Useful Bodies

Humans in the Service of Medical Science in the Twentieth Century

Edited by Jordan Goodman,
Anthony McElligott, and Lara Marks

The Johns Hopkins University Press
Baltimore and London

103. As mentioned, the Large Area Concept had been discussed at the Tripartite conferences prior to the tests.

104. G. L. Mandell, J. F. Bennett, and R. Dolin, *Principles and Practice of Infectious Diseases*, 4th ed. (London, 1995), 1890–94. Less anachronistically, the meningitis observation was recorded in the scientific literature in 1963, the allergic reaction of detergent workers in 1969. See also Leonard Cole, *Clouds of Secrecy: The Army's Germ Warfare Tests Over Populated Areas* (Savage, MD, 1988) for a similar argument about U.S. outdoor trials.

105. B. Spratt, *Independent Review of the Possible Health Hazards of the Large-Scale Release of Bacteria During the Dorset Defence Trials* (Oxford, 1999).

106. C. E. Stein, S. Bennett, S. Crook, and F. Maddison, "The Cluster That Never Was: Germ Warfare Experiments and Health Authority Reality in Dorset," *Journal of the Royal Statistical Society, Series A* 164 (2001): 23–27. The authors note that interpretation of their results—which compared observed and expected levels of miscarriages, still births, congenital malformations, and neurodevelopmental disabilities—is limited by "a dependence on the calculation of expected health events, which are not routinely recorded, inconsistencies in definitions of the health events in the literature, inaccuracy of exposure ascertainment up to 38 years after the event, the calculation of rates from small numbers of observations and the inclusion of multiple generations in the study" (26).

107. See, for example, H. Wigodsky and S. Keir Hoppe, "Humans as Research Subjects" in *Birth to Death: Science and Bioethics*, ed. D.C. Thomasma and K. Thomasine (Cambridge, 1996); J. E. Sieber, *Planning Ethically Responsible Research: A Guide for Students and Internal Review Boards* (London, 1992); R .E. Bulger, E. Heitman, and S. J. Reiser, eds., *The Ethical Dimensions of the Biological Sciences* (Cambridge, 1993); Bernard Barber, "Experimenting With Humans," *The Public Interest* 6 (Winter 1967): 91–102.

108. In particular, the Tuskegee syphilis experiment. See J. H. Jones, *Bad Blood: The Tuskegee Syphilis Experiment* (London, 1993).

109. Sheila Jasanoff, "Product, Process, or Programme: Three Cultures and the Regulation of Biotechnology," in *Resistance to New Technology: Nuclear Power, Information Technology and Biotechnology*, ed. M. Bauer (Cambridge, 1995): 311–31.

CHAPTER THREE

Whose Body? Which Disease?

Studying Malaria while Treating Neurosyphilis

Margaret Humphreys

In 1931 Sir Henry Hallett Dale, the British physiologist whose work on neurotransmitters made him justly famous, heard a stimulating paper at the Royal Society of Tropical Medicine and Hygiene. Its topic, the use of malaria as a treatment for neurosyphilis, was interesting enough, but what really roused him to comment during the discussion afterward was the splendid opportunity this therapy offered to experiment, with no moral qualms, on a disease in humans. Since the production of malaria was a therapeutic measure of benefit to the patient, it was unambiguously justifiable. So "the ordinary moral difficulty, the ordinary complications which beset the work of a clinician, the ordinary dilemma of choosing between the advantage of the patient and the obtaining of new knowledge was absent in a peculiar sense in this particular case." Dale noted with admiration that "the opportunity had been given . . . of studying malarial infection as an experimentally-produced condition, as an investigation into the natural history of the infection." There must have been at least a tinge of envy in his voice when he labeled this capability as unique, for he "doubted if any other such existed in medicine, and he thought that here was the brightest hope for experimental therapeutics."[1]

From the 1920s on, physicians treating neurosyphilis began routinely to inject malaria parasites into their patients with the hope that the resulting high fevers would kill the syphilis spirochete in the central nervous system. Neurosyphilis, the late state of syphilis in which peripheral neurological dysfunction was often accompanied by insanity and dementia, did not respond to the arsenicals used for the treatment of milder, earlier disease. The malaria produced was real malaria, and it offered researchers an opportunity to study this disease in a controlled setting. Even though malariatherapy was "state of the art" for neurosyphilis treatment in the 1920s and 1930s, it is not quite true that researchers on malaria approached their induced subjects totally devoid of those "ordinary moral difficult[ies]" of which Dale spoke. This chapter explores the ethical and scientific issues raised by just such a research project in the work of Mark Boyd, a Rockefeller Foundation malariologist stationed in north Florida during the 1930s and 1940s.

Research on malaria was not at all what Julius Wagner-Juaregg, the inventor of malariatherapy, had in mind. This Viennese psychiatrist had been seeking a cure for the insane stages of neurosyphilis since the late 1880s, and in 1917 he tried the injection of malaria parasites.[2] Most historians have, in turn, focused on the syphilis story, with varying opinions about the efficacy of fever therapy. For example, three epidemiologists published an essay in 1992 in the *Journal of the American Medical Association* that attempted a meta-analysis of articles on neurosyphilis treated with malaria. The authors concluded that malarial fevers did not produce long-term benefit to syphilis patients, although with the caveat that there were no case-controlled trials that addressed the question with the rigorous standards set by modern science.[3] Other scientists have disagreed, citing the consistency of improvement rates seen in multiple studies.[4] Historian Joel Braslow considered malariatherapy as a part of his broader work on the history of psychiatric treatment in the early twentieth century. He drew the interesting conclusion that once psychiatrists had a treatment for this particular form of madness, they started speaking of their patients with more humanity and compassion. The availability of an apparently successful therapy changed not only clinical behavior but also clinical attitude.[5] From the point of view of the history of syphilis or the history of psychiatry, the advent of malariatherapy was an important episode in the development of somatic therapeutics.

Most contemporary medical writers of the 1920s, 1930s, and 1940s saw

it that way as well. Their focus was on syphilis and on how well fever therapy alleviated the symptoms of advanced disease. Researchers attempted other means of raising the body temperature, such as infusing typhoid vaccine or heating the body with various mechanical devices. Malaria was merely one way to reach a fever high enough to roast the spirochete without killing the patient. Wagner-Juaregg, who won the Nobel Prize in 1927 for his discovery, had tried a variety of substances before hitting on malaria. At first he used tuberculin, Robert Koch's wonder drug for tuberculosis in 1890, until it was discredited as dangerous and ineffective. Wagner-Juaregg tried various other means to induce fever, including the injection of typhoid vaccine, streptococci, and staphylococci. None worked as well, or as safely, as malaria.[6]

Malariatherapy, or fever therapy more generally, became something of a therapeutic craze in the second quarter of the twentieth century. One textbook on fever therapy technique warned in 1939, "Like any new form of therapy, therapeutic fever has been tried indiscriminately in most of the diseases of mankind. . . . The enthusiasm and will to believe of many workers has far outweighed their clinical acumen." One thing was clear, however. "The therapeutic efficacy of these methods in certain diseases, such as neurosyphilis, has been established beyond any reasonable doubt."[7] Popular science writer Paul de Kruif believed malariatherapy had so revolutionized the treatment of neurosyphilis that he accorded Wagner-Juaregg the stature of a medical hero, putting him alongside the likes of Semmelweis and Banting. Creating "friendly fevers" in patients with neurosyphilis offered new and exciting hope to these otherwise hopeless victims of neurological degeneration.[8] Most physicians used the *vivax* malaria parasite, which causes significant fever spikes but is rarely fatal, rather than *falciparum*, which could cause coma, renal failure, and death.

