Journal of the History of Biology (2016) 49:359–395
DOI 10.1007/s10739-015-9421-8

Patterns of Infection and Patterns of Evolution: How a Malaria Parasite Brought "Monkeys and Man" Closer Together in the 1960s

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Abstract. In 1960, American parasitologist Don Eyles was unexpectedly infected with a malariaparasite isolated from a macaque. He and his supervisor, G. Robert Coatney of the National Institutes of Health, had started this series of experiments with the assumption that humans were not susceptible to "monkey malaria." The revelation that a mosquito carrying a macaque parasite could infect a human raised a whole range of public health and biological questions. This paper follows Coatney's team of parasitologists and their subjects: from the human to the nonhuman; from the American laboratory to the forests of Malaysia; and between the domains of medical research and natural history. In the course of this research, Coatney and his colleagues inverted Koch's postulate, by which animal subjects are used to identify and understand human parasites. In contrast, Coatney's experimental protocol used human subjects to identify and understand monkey parasites. In so doing, the team repeatedly followed malaria parasites across the purported boundary separating monkeys and humans, a practical experience that created a sense of biological symmetry between these separate species. Ultimately, this led Coatney and his colleagues make evolutionary inferences, concluding "that monkeys and man are more closely related than some of us wish to admit." In following monkeys, men, and malaria across biological, geographical, and disciplinary boundaries, this paper offers a new historical narrative, demonstrating that the pursuit of public health agendas can fuel the expansion of evolutionary knowledge.

Keywords: Parasitology, Malaria, Evolution, Public health, Primates, Ecology, Zoonosis, Experimental medicine, Lab-field border, National Institutes of Health

In 1960, parasitologist Don Eyles was in the midst of a series of malaria experiments on rhesus macaques. Under the auspices of the National

* This essay is part of a special issue entitled 'Ecology and Infection: Studying Host-Parasite Interactions at the Interface of Biology and Medicine.'

Institutes of Health (NIH), his Memphis laboratory aimed to understand human malaria infection. Previous work had convinced malariologists that macaques could not host the human malaria parasite *Plasmodium vivax* (Hegner, 1928). Fortunately, however, a monkey-specific parasite, *Plasmodium cynomolgi*, was considered similar enough to *P. vivax* to effectively model human malaria infection (Eyles, 1960). Eyles and his team later admitted that they had treated their malarious mosquitoes casually, considering their itching bites a mere nuisance (Eyles et al., 1960). As his supervisor G. Robert Coatney explained it, ''erroneously we thought malaria in the monkey was for monkeys and malaria in man was for people'' (Coatney, 1985, p. 10). Eyles was duly surprised when he fell ill with fever soon after the experiment, and several days passed before he seriously entertained the possibility that he had contracted malaria. When he finally examined his own blood films, he was perplexed to see that he had been infected with ''monkey malaria.''

A regimen of chloroquine handily cleared Eyles' malaria – but not before he had drawn 20 milliliters of his own blood, the first component in a new series of experiments that would transform the identity of ''monkey malaria'' for this team of malariologists. One inadvertent laboratory infection did not necessarily imply a public health threat, but it did present a string of perturbing questions to Coatney, Eyles, and their colleagues: Could mosquito vectors reliably transmit monkey malaria to human subjects? Could they perhaps even transmit the parasite *between* human subjects? Did human infection with monkey malaria actually happen in Malaysia, where the monkey parasite *P. cynomolgi* was first isolated? Pursuing these questions would require the efforts of multiple teams of parasitologists, working in the United States and Malaysia, conducting human experimentation, opportunistic collection, and ecological field trials.

However, this inquiry into monkey malaria did not stop with the medically relevant questions listed above. Coatney and his colleagues also extended their inquiry into the domain of biology, asking what a shared malaria parasite implied about ecological and evolutionary relationships between monkeys and humans. Host animal relationships had assumed practical importance for parasitologists since the inception of their field in the late nineteenth century. As in other medical fields, like bacteriology, they sought experimental animals that could act as 'proxies,' 'surrogates,' and 'stand-ins' for human medical conditions.[1]

[1] For more on extrapolation between animal and human bodies in medical research, see Guerrini (2003), Asdal (2008), Leonelli and Ankeny (2011), Löwy (1992, 2003), Birke (2012), Bresalier et al. (2015).

This search was not a straightforward one, though. The extrapolation of findings from nonhuman to human bodies was based upon an assumption of evolutionary relatedness, the basis for a posited biological symmetry; but at the same time, many parasitic organisms had evolved the ability to infect only very specific host animals, undermining scientists' efforts to find nonhuman models for human diseases.[2] The resulting struggle to find suitable, effective experimental animals became central to the practice of parasitology and it represented an intersection of medical and evolutionary questions ripe for exploration. Most critically, it was at this intersection that parasitologists came to engage with animals of many different species, in many different contexts, and to ask questions about the biological relationships between them.

While scholars have previously documented the application of evolutionary concepts to medicine (Bynum, 1983, 2002; Méthot, 2011; Buklijas and Gluckman, 2012), and recognized parasitology as a field that bridged medicine and natural history (Harden, 1985; Li, 2002; Anderson, 2004), they have almost entirely overlooked the ways that the study of animal disease has itself generated evolutionary insights.[3] Most importantly, these historical narratives portray medical researchers and evolutionary researchers as inhabitants of distinct disciplinary silos, with separate agendas. The case of parasitology offers a new historical narrative, demonstrating that medical research and evolutionary reasoning may be pursued in tandem. More specifically, it shows that public health agendas can fuel the expansion of evolutionary knowledge.

Central to parasitological practice was the examination of a broad range of animal species, which were tracked or acquired in forests, zoos, and human households, to name only a few contexts. The diversity of species employed was necessitated by the demands of host specificity: Parasitologists worked in the laboratory and in the field to determine how and why different parasites could be transferred (or *not* transferred) between two different animal species. This practical experience induced them to ask questions about the biology of these animals, hypothesizing about their ecological and evolutionary proximity to each other in order to explain the results of their medical experimentation. Thus they began to use patterns of infection to infer patterns of evolution, a practice identified

[2] As Ilana Löwy writes, "[n]o simple correlations were found between the susceptibility or resistance to a pathogenic germ and proximity on the phylogenetic [evolutionary] ladder" (Löwy, 2003, p. 437). Even heavily standardized model organisms, bred specifically for the purposes of hosting human diseases, remain "largely mysterious products of millennia of evolution," with the capacity to "surprise" researchers in the laboratory and beyond (Leonelli and Ankeny, 2011, pp. 315–316).

[3] For an exception, see Méthot (2012).

as the ''host–parasite method'' in the 1920s (Metcalf, 1929). Reciprocally, evolutionary relationships could also be used to predict potential parasitic infections or disease threats (von Ihering, 1891; Kellogg, 1913; Darling, 1921; Ward, 1926; Metcalf, 1929; Baer, 1940, 1952, 1957; Cameron, 1952).

Essential to both of these modes of the ''host–parasite method,'' working in either direction of inference, was a direct engagement with the lives of animals. The history of monkey malaria offers an especially opportune example of this parasitological practice. Malariologists believed that cross-infection between monkeys and humans was nearly impossible. Thus, the jarring reality of Eyles' accidental infection with monkey malaria in 1960 had a host of ramifications directly relevant to both public health agendas and assumptions about primate evolutionary relationships, bringing the biological reality of the experimental animals into stark relief. The malariologists who performed this research scrutinized all the organisms involved, from the protozoan parasites to their mammalian hosts, and they followed them over geographical, biological, and disciplinary boundaries. Coming at a time when strategies for malaria control and ideas about primate evolution were both in flux, the history of this project demonstrates how evolutionary relationships could be worked out as part of a public-health agenda.

In the first section of this paper, I explore the selection of research subjects for the experimental program that took shape in the wake of Eyles' accidental infection in 1960. I place these subjects in the broader context of the early-twentieth century search for appropriate malaria models and malariologists' struggle with host specificity in their parasite. During this time, a transition away from avian models began, as it became possible to employ primate and other mammalian models. One especially apposite element of this history was Coatney's use of human subjects *as models for monkey malaria*. Through this reversal of a typical medical research protocol, an equivalency was wrought between monkeys and humans; and this equivalency turned the conundrum of the malaria parasite's host specificity into a larger complex of questions about ecological relationships and evolutionary distance between humans and other species of primates. Unlike typical laboratory experimental models, which scholars have described as having ''no 'objective' counterparts in nature'' (Logan, 2002, p. 355), for Coatney and his group, understanding their experimental organisms – including humans, monkeys, and malaria parasites – in a natural context became paramount. The naturalness of cross-infection between monkeys and men was medically significant, thanks to its potential implications for disease transmission, and biologically intriguing, thanks to its implications for primate evolution.

