Manson-Bahr) who edited his 'manual of diseases of warm climates' was certainly aware of Lynch's report as he cited the paper in which the report was made [22]. The omission of Fijian *M. perstans* from Manson's tropical disease manual and elsewhere cannot therefore be viewed as a simple oversight on the part of the filarial worm establishment and thus the possibility that there were (presently unclear) well-grounded genuine scientific reasons to doubt the legitimacy of Lynch's report can not be reasonably ignored [5,16,23–31].

3. The disappearance of NG *Mansonella* parasitaemias from the scientific literature

In contrast to Lynch's reports of Fijian *M. perstans*, Manson's reports of *M. ozzardi* or a *M. ozzardi*-like parasite in NG were widely accepted and extensively cited during his life-time [12,16,21–25,32–38]. The reports appeared in the first edition of Manson's 'manual of diseases in warm climates' and in all subsequent editions he published up to and including the last he wrote before his death [16,22–25]. The disappearance from the mainstream scientific literature of these NG *Mansonella* parasites and the *M. perstans* that Cilento reported was a gradual process that seems to have begun with the publication of the 7th edition of Manson's Tropical Disease in which Manson's son-in-law (Manson-Bahr) effectively declared PNG free of *M. ozzardi* with the remark: 'As far as it is known, *Filaria ozzardi* (*F. ozzardi*) is confined to the West Indies and South America' [26]. This revised distribution is not accompanied by a retraction of Manson's original reports and occurred at the same time that the book began formally synonymizing *Filaria demarquayi* (*F. demarquayi*) and *F. demaraquaii* with *F. ozzardi* (see Table 1)—all of which are today regarded as synonyms of *M. ozzardi* [26]. Manson-Bahr's remarks can be seen as a natural progression of the revisions that Manson himself carried-out to the previous editions of this book. In the first edition of this manual it appears Manson is actually naming the PNG microfilariae *M. ozzardi* (under the synonym *F. demarquaii*) (see Table 1). As early as the second edition (published in 1900), however, signs of Manson's reticence to name the PNG microfilariae as *M. ozzardi* are evident as Manson introduces the caveat that (before PNG *M. ozzardi* parasites can be classified as such) adult forms need to be: 'discovered and compared' (to other filarial parasites) [16]. Manson's growing reticence is evident from the qualification he added to this caveat in the 5th and 6th editions of his book from when he begins to write that adults need to be 'discovered and carefully compared' [24,25]. By the 11th edition of the book Manson-Bahr is referring to these very same PNG parasites as belonging to a similar or related species and remarking that *M. ozzardi* is difficult to distinguish from the *M. perstans*, which by this time he is acknowledging probably also occur in the island. Manson's grandson's filarial parasite distribution map also acknowledged the occurrence of *M. perstans* on the Dutch side of NG, however, he made no mention of any parasitism-causing *Mansonella* parasite occurring anywhere on the island within the text of the book he edited [20]. In-line with the rest of mainstream scientific literature and Hawking and Denham who asserted in their 1970s WHO report that '*Wuchereria bancrofti* (*W. bancrofti*) periodic type is the only human filarial worm present' in the PNG [39], Manson's Tropical Disease had wiped all *Mansonella* parasites clean from the Eastern Hemisphere of their maps by the 20th edition of their book [28].

4. A modern perspective on Manson's descriptions of parasitaemia-causing filariae from PNG

There are presently no parasitaemia-causing microfilariae matching Manson's description thought to occur in PNG, the Pacific region or in fact anywhere in the Eastern Hemisphere [1,5,6]. Just like today, at the time of Manson's first report of *M. ozzardi*-like parasites, *W. bancrofti* was the only parasitaemia-causing filaria thought to occur in PNG and then, as now, these two parasites were regarded as easy to discriminate on the basis of microfilariae alone and thus the possibility that Manson repeatedly misidentified *W. bancrofti* as *M. ozzardi*-like parasites seems even less likely than the possibility that *M. ozzardi*-like parasites are routinely being misidentified as *W. bancrofti* today. Owing to the difficulty in obtaining adult specimens, since Manson's death very few (if any) adult *M. ozzardi* have been recovered from humans and contemporary accounts of their distribution are based almost entirely on the identification of microfilariae alone [1,5,6]. Since the advent of molecular systematics, however, it has been possible to look for filarial parasite diversity below the level visible from microfilariae morphology (without obtaining adult specimens) by comparing fast evolving DNA sequences like the CO1 and certain rDNA sequences of the parasites [1,10,40–46]. While this approach to the parasite identification has not been as widely used as it could or should have been, it has been used and to date there is evidence for just two

Table 1
Manson's reporting on *M. ozzardi*-like parasites from Papua New Guinea.

