PATRICK MANSON AND THE DISCOVERY AGE OF VECTOR BIOLOGY

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ABSTRACT. There have been few scientists who have had a greater impact on the history of vector biology than Sir Patrick Manson (1844–1922). By demonstrating that mosquitoes became infected with microfilariae in the process of taking a blood meal, he became the first to prove an association between insects and pathogens causing human and animal diseases. He also contributed substantially to the discovery of mosquito transmission of malaria parasites and was a principal force behind the founding of the London School of Tropical Medicine and the Royal Society of Tropical Medicine and Hygiene. Manson's career is reviewed in historical context as well as in relation to modern concepts of vector biology.

INTRODUCTION

I consider it a great honor to have been selected by the American Mosquito Control Association to present this year's memorial lecture, and a privilege to memorialize the contributions of Sir Patrick Manson to the field of vector biology and mosquito control. I will attempt to review the life and scientific career of this unusually productive physician and scientist, examine the significance of some of his original discoveries, and place these discoveries into the context of our current understanding of the biology of arthropod-borne diseases. We are presently in an exciting period of advances in our understanding of the epidemiology of vector-borne diseases, spurred by the availability of research tools that existed only in the imaginations of scientists just 15–20 years ago. However, these advances have their roots in painstaking research done using primitive experimental methods and equipment over 100 years ago. We owe much to the pioneering workers who were active from about 1875 to 1915. I have called this 40-year span the discovery age of vector biology. Entering this period, the role of arthropods as vectors of disease pathogens was unknown. Known human pathogens were restricted to helminths which could be seen either with the unaided eye or with microscopes of low magnification (by today's standards), and the role of invertebrates as intermediate hosts of parasites was just being discovered. Leuckart had shown between 1858 and 1867 that *Cyclops* was the intermediate host of a fish nematode. Pasteur had not yet expounded the germ theory of disease, and the etiology of microbial diseases was unknown. Numerous theories had been put forward concerning the relationship between insects and some human diseases. Philip and Rozeboom (1973) provided a detailed account of these early observers, referred to by Boyce (cited in Philip and Rozeboom 1973) as "John the Baptists." However, as of 1875, no one had demonstrated experimentally any connection between insects and human disease pathogens. By 1915, which I have chosen as the close of the discovery age, the relationship between arthropods and Texas cattle fever, nagana, malaria, yellow fever, dengue, plague, Rocky Mountain spotted fever, relapsing fever, trypanosomiasis and typhus had been defined and demonstrated. The period ended with the discovery of sand fly transmission of bartonellosis by sand flies by Townsend, and the development of *Loa loa* in *Chrysops* by Leiper. By 1918, the general framework of the field of medical entomology was essentially complete. A class held in 1918 to train entomologists in the subject to prepare them for possible insect problems in troops fighting in World War I bears a remarkable resemblance to the latest available medical entomology textbooks, complete with definitions of mechanical and biological transmission mechanisms (Pearce 1918). If there is one individual who can be identified with the beginning of this amazing period, it is Dr. Patrick Manson (Fig. 1).

LIFE AND CONTRIBUTIONS OF MANSON

Patrick Manson was born October 3, 1844, in Aberdeenshire, in northern Scotland. His father was the laird of a large estate called Fingast and a local banker. As a young man, Manson had a keen interest in natural history, including insect life (Manson-Bahr and Alcock 1927). He was educated at the University of Aberdeen, receiving an M.B. degree in 1865 at the age of 21 and an M.D. a year later. One of his first posts was as medical officer to the Chinese Imperial Mar-

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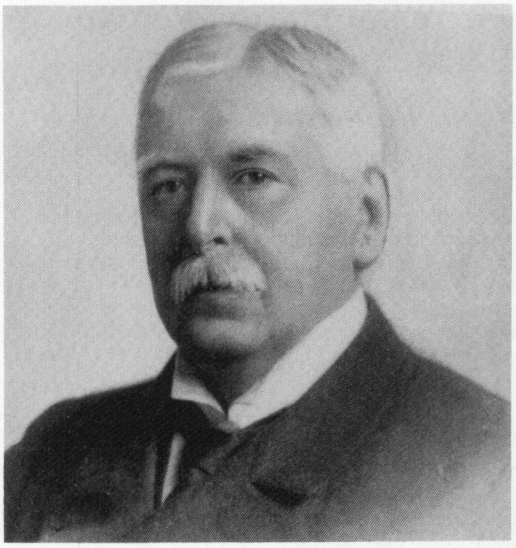

