Malaria: Origin of the Term “Hypnozoite”

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Abstract. The term “hypnozoite” is derived from the Greek words hypnos (sleep) and zoon (animal). Hypnozoites are dormant forms in the life cycles of certain parasitic protozoa that belong to the Phylum Apicomplexa (Sporozoa) and are best known for their probable association with latency and relapse in human malarial infections caused by Plasmodium ovale and P. vivax. Consequently, the hypnozoite is of great biological and medical significance. This, in turn, makes the origin of the name “hypnozoite” a subject of interest. Some “missing” history that is now placed on record (including a letter written by P. C. C. Garnham, FRS) shows that Miles B. Markus coined the term “hypnozoite”. While a PhD student at Imperial College London, he carried out research that led to the identification of an apparently dormant form of Cystoisospora (synonym: Isospora). In 1976, he speculated: “If sporozoites of Isospora can behave in this fashion, then those of related Sporozoa, like malaria parasites, may have the ability to survive in the tissues in a similar way.” He adopted the term “hypnozoite” for malaria in 1978 when he wrote in a little-known journal that this name would “… describe any dormant sporozoites or dormant, sporozoite-like stages in the life cycles of Plasmodium or other Haemosporina.” At that time, the existence of a hypnozoite form in the life cycle of Plasmodium was still a hypothetical notion. In 1980, however, Wojciech A. Krotoski published (together with several co-workers) details concerning his actual discovery of malarial hypnozoites, an event of considerable importance.

Keywords: hypnozoite, Isospora, malaria, Plasmodium ovale, Plasmodium vivax, relapse

Three decades ago, Wojciech Krotoski and his colleagues reported the discovery of an apparently dormant, uninucleate stage in the life cycle of
the malarial parasite, *Plasmodium* (Krotoski et al., 1980). This preliminary work was followed by a series of impressive confirmatory experiments. The researchers used the term “hypnozoite” for the newly recognized form of the organism, which is thought to be responsible for the important phenomena of latency and relapse in malaria (Krotoski et al., 1982a) and is a “hidden obstacle to malaria elimination” (Wells et al., 2010). The name “hypnozoite” has in the meantime become established internationally in the literature on parasitology and tropical medicine. Despite its widespread and standard use, the origin of the word is at present shrouded in mystery. The purpose of this article is to place relevant details on record.

Work that I carried out in the 1970s at Imperial College London on the protozoan parasite *Cystoisospora* (synonym: *Isospora*) revealed that its extraintestinal stage is sporozoite-like (Mehlhorn and Markus, 1976). Attention was drawn as follows (Markus, 1976a) to the significance of this finding if extrapolated to the incompletely elucidated (at the time) plasmodial life cycle: “If sporozoites of *Isospora* can behave in this fashion, then those of related Sporozoa, like malaria parasites, may have the ability to survive in the tissues in a similar way.” Garnham (1985) might be the only author who has since highlighted this indirect prediction. In 1976, the concept of the occurrence of dormant malarial parasites in the liver and/or elsewhere was still a hypothetical idea.

As was explained in the abovementioned letter (Markus, 1976a) to the Editor of the *Transactions of the Royal Society of Tropical Medicine and Hygiene*, the dormant, sporozoite-like, cystoisosporan form had been named a “dormozoite” (Markus, 1976b). It would seem that the late P. C. C. Garnham, MD, CMG, FRS, received the manuscript of the letter to review. I had not sent or shown the manuscript, which *inter alia* cited one of Garnham’s erudite publications, to anybody. It was mailed directly to the Editor of the *Transactions*, and was not available from any other source. Professor Garnham was considered by many people to be the world’s most distinguished protozoologist. For this reason, but particularly in the light of the subject of the letter, he would certainly (and correctly) have been the most logical choice of referee by the Journal’s editorial office. Garnham (1977) commented as follows on the use of “dormozoite” for the extraintestinal form of *Cystoisospora*; and his paper listed my letter as being in press: “Markus (1976[a]) has introduced the term ‘dormozoite’ for this stage of the parasite; if adopted, this hybrid word should be corrected to ‘hypnozoite’.” Some authors have attributed the name “hypnozoite” to Garnham on the basis of this single sentence (which had no research background or