During the 1920s and 1930s malariatherapy was extensively employed both in Europe and in the United States. At St. Elizabeth's mental hospital in Washington, D.C., for example, 2,158 persons were treated with malaria between 1922 and 1936. A physician at the state mental hospital in Bolivar, Tennessee, surveyed multiple American institutions in the early 1930s and could report an analysis of 8,354 such cases. In England, 821 patients with advanced neurosyphilis had been given malaria by 1926, and by the end of 1929 that number had reached 3,155. In general, about one quarter to one third of the patients improved enough to go home, and another third showed improvement. Anywhere from 1 to 10 percent died

during the therapy, although determining who actually died of the therapy was difficult, since these patients were already significantly ill of a fatal disease when the malariatherapy began.[9] There can be no doubt that from 1920 to 1945, malariatherapy for neurosyphilis represented the best that medical science had to offer for the neurosyphilis patient.

Most patients who received malariatherapy did so within mental hospitals, although a few private patients were treated at home. The physicians managing their care were specialists in mental disorders, not in malaria. So in most cases, if research was done at all, the focus was on syphilis, its neurological sequelae, and its response to various therapies. In a few instances, however, there were malariologists associated with the process, and this allowed for research on an artificially created and hence tightly controllable experimental disease. In England, S. P. James, a specialist in tropical disease who had retired from the Indian Medical Service and advised the government on tropical disease issues, supervised such research.[10] In the United States, the Rockefeller Foundation funded Mark Boyd's malaria work in the South, and in 1931 he initiated malariatherapy at a Florida mental hospital with the direct aim of studying malaria, not syphilis.

There were two methods of artificially inducing malaria, and both had their drawbacks. For either method, one first needed to acquire a patient with active malaria parasites to be tapped from his or her bloodstream. That patient had to be willing to delay treatment long enough for the parasites to be harvested. Then the process could go in one of two ways. The malaria blood could be drawn up in a syringe and directly injected into the syphilis patient, or the malaria source could become grazing ground for deliberately applied mosquitoes. Then those mosquitoes could be kept alive in cages long enough for the malaria parasite to go through its mosquito life cycle, an incubation time of one to two weeks. When the mosquito was ready, it could be applied to the syphilis patient. Variations on these two schemes were also possible, as in preserving the blood specimen and transporting it on ice or storing it. The mosquitoes could likewise be put under hibernation conditions and then activated for later use. Once the syphilis patient demonstrated malaria symptoms and parasites in his or her bloodstream, the process could begin again. Some hospitals kept a single strain of malaria alive for years by successfully passing it through one patient to another.

A word about the parasite's life cycle is necessary to clarify the difference between these two techniques. Under natural conditions, the infected mosquito injects malaria sporozoites with the saliva she inserts when she bites. The sporozoites enter the human body and go through various transformations. After a period of time in the liver, the parasite then moves into a red cell cycle in which it invades the red blood cell, multiplies, ruptures the cell, and then finds new cells to attack. The parasite, now called a trophozoite, may continue in this cycle, or it can transform into a male or female gametocyte, the sexual form of the malaria plasmodium. The female mosquito then takes up gametocytes with her blood meal. They mate in the mosquito's stomach, burrow through the wall, go through some more stages, and emerge as sporozoites in her saliva, ready to start a cycle again. So while the mosquito injects sporozoites, the prominent form present in the directly transmitted blood of the malaria patient is the trophozoite. Not surprisingly, the malaria cases induced by these two means have different clinical courses.

There are advantages and disadvantages to each technique. Blood taken from a malaria patient and directly injected into another person will carry malaria but will also carry all the other blood-borne diseases the malaria patient has. While physicians were not worried about AIDS in those early days, they did fear the transmission of hepatitis as well as strains of syphilis spirochetes that might worsen the receiving patient's condition. For these reasons direct transfer of malaria blood in order to create fevers in syphilitic patients was banned in England and was questioned elsewhere. What the technique had going for it was simplicity. It took very little training to learn to withdraw a few milliliters of blood from one arm and inject it into another's veins. The blood specimen could be transported on ice across hundreds of miles and maintained in cool storage until needed. The symptoms of malaria came on quickly, since the parasite was being introduced mid-cycle, as it were, having already gone through its early cycles elsewhere. The fever spikes were not as long-lived though; and some physicians believed that to cure neurosyphilis, the patient had to endure ten, fifteen, or even twenty bouts of chills and fever. In spite of these drawbacks, the direct blood injection route was the dominant form of malariatherapy induction in the United States and Europe.[11]

To induce malaria by laboratory-controlled mosquito bites was much more difficult, although the infection created mimicked natural conditions much more closely. Malariologists, who tended to oversee malariatherapy with mosquitoes, had to learn how to preserve mosquitoes rather than

killing them. First, anophelines had to be gathered from the wild, then kept alive and encouraged to breed. Once a set of them had fed on a patient with malaria, the mosquitoes had to be nurtured at a temperature optimal for both parasite reproduction and mosquito livelihood. This proved much trickier than expected, and entire cohorts of mosquitoes could die if conditions were not right. Then the "loaded" mosquito had to be convinced to bite the neurosyphilis patient. The mosquitoes were controlled by trapping them in jars open at the ends and covered with gauze. The gauze side was applied to the recipient's skin, which was sometimes pre-warmed to increase its surface circulation and attractiveness for the mosquito. The mosquitoes fed on sugar solutions to keep them alive between blood feedings; and the laboratory personnel had to balance sufficient nutrition with sufficient hunger, so that the mosquito lived but was also interested in taking a blood meal when offered. This process was further complicated by uncertainty about the infectiousness of the mosquito. Only after the mosquitoes had been applied to the patient were they dissected for evidence of sporozoites in their salivary ducts. If they had fresh blood in their gastrointestinal tracts and if there were sporozoites in their salivary glands, then it could be said with probability that the patient had received a dose of malaria parasites. This was all much more trouble than just injecting a small quantity of blood that was known to contain living organisms.

The positive aspects of this mode of malaria transmission were multiple, however. Since only the malaria parasite made it from the mosquito's stomach to her salivary glands, other contaminants of the donor blood were left behind. The induced malaria case was completely analogous to "wild" cases incurred outside of laboratory conditions, since the parasite entered the bloodstream in the sporozoite form and then proceeded through all of the normal human life cycle stages. So these patients presented a wonderful opportunity for studying malaria in closely controlled conditions. In particular, the time of infection could be determined with precision, whereas in nature the situation was much more confusing, since the patient might be exposed repeatedly to mosquito bites. The resulting infections could involve two or more different parasites or strains. Or, after multiple episodes of disease, the host and parasite could come into the sickly equilibrium of chronic malaria.