Edition	Year	Section title and quote
1st	1898	FILARIA DEMARQUAII In examining blood, sent me by Dr. Newsam, from natives of St. Vincent, West Indies, I found this blood worm in several individuals …. I have recently met with, apparently, the same parasite in the blood of natives of St. Lucia, W.I. and of New Guinea. It is quite possible that the sharp-tailed filaria (*f. Ozzardi*) of British Guiana is the same species.
2nd	1900	FILARIA DEMARQUAII. I have also found a minute, non-sheathed, sharp-tailed embryo filaria in the blood of natives of New Guinea likewise closely resembling *F. demarquaii*. Whether these various minute sharp-tailed, non-sheathed embryos belong to one or to several species is impossible to decide until the parental forms have been discovered and compared.
3rd	1903	FILARIA DEMARQUAII, Manson, 1895. I have also found a minute, non-sheathed, sharp-tailed embryo filaria in the blood of natives of New Guinea closely resembling *F. demarquaii*. Whether these various minute sharp-tailed, non-sheathed embryos belong to one or to several species is impossible to decide until the parental forms have been discovered and compared.
4th	1907	FILARIA DEMARQUAII, Manson, 1895. I have also found a minute, non-sheathed, sharp-tailed microfilaria in the blood of natives of New Guinea closely resembling *m.f. demarquaii*. Whether these various minute sharp-tailed, non-sheathed embryos belong to one or to several species is impossible to decide until the adult forms have been discovered and compared.
5th	1914	Under the section: *Microfilaria demarquaii*, Manson, 1895. I have also found a minute, non-sheathed, sharp-tailed microfilaria, closely resembling *m.f. demarquaii*, in the blood of natives of New Guinea. Whether these various minute sharp-tailed, non-sheathed embryos belong to one or to several species is impossible to decide until the adult forms have been discovered and carefully compared.
6th	1917	Under the section: *MICROFILARIA DEMARQUAII*, Manson, 1895. I have also found a minute, non-sheathed, sharp-tailed microfilaria, closely resembling *m.f. demarquaii*, in the blood of natives of New Guinea. Whether these various minute sharp-tailed, non-sheathed embryos belong to one or to several species is impossible to decide until the adult forms have been discovered and carefully compared.
7th	1921	Under the heading *Filaria ozzardi*, Manson, 1897. Synonyms: *F. demarquayi*, *F. juncea*, Railliet. 'It was first thought that smaller embryos from the natives of St. Vincent represented a different species, distinguished by Manson as *F. demarquayi*, but it is now generally recognised that only one species exists. As far as it is known, *F. ozzardi* is confined to the West Indies and South America.'

The underlining used here on the word 'careful' introduced here is for stress and do not exist in the original quote.

parasitaemia-causing sheathless filarial parasites—named *M. ozzardi* and *M. perstans*—which are the same two sheathless parasitaemia-causing filaria which Manson was aware of at the time of his death [1,4–6,10,40–46]. Today, both *M. perstans* and *M. ozzardi* parasitaemias are most often diagnosed using almost the same criteria that Manson used, namely using the morphology of the microfilariae and their absence of periodicity in the blood [4–6,15]. Morphologically, *Mansonella* genus microfilariae that cause parasitaemias can be discriminated from the other known parasitaemia-causing filarial parasite species and from each other by their size, their absence of a sheath and their tail shape [1,4–6,15,45].

5. The absence of *M. ozzardi*-like parasites from modern PNG filarial maps

As human *Mansonella* parasites are not known to be vectored by mosquitoes, *W. bancrofti* transmission monitoring of wild-caught mosquito vectors is unlikely to detect or be affected by the existence of occult *M. ozzardi*-like filarial populations [2,4–6]. Similarly as *Mansonella* parasitaemias are mostly or entirely asymptomatic, and certainly have no clearly defined symptoms to diagnose them, clinicians are in no position to diagnose infections without blood tests [2,4–6]. Blood examinations are thus the only method that parasites might be expected to be detected [2,4–6]. Over the last 15 years, filarial parasite mapping in PNG has been done almost exclusively using immunological assays that test blood samples for circulating *W. bancrofti* antigens and most recently predominately with ICT cards, which would not reveal the presence of an unexpected *M. ozzardi*-like parasite [46–49].