Fig. 1. Sir Patrick Manson, at the height of his career, 1905 (Credit Cassel & Co., London—Manson-Bahr and Alcock. 1927. The life and work of Sir Patrick Manson).

itime Customs in Takao, Formosa. He soon moved to the port of Amoy, China, where he began his research on human filariasis. Manson was a physician, and his first interest involved the cause of human diseases. He was especially interested in a disease which affected many Chinese in Amoy causing the symptoms of chyluria (milky lymph fluid in the urine) and elephantiasis. Manson returned to London in 1874 as a form of study leave, and learned of a discovery by T. R. Lewis that microfilariae were associated with these symptoms in India. Garnham (1971) reported that during one such leave Manson would sometimes work at the opposite side of a table at the British Museum from Karl Marx, one writing *Das Kapital*, the other "Notes on filaria disease in Amoy." Upon his return to China, he discovered microfilariae in Chinese patients with these symptoms. He reasoned that the microfilariae were the "young of some other animal," that being the adult filarial worm, and since no intermediate forms could be found in human hosts, that some other animal must serve as intermediate host, and that animal ought to be the mosquito. This reasoning was strengthened when, in 1872, he discovered that microfilariae were not always present in the blood of filariasis patients, but that a diurnal periodicity existed. Since the microfilariae were present in greatest numbers at night, a night-biting mosquito must be the intermediate host. Manson allowed *Culex quinquefasciatus* mosquitoes to bite a microfilaremic patient, then carefully dissected lots of the mosquitoes at intervals to observe the developing parasites. He made detailed observations and noted morphological changes in the parasites as they grew in size. He also noted that the microfilariae shed their sheaths once they reached the mosquito gut (Harrison 1978). These experiments and accompanying observations assured Manson a place in history. As always, though, there is a sidebar to the story, and one which mosquito biologists will appreciate. At the time Manson was conducting his epoch-making experiments, relatively little was known about the biology and classification of mosquitoes. Since this has seldom been emphasized by historians, it bears attention. Harrison (1978) in his excellent history of malaria research, leaves one with the impression that there was information available on the biology of mosquitoes which Manson ought to have been aware of. It is doubtful that much was available even in London, let alone in Amoy. *Culex pipiens* and *Aedes aegypti* were the first mosquitoes to be described in the present taxonomic system, by Linnaeus in 1758 and 1762, respectively. The genus *Anopheles* was not recognized until 1818, by Meigen. (*Anopheles claviger* had been described by Meigen in 1804 as a *Culex*). *Culex quinquefasciatus* was described in 1823 by the American entomologist Say. By 1805 only 15 species of mosquitoes appeared in Fabricius' revision of the Diptera (Fabricius 1805). No taxonomic work on mosquitoes was to appear before 1901 until the publication of Theobald's world monograph (Theobald 1901). Those interested in a historical account of writings on mosquito biology should read Chapter 1 of Christophers' book on *Aedes aegypti* (Christophers 1960). By 1870 several authors had described and illustrated the life cycle stages of mosquitoes, the most elegant drawings being those of Swammerdam. However, at this time literature on mosquito biology and ecology was scattered and mostly anecdotal. In speaking of the many scattered reports which appeared in publications such as *Nature* and the *Entomologist's Monthly Magazine* from 1850 to 1900, Christophers (1960) remarked: "These communications further show very strikingly how complete has been the change in character of the literature on mosquitoes from the year 1900 or so onwards." Thus much of what Manson learned about the handling of mosquitoes and their experimental use was self-taught. He recognized different species of mosquitoes in the vicinity of Amoy, but did not know their scientific names. It is not surprising, then, that Manson believed that mosquitoes lived but a short time and died shortly after laying eggs on a water surface. He also failed to appreciate that female