In the second section of my paper, I will follow Eyles and his colleagues as they exited the lab and entered the field in Malaysia,[4] reconstructing the ecological reality of both monkey malaria and its hosts, and collecting data that would demonstrate that human infection with the monkey parasite was more than a "laboratory curiosity" (Contacos and Coatney, 1963, p. 914), and was in fact a "true zoonosis," contractible by natural means. This history of monkey malaria is one more instantiation of the "lab-field border," as Robert Kohler has called it (Kohler, 2002). As in Kohler's account, the definition of what is "natural" shifted, relative to the context and goals of the research project as it developed. As the apparent naturalness of malaria cross-infection between rhesus monkeys and humans gained credibility, it brought these two primate species into closer proximity in the minds of Coatney and his colleagues.

Thus, as they enriched the ecological picture of primate malaria in nature, malariologists also came to appreciate that "natural" infection had as much to do with the evolutionary history of hosts as with the supposed naturalness of an experiment's context or mode of infection. In the final section of the paper, I show how the parasitologists involved in this research transmuted the medical characteristics of malaria infections, including susceptibility and transmissibility, into evolutionary characters. Eyles' accidental infection occurred in a climate where it was *assumed* that humans were not susceptible to monkey malaria. In throwing this assumption into question and following a simian parasite across the species boundary, parasitologists also formulated an evolutionary argument that "monkeys and man" were, in Coatney's words, "more closely related than some of us wish to admit" (Coatney, 1963, p. 877). My account demonstrates that Coatney's striking conclusion was wrought from the most pressing questions and central practices of parasitology, in which evolutionary insights have long been drawn from medical practices and medical insights from evolutionary practices.

Modeling Parasitic Disease: Monkeys, Malaria, and Men in the Lab

Coatney's post-war malaria research coincided with a newfound capacity to use mammalian experimental models in malariology, including rodents and nonhuman primates, thus marking a shift away

[4] Eyles and his team worked in peninsular Malaysia, which was known as Malaya until 1963, when it was incorporated into the newly formed country of Malaysia (which also includes Singapore and Sarawak, on the island of Borneo). As the research discussed here spans the period of transition from Malaya to Malaysia, I will refer to the country as Malaysia, for simplicity's sake.

from traditional bird malaria models (Slater, 2009, pp. 39–42; Cox, 2010). Since Darwin, the extrapolation of knowledge from nonhuman to human bodies has often been rooted in a notion of evolutionary relatedness (Bernard, 1865; Guerrini, 2003; Bresalier et al., 2015). Thus another primate might seem the ideal experimental model for human malaria, based upon the assumption that close familial relationships result in easy cross-infection between species. However, parasitic cross-infection has never followed such straightforward phylogenetic rules, and even closely related organisms might prove immune to each other's parasites. This has been especially true in malaria research, thanks to the parasite's relatively high level of host specificity. In other words, most early attempts to infect monkeys with human malaria failed (Hegner, 1928, p. 238). To make matters worse, the challenges of procuring and maintaining healthy populations of nonhuman primates for experimental use were nearly insurmountable until the mid-twentieth century, when breeding colonies in the United States were established (Carpenter, 1940; Schmidt, 1979; Rawlins and Kessler, 1986; Dukelow and Whitehair, 1995; Montgomery, 2005).

By contrast, birds were easily obtained and reared, and their malaria parasites were readily isolated. (Slater, 2005a, 2009). For malariologists, an exact correspondence between avian and human parasites was unnecessary. In fact, "the avian malarias were distinct [from the human malarias] in morphological and phylogenetic detail," Slater writes, and "they could be viewed as congruent only if viewed over the course of the whole life cycle of the [parasitic] organism, in its many stages and forms, and in many locations and transformations, including at times consideration of the role of vectors and the response to drugs" (Slater, 2005a, p. 291). In other words, the apparent impossibility of finding a closer evolutionary correlate to human malaria infection required a special mode of argumentation, a formulation of "congruence" that would emphasize the parallels between human and avian parasites and trivialize the divergences. The lack of better options, the ease of maintaining birds in the laboratory, and the perception of symmetry between the avian and human parasite life cycles all contributed to making bird malaria fundamental to the biomedical understanding of malaria through the 1930s (Slater, 2009, pp. 39–58). However, it left open the question of how the evolutionary relationships of hosts were related to their susceptibility to malarial infection – a problem that was simultaneously practical, experimental, and theoretical, and to which parasitologists would turn afresh after Eyles' unanticipated infection with monkey malaria.

G. Robert Coatney was one malariologist who was well aware of the complex association between the evolutionary proximity of hosts and the chances of experimental cross-infection amongst them. In the 1950s and 1960s, Coatney would take advantage of the growing availability of primate experimental models, as in the laboratory where Eyles was infected; but three decades earlier, he had launched his early career with an *avian* experimental model. Trained in the traditions of parasitology, with an emphasis on both zoology and medicine, Coatney worked as a biology professor at Nebraska State Teachers College in the 1930s. When he wasn't teaching, he was combing the Nebraska landscape, seeking a new model for malaria research amongst wild bird populations. After years of collecting and screening birds for malaria, he finally identified a malaria infection from a mourning dove. First he attempted to transfer the parasite to the canary (a typical malaria laboratory model) but he found that the infection dropped off rapidly. So he changed tack, shifting to a pigeon host, and was rewarded: The parasite flourished in his new model and, thanks to his success, the Public Health Service subsequently offered him a job (Coatney, 1985).[5] As he reported in a 1938 paper in the *American Journal of Epidemiology*, the "close zoological relationship existing between doves and pigeons" had suggested to him that pigeons might serve as a better laboratory host for a strain of malaria isolated from doves (Coatney, 1938, p. 382). In other words, early in his career, long before he had begun working with primate malaria models, Coatney was already considering how evolutionary distance between different host species was related to parasitic cross-infection, and could be employed to make more effective experimental choices.

Soon after Coatney joined the Public Health Service, patterns in malaria experimental models began to shift. Work in the 1940s revealed that mammalian malaria life cycles include a stage that is quite different from avian malaria life cycles – a dormant form that lodges in the mammalian liver, a finding that undermined the acceptability of birds as proxies for humans.[6] British parasitologists Percy Cyril Claude (P.C.C.) Garnham and Henry E. Shortt, of the London School of Hygiene and Tropical Medicine, had uncovered this "exoerythrocytic cycle" while studying a rhesus macaque infected by *Plasmodium cynomolgi* (Shortt and Garnham, 1948).

[5] In 1935, only a few years after Coatney isolated a plasmodium from a pigeon, chicken malaria, *P. gallinceum*, was isolated and identified and it soon became an extremely common model (Slater, 2009, p. 53), although, according to Coatney, the USDA would not allow the importation of this parasite until the advent of World War II made it imperative (Schmidt, 1979, at 13:52).

[6] As opposed to the avian malaria parasites, where this stage takes place in a variety of other tissues (Lainson and Killick-Kendrick, 1997, p. 179).

Immediately after infecting a new mammalian host, malaria becomes temporarily dormant and enters the host's liver. From a clinical standpoint, the parasite is concealed, since blood drawn at this time will show no sign of infection. Shortt and Garnham confirmed the generality of their finding with a biopsy of the liver of human mental patient, whose advanced syphilis was being treated with malarial fever, which was a common treatment at the time, developed during the interwar period, prior to the advent of antibiotics (Wagner-Jauregg, 1927; Coatney et al., 1971).

Avian malaria researchers were dismayed by this clear demonstration that a major stage in the life cycle of human malaria was so distinct from that of avian malaria, thus challenging the perception of congruence upon which the avian malaria model rested. In fact, some initially questioned the validity of these new observations and suggested that Shortt and Garnham had observed an artifact peculiar to their method of experimental malaria inoculation or a product of previous biopsies performed on the monkey's liver (Eyles, 1960, pp. 553–554). While most malariologists accepted Shortt and Garnham's claims, it was at least a decade before the question was completely laid to rest and Shortt and Garnham vindicated. Nonetheless, the notion that birds could effectively model human malaria had been undermined. Even disregarding the claims of Shortt and Garnham, the avian model could not be used to accurately test the *toxicity* of anti-malarial drugs for human subjects – in this respect, the physiology of a bird was understood to be too far removed from that of a human (Slater, 2005a, p. 289).

To make matters worse, fear that quinine supplies might be cut off during World War II meant that the turnaround time from drug development to implementation in the field seemed desperately short. Thousands of potential antimalarial drugs awaited testing, and the safety of these compounds could not be adequately gauged through avian models. Slater refers to this need as one motivation for the development of primate malaria research models during this period (Slater, 2005a, p. 289), but it is clear that there were still very few reliable sources of monkeys for toxicity trials in 1944. Most large-scale primate trials required researchers to travel to Asia and make direct contact with monkey-trappers and then personally supervise their transport across the globe. The necessity of a lengthy sea voyage during the war made this prospect seem even less reasonable.[7] Coatney, who was in charge of the federal effort to test antimalarials at this time, knew

[7] The acquisition of macaques and other primates for research in 1944 was not much different from Carpenter's description of sourcing macaques to stock his colony on Cayo Santiago (Puerto Rico) in 1938 (see Rawlins and Kessler, 1986, pp. 16–19).

that he needed a reliable source of human research subjects who could trial the drugs that had proven most promising in nonhuman models.