The malaria research community in the United States was rather slow to take advantage of this opportunity. While physicians in England had already infected thousands of neurosyphilis patients by means of "loaded"

mosquitoes by 1930, no Americans were engaged in similar practices. Malariatherapy flourished, but it was of the direct-injection sort, which made the resultant cases of little use to the researcher interested in malaria and not syphilis. The Rockefeller Foundation decided to remedy this defect; and in the spring of 1931, it sent malariologist Mark Boyd (1889–1968) to Tallahassee, Florida, to open a malaria research station. Boyd had been employed by the Rockefeller Foundation since the early years of Rockefeller-funded research on malaria in the American South after World War I. Aside from occasional research trips to other malarious areas such as Brazil, Jamaica, and Sardinia, he had been working as a malariologist in the United States since then.

Boyd carried out his research in Tallahassee in cooperation with the Florida State Board of Health. Wherever he was stationed, Boyd sent quarterly diaries to his superiors at the Rockefeller Foundation in New York City. These accounts have personal detail (such as the death of a relative and his trip to the funeral) as well as information on the difficult research problems facing Boyd. This was a standard format for Rockefeller medicine men when away from home base; it was the way the foundation tracked its workers and kept abreast of their achievements and setbacks.[12]

The Boyd diaries offer an interesting window into the ethical scruples of one researcher in the early 1930s. These were the same years when physicians in the U.S. Public Health Service decided to continue a syphilis study carried out in Tuskegee, Alabama, as an "observation only" project with no apparent moral qualms at all.[13] Boyd, on the other hand, was overtly anxious about the health of his malaria patients, both those who served as donors and those who received the parasites. His donor cases were paid volunteers who cooperated on the assumption that delaying treatment would not significantly damage their health. Boyd may have been marginally less concerned about the syphilis patients, but still he appears to have been more worried about the immediate effects of malaria in them than were their treating physicians at the mental hospital. While Boyd had made a career out of preventing and treating malaria, he was new to the field of syphilis therapy. It may have come naturally to him to value treating malaria above treating syphilis, even while he was eager to study the natural course of malaria.

Boyd's first challenge was to get the superintendent of the nearby state mental hospital in Chattahoochee to cooperate with his plans for malariatherapy. The superintendent was enthusiastic and willingly offered up his

many neurosyphilis patients for treatment. The hospital had both black and white patients, housed in wards segregated by race and sex. Since malariatherapy was a much-sought-after treatment in the early 1930s, it is not surprising that Boyd chose white patients for his preliminary experiments.

Boyd's position within the hospital's hierarchy was a curious one. He was not the physician who attended the syphilis patients and was only in an advisory or consultant role regarding their care. He or his assistant might apply the mosquitoes, but they did so under the direction of the state hospital physicians. Boyd himself actually spent very little time at the hospital and instead sent his assistant and co-worker, Warren Stratman-Thomas, to do the relevant work there. When controversy arose around issues of patient care, Boyd and Stratman-Thomas had to yield to the hospital's physicians. While they were malaria subjects to Boyd and Stratman-Thomas, they were first and foremost syphilis patients to the hospital's physicians.[14]

Having established a working relationship with the mental hospital and hence acquired experimental/therapeutic subjects, Boyd's next task was to find a source of malaria parasites. This proved an unexpectedly difficult task. North Florida was notoriously malaria-ridden in the 1930s, but Boyd needed not just any malaria patient. His human parasite reservoir had to meet several criteria: (1) have *vivax* (and definitely not *falciparum*) malaria; (2) have a case that had as yet received no treatment; (3) be willing and able to forego treatment for some period of time so that parasites could be harvested from the blood stream; and (4) be willing to have his or her blood drawn. Even the poorest of Florida's impoverished population could usually find a few dimes to buy a bottle of chill tonic. Although the quinine content of such patent medicines was low, it was enough to suppress the parasites and make acquisition of them from the patient's bloodstream unreliable. Finding a virgin case would occupy Boyd and Stratman-Thomas for much of May 1931.[15]

Boyd had a separate task to keep him busy during that summer. He had to acquire mosquitoes and build a housing unit for their preservation and propagation. This too proved much more challenging than he had anticipated. Upon first reading a diary entry dated July 14, 1931, one might be puzzled. It mentioned Cain, one of the research center's employees: "Cain conferred with sheriff of Jefferson Co., re theft of our pig. Interview not productive." It was not immediately clear why Boyd's group was keeping

a pig or why they kept buying new ones to replace those stolen. It turned out that the pig had an important job. It was housed in a remote swampy corner of the county and served as bait to attract *anopheles* mosquitoes. Once captured, the mosquitoes were transferred to the insectary. But they could not keep a man out there all the time watching that pig, and no matter what pen and padlock were devised, some of the locals managed to bring home the bacon.[16]

The insectary also gave Boyd a lot of trouble. His initial incubator would not maintain the proper temperature. In early 1932 a much fancier model finally arrived after he had begged funding for it from the home office. That incubator proved a disappointment as well. It broke down almost immediately, and no local workmen could be found who knew how to fix such a sophisticated piece of equipment. There was a high learning curve in terms of the acquisition of information on how best to raise a mosquito to become a malaria transmitter. Boyd found, for example, that the optimal temperature for developing parasites was also one that promoted mosquito mortality. The malaria parasite could kill the mosquito if it multiplied too rapidly, it appeared. Feeding the mosquitoes offered another challenge. At one point he resorted to letting uninfected insects feed on the arm of the laboratory technician, a practice that one colleague denounced as inhumane.[17] In spite of all of these difficulties, Boyd was able to keep enough mosquitoes viable to carry out a series of malaria inoculations at the state mental hospital.

In early May, Boyd commenced giving malariatherapy by taking a young woman named Mabel over to the mental hospital, extracting some of her parasite-rich blood, and injecting 2.5 cc. into a woman with syphilis. Then he gave Mabel ten dollars and arranged for her to be given quinine. It is unclear why Boyd did not let mosquitoes feed on Mabel in order to start the mosquito-transmitted therapy—perhaps she was too ill, or perhaps she was unwilling to be made use of in such a way. In any event, his next malaria case was an 18–year-old white boy, whose parents brought him into Tallahassee to be fed on by mosquitoes. Boyd was very pleased with this source of parasites, calling him an "ideal subject."[18]

There were problems from the start, however. The boy had a severe outbreak of fever blisters on his face, which worsened with each malarious fever spike. Boyd had a local physician evaluate him to see if it would be safe to withhold treatment for a few days, especially since his blood was so rich in parasites. The local doctor said they could go ahead, and the

mosquitoes were applied. The next day Boyd's anxiety continued, and he again asked the local physician to judge whether the boy could endure another chill. Again the doctor said it was all right, and more mosquitoes feasted on the boy's blood. Although Boyd had planned on giving the boy quinine after another day of mosquito feeding, he could not stand by while the adolescent's illness continued unabated. Boyd brought him some warm clothing and gave him quinine one day early. In the same week Boyd evaluated another malaria case but found her to be comatose. He not only advised immediate treatment, but he took quinine out to the woman himself. Clearly, it was hard for him, a malariologist, to stand by and not treat cases of malaria.[19]