mosquitoes could be kept for extended periods of time by providing water and a source of carbohydrates. For whatever reason, he thought that mosquitoes in nature, as was the case with his captive mosquitoes, took a single blood meal and laid but a single batch of eggs in their lifetimes. He thus reasoned that filarial larvae escaped into the water from the bodies of dead mosquitoes and that human hosts were infected by drinking water infested with filarial larvae. Thus Manson went astray in attempting to discover the complete life cycle of the filarial parasite of man. That he failed to do so in no way minimizes the importance of his monumental discovery, however. When viewed in the context of the time when it was made, and the resources available to Manson at the time, the discovery is even more amazing. However, had Manson demonstrated the complete transmission cycle, the significance of his discovery would have been unchallenged, and he would have avoided some of the adverse criticism he received later by some of his contemporaries and by some historians.

In 1883, while Manson was still working on filarial development in mosquitoes, a reviewer for the journal *Veterinarian* made the suggestion that the mosquito might transmit filarial larvae to human hosts in the course of biting. Unfortunately, Manson did not see these remarks (Manson-Bahr and Alcock 1927), and it was not until 1900 that Low confirmed mosquito transmission of filarial larvae.

Manson moved to Hong Kong in 1883, thus bringing to a close the most productive period of his research on filariasis. In Hong Kong, Manson founded a medical society, a dairy farm and a school of medicine (Manson-Bahr and Alcock 1927). In 1889, he moved back to Scotland to retire. His retirement lasted only until 1890, when he moved to London to open a medical practice. He also set up a crude laboratory in his home and continued to study various kinds of biological specimens sent to him from abroad.

In 1892, Manson received an appointment at the Seaman's Hospital in London. He was given charge of a ward at the Albert Dock Hospital. He also established a small laboratory there which was to become the nucleus for the London School of Tropical Medicine. It was at this time that Manson first learned about malarial parasites and developed his "mosquito theory" of malaria transmission. Manson was, in the words of Harrison (1978), "possessed of a truly creative mind that was always perceiving connections and resemblances between disparate phenomena. . . ." Having been shown malarial parasites by a Dr. Plimmer, Manson drew parallels between these parasites and filariae. His mosquito theory relied heavily upon his observations of exflagellation, first observed by Laveran. It also paralleled his erroneous perception that mosquitoes served only as intermediate hosts of these parasites, and not as agents of transmission. In spite of its faults, Manson's theory involved several original and important insights: One was that if blood containing malarial parasites were to be taken in by mosquitoes, then in the gut a transformation of the parasite would occur leading to a life form capable of infecting a human host. Another was that this transformation would only occur in certain species of mosquitoes. It remained for McCallum in America to show in the case of *Haemoproteus* in birds that the "flagellae" were male forms and that female forms were also present, with fertilization taking place in the invertebrate host (Garnham 1971). In 1894, a young surgeon by the name of Ronald Ross visited Manson at his home, beginning a collaboration which was to last 4 years, involve constant exchanges of letters (about 100) and specimens, and culminate in the demonstration, by Ross, of mosquito transmission of malaria. As late as 1896, when Bignami forwarded his own mosquito hypothesis, Manson still believed that mosquitoes did not transmit malaria directly because they fed on blood only once. However, Bignami believed although mosquitoes transmitted malarial parasites to people, they did not become infected from people (Harrison 1978).

Manson's involvement with malaria transmission by mosquitoes culminated in a series of experiments carried out in London and Rome in 1900. Manson designed these experiments to prove to skeptics a transmission mechanism which he now regarded to be an established scientific fact as a result of Ross' research. He had some anopheline mosquitoes infected by feeding on patients with *Plasmodium vivax* at the Santo Spirito Hospital in Rome brought to London, where they were permitted to bite his oldest son and a laboratory assistant. He also organized an expedition, conducted by Low, Sambon and Terzi, in which these individuals were protected at night by mosquito-proof quarters at the Roman Campagna at the mouth of the Tiber River. After staying there during one entire malaria season, they did not come down with malaria, although most everyone else in the area did (Manson-Bahr and Alcock 1927).