Fortunately for Coatney, the common use of malarial fever against the dementia and paralysis of advanced syphilis provided a source of human subjects, circumventing doubts about the use of nonhuman experimental subjects. Early in the war, he began antimalarial trials with the patients of St. Elizabeths Hospital in Washington, D.C., who were already undergoing treatment with *P. vivax*, the human malaria parasite. As the war progressed, however, the demand for human subjects increased. In 1943, a colleague mentioned the possibility of using prison inmates in this research, and Coatney was immediately interested in the prospect. Using his medical and political connections, he was soon able to secure the cooperation of a federal prison in Atlanta, where he began infecting prisoners in March 1944 (Schmidt, 1979; Coatney, 1985). Describing the project in 1966 for a *New York Times Magazine* cover article, science journalist C.P. Gilmore wrote, ''In the more than two decades since [the project began], the units have been responsible for much of the progress, both in antimalarial drugs and in fundamental knowledge of the disease itself'' (Gilmore, 1966, p. 47). Quoting Coatney, Gilmore reported that 3000 inmate volunteers had participated in the project at the Atlanta penitentiary during that period. Most prominently, it was this location that demonstrated the safety of Chloroquine, a successful antimalarial for more than fifteen years, until the parasite evolved resistance to the drug (Gilmore, 1966, p. 52). After the war, alternate models for malaria research proliferated, thanks to the discovery of several rodent malarias and the increasing supply of nonhuman primates for biomedical research (Slater, 2005a).[8] But the success of Coatney's prison research scheme allowed him to continue his human experimentation, in tandem with primate and other nonhuman malaria research.

The initiation of the World Health Organization (WHO)'s global malaria eradication program in 1955 further secured Coatney's access to multiple experimental populations for his malaria research. The history of this program and its ultimate failure and cessation in 1969, fourteen years after it was initiated, has already been told.[9] For my purposes, the global drive toward malaria eradication provides an important context for the monkey malaria story, providing a powerful justification for the funding

[8] Slater (2005a, pp. 270, 289, 293) on the increasing use – and necessity – of nonavian models for malaria. Guerrini (2003, pp. 117–120) describes the general increase in the use of primates, especially rhesus macaques, in the first half of twentieth century. Also, see again, on the topic of breeding colonies of primates: Carpenter (1940), Rawlins and Kessler (1986), Dukelow and Whitehair (1995) and Montgomery (2005).

[9] See, for example, Packard (2010, pp. 150–176).

that made this extended project possible. From its inception, the program had been plagued by challenges and doubts. However, Eyles' infection presented the possibility that malaria eradicated from a human population might return later, thanks to a hidden and inaccessible animal reservoir. Thus, the breaking down of the species barrier between macaques and humans within Coatney's NIH lab had repercussions far beyond its walls: *If* simian species of malaria could easily pass from monkeys to humans via mosquito vectors, this alone could prove fatal to the WHO's plans for malaria eradication. As malariologist McWilson Warren recalled in a 2005 interview with Slater, "On a worldwide basis, at this time, the commitment to malaria eradication had become a major issue," and threats to this goal had to be taken seriously. "Geneva [the headquarters of the WHO], London, and Washington were really, very spooked about the whole business [of Eyles' infection with monkey malaria,] because suddenly if there was a significant level of malaria in non-human primates infectious to man, then the concept of eradication had biologically gone down the tubes: Under the circumstances, there seemed to be no possibility that human malaria could be eradicated" (Slater, 2005b, p. 9).

Thus, when Eyles was unexpectedly infected with monkey malaria in 1960, a reliable experimental protocol and a pool of human subjects were immediately available, and Coatney's team began testing the transmission of malaria from monkeys to humans. While previous attempts to cross-infect between monkeys and humans had been performed in the first decades of the twentieth-century, mostly without success, never had such a large-scale cross-infection project, with hundreds of human subjects, been attempted.[10] From the 20 mL of blood he had drawn from himself, Eyles first inoculated a macaque in his own lab. The remainder of the blood was sent to Atlanta, to be immediately administered to volunteers from the inmate population. And within days, all of the experimental organisms – macaques and inmates alike – showed signs of malaria infection (Eyles et al., 1960).

Prominent in this project from the beginning was an emphasis upon the *natural* status of the team's laboratory experimentation. Only two years earlier, in 1958, the Joint WHO/FAO Expert Group on Zoonoses had assembled to assess the risks to human health posed by nonhuman animal disease, generating an official definition of "zoonoses," as those diseases that were "naturally transmitted" between animals and humans (WHO, 1959, p. 6).[11] Embedded as he was in the Public Health Service, funded by

[10] For a representative example of past such experiments, see Clark and Dunn (1931).

[11] It should be noted that this report makes no mention of the possiblity that malaria might be a zoonosis, and despite the work of Coatney's group, malaria continues to be left out of subsequent reports.

the NIH, and overseeing the WHO Expert Committee on Malaria in both 1958 and 1960,[12] it fell to Coatney to create the most "natural" conditions possible in his experiments, in order to directly address the urgent public health concern with zoonotic malaria.

Coatney felt this pressure acutely. In his mind, *P. cynomolgi*, monkey malaria, had already "qualified *experimentally* as a zoonosis" (Beye et al., 1961, p. 315),[13] by means of the experimental prison infections that immediately followed Eyles' infection. But Coatney also expressed concern about critics who "implied that the establishment of a *cynomolgi* parasite in man was nothing more than a laboratory curiosity" (Contacos and Coatney, 1963, p. 914). In other words, unlike a typical laboratory experimental model, which scholars have described as having "no 'objective' counterparts in nature" (Logan, 2002, p. 355) establishing the natural complement of this experimental model became absolutely essential to Coatney's group.

One method of attempting to recreate "natural conditions" in the laboratory was to import organisms directly from their original environment. In general, the experimental animals used in American and English malariology were not heavily standardized. Of the malaria research in the first decades of the twentieth century, Slater writes, "the birds, parasites, and insects that made up these complex, multiorganism malaria models were not highly inbred, and often were creatures of the wild or the market" (Slater, 2005a, p. 264). This was also true of most of the monkeys used in the experiments overseen by Coatney. Indeed, throughout the first half of the century, most primates for biomedical research were imported directly from India or other locations in Asia. Malariologists and their family members recall collecting primates for research, accompanying trappers on expeditions or seeking them in public marketplaces (Slater, 2005b, pp. 13–16 and 20; Eyles, n.d., p. 93). After all, it was not until 1962 that the first Regional Primate Research Center opened in the United States, ushering in an era of locally bred primates for research.[14] Until that time, the rhesus macaques of malaria laboratories were typically only one degree removed from their natural environment.

Even the malaria strain used by Coatney's group appears to have been a step closer to "nature" than the strain used in other labs in the

[12] In 1958, Coatney represented the NIH as a WHO consultant (WHO, 1959) and in 1960 he was a member of the committee (WHO, 1961a, b).

[13] My italics.

[14] Eventually there was would be seven of these centers, scattered throughout the U.S. (Dukelow and Whitehair, 1995, pp. 1–2).

United States. While most American malariologists in the late 1950s shared a strain of the monkey parasite *P. cynomolgi* that had been isolated from an infected macaque seventeen years earlier, Eyles had a new strain, which P.C.C. Garnham had taken from a macaque in Malaysia in 1957 (Eyles et al., 1960, p. 1812). After 1960, Coatney and others hypothesized that the newer strain of the parasite was able to jump hosts, from monkeys to humans, because of its more recent wild origin. In other words, the older strain had been used as a laboratory model for too long – it was domesticated and no longer held many of the properties that tied it to its natural ecological existence. While not engineered in the same sense as a standardized organism, the strain's long perpetuation in the contrived environs of the laboratory had separated it from its natural origin and converted it into a tool of the laboratory.[15] By contrast, the newer strain of monkey malaria challenged the assumptions and artificial strictures that scientists had attempted to place upon it; it retained a wild quality even within the laboratory, a fact that the malariologists involved in subsequent experimentation appeared to appreciate.

Soon enough, Coatney's group made the conscious decision to import a *naturally infected* simian host as well: After the initial set of trials with Eyles' infected blood, an infected macaque was trapped in Malaysia and shipped to the U.S., where its parasite was transferred to six new human inmate volunteers. Three inmates received the malaria parasite by mosquito bite while the remaining three all received it via an injection of the infected monkey's blood – and all of these were also infected (Contacos and Coatney, 1963). After this set of experiments, Coatney and his colleagues were increasingly confident that their strain of malaria was no mere "laboratory curiosity."