Boyd was also very concerned about the initial syphilis patients who were treated with malaria. He felt frustrated due to his lack of control over their care once the parasites had passed into their bloodstreams. He sent Stratman-Thomas to make daily rounds on the malaria patients at the mental hospital. When one early case developed pus in his urine, Boyd wanted to at least "interrupt" the case with a brief dose of quinine. The psychiatrists at the hospital, who were trying to give the syphilis patients as many fever spikes as possible to control their underlying disease, did not agree, and the quinine was not given. Their concern was that the syphilis patients should receive the strongest possible dose of the curative syphilis therapy. A few days later another induced malaria case became dangerously ill. Boyd recorded in his diary: "S[tratman-] T[homas] reports that Mrs. C____ had several convulsions this morning, though he quotes Dr. Cobb as expressing the opinion that her condition is not serious and ascribes these symptoms to her paresis. I instructed S. T. to call hospital and order to have her given 30 gr. Quinine today. Also emphasized to S. T. that we must not permit any chances to be taken with the inoculated cases. Said that we could not under any circumstances permit an induced infection to continue unchecked if it in any way jeopardized the patient."[20] This patient did receive quinine, although not until more days had passed, so perhaps the psychiatrists offered some resistance. Another case was interrupted a few days later because his condition worried Boyd as well.[21]

Bad luck continued to dog Boyd in these early trials of malariatherapy. Another syphilis patient became seriously ill after receiving malaria. He had come into the hospital completely demented, signifying advanced neurosyphilis. During the malariatherapy the patient became very ill, perhaps because of an abscess on his thumb. When Boyd saw how sick the patient

was, he ordered intravenous quinine. "Got in touch with Dr. Robertson, staff member on temporary duty, who gave 5 gr. quinine bichloride intravenously. Patient died within 5 minutes." Although Boyd was distressed by the death, he was also angry, since it incriminated the malariatherapy unfairly. This episode opened Boyd to the charge that malaria had killed the patient, even though he attributed the death to septicemia from the man's thumb infection. He, in turn, blamed the hospital's physicians, who had heretofore selected the patients for malariatherapy. This would have to stop. "In the past we have infected cases assigned to us by the hospital staff, . . . [leaving us to act] as a nurse would in applying prescribed treatment. In the future we will advise against the inoculation of any who are not in good physical condition." Although a few more deaths as well as "interruptions" of malariatherapy are recorded in the diaries, after the summer of 1931 the process seems to have gone much more smoothly.[22] Still, when Boyd and Stratman-Thomas described their technique in a 1933 article, they concluded with a cautionary note: "Although malaria therapy is most beneficial in many cases, it must be regarded as a heroic form of medication and should be employed with discretion."[23]

Boyd and Stratman-Thomas published several papers in which they described the research they did on *vivax* malaria through the medium of the mental hospital clientele. They were interested in immunity to malaria, so they studied what happened when patients were reinocculated with the same strain as they had been given initially. They found that the reinocculated patients (and not the controls who were exposed to the strain for the first time) remained free of disease, thus proving the existence of at least short-term immunity to particular *vivax* malaria strains. If, however, the patients who had received one strain were challenged with a second, they responded just as vigorously as if they had never had malaria. So Boyd and Stratman-Thomas were able to show that immunity to *vivax* malaria was strain-specific.[24] In a second article they reported on attempts to determine what quantity of mosquito bites was necessary to induce a case. They had found that mosquitoes varied in the number of sporozoites carried (and hence injected). The rate and quality of infection depended directly on the density of parasites in the mosquito, not on the number of mosquitoes applied or the number of bites.[25] Such information helped explain why some mosquito bites did not "take," but it had little practical application beyond the ranks of those attempting to induce malaria in syphilis patients.

Boyd and Stratman-Thomas had discovered something important, however, something that James in England was unlikely ever to see. They had black patients with neurosyphilis in their hospital population, and had a "devil of a time" giving them *vivax* malaria. At first they thought the mosquitoes were "bad" in some way—not full of parasites, or not biting properly, or held at the wrong temperature, or something. But mosquitoes from that same batch had no trouble infecting whites. In the fourteen months following June 1931, they had inoculated seventy-seven white patients with *vivax* malaria, and eight black patients. Of the eight, only three had any symptoms at all, in spite of large doses of sporozoites. "In the three [N]egro patients who were successfully inoculated, the clinical course of the infection was of exceptional mildness, so that little therapeutic benefit was to be expected," reported Boyd and Stratman-Thomas. Two of these patients had mild malaria attacks that lasted less than a week; the third showed symptoms eighty-five days after inoculation and then had fevers only to 100°F.[26] Boyd and Stratman-Thomas had discovered the innate African American immunity to *vivax* malaria.

The possibility that African Americans were less susceptible to malaria than whites had been suspected since the early years of the African slave trade. During the first centuries of Pan-American settlement, malaria limited the exploitation of the rich soils of the tropical and subtropical zones. While *vivax* malaria had come to the New World from Europe, the Africans brought *falciparum* malaria in their unwillingly transported bodies. The result was that wherever whites and blacks mixed in the Tropics, severe malaria followed, mowing down Europeans while apparently sparing black people. Europeans were familiar with the fever spikes of *vivax*, but most had not seen the malicious and deadly malaria that came to characterize the American colonies in a coastal band from South Carolina, through the Caribbean, down the Mexican coast, and into Latin America. These colonies quickly acquired a reputation as unhealthy and feverish, spurring the development of the African slave trade. White workers avoided the sickly lands where possible; Africans were forcibly brought there, and at least managed to escape, by and large, from the ravages of the local fevers. Thus, when colonial and antebellum apologists for slavery argued that black people were particularly suited to labor on their hot, humid plantations, their argument had some basis in fact.[27]

Awareness of racial variability with regard to malaria served a strong social purpose in arguments supporting slavery. Given their tolerance of

malaria, this line of reasoning went, blacks were destined by God and biology to labor under tropical conditions not suited to white people. After the U.S. Civil War, discussion of this phenomenon largely faded from the medical literature on race and on malaria. By 1900 when white physicians discussed "the Negro health problem," they were addressing the appalling mortality figures that characterized the black population, especially those living in cities. The principal culprits were tuberculosis and venereal disease, diseases made all the more disturbing because of the possibility of transmission to the white race: blacks were ubiquitous in white households, serving as maids, caring for children, and waiting on tables. Blacks were no longer seen as having a feature that made them healthier than whites, but rather as being particularly diseased and dangerous. Some even argued that the race had so degenerated since the years of kindly paternalistic care by slave owners that it was in danger of extinction.[28]

Furthermore, it was widely evident in the twentieth-century American South that blacks suffered disproportionately more from malaria than whites did. Over and over again, mortality statistics showed more blacks than whites dying of malaria, often in ratios as high as two to one. For example, a researcher for the U.S. Public Health Service, Kenneth Maxcy, found twice as many cases of splenomegaly (a sign of malaria) among black Mississippi delta school children as among white.[29] This difference was also borne out in studies that looked at parasite rates between the races. Although one can argue that these statistics have various biases, it remains clear that public health officials and the public at large saw the black population as more at risk for malaria than the white one. When the researchers compared black and white, the blacks usually equaled, if not much exceeded, the parasite rates of whites. Of course such percentages were very much dependent on the population surveyed, but it at least indicates that public health researchers had no problem finding abundant malaria infestation among southern blacks.[30]

So expectations about blacks and malaria in the early 1930s did not predict that it would be hard to give them malaria. They seemed to get it just fine out in the swampy southern world. The fact that most of those cases were caused by *falciparum* parasites was obscured by a variety of factors. Very few doctors in the American South were equipped with the knowledge, the microscope, or the inclination to make an accurate diagnosis. Many poor blacks never saw a doctor, preferring to dose themselves with patent medicines containing quinine if they sought any treatment at all.