Historians have argued for years about the significance of Manson's role in the discovery of mosquito transmission of malaria, especially in contrast with that of Ronald Ross and Battista Grassi. Ross stated, in 1900: ". . . it was Manson's theory, and no other, which actually solved the problem" (Harrison 1978). Manson himself,

in 1909, said he should get credit not for the mosquito theory, but for having discovered Ronald Ross (Manson-Bahr and Alcock 1927). Harrison (1978) states: "Both talents, and both men [Manson and Ross] were essential to the work." I believe this to be an accurate assessment.

The discovery of the development of bancroftian filariae in mosquitoes and his participation in malaria research were not the only contributions Manson made during his career. While in Amoy he discovered new species of filariae in domestic fowl, crows and magpies. His work with magpies was done at considerable risk because the bird was considered sacred in China. It was believed that an ancient Emperor had entered a magpie (Manson-Bahr and Alcock 1927). Later, Manson contributed to the discovery of the lung fluke, *Paragonimus westermani*, and he predicted that *Chysops* were vectors of *Loa loa* 21 years before Leiper was able to demonstrate the fact. In 1897, he demonstrated exflagellation in malarial parasites after discovering that the addition of borax to methylene blue would enable the visualization of chromatin. This was known as Manson's stain, and was developed further by Romanowsky and Leishman to become the well-known stains of those names. In 1902, Manson discovered a new species of fluke, named by Sambon *Schistosoma mansoni*. He also made original discoveries in leishmaniasis and trypanosomiasis.

Because Manson was concerned about the slow movement of scientific information relating to tropical medicine, he felt that a school of tropical medicine should be founded. He was particularly distressed that it was not until his return to London in 1893 that he first learned about Laveran's discovery of malaria parasites in 1880. He began to organize such a school in 1897. The London School of Tropical Medicine was established in 1899, in connection with the Seaman's Hospital at Albert Dock. In 1920, the School was moved into a new building in the University Quarter of London. In the final years of Manson's active professional life he devoted much time and effort to teaching and to the administration of the School. In 1898 he wrote the first edition of the textbook *Tropical Diseases*. Over the next 23 years, 6 more editions appeared. His son-in-law Philip Manson-Bahr wrote editions 7 through 16. *Manson's Tropical Diseases* is now in its 19th edition. In 1907, Manson was responsible for the founding of the Royal Society of Tropical Medicine and Hygiene (then called the Society of Tropical Medicine). Manson was the guiding force behind many projects in tropical medicine, and brought many famous parasitologists to the London School: Leiper, Wenyon, Low, Castellani, Daniels and Manson-Bahr (Garnham 1971).

Manson received many awards during his life. He was knighted in 1903, and died April 9, 1922. Alert to the end, he quoted poetry to those at his bedside just before he died.

Many parasites and mosquitoes have been named in his honor, including the genus-*Mansonia*, *Schistosoma mansoni* and *Mansonella*. At the time of his death, he had published over 160 scientific articles.

Although after his death in 1922, Manson had his detractors, it is difficult to minimize the significance of his pioneering discoveries. That they were made in crude surroundings and in virtual isolation from the scientific community of his day bears testimony to the remarkable effort they required. Manson was a genuine pioneer in the field of tropical medicine and parasitology. He will always be marked in some historians' minds by the discovery which he did not make: that the mosquito not only serves as a host of filarial parasites, but as a vector as well. Nevertheless, Manson's research in China involving mosquitoes, their biology and their role as hosts of parasites, paved the way for all that followed.

Manson was not only the first to demonstrate a role for mosquitoes in the life cycle of human pathogens, he was also the first to point out that mosquitoes varied from species to species in their ability to serve as intermediate hosts. This, he showed, was partly because mosquitoes differed in their daily biting cycles, but also because filariae would not develop in some species. He tested 4 species of mosquitoes in Amoy, and found that filariae "miscarried" in all but one, *Culex quinquefasciatus* (Manson-Bahr and Alcock 1927). Here is the advice Manson gave Ross in a letter written in 1895: "Another hint I would give you. Send specimens of the mosquito for identification of species. Probably different species of mosquito modify the malaria germ that the differing degrees of virulence depend on the different species of mosquito that has served as alternative host to the parasite" (Manson-Bahr and Alcock 1927). These observations are actually the forerunners of modern concepts of vector capacity and vector competence.

