Manson's triple error

DELAPORTE F.*

Summary:

The author discusses the significance, implications and limitations of Manson's work. How did Patrick Manson resolve some of the major problems raised by the filarial worm life cycle? The Amoy physician showed that circulating embryos could only leave the blood via the percutaneous route, thereby requiring a bloodsucking insect. The discovery of a new autonomous, airborne, active host undoubtedly had a considerable impact on the history of parasitology, but the way in which Manson formulated and solved the problem of the transfer of filarial worms from the body of the mosquito to man resulted in failure. This article shows how the epistemological transformation operated by Manson was indissociably related to a series of errors and how a major breakthrough can be the result of a series of false proposals and, consequently, that the history of truth often involves a history of error.

KEY WORDS : filarial worm, life cycle, history, Manson P.

BACKGROUND

The events are well documented. In 1863, Demarquay found worm-like organisms in the milky fluid extracted by aspiration of a scrotal mass. In 1866, in Bahia, Wücherer examined the urine of a patient with chyluria and observed the presence of small filarial worms. In 1872, Lewis showed that the microscopic haematozoan discovered by Wücherer in a patient's chylous urine was also present in blood, hence the name coined by Cobbold: *Filaria sanguinis hominis*. Soon after, Lewis detected this organism in the blood and chylous urine of about 20 patients. The embryo was enclosed in a delicate sheath, closed at both ends.

At that time, the parasite was only known at the egg or embryo stage. In 1876, in Brisbane, Joseph Bancroft found an adult worm in a lymphatic abscess of the arm and, shortly afterwards, found another four worms in a hydrocele of the spermatic cord. He reported his discovery to Cobbold, who published this finding in 1877, and called the parent of embryonic forms *Filaria bancrofti*. This worm is as narrow as a hair and about ten centimetres long. In the following year, Lewis also observed an adult and sexual filarial worm in a young Bengalese patient that he operated for elephantiasis of the scrotum. Manson confirmed Bancroft's discovery by finding parental forms of the small worm in various regions of the body of his patients and described the various parts of the worm: head, neck, oesophagus, vagina, intestine and tail. So, by 1877, it was known that the embryos found in blood and urine were the offspring of an adult worm that lived in lymphatic vessels.

Lewis thought that chyluria was due to obstruction of lymphatics by these parasites, resulting in dilatation and rupture of lymphatic vessels into the walls of renal cavities. A whole series of diseases was finally elucidated with the discovery of these small nematodes. Manson attributed the disease known as Elephantiasis arabum to *Filaria bancrofti*. He also considered that hydroceles, genital cysts, lymphatic varicosities and hypertrophy of the scrotum to be various syndromes due to the same disease process. These coiled balls of worms induce more or less complete obstruction of lymphatic vessels, resulting in inflammatory reactions causing thickening and induration of surrounding tissues. Deformities then become permanent and these disorders usually result in elephantiasis of the scrotum.

In 1879, the Amoy physician was already in a position to summarize the history of the search for the parasite responsible for filariasis. Lewis discovered the embryonic form of the nematode and Joseph Bancroft discovered the adult form, but Manson was the first to describe the metamorphosis of the small worm and establish its life cycle, at least in part. First of all, he showed that development of embryos cannot take place in the host which already contains adult forms. In entozoa, eggs only start to develop once they have left the host infested by their parents; similarly, filaria embryos must also escape from this host. This conjecture was based on an analogy, but it very rapidly became a solid hypothesis, as Manson calculated that the vessels of a dog infested by *Filaria immitis* could contain as many as two million embryos. Assuming that the animalcules started their growth in the dog, their

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total weight would exceed that of the dog before they had reached one hundredth of the size of the adult worm. This absurdity comprised another: "*The death of the host would imply the death of the parasite before a second generation of filariae could be born, and this of course entails the extermination of the species; for in such an arrangement, reproduction would be equivalent to death of both parent and offspring, an anomaly impossible in nature*" (Manson, 1877, p. 9).