While monkeys and malaria could both be physically imported from Malaysia, defining a "natural infection" in a human prison inmate population had much to do with the experimental protocol put in place. Images from the 1966 *New York Times Magazine* article give a sense of how human subjects in the prison were viewed and employed. A photo on the first page shows the project's mosquito breeding facilities, with a caption reading, "Rabbits and monkeys, as well as human volunteers, are used in the search for drugs to combat the disease" (Gilmore, 1966, p. 44). While humans are set apart in this phrasing, the clinical gaze of the camera lens in the series of photos that follows seems to equate the

[15] The "domestication" of malaria in this case is reminiscent of the first stages of the process described by Robert Kohler in his earlier work, when wild *Drosophila melanogaster* entered the laboratory, was domesticated, and was subsequently transformed into an iconic standardized experimental model (Kohler, 1994).

rabbit with the faceless body parts of the inmate volunteers – most notably their bared forearms, against which white-coated laboratory technicians hold vials containing malarious mosquitoes.

These vials held the key to mimicking nature: that is, via the *natural route* of malaria infection. Previously, many such transmission experiments had taken place using blood inoculation. After all, as of 1960, virtually nothing was known of the *natural vectors* of monkey malaria; these would not begin to be elucidated until Coatney himself sent a team of scientists into the field in Malaysia. Blood inoculation was, in the first place, apparently less effective than infection by mosquito vector. More importantly for Coatney's purposes, though, blood inoculation did not represent what happened in *nature*.

Thus, as experimentation proceeded in the Atlanta Federal Penitentiary, efforts were directed in particular at demonstrating mosquito transmission of the monkey malaria parasites. Figure 1 is an example of a diagram the team produced to trace the passage of malaria parasites between hosts. While some transmissions were achieved via blood inoculation, many more infections were transmitted by mosquito vector. The complex chain of infection reveals how freely the "monkey malaria" parasite could be passed between both monkeys to humans.

Coatney's team quickly demonstrated that every permutation of this cross-infection was possible – at least in the laboratory. And indeed, it's clear that the prison trials were run as a very strict laboratory. As Collins recalled from his time working at the prison, it "was a totally controlled environment," which essentially converted the human inmates into experimental laboratory animals (Slater, 2005c, p. 9).[16] An argument for the congruence of malaria infection between monkeys and humans, and the concomitant conversion of human subjects into laboratory animals, was only advanced when the aforementioned wild-

[16] I would suggest that it was possibly a better-controlled environment than Eyles' lab, where infected mosquitoes were able to escape experimental protocols and infect experimenters. This experimental picture reflects Nathaniel Comfort's analysis of the related research program at Stateville Penitentiary in Illinois, which was launched shortly after the Atlanta program. Indeed, he discusses the transformation of inmates into objects for research, a process aided by the fact of their incarceration, which had already removed a degree of agency and individuation (Comfort, 2009). Even outside the prison context, researchers have been known to equate human clinical research subjects with laboratory animals, as Susan Lederer has described (Lederer, 1997, p. 123). But the prison offered a level of standardization and control that would have been virtually impossible in any other population of human research subjects. Thus, it's no surprise that experimental volunteers in prison might be even more thoroughly converted into "analytic objects" than other humans participating in clinical research (on "analytic objects," see Lynch, 1988, pp. 265–266).

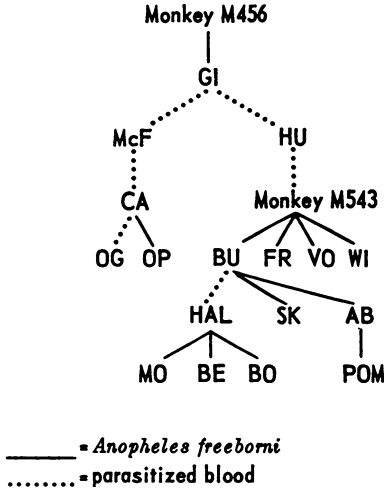

Figure 1. Diagram of a series of transmission experiments undertaken at the federal prison in Atlanta. *P. cynomolgi* was passed repeatedly between macaques and humans, the latter of which are denoted by initials. Solid lines indicate transmission via mosquito (*Anopheles freeborni)*, while dotted lines indicated transmission via blood, from an infected subject to an uninfected subject (Contacos et al., 1962, p. 189). Image provided courtesy of the *American Journal of Tropical Medicine and Hygiene*

infected macaque was imported into the laboratory and the inmate population was used to study the parasite it carried (Coatney, 1963). This trial entailed the reversal of the standard method of identifying the specific causal agent of a human infection: Instead of isolating a parasite from a human and transmitting it to an experimental laboratory animal for verification, Coatney's team transferred a parasite from a monkey to a human for precisely the same reason. This striking inversion of Koch's postulate clarifies the status of the human inmate volunteers, who had become subjects of experiments designed to study the disease of a nonhuman animal.

The deeper evolutionary implications of this inversion were also apparent. Coatney would claim decades later that that the "greater question" apparent at the time had direct bearing upon the evolutionary relationships between primates, asking, "is monkey malaria a true zoonosis, an anthroponosis, or both?" (Coatney, 1985, p. 10). In other words, not only were humans susceptible to "monkey malaria," but the possibility now existed that the disease had actually *originated* with humans. This perspective represented a new fluidity in perceived biological and disease relationships between humans and monkeys, a chink in the boundary separating us from other primates, and the advance-

ment of an argument for our proximity to and symmetry with them. More specifically, however, it indicated a more nuanced definition of ''natural'' infection, hinging not only upon *where* infection took place, but also *when*, in evolutionary time, the infection had become possible. This was the critical question of host specificity, in which the susceptibility to infection was used to understand evolutionary relationships. In the next two sections of the paper, I show that understanding the malaria infections of primates was not just about public health and understanding the mechanism of malaria infection; it was equally about inferring evolutionary relationships and distance between hosts and understanding the ecological requirements of the malarial parasite.

Following Monkey Malaria Back into "Nature"

As the transfer of parasites between monkeys and men continued apace in the prison and laboratory in the U.S., ecological questions about monkeys, malaria, and humans became more pressing. The only way to pursue these questions was to follow the erstwhile-decontextualized experimental organisms back into their natural context: the forests of Malaysia. Within the year following his recuperation from malaria, Eyles, his family, and a number of NIH colleagues relocated to Kuala Lumpur. The city proved an ideal setting for this research, thanks to its ease of access to the forests where monkey malaria, *P. cynomolgi*, would most likely be found. McWilson Warren, a parasitologist heavily involved in this phase of the research, recalled that one ''could travel 15 miles out of the city and it was pure jungle at that time'' (Slater, 2005b, p. 19). The city was also home to the Institute for Medical Research (IMR), a renowned British institution dating back to 1900, which gave Coatney's NIH team a chance to collaborate with expert tropical disease researchers (Slater, 2005b, pp. 9–10). Moreover, the US Army Medical Research Unit also had an ''arrangement with [the] Malaysian government for bringing in funds from the outside'' to support research at the IMR. According to Warren, this ''was the means by which funds for the special program in which Don Eyles was going to be working were brought into Kuala Lumpur,'' and the NIH Far East Research Unity (FERU) was established (Slater, 2005b, p. 10).

The team began immediately to look for links between local populations of humans and monkeys, asking if they might serve jointly as hosts of the same species of malaria parasite. Public health concerns motivated the research, but in practice, the ensuing scientific interro-

gation took the form of natural history. Eyles had an M.S. in Biology from Emory University and a Sc.D. (Doctor of Science) from Johns Hopkins School of Hygiene and Public Health (Bruce-Chwatt, 1963). The latter was known for its medical zoology, developed by parasitologist Robert Hegner, who considered the field to be a "subdivision of zoology," with equally important "scientific and practical phases" (Hegner, 1924, p. 551). This foundation enhanced Eyles' standing as a naturalist, and it was this impression that he gave to his colleagues, who remember most strongly the breadth of his biological interests. Warren refers to Eyles as "the most accomplished, the most brilliant scientist/thinker that I ever had the opportunity to be around" (Slater, 2005b, p. 8).[17] Eyles' wife Mary was also trained as a biologist and worked with the team, helping to mist-net bats, in order to collect their malaria parasites (Slater, 2005b, p. 13). Her self-published memoir offers an invaluable window into the diversity of Eyles' interests, and she describes many happy years of botanizing and bird watching with her husband, before his untimely death in 1963, just as they were about to leave Malaysia (Eyles, n.d.).[18] Thanks to the broadly biological approach of Eyles and his colleagues, their work exemplified a dual medical and naturalistic approach, which can be seen in the research questions that they asked: What undiscovered species of monkey malaria parasites thrive in Malaysia? Can these parasites infect humans? Which species of mosquito serve as the natural vectors of *Plasmodium cynomolgi* and other Malaysian species of malaria? What types of habitat do these vectors prefer? And, finally, in their native habitat, will these vectors bite both monkeys and humans?

During the first three years of their research in Malaysia, Eyles and his team uncovered five new species of simian malaria and "some two dozen natural vectors of monkey malaria" (Coatney, 1968, p. 147), the first such vectors to be identified anywhere in the world (Eyles, 1963; Warren and Wharton, 1963). But their ecological mandate required more than simply the collection of indigenous mosquitoes; they needed to know if these simian malaria vectors were both able and likely to feed on humans. Instead of bringing these mosquitoes into the lab and forcing them to conform to experimental conditions, Eyles and his team wanted to observe them in their natural context. To do this, they had to develop

[17] Warren describes, for example, how Eyles led him on an expedition to collect microscopic snails, from which they later wrote a paper on divergence in shell patterns of different local snail populations (Slater, 2005b, p. 13).