Even when public health researchers did parasite surveys, going into schools or communities and getting blood smears from the population, the fact of racial differentiation by parasite was not recognized. Distinguishing the parasites under the microscope is not always easy. Furthermore, as Boyd and Stratman-Thomas showed, black people could have parasites in their bloodstreams but show no clinical signs of infection. So parasite surveys tended to overestimate the prevalence of *vivax* malaria in the black population, if it was measured at all.

It was not until 1975 that the mechanism of African American resistance to *vivax* malaria was sorted out. In that year a researcher showed that about 95 percent of sub-Saharan Africans have a characteristic of their red blood cells that causes them no apparent harm. Their red blood cells are missing a cell wall structure called the Duffy antigen. Without this structure, the *vivax* parasite apparently cannot gain entrance into the red blood cell. This represents an absolute immunity: bearers of "Duffy-negative" red blood cells will never have a case of *vivax* malaria, although under certain circumstances they may have the parasites swimming in their bloodstreams. They can, in other words, be infected but not sick.[31] This trait should not be confused with the myriad of genetic defects that protect many Africans from *falciparum* malaria. The most famous of these, the sickle-cell trait, makes it more likely a child will survive early *falciparum* infections and makes the resultant disease less hazardous, even in adults. This and other hemoglobin abnormalities help protect many blacks from *falciparum* malaria, but the protection is only partial, not absolute.[32]

This complex situation with regard to malaria immunity explains the variant disease mortality in the early years of New World colonization and conquest. African Americans were better able to survive *falciparum* infection than whites due to inherited genetic traits (as well as acquired immunity from a childhood spent exposed to malaria). While blacks gave deadly *falciparum* to whites, they were largely unscathed by the *vivax* malaria that whites carried to the New World. The role of sickle-cell trait and other hemoglobin variants in determining the malaria death rate was not demonstrated until the 1950s, so Boyd and Stratman-Thomas were the first to establish the existence of a racial resistance to malaria. Their work did not light any ideological fires, however, and was received quietly by the research community. Still, the fact of partial resistance paved the way for other researchers, who ultimately established the presence of genetically determined malaria resistance and immunity.[33]

Although Boyd recognized that his discovery about blacks and *vivax* malaria was significant, it did not help him in treating them for neurosyphilis. But it did set up an enticing opportunity. So far he had been careful to exclude *falciparum* parasites, knowing how dangerous they were. But there was much he wanted to learn about *falciparum*, so the fact that syphilitic blacks could not benefit from *vivax* and might benefit from malaria therapy, helped him justify the use of this heroic course. The relative immunity of African Americans to *falciparum* was unknown to him, although he would have recognized the existence of acquired immunity in adults who had grown up in a malarious area. He eagerly, perhaps too eagerly, embraced the opportunity to study the natural history of *falciparum* with the same degree of control as he had found with *vivax* malariatherapy patients. Accordingly, in late October 1931, he gave his first dose of *falciparum* to a black man suffering from neurosyphilis.[34]

Boyd was very anxious about the series of patients he injected with *falciparum* over the next couple of weeks. He ordered Stratman-Thomas to sleep over at the hospital so their care could be carefully monitored. After the initial rounds of fever went satisfactorily, Boyd relaxed his watchfulness. Then, on November 21, "S.T. called about 6 p.m. to say that had just received message from hospital that J____, one of our falciparum cases had had a temp. of 105°[F] for 4–5 hours and was then in a coma. T. said he asked Dr. Watson to give intravenous quinine immediately." Note again that the care of the malaria patients was only indirectly in the hands of Boyd and Stratman-Thomas. Boyd sent Stratman-Thomas out to Chattahoochee to examine the patient, where he found that the patient had died before the quinine could be administered. Later *falciparum* patients died as well, although Boyd often attributed their deaths to causes other than malaria.[35]

These deaths did not dissuade Boyd from further use of *falciparum*. By 1935 he had inoculated seventy-two black patients with this strain of malaria and reported on his results in the *American Journal of Tropical Medicine*.[36] Of this group sixty developed cases of *falciparum*, four died, and forty-nine had to have their fever bouts interrupted with quinine before the desired number of fever spikes had occurred. The criteria for termination were either parasite counts over 100,000 per cubic millimeter of blood inspected, or a fever above 104°F. (The more dense the parasites, the more severe the disease, the more likely death will ensue.) There were four white patients in the cohort receiving *falciparum* (chosen because they were

refractory to *vivax*), although Boyd does not draw any conclusions regarding racial susceptibility since the white sample was so small. He found that one mosquito bite could be sufficient to cause a case of *falciparum* and that increasing the dosage of parasite did not effect the course of the disease. He also published extensive data on the duration of *falciparum*, the number of fever peaks, and the pattern of febrile episodes. Finally, Boyd noted that the *falciparum*-induced fever therapy was just as effective in neurosyphilis as that obtained from *vivax*.

In 1938 Boyd and colleagues published a paper summarizing their experience with patients at the Chattahoochee state mental hospital. Just over two hundred patients had been injected with malaria parasites, 75 percent via mosquitoes and 25 percent via direct intravenous inoculation, as well as being given the standard medical treatment with arsenicals. In addition to using *vivax* and *falciparum* malaria, Boyd had also injected some cases with quartan, or *malariae* malaria.[37] He found that these latter patients did well, but keeping the quartan strain alive and active was very difficult. Although one quarter of the malariatherapy patients were dead at the time Boyd was writing, he believed only 7 percent of deaths were due to malaria. In comparison, only 45 percent of the patients treated with medication alone were still alive. All told, in the malaria group, 31 percent were deemed "in remission," 23 percent "improved," and 19 percent "unimproved" (with 25% dead). "The mortality experience in the 2 races is similar," Boyd and colleagues reported. Since "in remission" meant, by definition, that the patient was well enough to go home, "the remission rate among colored persons was actually better than shown, as the furloughing of many colored patients who showed satisfactory improvement was impracticable for lack of guardians."[38] In summary, Boyd and colleagues concluded, "Malaria therapy combined with chemotherapy gives very much better results in the treatment of neurosyphilis than chemotherapy alone."[39]

So Boyd saw himself as providing a valuable therapeutic option to these patients, and hence he justified his use of them as experimental subjects. It is interesting to note that they were someone else's *patients* (the doctors at the mental hospital), and mainly for him *subjects* of his research. Still, he could not maintain the cool researcher objectivity that would be expected if he only saw them as research objects. He was quite worried about causing harm to either the sources of his parasites or to their recipients, although some of this concern may have arisen less out of compassion than

out of concern for the good name of the Rockefeller Foundation. This issue came particularly to the forefront when private patients, not inmates of the state mental hospital, applied to Boyd's group for malariatherapy.[40] In January 1934, for example, a patient from Tampa showed up at the malaria research station for inoculation. "The usual release form was secured from patient and 3 mosquitoes fed."[41] Nowhere else did Boyd mention such a release or consent form, so it is not clear if he required it only for nonhospital patients or for everyone. Many of the hospital patients were too demented to make any decisions for themselves, and the acquisition of consent from relatives was only mentioned in regard to securing autopsies, not to giving malariatherapy.