RELEASE OF MICROFILARIAE

To continue their development and ensure propagation of the species, embryos must leave their primary host, hence the idea of a life cycle in which the first phase consists of release of microfilariae. The eggs or embryos of endoparasites are generally expelled with excretions and continue their development either in the environment in which they were deposited, or in the body of an animal that has fed on that environment. Manson briefly thought that filaria embryos might be released in excreted fluids, as several observers had noted the presence of small organisms in chylous urine. However, this mode of release is related to an inconstant disease process. An operation essential for propagation cannot be left to chance. Manson had another reason to consider an external factor: embryos are not equipped to leave the circulation, as they are trapped in their sheath, and are passively transported by the blood. Manson's belief in a wise and provident Nature led him to look for a route of escape that differed from that of most other endoparasites. He proposed the following alternatives: either the microfilariae were all expelled together or one by one. In the first case, the embryos would have to be removed with a piece of human flesh and *Filaria sanguinis hominis* would then be like *Trichina spiralis*. "*But in few countries is human flesh devoured in so wholesale a fashion as would warrant us supposing that Filaria sanguinis hominis was similarly treated*". Manson rejected the analogy based on the assumption of cannibalism and considered that embryos had to be expelled one by one. Furthermore, the fact that embryos resided in the blood provided a clue. The first phase of the parasite's life cycle takes place in blood and the following phase must take place in the body of an animal that removes this blood: a blood-sucking animal. What animals are free at all ages and hungry for blood? "Thus, then, the privilege will be confined to a very limited number of animals – the blood suckers. This includes the fleas, lice, bugs, leeches, mosquitoes, and sandflies" (Manson, 1881, p. 290) The most likely insect would have to be commonly found in regions affected by filariasis, which is confined to tropical and subtropical regions. The insect that removed the parasite from the human host would have to have a similar geographical distribution and would have to share the same habitat. Fleas, lice, bedbugs, leeches and sandflies could be excluded, as they are found everywhere. That left mosquitoes, or, more specifically, species of mosquitoes that lived in hot, humid regions. Two species are frequently found in zones with a high prevalence of filariasis. Manson chose the more common species, noting that the distribution of elephantiasis corresponded to that of the *Culex* mosquito; these insects were abundant in the zone of the disease.

Manson already knew, in 1877, that he had selected the right species. He allowed the insect to bite individuals whose blood was infested with embryos. He found four times as many larvae in the mosquito's body than in the same volume of blood extracted with a needle: "*From this it would appear that the mosquito has the faculty of selecting the embryonic filariae; and in this strange circumstance we have an additional reason for concluding that this insect is the natural nurse of the parasite*" (Manson, 1877, p. 11). In 1879, Manson established that the microfilariae were adapted to the mosquito's nocturnal feeding habits. The periodicity of the life of embryonic filariae constitutes a remarkable example of adaptation. The filariae start to appear in growing numbers in the peripheral circulation at the end of the day. Their number increases until midnight (300 to 600 parasites in a drop of blood). After midnight, the number of parasites starts to decrease and the filariae disappear from the peripheral circulation in the morning and remain absent for the rest of the day. This led to Manson's famous "law of periodicity", which confirmed Manson's choice of the *Culex* mosquito as intermediate host of the filaria. Embryos clearly need to escape from the blood circulation in order to continue their growth and perpetuate the species.

These insects simply needed to be dissected at various times in order to define the life cycle of microfilariae. At the beginning of the first stage, the filaria presented the same appearance and movements as in the human host. The sheath becomes more visible and a buccal ridge can be distinguished. One hour after ingestion, the filaria sheds this sheath: the mouth crease becomes more apparent, and the whip-like movements continue. Very rapidly, the larval stage then begins. Manson observed separation of the tail and the firsts outline of the mouth. The body shrinks, thickens and becomes transparent and the alimentary canal then appears. The final stage is characterized by accelerated growth. The body reaches its maximum thickness at the end of the sixth day and, after one week, the embryo ingested by the mosquito reaches maturity: "*This formidable looking animal is undoubtedly the* Filaria sanguinis hominis *equipped for independent life and ready to quit its nurse, the mosquito*" (Manson, 1877, p. 13).

However, there was still a missing link in the parasite's life cycle: how do the adult forms reach the human lymphatic system? In hindsight, the answer to this problem of vectors appears perfectly logical, but things were not quite so simple for those who applied this logic for the first time in the history of medicine. The solution appeared to be obvious to Manson: as the mosquito dies in water soon after laying its eggs, the filariae no doubt left the dead mosquito to enter the water and start an independent life. Man would subsequently become infested by drinking water contaminated by the filariae. The invention of this mode of contamination is based on a triple error. The first error concerns the gap in the knowledge concerning the mosquito's habits. The second is based on the perception of the mosquito as a nurse. The third is based on an analogy with the life cycle of the Guinea worm.