[18] Sadly, Eyles died of a heart attack just after he and his family boarded a boat in Penang that was to take them back to the United States (Bruce-Chwatt, 1963; Eyles, n.d., p. 131).

original experimental field methods. Mosquito collection took place at night, from sunset to sunrise, using nets stitched together into traps by a seamstress they found working just down the street from the IMR. Asked where they had acquired their mosquito trapping methods, Warren replied, "All these technologies were new with us" (Slater, 2005b, p. 18). The traps were erected both at ground level and in the canopy of the forest, and baited with both live humans and monkeys. In other words, monkeys in cages and human volunteers on platforms would spend long nights in the forest, simply waiting for hungry mosquitoes to home in on their bare skin (Warren et al., 1970). In each case, trapped mosquitoes were identified and dissected. Where crossover occurred between the species of mosquito captured in monkey-baited and human-baited trips, it was assumed that the species was attracted to both monkeys and humans. Thus, the malaria carried by these species of mosquito could plausibly be passed between monkeys and human. This combination of opportunistic collecting and experimentation was an explicit attempt to follow host animals and their parasites: first across geographical boundaries, from the United States to Malaysia, tracking both monkeys and humans; then across ecological boundaries, crossing zones of the forest to track the movements of both mosquitoes and malaria parasites; and finally across the boundaries that separate the bodies of different animal species, in order to understand what conditions could make cross-infection possible.

In these attempts to follow both human and nonhuman primates, Eyles, Warren, and their colleagues also had a good deal of direct contact with local populations of both species. In his interview with Slater, Warren recalled his experiences collecting primates for research with Eyles and with regional animal trappers (Slater, 2005b, p. 18). Local villagers also kept monkeys and gibbons as pets, and these could be adopted into the experimental program if they were discovered to carry a malaria infection (Slater, 2005b, p. 20). The sense of proximity between humans and nonhuman primates is only heightened by the accounts that Warren and Mary Eyles gave of the connection between the Eyles family and their pet gibbon, Watu (pictured with Don Eyles in Figure 2).[19] The NIH researchers were immersed in local nature, which included insects and plants, nonhuman primates and a great variety of human ones from both local towns and far-flung forest villages, including hunters, trappers, pet-owners, and tradespeople.

[19] Mary Stipe Eyles writes in her memoir that in Eyles' initial visit to Malaysia in 1963, he also traveled to Bangkok to purchase monkeys for their experiments, "and a little gibbon clung to the edge of the cage and kept calling to him. So Don bought him" (Eyles, n.d., p. 93). See the caption of Figure 4 for Warren's account.

Figure 2. Don Eyles and the pet gibbon, Watu, whom he acquired while in Bangkok, purchasing monkeys for experimentation. McWilson Warren recalls: "He was a pet of the Eyles and absolutely devoted to Mary Eyles. When Don and Mary left, they left the gibbon with me…I would feed this animal everything one could think of, trying to keep it going, but it pined away, it died. I could not get it to eat anything. Once Mary was no longer there, if refused to eat and it starved to death" (Slater, 2005b, pp. 20–21). This sense of closeness between parasitologists and their primate research subjects is not unusual. A similar image of P.C.C. Garnham, holding a chimpanzee, marks the opening of a volume of dedicated to him on his 80th birthday, suggesting how important such inter-primate relationships were in his research (Canning, 1981). Not all researchers literally took nonhuman primates into their families, as Eyles did, but many regarded them as such anyway; for example, British parasitologist Clifford Dobell referred to his research subjects as his "monkey-family" in journal articles (Dobell, 1933, p. 456). Photo provided courtesy of Don Eyles, Jr

Through their work in the field, following mosquitoes and malaria parasites, the researchers quickly realized that the vectors that regularly carried the monkey malaria parasite, *P. cynomolgi*, were attracted to both humans and monkeys, and would readily bite either one. Nevertheless, screen as they might, Eyles, Warren, and their colleagues could detect very

few active monkey malaria infections in the local human population. In one trial, Warren collected the blood of over 1100 people from the surrounding populations and, pooling the samples into groups of 10, he inoculated over 100 malaria-free rhesus macaques. Not a single monkey malaria infection was recovered in this experiment (Warren et al., 1970).

Because monkey-malaria vectors seemed equally likely to bite both monkeys and humans, the research team left the laboratory behind and headed to an environment where mosquitoes were most likely to encounter both species of potential host animal, travelling on foot to make contact with forest-dwelling human populations. Mary Eyles accompanied them on one such trip, describing the hike, in which scientists lugging microscopes created a "human rope" to ford a river. "The purpose of the trip was to take blood smears," she wrote, noting, "By letting the aborigines look in the microscope, they became interested and friendly. The scientists also took cigarettes and candy in for good will" (Eyles, n.d., pp. 109–110). In his *New York Times* Magazine piece, Gilmore would refer to these forest-dwelling populations of humans as *reservoirs* – a term usually applied to nonhuman animal populations harboring human disease – writing that "such untreated populations [of humans] continue to be reservoirs of infection that can break out into neighboring regions at any time" (Gilmore, 1966, p. 59). In other words, like the inversion of Koch's postulate that Coatney's team enacted in the laboratory, the hypotheses of Eyles and his team in the field were based on a similar inversion, testing whether *humans* could serve as "reservoirs" for a *monkey* parasite. Nevertheless, despite the researchers' efforts to reach deep into the forest, where monkey and human populations were in close proximity, these human blood samples still did not produce a single infection in any of the inoculated monkeys back in Kuala Lumpur (Warren et al., 1970).

The team proposed a plausible explanation for this apparent lack of human exposure. While their collection experiments demonstrated that simian malaria vectors happily bit human hosts, these mosquito species also tended to spend most of their time high in the forest canopy, a niche in the forest not visited by the typical human. In other words, Warren, Eyles, and their colleagues were finding that the habitats of humans and indigenous simian malaria vectors did not overlap to a significant extent, even in the deep forest (Warren et al., 1970). This was an important ecological conclusion, with public health ramifications. While it did not eliminate the danger of malaria reservoirs in forest populations of primates, it did suggest that cross-infection between monkeys and humans was unlikely under existing social and ecological conditions.

A second plausible explanation, *not* mutually exclusive with the first, was that humans could develop some degree of immunity to the malaria

parasite (Coatney, 1968). In other words, local human and monkey populations had become true joint hosts of the same parasite. And, as scattered evidence of cross-infection accumulated within Malaysia, it mostly came from the incursions of travelers into the deeper recesses of the jungle. These travelers were almost invariably foreign visitors, not indigenous people – providing some support for this immunological explanation. To understand the dynamics of how this malaria parasite was shared and communicated across the ''species boundary,'' the researchers would have to focus on following humans who had themselves crossed geographical boundaries, into new ecological zones, where they would be exposed to unfamiliar parasites.

In an attempt to do just this, one collaborator on the project, a Dr. Bennet, volunteered to act as an immunologically ''clean'' human subject, allowing an infected simian malaria vector to bite him (Coatney, 1968). While this experiment was much like those carried out already in the U.S., there was a critical difference that reflected the group's desire to understand infection in nature: The vectors used in Memphis and Atlanta were typical experimental vectors, not the mosquito species found in the ecological context where the malaria strain had originated. Thus, when Bennet was successfully infected, it was the first time an indigenous Malaysian mosquito had been shown to transmit simian malaria to a human. And yet – it was still an *experiment* and Coatney felt he had to qualify his results, writing, ''Even with this demonstration, the original question remain[s]; namely, does it happen in nature?'' (Coatney, 1968, p. 148). The ideal demonstration in Coatney's eyes would be an infection resulting from ''natural'' human movement, a geographical shift completely unrelated to the experimental conditions that his team had established in Malaysia.

Coatney did not have to wait long to find just such a human, with just such a ''natural'' infection. In 1965, the same year that the report of Bennet's infection was published, a 37-year-old surveyor for the U.S. Army Map Service took a short visit to peninsular Malaysia. He travelled on to Thailand, where he started to feel ill. It was not until he returned to the U.S. that his doctor suggested he might have malaria – the most severe form of human malaria parasite, in fact, *P. falciparum*. Fortunately, the surveyor was referred to the Clinical Center of the NIH for a confirmation of the diagnosis. The NIH doctor who examined him knew of Coatney's simian malaria research project and referred his patient onward. Examining the surveyor's blood microscopically, Coatney more capably discerned the species of the malaria parasite: Rather than a human parasite, the culprit was *P. knowlesi*, another

parasite of macaques. The surveyor's case was the first report of a human infection with monkey malaria *in nature*. In reporting the case, Coatney and his colleagues were unambiguous about the status of the infection: "This report of a naturally acquired malaria infection in man transferable to monkeys represents the first proof that simian malaria is a *true zoonosis*" (Chin et al., 1965, p. 865).[20] For them, both practically and theoretically, this monkey malaria parasite had breached a critical medical and biological separation between humans and nonhuman primates.