The only other insight into Boyd's worries about liability came in this comment written in December 1932: "FFR received wire from JAF about liability of RF if we do inoculations of private paretics [neurosyphilis patients] in Ala. and Ga. FFR not inclined to view as desirable."[42] FFR was Frederick F. Russell, director of the International Health Division and one of Boyd's superiors within the Rockefeller Foundation (RF); JAF was John A. Ferrell, who had supervised the earlier malaria campaigns funded by the Rockefeller Foundation during the 1910s and 1920s, and so was considered an in-house expert on the disease.[43] Boyd, in other words, was being ordered not to treat private patients from Alabama and Georgia since that would put the Rockefeller Foundation at too much risk, not only strictly because of legal liability but also because of possible negative publicity.

One ethical issue not addressed directly in either Boyd's published papers or in the diaries was the possibility that hospital-induced malaria could spread to the surrounding community. Indeed, Stratman-Thomas himself acquired malaria while working in the mental hospital. Although the white wards were screened, the black wards were not made mosquito-proof until 1935.[44] The only mention of concern about this community hazard is a cryptic entry in Boyd's diary for November 20, 1932: "ST got an autopsy on a child dying from malarial hematuria living near Chattahoochee, we paying $15.00 toward burial."[45] Given the presence of bloody urine, a sign of renal failure, the child probably died of *falciparum* malaria. Did Boyd pay $15 toward her funeral costs only to have the opportunity to do an autopsy on a malaria case? That is possible, but there is nothing further recorded about the autopsy or about why the case might be particularly interesting. Or did he feel some guilt at the prospect that the infecting *falciparum* parasites had come from one of his malariatherapy patients and

was, in effect, paying the parents off? I suspect the latter, but there is no further information about community malaria cases to support my conclusion.

Although the idea of giving malaria to cure another disease seems strange to us today, it was an accepted therapy for a devastating disease when Boyd took it up in the 1930s. In fact, it still has some appeal for patients with modern, incurable diseases, as evidenced by a Mexican clinic that offered malariatherapy for late-stage Lyme disease in 1989 and a recent Chinese trial of using malaria to treat AIDS.[46] Boyd's methods do make one uneasily aware of the slippery slope that might lead researchers to induce malaria in patients with no underlying disease in order to test medications or perform other research on malaria. This indeed happened during World War II. Conscientious objectors and prisoner volunteers in the United States agreed to receive malaria so that new medications could be tried out on them and older medications tested for appropriate dosage intervals and quantities. The Nazis took it one step further. When the need to control malaria among German troops stationed in the southern areas of Europe and Southwest Asia became acute, German doctors turned from testing malaria drugs on syphilis patients and volunteers to using inmates at concentration camps. The physician who had supervised these studies at Dachau was hanged in 1946 after his meticulously detailed records survived the camp's liberation. During his trial he defended himself by saying, "I admit that people had to suffer because of each experiment, mostly from depressions. Yet, the scientific interest to protect millions of people from this disease and to save them was predominant."[47]

There has been a recent analysis of the ethical aspects of using malariatherapy research data, although not in regard to Boyd's work. In 1999 the *American Journal of Tropical Medicine* published a series of papers by William Collins and Geoffrey Jeffrey that used retrospective analysis to describe the course of 474 subjects who received *falciparum* malaria at two mental hospitals in the American South between 1940 and 1963. All subjects were patients diagnosed with neurosyphilis. The authors' intention was that their data base of induced infections could provide essential information about the natural history of *falciparum* malaria to be used by researchers studying malaria vaccines.[48]

Accompanying the articles presenting this data was an essay entitled "Another Tuskegee?" by ethicist Charles Weijer of Dalhousie University.

He asked whether it was ethical to use the information that Collins and Jeffery presented. Similar questions have been asked, for example, about the use of Nazi medical research, since its subjects were unwilling prisoners who were frequently harmed or killed during the experiments. Weijer drew several conclusions about the malariatherapy research. First, he noted that 60 percent of the malariatherapy patients were black, and 40 percent were white. Hence, he felt that blacks were not selectively targeted for the research, unlike in the Tuskegee case. Second, he pointed out that the patients or their families gave consent for treatment within the hospital and that malariatherapy was a standard treatment of the day. Finally, he argued that since the subjects were clinical patients receiving appropriate care for their illness, they could not simultaneously be research subjects. He made the distinction based on whether the malariatherapy patients received extra interventions for research purposes that they would not otherwise have received, and he concluded that the answer was no. Altogether, he found that Collins and Jeffery "present data that will be invaluable to future malaria research . . . in an ethically supportable manner."[49]

One aspect of Weijer's analysis is based on a misunderstanding of the Collins and Jeffery data. They tell us that a total of 1,053 patients received malariatherapy and that roughly 60 percent of these patients were black. Yet their four papers all look at the subset of the 1,053 patients who received *falciparum* parasites—474 patients. We are not told the racial breakdown of this population. In total there were 635 black patients who received malaria of any kind. It is likely that all, or almost all, of the 474 *falciparum* patients were black, with most of the remaining 161 black patients receiving *Plasmodium malariae* (the parasite of quartan malaria). As a 1941 description of the malariatherapy program at the South Carolina State Hospital (one of the two analyzed by Collins and Jeffery) noted, "In Negroes tertian malaria [*vivax*] does not develop with any degree of success."[50] So Weijer missed the point that almost all of the patients who received the most dangerous of malarias were black, and he failed to analyze the ethical implications of this fact. He provided no guidance about the willingness of physicians, including Boyd, to give *falciparum* to black patients. Was it made easier because the recipients of this heroic therapy were slightly less valued as human beings than white patients? Perhaps, but there is no evidence here to support this conclusion. Certainly Boyd, for one, was acutely aware of the dangers of this potentially deadly parasite.

Whether his anxiety as a researcher was balanced by his conviction that this was best for the patient who had no other way to benefit from malariatherapy is something that his diaries and papers do not reveal.

Weijer's distinction between research subjects and clinical patients is interesting and raises questions about Boyd's work. Did his patients receive any interventions that would not have otherwise happened because they were subjects of his study? Well, yes—they received malariatherapy. Florida State Hospital did not provide this sort of treatment at all prior to Boyd's arrival. Whether this was good or bad depends on the unanswered question about the treatment's efficacy. This aside, the issue is more complex in the Boyd case than in the one analyzed by Weijer. The patients described in Boyd's work had two distinct sets of practitioners providing care for them. One set, the doctors at the Florida State Hospital, had as their primary goal the treatment of syphilis, and they were willing to subject patients to dangerous levels of malaria in order to maximize the conquest of neurosyphilis. Boyd, on the other hand, had inherent conflicts in his goals. He wanted to gather data on the natural history of malaria, but at the same time, he wanted the patients to endure only safe levels of malaria, particularly since he himself had given it to them. If anything, the physicians directly responsible for the medical care of the Chattahoochee patients appear to have been more callous about their suffering (and accepting of potential death) than the researcher who might be assumed to be the more distant and uncaring participant.