THE FIRST ERROR

The first error concerns the mosquito's habits. At the time, it was believed that after the female mosquito had ingested its blood meal, it withdrew to a place near water to digest its meal, lay its eggs and die. Manson subsequently deplored the absence of books that would have given him the right information, *i.e.* that female mosquitoes can ingest several blood meals: "*A regrettable mistake, the result of a want of books, was my belief that the mosquito died soon after laying her eggs*". But Manson also knew that he did not really have to justify his blunder: "*For this error, I was not altogether to blame, for those books of natural history to which I had access gave little or no information about these insects, whilst one misled me by a very positive misstatement*" (Manson, 1922, p. 159b). It is easy to imagine what Manson must have read when we see what Blanchard continued to write, in 1890, in his *Traité de Zoologie Médicale*: "*It only takes two minutes for the mosquito to fill with blood. Unable to support sustained flight due to the weight of its distended abdomen, it settles, as if exhausted, close to stagnant water: it digests the blood that it has sucked and matures its eggs. After four to five days, these operations are completed and the mosquito then hovers over the water and lays its eggs on the surface of the water. After laying its eggs, the mosquito then falls into the water and dies*" (Blanchard, 1890, p. 48)

The Amoy physician imagined a fairly complicated system to account for transmission of the filariae. After the primary host, the mosquito, he felt compelled to add drinking water as the intermediate vector, therefore constituting an alliance between a completely new route, an active mosquito, and a classical route, drinking water. The female mosquito consumes a single blood meal, digests it and then dies in the water in which she laid her eggs. To explain this lack of information, we need to apply to the mosquito Canguilhem's description of wild animals: "*Not only are they an outlaw of domestication for man, but they are also a potential enemy. Vital competition contradicts the contemplative attitude, the theoretical relationship between man and animal*" (Canguilhem, 1968, p. 215). This view is supported by Milne-Edwards's description of the mosquito's habits: "*In the evening, they hover in large swarms and emit a sharp droning sound. We all know how much they want our blood. To feed on us, they pierce our skin with the fine-toothed bristles of their sucker, and they leave a poisonous liqueur in the bite, which causes severe irritation and often considerable swelling. It has been observed that it is only the females which torment us in this way, and their attacks are especially threatening in hot climates. They are called mosquitoes*" (Milne-Edwards, 1834, p. 951). Claus, quoting Milne-Edwards' description in his *Traité de zoologie* (1884), goes as far as to say that female mosquitoes constitute "a real scourge".

It was unthinkable to attribute to these insects, already perceived as being harmful, an even more harmful role of spreading a terrible disease like lymphatic filariasis. It was difficult to imagine that the alliances between living beings could be so detrimental to man. We know that the identification of adaptations was usually guided by observing positive harmonies. For example, the garden was perceived as a peaceful and charming laboratory in the context of domestication of plants and animals. The theory of pollination invented by Sprengel constitutes a model of explanation based on recording examples of finality. Sprengel showed that the complex nectar-gathering behaviour of the insects also had another purpose: by transporting pollen, insects ensured the perpetuation of plant species. As a result of this remarkable collaboration, man was the ultimate beneficiary by collecting honey. By overestimating the mutual advantages between man and animals, man was obliged to exclude any possibility of dangerous, disastrous or even fatal alliances.

It is very possible that the principle of finality, which had appeared to be so useful to explain the exit of embryos, finally constituted an epistemological block. Manson said that embryos were adapted to the nocturnal activity of mosquitoes: "*It is marvellous how nature has adapted the habits of the filariae to those of the mosquito. The embryos are in the blood just at the time the mosquito selects for feeding*". But doesn't he go just a little too far when he notes that mosquitoes "*are designed*" to ensure the exit of embryos? In order to account for the considerable number of larvae present in the insect's stomach, it was perfectly legitimate to describe their behaviour: "*When the mosquito* *penetrates a blood vessel, the passing embryos, lasking about as is their habit, entangle themselves on the proboscis and get sucked up*". However, it is surprising to find that Manson associated this phenomenon with "the selecting faculty of that insect" (Letter from P. Manson to T. Spencer Cobbold, Amoy, 20 June 1879, cited in Manson & Alcock, 1927, p. 51-52). More exactly, it is surprising to find that he considers that the mosquito has a faculty of choice to select filaria embryos. Perhaps in his efforts to find an explanation, Manson borrowed a little too much from teleology.