Throughout this account of monkey malaria research, the gold standard of *natural* zoonotic infections shifted gradually. First, the wild nature of the malaria strain lent Coatney's team's experiments the authenticity of nature. Next, a naturally infected animal was imported to an NIH lab. In the prison research setting, the natural mode of infection was paramount. Like many twentieth-century scientists addressing biological questions, Coatney was attempting to meet the ideals of the laboratory – striving for results that could be generalized, even universalized – while also attempting to mimic natural conditions (Kohler, 2002). Finally, bowing to the strictures of the WHO's definition of zoonosis, it became necessary to see how infection happened "in nature" itself. But even then, nature proved elusive, when the local populations of humans were not demonstrably infected with monkey parasites. The notion that these populations were regularly exposed to monkey malaria and were, in effect, joint hosts of the parasite along with local monkey populations, was supported by the easy infections of nonimmune outsiders like Dr. Bennet. Still, it was not until an unsuspecting traveler met a mosquito infected with monkey malaria that the principle was finally demonstrated in Coatney's mind. Perhaps most importantly, that unsuspecting traveler had his infection diagnosed by a malariologist expert enough to discern between *virtually indistinguishable* human and monkey malaria parasites. Only after all of this was Coatney ready to declare that monkey malaria was a "true zoonosis."

This redefinition of simian malaria had serious ramifications, not only for the future of malaria eradication, but also for the researchers' understanding of relationships between humans and nonhuman primates. Practically speaking, it is easy to see this effect in the experimental record. Prior to commencing the surveyor's treatment, Coatney had samples of the man's blood sent to Atlanta, where it was inoculated into both human prison inmate volunteers and monkeys, just as they had done with Eyles' blood five years earlier. And, just as in 1960, the

[20] Italics in original.

infections were successful. Again, human subjects were placed in the role of laboratory animals, using humans and nonhumans in parallel.

In retracing the parasite's path, from his lab in the United States back to peninsular Malaysia, Eyles and his team were fleshing out the ecological and evolutionary landscape of these organisms. Where once they had been circumscribed by the experiments into which they were slotted, now primates and their parasites were again seen as meaningful biological entities, embedded in their own biological reality and history, linked by the reconfiguration of the host specificity of the malaria parasite. This revivification of malarial macaques as ecological entities, along with the continued reversal of human and monkey roles in both the lab (where humans served as laboratory animals) and field (where human populations could be reservoirs for nonhuman disease), wrought an increasing degree of symmetry between human and nonhuman primates. In the final section of this paper, I will draw out the ramifications of this process, examining how the altered conception of malaria host specificity changed parasitologists' ideas about primate evolution and brought ''monkeys and man'' into closer proximity.

Using Parasitic Infection to Reconstruct Evolutionary Relationships

When Eyles was infected with ''monkey malaria'' in 1960, his research program was already based upon a basic assumption of symmetry between humans and other primates. At the same time, a biological boundary was perceived between monkey malaria and human malaria, firmly grounded in the belief that ''malaria in the monkey was for monkeys and malaria in man was for people'' (Coatney, 1985, p. 10). This apparent paradox was an outgrowth of the parasitological practices of the preceding decades, in particular the ''host–parasite method'' (Metcalf, 1929), which placed importance both on inferred evolutionary relationships between species *and* on empirical evidence of infection. In other words, parasitology was a domain where the traditions of natural history and taxonomy converged (and sometimes conflicted) with laboratory- and field-based medical research. Following primates and their malaria parasites as they move across this historical domain provides an opportunity to analyze how these different modes of science were pursued in concert and how their interaction shifted the taxonomic and disease identities and evolutionary relationships of the organisms that parasitologists studied.

G. Robert Coatney had already applied the logic of the ''host–parasite method'' in the 1930s, when he chose the pigeon as an experimental

host for his unique dove-derived avian malaria strain and explained the choice using the birds' evolutionary proximity (Coatney, 1938). Three decades later, he perpetuated it still, writing that "the great evolutionary gap" between monkeys and humans explained the challenges parasitologists faced passing malaria parasites between the species (Coatney 1968, p. 148). Yet, such sizeable gaps were repeatedly spanned by malaria parasites in the 1960s, creating points of tension between taxonomic designations and phylogenetic inference, on the one hand, and empirical medical evidence, on the other.

For Coatney and his colleagues, these points of tension were opportunities for parasitological evidence to shed light on primate phylogenies. The precedent for using parasitic infection to understand primate evolution had been set as early as 1928, when Johns Hopkins protozoologist and proponent of the host–parasite method Robert Hegner wrote, "If the proposition that close relationships of parasites indicate a common ancestry of their hosts is valid, then the facts available regarding the protozoan parasites of monkeys and man furnish evidence of importance in favor of the hypothesis that monkeys and man are of common descent" (Hegner, 1928, p. 242; Mason Dentinger, 2013, 2014). Work on a variety of other parasites was also brought to bear on the descent of primates,[21] and by the time Solly Zuckerman published *Functional Affinities of Man, Monkeys, and Apes* in 1933, "The Diseases and Parasites of the Primates" merited its own chapter, alongside those comparing the reproduction, blood, behavior, and sensory organs of primate species. Zuckerman expressed concerns about "phylogenetic speculations based on comparative host–parasite studies," but admitted that the "fame of this phylogenetic method has grown to such proportions that it cannot be passed over" (Zuckerman, 1933, p. 80).

Throughout the 1950s and 1960s, primate phylogenies were in dispute, and the newer laboratory methods seemed to complement and challenge traditional phylogenetic methods in equal measure. The application of serological techniques to primate kinship had already suggested that humans might have closer ties to chimpanzees and gorillas than previously imagined (Proctor, 2004; Hagen, 2009, 2010; Strasser, 2010; Delisle, 2012). As such, it's unsurprising that Coatney and his colleagues might see parasitic cross-infection between humans and monkeys in a new light: Did the restructuring of evolutionary relationships in the primate lineage mean that monkey malaria was indeed more of threat to humans? And, conversely, could these infections provide corroboration for other innovative phylogenetic techniques? While these parasitologists believed that

[21] E.g., Darling (1921) on hookworm.

their field had contributions to make to evolutionary thinking on a broader scale, there is little evidence – outside of Zuckerman's inclusion of the method in his volume – that their ideas about host animal evolution directly influenced evolutionary thought beyond the domain of parasitology.[22] Thus, the importance of this historical case does not rest upon the impact parasitology had upon evolutionary biology, but upon the hybridization between medical and evolutionary research practices that was integral to the field of parasitology itself.

As such, host specificity is historically interesting not only as a defining concept in parasitology, but also as a crucial point where medical and evolutionary research goals were fruitfully linked together. P.C.C. Garnham, who had been associated with Coatney's project since he contributed his freshly isolated strain of *Plasmodium cynomolgi* for Eyles' laboratory experiments in 1960, was instrumental in this regard, greatly expanding the evolutionary relevance of primate malaria cross-infection.[23] When Coatney convened a special symposium on simian malaria in 1963, in conjunction with a meeting of the International Congress of Zoology, Garnham numbered amongst the contributors, which also included Warren and Eyles.[24] Having begun his career in the 1920s studying medicine at St. Bartholomew's in London and at the London School of Hygiene and Tropical Medicine (LSHTM), Garnham then worked as a colonial medical officer in Kenya for more than two decades, pursuing the malaria parasites of African monkeys. His interest in nonhuman malaria parasites and his additional knowledge of entomology exemplified the breadth and depth of his interest in parasite natural history, which was further borne out in the second phase of his career, when he returned to London as a Reader in Medical Protozoology at LSHTM, and later Head of the Department of Parasitology (Lainson and Killick-Kendrick, 1997). Three years after the 1963 symposium on simian malaria, Garnham would publish *Malaria Parasites*

[22] However, even an evolutionary biologist of the caliber of Ernst Mayr saw that parasitic infection might yield insights into host evolution (Mayr, 1952, pp. 139–140), and he collaborated with Swiss parasitologist Jean Baer to convene on conference on the topic, bringing together parasitologists and other zoologists (Baer, 1957; Mayr, 1957).

[23] As Coatney's malaria project expanded in the early 1960 s, Garnham continued his association with various members of the team, corresponding extensively with Eyles and contributing to the group's effort to understand the relationships between different species of malaria and different species of hosts. For example, see letters in folder PP/PCG/D/59, Papers of P.C.C. Garnham, Wellcome Collection.

[24] Eyles had passed away earlier in the year, but his paper, "The Species of Simian Malaria: Taxonomy, Morphology, Life Cycle, and Geographical Distribution of the Monkey Species," was included posthumously in the publication of this special session (Eyles, 1963).

and other Haemosporidia, which was considered the definitive volume on plasmodium biology and taxonomy. However, his expertise and interests ranged far beyond malaria, and he studied a vast array of parasites and wrote on many different aspect of parasitology throughout his long career, with a particular interest in the evolution of parasites and parasitism.[25] Garnham's work represented precisely the sort of synthetic analysis that could address points of intersection between infectious disease and evolutionary history.