Although, intuitively, light-microscopy-based malaria blood surveys might be thought to detect filarial parasites if any were present and such surveys have detected *M. ozzardi* in the past, this type of survey cannot reasonably be expected to have found *Mansonella* parasites in PNG [50]. This is because malaria parasites are found using high-magnification objectives rather than the low magnification objectives that are used to find filarial parasitaemias [51–53]. Sir Patrick Manson actually advocated the need for schools of tropical medicine (before the London School

of Hygiene and Tropical Medicine and the Liverpool School of Tropical Medicine existed) using this counter-intuitive fact as an example of the sort of thing that needs to be taught. In his address on 'the necessity for special education in tropical medicine' Manson is reported as saying: 'filariae should be sought with an inch objective otherwise they will be missed' and that although 'in searching the blood for filaria—a large field is indispensable' this 'self-evident fact' is one that 'He (the student of tropical medicine) seldom arrives at spontaneously' [51–53]. Microscope based filarial surveys—which the WHO presently recommends should use a 10× objective to find *W. bancrofti*—should, however, quite reasonably, have been expected to also have found Manson's *M. ozzardi*-like parasites if any had occurred in the tested blood samples [51–53]. Trained microscopists should have no problem discriminating between the much larger periodic sheathed *W. bancrofti* and the unsheathed *M. ozzardi*-like parasites that Manson reported even if they were not expecting to see them [15,53].

In a 2013 review about lymphatic filariasis in PNG, 155 microscopy-based filarial surveys from PNG were reported to have been conducted between 1980 and 2011, without any new reports of *Mansonella* or *Mansonella*-like parasites causing parasitaemias in the area [47]. Similarly, in two other detailed reviews of microfilarial surveying covering the period from Manson's first report of *M. ozzardi* in 1897 up to Hawking and Denham's 1971 WHO report declaring *W. bancrofti* as the only filarial parasite to occur in PNG, only Seligmann (1901) and Cilento (1923) have provided first-hand accounts of *Mansonella* parasites causing parasitaemias [12,13,18,39,54]. The primary source data supporting the contemporary existence of *Mansonella*-caused parasitaemias occurring in NG cannot be, therefore, regarded as strong. Likewise, however, when this survey data is assessed by geography, it can be seen that the localities that the parasites were first recorded in have not been rigorously surveyed and thus that the evidence that the parasites have been lost from NG is also not strong [39,47,54]. Between 1980 and 2011, there were no microfilarial surveys in the 'Central' Provence where Seligmann's report first originated and there seems to have been just one survey conducted in the Provence (in 1936) after his report [47,55]. Although it is more difficult to be sure where exactly the *M. ozzardi*-like parasites that Manson recorded as deriving from the 'north-east coast' of NG originated, it is also likely that this locality has also not been rigorously surveyed [12,39,47,54]. At the time of Manson's report what is now known as the Northern or Oro province was the most north-easterly part of what was then British NG and thus this Provence is likely to be where the parasites he described came from [12,39]. Oro Provence, which is more than 20 000 km^2 in size, was surveyed at just one coastal locality (Oro Bay) between 1980 and 2011 and prior to this once at the inland town of Popondetta in 1966 [39,47,54].

Little is known of the epidemiology of *M. ozzardi*, however, from what is known it is clear that *M. ozzardi* can be stably maintained over long periods of time in very localized foci [11,12,36,37,50,56–58]. In at least three of the Caribbean islands where *M. ozzardi* has been recorded (St. Vincent, St Lucia and Nevis), the parasites seem to have been stably maintained with just a single village focus [12,36,37,49,55]. And in almost all of the islands where the parasites' distribution has been studied, it appears that their distribution is localized to just one or two areas [11,12,36,37,50,57,58]. While most of the Caribbean islands have not been well-sampled since the 1940s, the evidence that the parasites can be maintained (even with ongoing anti-filarial mass-drug distribution) has been clearly shown in both Trinidad and Haiti [11,36,37,50,57,58]. In Haiti, where most of the recent Caribbean surveying has occurred it is apparent the parasites have been maintained in the island for over 90 years [11,36,37,56,58]. If the known *M. ozzardi* epidemiology in the Caribbean is taken as a guide for what could be happening in NG, the possibility of occult *M. ozzardi* or *M. ozzardi*-like parasitaemias continuing to occur in localized foci of NG is difficult to rule out.