THE SECOND ERROR

The second error, complementary to the first, stemmed from the belief that the metamorphosis of the filaria was complete after one week. We would be wrong to suggest that Manson was a poor observer or lacked perspicacity on the pretext that he gave a partial, incomplete description of the filaria life cycle in the body of the insect. The time required for larval development had to correspond to the interval of time between the blood meal and the death of the mosquito. This second error was not only due to ignorance about the mosquito's habits, but was largely due to the role that Manson attributed to the mosquito, the role of a nurse. In the various studies concerning the mode of contamination of filariasis, this idea constituted a real locking mechanism, as can be seen from a more distant viewpoint.

In the Classical Age, generation was identified as growth and fertilization as nutrition. The concept of "metamorphosis" referred to the development of a preformed organism. The passage from the larva to the butterfly consisted of shedding the layers that masked the presence of the butterfly inside the larva. Naturalists considered that the caterpillar already presented rudimentary wings, antennae and feet. The caterpillar was present in the form of a chrysalis, which was only the butterfly still wrapped in its sheathes. Hence the Latin name of *pupa* which means "doll, little girl". When the study of the behaviour of insects revealed that larvae were raised by worker insects, these insects were then described as *nurses*. In relation to ants, Réaumur wrote: "*Mothers lay their eggs; the baby ants that hatch from these eggs are the object of very attentive care by the workers, which are their nurses, and among all insects, and possibly among all men, it would be difficult to find nurses that are so attentive to their infants*" (Réaumur, 1939, p. 228). Bonnet described the various modes of reproduction in fleas, either by mating, as they are oviparous in Winter, or without mating, as they are viviparous in Summer. Fertilization in Winter compensates for the lack of heat which ensures hatching of eggs in the mother's stomach during warm weather. However, regardless of the modalities of reproduction, fleas are derived from eggs and generation is assimilated to the progressive exhibition of preformed beings.

In the following century, the term generation no longer meant the growth of a germ until the state of a new individual distinct from the parent. The process which preserves a living being and which determines its growth was distinguished from that which determines formation of the body by generation and vegetation. This distinction was derived from a new philosophy of living forms. The concept of metamorphosis was then used to describe the life cycle of the larva, *i.e.* acquisition of the shape and structure of the adult individual by a process of larval development. The individual being was always the same from embryo to adult, but presented various forms. Steenstrup proposed a theory of alternating generations. In particular, he showed that certain parasites give birth to beings that did not resemble their parents and that the parent form only reappears after a series of asexual generations. Steenstrup called the asexual individual which, by means of gemmation, gives birth to the sexual individual *amme* (wet-nurse in English) and the individual which gave birth to the nurse a *groβ amme (*parent-nurse).

When Manson attributed the role of nurse to the mosquito, he used a concept that did not have exactly the same meaning when it was used to describe worker ants in an anthill or sporocysts and rediae, which live as parasites inside a mollusc and which produce cercariae. However, it is of little importance whether the offspring dependent on nurses live outside of the nurses, like ant larvae, or inside the nurses, like cercariae derived from sporocysts and rediae, the essential point is that, in both cases, nurses exert a momentary, temporary and provisional activity either by ensuring larval development of ants, or by disappearing after having expelled the asexual forms which they have produced by budding or gemmation.

It is clear that the concept of nurse constituted an unprecedented breakthrough in the history of the formation of the concept of vector and an equally dramatic obstacle. Describing the mosquito as a nurse referred to the fact that it was the organism in which filaria larvae developed, but this description also constituted an obstacle. The problem was no longer "how" did the filaria complete its life cycle in man, but "when" did the filaria have to leave its nurse. Death of the mosquito, maturity of the filaria and its migration in water therefore constituted a solid body of evidence. It took about another twenty years to refute this evidence, the time required to allow a decisive reversal of medical thought and to understand that larvae do not leave the insect, but are released by the insect. The insect was then perceived as a fully fledged intermediate host. Ross was awarded the Nobel Prize for this discovery, but Manson really deserved this Prize for having set the stage for this discovery.