In his contribution to the symposium, Garnham took the subject of simian malaria as a launching point from which he could address the taxonomic and phylogenetic instability of all primates. In the style of the host–parasite method established by a previous generation of parasitologists, Garnham transmuted the medical qualities of infectivity and susceptibility into characters useful for other types of zoological inference. He provided a graphic representation (Figure 3) of how medical research might be used to mutually inform evolutionary research, correlating infectivity/susceptibility with a posited primate evolutionary tree. Instead of setting humans and their associated parasites apart from all nonhuman primates and their parasites, Garnham's tree drew the malaria parasites of apes and humans into close proximity, while placing those of monkeys at a greater evolutionary distance. He drew on contemporary paleoanthropological research, including serological methods, when he wrote: "There is evidence today that the chimpanzee and gorilla are closer to man than the other so-called higher apes," arguing that the clustering apparent in patterns of malaria infection could be used to bolster this hypothesis (Garnham, 1963, p. 905). Finally, he went on to propose points in the shared evolutionary history of primates and their malaria parasites where both lineages jointly diverged, establishing an evolutionary narrative that accounted for both hosts and parasites (see Figure 4).

Before the end of the decade, Coatney would follow Garnham's lead in making strong zoological claims based upon disease transmission between host species. Where Garnham used evidence of parasitic cross-infection to infer a closer relationship between humans and apes, Coatney argued that humans and chimpanzees shared *identical* parasites, where previously parasitologists had recognized separate "counterpart" malaria species. Like other protozoan parasites of primates, the malaria parasites that infect humans and chimpanzees often appeared morphologically and functionally indistinguishable (Bray, 1963).[26] Despite this appearance,

[25] See, for example, Garnham (1959, 1971).

[26] On the generality of shared morphology between monkey and human protozoan parasites, see Hegner (1928) and Dobell (1933).

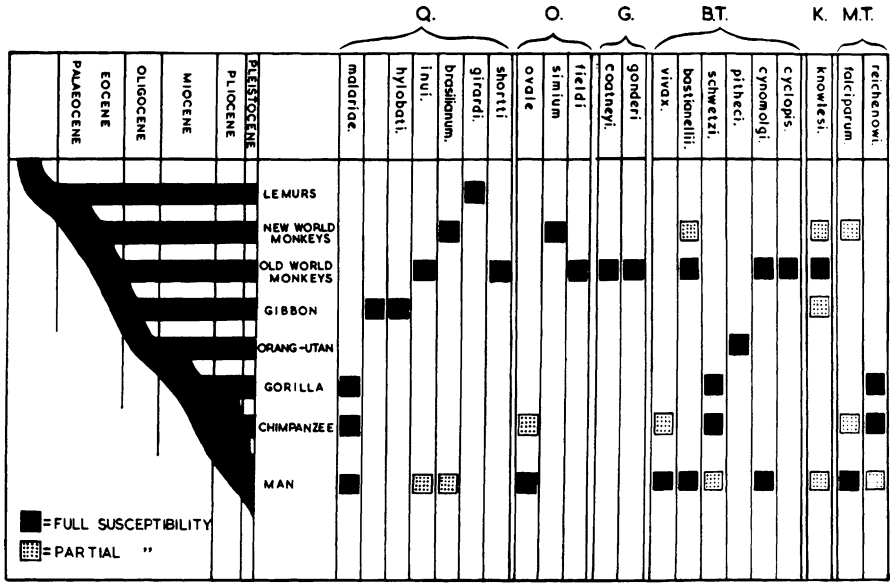

Figure 3. From Garnham (1963, p. 910). Image provided courtesy of Allen Press Publishing Services

however, malariologists, like other protozoologists, assigned different species identities to these parasites, by virtue of their discovery in the bodies of human or chimpanzee hosts. In some cases, this division seemed justified, as the apparently indistinguishable parasites proved to resist cross-infection between the different species of primate host.[27] But in other cases, counterpart parasite species were morphologically identical *and* they could infect humans and chimpanzees with equal facility.

P. malariae of humans and *P. rodhaini* of chimpanzees represented just such a pair of counterpart species. "When *P. rodhaini* is given to man via inoculation of parasitized blood it produces a clinical picture typical of *P. malariae*," Coatney wrote in 1968. "It is clear, then, that the quartan parasite of man [*P. malariae*] and of the chimpanzee [*P. rodhaini*] are actually *the same parasite*,[28] as suggested by Rodhain as early as 1940, and should [both] be considered as *P. malariae*" (Coatney, 1968, p. 149). Coatney had taken the results of medical experimentation on cross-infection and used them to make a taxonomic argument for collapsing the two counterpart parasite species into one. But why had these parasites been given separate species designations in the first

[27] As in the case of *P. falciparum* and *P. reichenowi* (Coatney, 1968, p. 149).

[28] My italics.

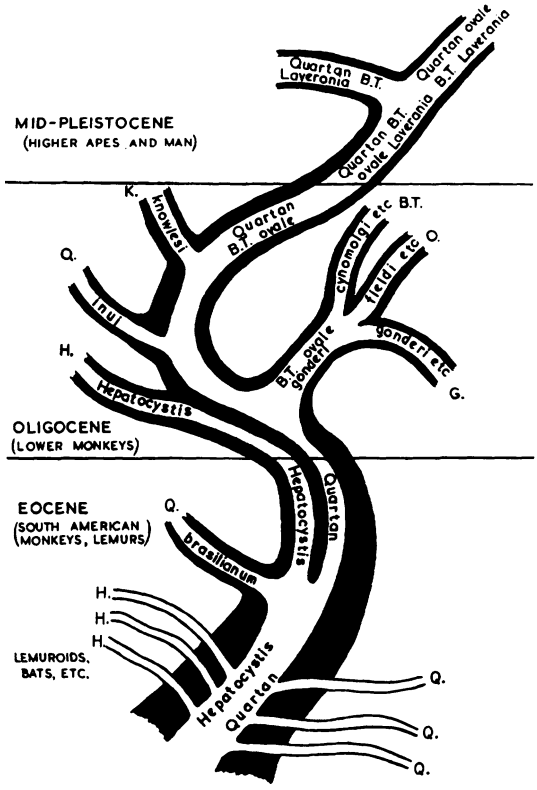

Figure 4. From Garnham (1963, p. 909). This diagram implies what biologists today would call "coevolution" of hosts and parasites. At the time, this concept and word was not in usage (with one exception: Mode, 1958), though it would soon gain currency with the development of the field of "coevolutionary studies" (Mason Dentinger, 2009). Image provided courtesy of Allen Press Publishing Services

place? And if Rodhain had suggested they were identical in 1940, why did Coatney have to argue for their similarity again in 1968? The apparent resistance to Rodhain's hypotheses provides evidence that previous to the 1960s, parasitologists had seen a definite species boundary between chimpanzees and humans. Moreover, Coatney could not let the argument rest even in 1968, asserting again, only three years later, that "*P. rodhaini* most likely does not exist but *P. malariae* does, and it infects man and apes…It apparently goes from man to ape and from ape to man with no detectable alteration in morphology or life pattern"(Coatney, 1971, p. 798).[29] In this, Coatney was making an

[29] Even today *P. rodhaini* is often described as a parasite of apes, even when its synonym with *P. malariae* of humans is subsequently acknowledged (Abee et al., 2012).

argument that joined together his medical understanding of malaria infection with evolutionary inference, arguing simultaneously that chimps and humans were closely related and that their malaria parasites, once thought distinct, were actually the same species.

For Coatney, linking taxonomic identity to the history of host–parasite associations had repercussions in the realm of public health and beyond. If *P. malariae* of humans and *P. rodhaini* of chimpanzees are one and the same, he wrote in 1968, "either this simian parasite became adapted to early man, or the exchange of this parasite between chimpanzee and man has been taking place for thousands of years. In the same vein, once the parasite was acclimated to man, it was available for transfer back to the chimpanzee. In other words, this simian malaria is a zoonosis of long standing and, more recently, under favorable conditions, an anthroponosis as well" (Coatney 1968, p. 149). The easy communication of disease that Coatney described would surely present a challenge to anyone still championing the failing project of worldwide malaria eradication. Yet, Coatney's account asserted something more than his notion that malaria was a historical breaker of species boundaries. It also conveyed what he saw as the ecological and evolutionary proximity of humans and chimpanzees. Coatney, like Garnham, believed that shared parasitic infections between humans and chimpanzees contained evidence for their shared evolutionary descent. Unlike Garnham, however, Coatney did not attempt to provide a graphic phylogenetic representation in support of his position. Instead, he concluded his paper poetically, quoting century-old verse, originally published in *Punch* in 1861 (Coatney, 1968, p. 152):

> *Am I satyr or man?*
> *Pray tell me who can*
> *And settle my place in the scale;*
> *A man in ape's shape,*
> *Or anthropoid ape,*
> *Or a monkey deprived of a tail?*

For Coatney, then, recognizing the surprising *lack* of host specificity in primate malaria parasites was a watershed in two interconnected ways: First, it constituted an unrecognized public health threat; and second, it prompted a realization of his own proximity to other primates. While the versification of this dual insight added a personal note to Coatney's case, it was, at the same time, just an extension of the decades of research that had preceded his own, which had linked together medical and evolutionary questions and research agendas in the pursuit of parasitology.