MODERN CONCEPTS

Although the idea of vector specificity has been with us for over 100 years, only rarely have particular patterns been fully described, let alone explained. Huff (1929), working with bird malaria, was one of the first to provide evidence that susceptibility of arthropod vectors to infection by pathogens is under genetic control. Sub-

sequent workers showed that populations could be selected for susceptibility, and also that considerable variation in susceptibility exists among populations of a number of vector groups. In the case of several parasitic diseases, genetic mechanisms for control of susceptibility have been described (Lehane 1991).

For arbovirus diseases, sorting out environmental factors of vector capacity from physiological factors of vector competence has a long way to go. This is partly because of the complexity of both vector and pathogen complexes, with hundreds of viruses already described, and probably many more to be described. Just last year the first evidence of a genetic control mechanism for vector susceptibility to an arbovirus was reported by Tabachnick (1991). The current status of our knowledge of vector-pathogen interactions in arboviruses was well stated by DeFoliart et al. (1987):

> Such mosaics of regional behavior underline the importance of detecting the existence of species complexes and intraspecific differences in population behavior. Intraspecific population differences in internal vector competence have been similarly documented for the vectors of a number of arboviruses. Possibly the most important concept emerging from arbovirus research of the past decade is that there are no simple stories.

I am involved in a research project with James Hardy, William C. Reeves and others at the UC Berkeley School of Public Health. This research is proving to us that vector relationships for California and Bunyamwera serogroup viruses in the western U.S. certainly do not represent a simple story. We sampled populations of *Aedes squamiger* from coastal salt marshes in California because this species is a "sister species" to *Ae. increpitus* and *Ae. fitchii.* Snowshoe hare (SSH) virus has been isolated from the latter species, and we thought *Ae. squamiger* might harbor either SSH virus or a closely related virus. We repeatedly isolated an as yet unnamed California serogroup (CAL) virus closely related to California encephalitis (CE) virus from *Ae. squamiger*, but nothing from its closest relative, *Ae. increpitus*, nor from any other species present in salt marsh habitats in California (Eldridge et al. 1991). To make matters more complicated, we found that populations of *Ae. increpitus* in California differed significantly in vector competence for this CE-like virus (Kramer et al. 1992), and on the basis of electrophoretic and morphological evidence, concluded that 3 species in the *Ae. increpitus* complex exist in California (Lanzaro and Eldridge 1992). Our studies with Jamestown Canyon (JC) virus to date suggest an equally complex array of mosquito populations and viral strains. Brust and Munstermann (1992) have recently shown that the *Aedes communis* complex consists of at least 3 species in the western U.S. About 65% of our isolates of JC virus have come from members of that complex in California. Before we can sort out the vector relationships for CAL serogroup viruses in California, we must answer a number of fundamental questions involving the evolution of mosquitoes as well as the evolution of viruses. We must also learn more about the underlying cause of vector competence in these populations for CAL serogroup viruses. Only then can the apparently anomolous patterns of vector susceptibility to infection be explained.

THE NEW DISCOVERY AGE

During the past few years there have many interesting developments involving the genetic and molecular basis of vector competence of arboviruses, with the pace of discoveries increasing in the past 2–3 years. In fact, we are in another discovery age in vector biology. This age holds the promise of discovering the underlying cellular mechanisms controlling the relationship between a wide variety of vectors and pathogens. As these mechanisms are defined, they can be meshed to biosystematic and ecological studies in a way which can explain not only the physiological basis of vector competence, but also the environmental basis for the broader questions of vector capacity. The editor of the *American Journal of Tropical Medicine and Hygiene* stated in the February 1992 issue: "The intimate relationship between the insect vector and the infectious agent it transmits remains a cornerstone of laboratory and field studies in tropical medicine."

I wonder if Patrick Manson ever imagined what he was starting when he was working in his laboratory in Amoy. I suspect he did, because he was a very creative and imaginative thinker. We owe him much, and again, I thank this association for the opportunity to share this tribute to his memory.

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