6. The possible impact of occult *M. ozzardi*-like blood parasitaemias in PNG on *W. bancrofti* epidemiological monitoring and control

Accurate filarial parasite distribution maps are key to the success of the Global Programme to Eliminate Lymphatic Filariasis (GPELF) [47,48,59,60]. Historically, lymphatic filariasis control efforts have made use of light-microscopy based microfilariae surveys, circulating antigen and antibody detection assays to plan control programs in PNG [47]. Since 2000, however, most mapping data have derived from circulating antigen assays and most predominately from diagnoses made with the immunochromatographic card test (ICT), which have been performed without the fear of other filarial parasite species affecting their accuracy [47]. Although the specificity of ICT cards has been tested against *M. ozzardi* parasites from Bolivia and ICT-based mapping of *W. bancrofti* has been carried out in co-endemic counties like Haiti, there are no guarantees that *W. bancrofti* elimination efforts would be unaffected by the existence of occult *M. ozzardi* or *M. ozzardi*-like parasitaemias in PNG or indeed the existence of such parasites in Haiti or beyond [61–63]. Preliminary testing of the ICT cards suggested that they did not cross-react with *Loa loa* and/or *M. perstans*, however, recent field studies in Africa have shown that they can [64]. Other immunological assays for *W. bancrofti* detection can and have been used for *W. bancrofti* diagnoses in the Pacific region, but none of the cross-reactivity testing of these tests could be regarded as much more rigorous than the ICT evaluations [65,66]. Cross-reactivity issues are also known to affect the security of antibody detecting immunological assays. For example, the ov16 antibody detection assay, which has been used effectively for onchocerciasis control and proven especially important for recrudescence monitoring throughout Africa and in many parts of Latin America, cannot be used safely in the Amazonia onchocerciasis focus because it can cross-react with *M. ozzardi*-positive sera [67,68]. Similarly, alternative anti-*O. volvulus* antibody detecting assays have also been shown to cross-react with *M. ozzardi*-positive sera from some geographic regions and not others [68].

Present plans for *W. bancrofti* elimination in PNG involve focussing resources and control efforts on the endemic areas. As Kairuku-Hiri district (where *M. ozzardi* were last recorded to occur) is classified as non-endemic for *W. bancrofti*, it is unlikely to be surveyed as part of the GPELF's existing plans [47]. Extrapolating from recent surveying efforts, it would seem, moreover, that even if the site were to be surveyed for the presence of *W. bancrofti*, it is unlikely that it would be surveyed with the sort of PCR or light-microscopy microfilarial surveys that might be expected to uncover the existence of *M. ozzardi* parasitaemias [47]. Because more than 1 000 ICT card

tests have been conducted in this district without *W. bancrofti* being detected, it is clear that *M. ozzardi* parasites have not previously impacted on *W. bancrofti* monitoring in Kairuku-Hiri district and so an argument could be made that the presence or absence of *M. ozzardi* or *M. ozzardi*-like parasites in this area (or indeed all of PNG) is irrelevant for GPELF efforts [47]. Even if this perspective is adopted, however, surveying the Kairuku-Hiri district for *M. ozzardi* or *M. ozzardi*-like parasites could still prove very useful to control efforts. This is because uncovering a *M. ozzardi* or *M. ozzardi*-like focus could provide a useful resource not only to confirm the security of ICT card testing in the area, but also as a useful resource for testing the security of other diagnostic tools such as Bm14-based assays which are likely to prove important for the recrudescence monitoring of the GPELF [47,48,59,60,66].

Because *M. ozzardi* or *M. ozzardi*-like infections have not been recorded from over 155 microscope surveys in the last 30 years, it is unlikely that they are presently common in PNG. It is, thus, likewise unlikely that they have had a major impact on *W. bancrofti* mapping efforts to date whether they still occur in PNG or not. It is, however, important to note that if such parasites do exist and interfere with the accuracy of lymphatic filariasis disease and disease-risk mapping efforts, their importance will only grow as the GPELF gets nearer its target and the number of *W. bancrofti* parasites in the PNG diminishes [47,48,59,60]. In light of this, whether surveys in Kairuku-Hiri district find the parasite or not, it may prove prudent for the GPELF to shift away from its present focus on immunological-based diagnosis of *W. bancrofti* blood infections in the PNG and begin to introduce at least some *W. bancrofti* DNA-detection based diagnostic techniques, with the capacity to detect more than one type of filarial parasite [44,46,49]. Many PCR tests of this nature have been developed and could be used for this purpose [44,46,49]. Tang *et al*. reported one such test that is presently being recommended for the detection of *O. volvulus* DNA [44] and which has recently been shown to be highly sensitive at detecting *M. ozzardi* blood samples [40,49]. This test has also been shown to be capable of amplifying *W. bancrofti* DNA and therefore could be, potentially, adapted to reliably diagnose *W. bancrofti* infections and distinguish them from any *M. ozzardi* or *M. ozzardi*-like blood parasitaemias [40,44,49].

Conflict of interest statement

The authors declare that they have no conflict of interest.

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