Conclusion

In 1971, the NIH published *The Primate Malarias*, a 300-plus-page volume summarizing the current state of knowledge, coauthored by Coatney and his colleagues from the primate malaria research project of the past decade. For each species treated in this volume, the life cycle, course of infection, host specificity, and immunological reactions of the host were compiled – an amalgam of zoological and medical data. In the first chapter, ''Evolution of the Primate Malarias,'' the authors wrote of the challenges inherent in the parasitology, ''since not only must the evolution of the protozoan be accounted for but the concomitant evolutionary development of both the vertebrate and invertebrate hosts as well'' (Coatney et al., 1971, p. 1). This pronouncement captured the complexity of the parasitological perspective, grounded in decades of comparative thinking and the host–parasite method, in which understanding evolution was considered ''more than an academic exercise.'' ''There are some very practical considerations to the evolutionary trends in the primate malarias'' (Coatney et al., 1971, p. 1), they wrote, thus closing the circle: Evolutionary insights could be drawn from medical practices and medical insights could be drawn from evolutionary practices.

For Coatney, linking ''practical considerations'' and ''evolutionary trends'' had been an integral part of his early parasitological training and practice in the 1930s, when he employed ''close zoological relationships'' between bird species to select his experimental model (Coatney, 1938, p. 382). After his move from avian malaria to primate malaria, he observed parasitologists' conviction that malaria cross-infection between humans and monkeys was impossible, and he surmised that it was based on the ''great evolutionary gap'' between these primates (Coatney 1968, p. 148). Finally, once it was clear that malaria parasites could easily cross this boundary, Coatney concluded ''that monkeys and man are more closely related than some of us wish to admit'' (Coatney, 1963, p. 877), indelibly linking disease susceptibility to evolutionary proximity.

Similarly, Coatney's dogged pursuit of zoonotic malaria also reflected the notion of human and nonhuman proximity, ending time and again with the possibility of *anthroponosis* – that is, humans transmitting their own malaria parasites to their primate relatives. Repeatedly, it seems, parasites traversed the species boundary, as in the case of the chimpanzee parasite *P. rodhaini*, passing ''from man to ape and from ape to man''(Coatney, 1971, p. 798). For Coatney, the

implications of this boundary-crossing were clear: Where once malariologists had perceived two separate species of parasite, by virtue of their isolation from different species of hosts, now there was only one species of parasite and a closer relationship between its joint host species, chimps and humans.

The notion of a single species of parasite, jointly hosted by different species of primates, suggested that a narrow focus on eradicating "human malaria" might not suffice to control the disease. Ultimately, however, the broader public health community seems to have paid little attention to the hard-won conclusions of Coatney and his colleagues. The WHO plan to eradicate malaria, initiated in 1955, faced doubts almost immediately, as resistance to antimalarials and DDT were quickly registered. But they continued to push this agenda for another decade, and it was not until 1969 that malaria eradication was called off. That is to say, the demise of malaria eradication was played out at precisely the same time that Coatney and his group were increasingly convinced that simian malaria presented a zoonotic threat to human health. Yet their work seems to have had little direct impact on WHO policy, even though Coatney himself served on the WHO committee in the years just before and after Eyles' infection (WHO, 1959, 1961a, b). Looking back on the malaria eradication program from the vantage point of 1971, Coatney recalled, "The record was clear. Three simian malarias would grow in man, and one…could produce grave disease. Even so, no one considered their zoonotic potential" (Coatney, 1971, p. 796).

In recent years, however, the public health community has come to reconsider simian malaria. Take, for example, *Plasmodium knowlesi*, the macaque parasite that infected a U.S. army surveyor traveling in Malaysia in 1965, and the case that Coatney and his colleagues had declared "the first proof that simian malaria is a *true zoonosis*" (Chin et al., 1965, p. 865). A 2008 editorial in the pages of *Clinical Infectious Disease* describes how "the zoonotic potential of *P. knowlesi* has, until recently, seemed limited, with only sporadic case reports of human infection." However, upon closer inspection of "what appeared initially to be an unusually high incidence of [the human parasite] *Plasmodium malariae*" in Borneo, a research team recognized that, in fact, a large proportion of these infections were actually *P. knowlesi* of monkeys (White, 2008, p. 172). In other words, monkeys and humans in Borneo already share this parasite to a great extent. The morphological differences between the human parasite *P. malariae* and the monkey parasite *P. knowlesi* might easily go unnoticed to the eye of a researcher who

assumes that a "monkey malaria" cannot breach what is often called the "species barrier."[30] By contrast, Coatney and his colleagues followed the trails of monkeys, men, mosquitoes, and malaria, and by working as both medical researchers and natural historians, they were able to observe how easily border-crossing could occur.

Once the boundary between "monkeys and man" was breached for Coatney, Eyles, and their colleagues, moving back and forth between the two species became an ordinary component of their experimental protocol, reflecting the typical parasitological practice of cross-infection between myriad species of animal host. Koch's postulate relied upon the use of nonhuman animal models to detect the identity of an infectious agent isolated from an ill human. But for these parasitologists, a *human model* could just as easily be used to detect the identity of an infectious agent taken from an animal. Their key practice was that of following organisms – parasites and hosts alike – and engaging directly with the circumstances of their lives. Thus a parasite's taxonomic identity and its constitution as a public health threat could simultaneously shift as a result of their practical investigation. Which mosquito species naturally host monkey malaria parasites and where do they live? What happens when humans enter the deep forest and encounter mosquitoes that readily bite both monkeys and humans? What direction does a parasite move in crossing supposed "species boundaries" between different primate species? And at what point in evolutionary history did a species of malaria parasite first make a leap between primate species? Taken together, these questions represent the duality of parasitology and its "host–parasite method," which advanced medical and evolutionary agendas simultaneously.

This historical narrative is distinct from previous accounts, which seek to understand the effect of evolutionary thinking upon medicine.[31] In contrast, this paper demonstrates that the intellectual and methodological traffic can also move in the opposite direction, enabling medical concepts to shape evolutionary practices. Malariologists were particularly well positioned for this form of scientific practice, as they had struggled for decades to find effective experimental models and were accustomed to considering the biological symmetry of human and nonhuman animals. Thus, like parasitologists of previous decades,

[30] The American Society of Tropical Medicine and Hygiene construes this discovery as a vindication of Coatney's work, writing in their newsletter that "It has taken over 45 years to fulfill the goal that Bob Coatney originally sent his people out to prove – that monkey malaria is a true zoonosis." (https://www.astmh.org/source/newsletter/index.cfm?fuseaction=Newsletter.showThisIssue&Issue_ID=11&Article_ID=367, accessed 6 July 2015).

[31] See especially Méthot (2011, 2012).

Coatney and his colleagues moved fluidly between practical challenges and evolutionary conceptions, and their medical mission, to fight malaria, manifestly shaped their ideas about the evolutionary relationships of hosts. Where Coatney and other malariologists had seen "monkey malaria" threatening human health, they came to see a parasite that could be jointly hosted by two different species of primate; and where they had seen separation, they came to see a continuity that reflected a shared evolutionary history.

Acknowledgments

This research was funded by the Wellcome Trust (grant 092719/Z/10/A), on the grant "One Medicine? Investigating human and animal disease." The insights and suggestions of my colleagues on this grant, including Abigail Woods, Michael Bresalier, and Angela Cassidy, have been invaluable. Many thanks also to Julie Hipperson, Gina Rumore, and Kim Mason, who all commented on drafts along the way, and to Georgina Montgomery and Rob Kirk, who both shared information about the use of primates in research in the early twentieth century. Thanks to the participants of the History of Science Society session (Boston, 2013) from which this paper originated, in particular Susan Jones, who provided useful commentary after the session, and Pierre-Olivier Méthot (with whom I organized the session) and Glady Kostyrka, both of whom have generously commented upon this paper. I thank Leo Slater for his advice when I was originally seeking more information about NIH malariologists and for his interviews with these scientists, which I could not have read without the help of NIH archivist Barbara Faye Harkins. Don Eyles' son, Don Eyles, Jr., kindly provided me with a copy of his mother's memoir, photographs of his family, and his own recollections of the time his father fell ill with malaria – not to mention meeting with me in Boston and attending my talk during the HSS meeting! My thanks to two anonymous reviewers, who provided a thoughtful critique of this paper. Finally, thanks always to my husband, Bryn Mason Dentinger, ever the sounding board for my ideas and arbiter of my work.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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