One final note should be made about Boyd's peculiar difficulty of inducing malaria in his African American subjects. His paper on the innate immunities of blacks to *vivax* caused no splash at all. It is cited appropriately by later works on the Duffy antigen that explained the immunity, but otherwise it does not appear in discussions about race and health issues that took place during the 1930s. It was a discovery that served no social purpose in its time. Southerners were no longer claiming that somehow blacks were particularly suited to toil in tropical climates as enslaved labor, since this antebellum argument had no function once the Civil War had made the issue moot. Boyd's discovery came a century too late for slavery's defenders. Social reformers who promoted the cause of black Americans likewise had little use for the information about *vivax* immunity. Their line of rhetoric blamed the various health problems of the black race on socioeconomic oppression; they specifically opposed the idea that blacks were biologically different and hence more susceptible to, say, tuberculosis. Instead, they argued that blacks were the same as whites biologically and would be just as healthy if they lived in adequate housing, ate nutritious food, and worked in safe environments.[51] Again, they had no use for Boyd's data, even though it could be touted as showing that blacks were actually stronger and more fit than whites in one respect. Boyd's research met an ideological void.

Joel Braslow has argued that malariatherapy tended to make psychiatrists see their neurosyphilis patients more as people and less as dehumanized, demented creatures suitable only for control and warehousing.[52] But it is certainly possible to argue the opposite point of view, especially if the physician approaching the patient was primarily interested in malaria and only secondarily in the treatment of neurosyphilis. In this case the patient becomes a subject and becomes vulnerable to potential abuse. Mark Boyd and his colleagues struggled against this inclination, while at the same time they appreciated the experimental gold mine that the neurosyphilis patients offered. It was not accidental that their patients/subjects suffered from one of the vilest social diseases known and were generally condemned by society for having that illness in the first place. This may have helped create a patina of "otherness" that made the creation of a research mentality possible. Yet Boyd resisted this impulse, and he seems to have retained his role as a caring physician, torn in his desires both to study and to treat malaria in spite of working with patients that would have stretched any definition of attractive humanity. His use of *falciparum* allowed him to offer black patients both the dangers and the rewards of malariatherapy and to pursue research on an otherwise inaccessible disease. But in so doing he continually faced Dale's dilemma of "choosing between the advantage of the patient and the obtaining of new information."

NOTES

1. Sir Henry Hallett Dale, comments following S. P. James, "Some General Results of a Study of Induced Malaria in England," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 24 (1931): 528.

2. [Julius] Wagner-Juaregg, "The Treatment of General Paresis by Inoculation of Malaria," *Journal of Nervous and Mental Disease* 55 (1922): 369–75; Magda Whitrow, "Wagner-Jauregg and Fever Therapy," *Medical History* 34 (1990): 294–310.

3. Stephanie C. Austin, Paul D. Stolley, and Tamar Lasky, "The History of

Malariotherapy for Neurosyphilis: Modern Parallels," *Journal of the American Medical Association* 268 (1992): 516–19.

4. Eli Chernin, "The Malariatherapy of Neurosyphilis," *Journal of Parasitology* 70 (1984): 611–17; Magda Whitrow, letter to the editor, *Journal of the American Medical Association* 270 (1994): 343; Henry J. Heimlich, letter to the editor, *Journal of the American Medical Association* 269 (1993): 211. There are enough immunological similarities between the syphilis and malaria organisms that the presence of malaria can generate a false positive result on syphilis testing. Such parallels could mean that malariatherapy did not act simply through temperature effects but also through stimulation of a specific immune reaction against the spirochete.

5. Joel T. Braslow, "The Influence of a Biological Therapy on Doctor's Narratives and Interrogations: The Case of General Paralysis of the Insane and Malaria Fever Therapy, 1910–1950," *Bulletin of the History of Medicine* 70 (1996): 577–608; Joel Braslow, *Mental Ills and Bodily Cures: Psychiatric Treatment in the First Half of the Twentieth Century* (Berkeley, CA, 1997).

6. Whitrow (n. 2 above). On the search for alternatives to malaria, see Albert Heyman, "The Treatment of Neurosyphilis by Continuous Infusion of Typhoid Vaccine," *Venereal Disease Information* 26 (1945): 2–8; and William Bierman, "The History of Fever Therapy in the Treatment of Disease," *Bulletin of the New York Academy of Medicine* 18 (1942): 65–75.

7. Jack R. Ewalt, Ernest H. Parsons, Stafford L. Warren, and Stafford L. Osborne, *Fever Therapy Technique* (New York, 1939), 3–4.

8. Paul de Kruif, *Men against Death* (New York, 1932), 249–79.

9. Theodore C. C. Fong, "A Study of the Mortality Rate and Complications following Therapeutic Malaria," *Southern Medical Journal* 30 (1937): 1084–88; William Kraus, "Analysis of Reports of 8,354 Cases of IMPF-Malaria," *Southern Medical Journal* 25 (1932): 537–41; S. P. James, "Epidemiological Results of a Laboratory Study of Malaria in England," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 20 (1926): 148–65; S. P. James, "Some General Results of a Study of Induced Malaria in England," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 24 (1931): 477–538.

10. James, "Some General Results" (n. 9 above).

11. Mark F. Boyd and Warren K. Stratman-Thomas, "A Controlled Technique for the Employment of Naturally Induced Malaria in the Therapy of Paresis," *American Journal of Hygiene* 17 (1933): 37–54.

12. Mark Boyd, Diaries, folders 468–470, box 48, Rockefeller Foundation Archives, RF 1, 100 Series, Rockefeller Archive Center, North Tarrytown, New York (hereafter cited as RAC). Archives director Darwin Stapleton and his staff made research in this archive consistently pleasant, efficient, and productive.

13. On the Tuskegee syphilis study, see James Jones, *Bad Blood: The Tuskegee Syphilis Experiment* (New York, 1981); and Allan M. Brandt, "Racism and Research: The Case of the Tuskegee Syphilis Study," *Hastings Center Report* 8 (1978): 21–29.

14. Boyd, Diaries, May 1931, RAC.

15. Ibid.

16. Boyd, Diaries, July 14, 1931, RAC.

17. Boyd, Diaries, July 7, 1933, RAC.

18. Boyd, Diaries, May and June 1931, RAC.

19. Boyd, Diaries, June and July 1931, RAC.

20. Boyd, Diaries, July 10, 1931, RAC.

21. Boyd, Diaries, July 26 and July 28, 1931, RAC.

22. Ibid.

23. Boyd and Stratman-Thomas (n. 11 above), 54.

24. Mark F. Boyd and Warren K. Stratman-Thomas, "Studies on Benign Tertian Malaria. 1. On the Occurrence of Acquired Tolerance to *Plasmodium vivax*," *American Journal of Hygiene* 17 (1933): 55–59.

25. Mark F. Boyd and Warren K. Stratman-Thomas, "Studies of Benign Tertian Malaria. 2. The Clinical Characteristics of the Disease in Relation to the Dosage of Sporozoites," *American Journal of Hygiene* 17 (1933): 666–85.

26. Ibid., 683–84.

27. Philip Curtin, *Death by Migration: Europe's Encounter with the Tropical World in the Nineteenth Century* (Cambridge, 1989).

28. Frederick L. Hoffman, "Race Traits and Tendencies of the American Negro," *Publications of the American Economic Association* XI (1896): 1–139; Marvin L. Graves, "The Negro a Menace to the Health of the White Race," *Southern Medical Journal* 9 (1916): 407–13; C. Jeff Miller, "Special Medical Problems of the Colored Woman," *Southern Medical Journal* 25 (1932): 733–39; L. C. Allen, "The Negro Health Problem," *American Journal of Public Health* 5 (1915): 194–203.