The concept of nurse, because it belongs to the field of animal ethology and the theory of alternating generations, could hardly be used as a founding element for a theory of vectors. In insects, the activity of nurses ensures preservation of the society to which they belong. In trematodes, nurses ensure their role at various phases of the life cycle that lead to the parent or adult form of the distomid. This concept of nurse remains indelibly marked by its original meaning: the fairly common practice in the middle class of using a wet nurse. In the context of the relationship between the mosquito and filaria larvae, it clearly involves adaptations between various zoological species. This relationship must therefore be considered in terms of the problem of intermediate hosts. Cobbold was aware of this point. At the time when Manson was still using the term *nurse* (in his article, "On the development of *Filaria sanguinis hominis*, and on the Mosquito considered as a Nurse", published in *Transactions of the Linnean Society*, Zoology, 1878, p. 304-311), Cobbold replaced the term "nurse" by "intermediate host": "The character of the changes undergone by the microscopic *Filariae*, and the ultimate form assumed by the larvae whilst still within the body of the intermediate host (*Culex mosquito*) are amply sufficient to establish the genetic relationship as between the embryonal *Filaria sanguinis hominis*, the stomachal *Filariae* of the mosquito, and the sexually mature *Filaria bancrofti*" (Cobbold, 1879, p. 366-367)

THE THIRD ERROR

It was obviously not enough to consider the mosquito as intermediate host in order to solve the problem raised by the life cycle of *Filaria bancrofti*, the study of cycles in one or several hosts, as already observed in helminths, also had to be put to one side. This brings us to Manson's third and last error, which helped to support the body of evidence that he had so laboriously elaborated. What happens between the time when the adult filaria is ready to leave the dead mosquito's body and the time it is found in man, its final host? "*This hiatus is not likely to be filled in, except by conjecture, conjecture founded, however, on, and borne out by, analogy*" (Manson, 1881, p. 293)

At this time, the only discovery concerning the life cycle of filariae had just been reported by Fedschenko and was based on analogy with the life cycle of a trematode. It was known, from time immemorial, that dracunculosis was caused by the Guinea worm or *Dracunculus medinensis*. The life cycle of the parasite presents an unusual feature: the female lives in the dermis and contains thousands of larvae that she releases in contact with water. Between 1868 and 1871, the Russian naturalist Fedschenko directed his research towards a crustacean, a hypothesis that had been suggested to him by Leuckart on the basis on the resemblance of *Dracunculus medinensis* embryos with those of *Cucullanus elegans*, a parasite of Perch. *Cucullanus elegans* embryos emigrate in the body of a small crustacean where they develop. They undergo a double moult in the visceral cavity of these small crustaceans, but they acquire their final organization in the intestine of the Perch, as the crustacean is swallowed with its cargo of larvae by the fish whose flesh is consequently infested with parasites. Cobbold had emphasized this point: "*What I had gathered from Fedschenko in conversation thus epitomises that which has since been much more fully stated by Leuckart; and it is only fair to add that the Russian traveller was led up to his discovery by the previous investigations of Leuckart concerning the young of* Cucullanus. *The Leipzig helmintholologist had, indeed, specially instructed Fedschenko as to the probable source of* Dracunculus. *It is often thus that science makes its clear advances, since a master-mind is needed to set others on the right track*" (Spencer Cobbold, 1879, p. 223)

Manson therefore established an analogy between the life cycle of *Filaria bancrofti* and the life cycle of *Dracunculus medinensis* that had just been elucidated. However, by choosing to elucidate the unknown by the known, Manson engaged his research into a dead-end. The conjecture was initially founded on an analogy: the Guinea worm completes its life cycle in the body of a small crustacean of the Cyclops genus, which is where the embryo undergoes metamorphosis from the larval state to become a young filaria. Man becomes infested by drinking water contaminated by the small crustacean. During digestion, the larvae escape from the small crustacean and travel through the duodenal wall to subsequently lodge in the dermis. It would have been absurd to propose ingestion of the dead nurse in the case of *Filaria bancrofti*, as the offspring had already left its body, as the filariae reach the adult stage at the same time as the female mosquito dies on the water after laying her eggs. The filaria then devours the insect's tissues and begins its independent life in water. It is probably *via* drinking water that it reaches its final host: "*The* Filaria... *escaping into the water in which the mosquito died [and] being swallowed, it works its way through the alimentary channel to its final resting place*" (Manson, 1877, p. 14).

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