29. Kenneth F. Maxcy, "Spleen Rate of School Boys in the Mississippi Delta," *Public Health Reports* 38 (1923): 2466–72.

30. For malaria statistics by race see, M. A. Barber, et al., "Prevalence of Malaria (1925) in Parts of Delta of Mississippi and Arkansas: Economic Conditions," *Southern Medical Journal* 19 (1926): 373–77; M. A. Barber and Bruce Mayne, "The Seasonal Incidence of Malaria Parasites in the Southern United States," *Southern Medical Journal* 17 (1924): 583–91; R. H. von Ezdorf, "Endemic Index of Malaria in the United States," *Public Health Reports* 31 (1916): 819–28; Mary Gover, "Negro Mortality," *Public Health Reports* 61 (1946): 259–65, 1529–38; ibid, 63 (1948): 201–13; ibid, 66 (1951): 295–305.

31. Martin D. Young et al., "Experimental Testing of the Immunity of Negroes to *Plasmodium vivax*," *Journal of Parasitology* 41 (1955): 315–18; Louis H. Miller et al., "Erythrocyte Receptors for (*Plasmodium knowlesi*) Malaria: Duffy Blood Group Determinants," *Science* 189 (1975): 561–63; Louis H. Miller et al., "The Resistance Factor to *Plasmodium vivax* in Blacks: The Duffy-Blood-Group Genotype, *FyFy*," *New England Journal of Medicine* 295 (1976): 302–4.

32. D. J. Weatherall, "Common Genetic Disorders of the Red Cell and the 'Malaria Hypothesis,'" *Annals of Tropical Medicine and Parasitology* 81 (1987): 539–48; F. Fleming, "Abnormal Haemoglobins in the Sudan Savanna of Nigeria," *Annals of Tropical Medicine and Parasitology* 73 (1979): 161–72; L. Luca Cavalli-Sforza, Paolo Menozzi, and Alberto Piazza, *The History and Geography of Human Genes* (Princeton, 1994), 146ff.

33. A. C. Allison, "Protection Afforded by Sickle-Cell Trait against Subtertian Malarial Infection," *British Medical Journal* 1 (1954): 290–94; A. C. Allison, "The Distribution of the Sickle-Cell Trait in East Africa and Elsewhere, and Its Appar-

ent Relationship to the Incidence of Subtertian Malaria," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 48 (1954): 312–18.

34. Boyd, Diaries, October 29, 1931, RAC.

35. Boyd, Diaries, November 21, 1931, RAC.

36. Mark F. Boyd and S. F. Kitchen, "Observations on Induced Falciparum Malaria," *American Journal of Tropical Medicine* 17 (1937): 213–35.

37. On the use of quartan malaria in neurosyphilis, see Bruce Mayne, "Note on Experimental Infection of Anopheles punctipennis with Quartan Malaria," *Public Health Reports* 47 (1932): 1771–73, and Bruce Mayne and Martin D. Young, "Antagonism between Species of Malaria Parasites in Induced Mixed Infections," *Public Health Reports* 53 (1938): 1289–91.

38. Mark F. Boyd, W. K. Stratman-Thomas, S. F. Kitchen, and W. H. Kupper, "A Review of the Results from the Employment of Malaria Therapy in the Treatment of Neurosyphilis in the Florida State Hospital," *American Journal of Psychiatry* 94 (1938): 1099–1114, quote at 1107.

39. Ibid., 1114.

40. On the treatment of nonhospitalized neurosyphilis patients, see Walter Freeman, "Therapeutic Malaria in Private Practice," *Southern Medical Journal* 24 (1931): 933–37.

41. Boyd, Diaries, January 13, 1934, RAC.

42. Boyd, Diaries, December 6, 1932, RAC.

43. On these trials, and the general history of malaria in the American South during the first half of the twentieth century, see my book, *Malaria: Poverty, Race, and Public Health in the United States* (Baltimore, 2001).

44. Boyd, Diaries, August 21, 1935, RAC.

45. Boyd, Diaries, November 20, 1932, RAC.

46. K. Mertz and K. C. Spitalny, "Imported Malaria Associated with Malariotherapy of Lyme Disease—New Jersey," *Morbidity and Mortality Weekly Report* 39 (1990): 873–75; "Self-induced Malaria Associated with Malariotherapy for Lyme-Disease—Texas," *Morbidity and Mortality Weekly Report* 40 (1991): 665–66. One physician in favor of studying the use of malariatherapy for central nervous system Lyme disease is Henry J. Heimlich. See his letter to the editor, *New England Journal of Medicine* 322 (1990): 1234–35. He also is involved in the Chinese AIDS effort. See Xiaoping Chen et al., "Phase-I Studies of Malariotherapy for HIV Infection," *Chinese Medical Sciences Journal* 14 (1999): 224–28; and Henry Heimlich et al., "Malariotherapy for HIV Patients," *Mechanisms of Aging and Development* 93 (1997): 79–85.

47. Wolfgang U. Eckart and Hana Vondra, "Malaria and World War II—German Malaria Experiments 1939–45," forthcoming in *Parassitologia*. The quotation is from Dr. Claus Karl Schilling, translated from the German by Eckart and Vondra.

48. William E. Collins and Geoffrey M. Jeffery, "A Retrospective Examination of Sporozoite- and Trophozoite-induced Infections with *Plasmodium falciparum:* Development of Parasitologic and Clinical Immunity during Primary Infection," *American Journal of Tropical Medicine* 61 (1999): 4–19; idem, "A Retrospective Examination of Secondary Sporozoite-and Trophozoite-induced Infections with *Plasmodium falciparum:* Development of Parasitologic and Clinical Immunity following Secondary Infection," *American Journal of Tropical Medicine* 61 (1999): 20–35; idem, "A Retrospective Examination of Sporozoite-and Trophozoite-induced Infections with *Plasmodium falciparum* in Patients Previously Infected with Heterologous Species of Plasmodium: Effect on Development of Parasitologic and Clinical Immunity," *American Journal of Tropical Medicine* 61 (1999): 36–43; idem, "A Retrospective Examination of the Patterns of Recrudescence in Patients Infected with *Plasmodium falciparum,*" *American Journal of Tropical Medicine* 61 (1999): 44–48.

49. Charles Weijer, "Another Tuskegee?" *American Journal of Tropical Medicine* 61 (1999): 1–2, quote at 2.

50. Bruce Mayne and Martin D. Young, "The Technic of Induced Malaria as Used in the South Carolina State Hospital," *Venereal Disease Information* 22 (1941): 271–76, quote at 272.

51. See, for example, Marion Torchia, "Tuberculosis among American Negroes: Medical Research on a Racial Disease, 1830–1959," *Journal of the History of Medicine and Allied Sciences* 32 (1977): 252–79; A. G. Fort, "The Negro Health Problem in Rural Communities," *American Journal of Public Health* 5 (1915): 191–93; W. E. Burghardt DuBois, *The Health and Physique of the Negro American* (Atlanta, GA, 1906); James A. Doull, "Comparative Racial Immunity to Diseases," *Journal of Negro Education* 6 (1937): 429–37.

52. Braslow (n. 5 above).