Parasites and Progress: Ethical Decision-Making and the Santee-Cooper Malaria Study, 1944-1949

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Parasites and Progress

ethical decision-making and the Santee-Cooper Malaria Study, 1944–1949

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ABSTRACT As part of a mid-1940s malaria research program, U.S. Public Health Service researchers working in South Carolina chose to withhold treatment from a group of subjects while testing the efficacy of a new insecticide. Research during World War II had generated new tools to fight malaria, including the insecticide DDT and the medication chloroquine. The choices made about how to conduct research in one of the last pockets of endemic malaria in the United States reveal much about prevailing attitudes and assumptions with regard to malaria control. We describe this research and explore the ethical choices inherent in the tension between environmentally based interventions and the individual health needs of the population living within the study domain. The singular focus on the mosquito and its lifecycle led some researchers to view the humans in their study area as little more than parasite reservoirs, an attitude fueled by the frustrating disappearance of malaria just when the scientists were on the verge of establishing the efficacy of a powerful new agent in the fight against malaria. This analysis of their choices has relevance to broader questions in public health ethics.

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Malaria remains one of the world's most frustrating public health problems. Since 1900 its mode of transmission has been understood, and means to interrupt its life course well known. But the disease continues to kill millions each year, and public health researchers continue to seek efficient ways to stop it. Scientists in the 1940s were equally determined to conquer malaria, as the disease had emerged as a major factor in troop effectiveness during World War II. Governments, both Axis and Allied, urgently sought either to interrupt the environmental transmission of malaria or to use medication to kill the malaria parasites in the human body (Harrison 1978; Litsios 1997). When these research trajectories crossed paths, researchers had to make difficult decisions about treating the individual or, perhaps to greater effect, treating the environment.

This issue was particularly pressing within the United States. The U.S. Public Health Service (USPHS) had created the Malaria Control in War Areas agency (MCWA) to fight malaria in the American South, and U.S. military physicians engaged malaria in North Africa, Italy, and the Pacific theater. Ironically, just as malaria was assuming importance in the war, the disease was in steep decline within the continental United States. This meant that sites for research on environmental modification or pharmacological intervention suddenly became rare, even in the American South (Humphreys 2001). Thus, when USPHS researchers chose to investigate the usefulness of a new pesticide against the malaria mosquito, they had only one site to choose from, the area around the Santee-Cooper Reservoir in South Carolina.

In the mid-1940s, USPHS researchers, in collaboration with public health officials from South Carolina, launched a study of the effectiveness of DDT (dichlorodiphenyltrichloroethane) in clearing the Santee-Cooper Reservoir area of malaria. They initially planned to withhold treatment from those persons in the study area with active cases of malaria, so that the impact of DDT alone could be properly assessed. This population was for the most part black, poor, and infected with falciparum malaria. While it is probably true that the physicians running the Santee-Cooper study, all of whom were white, were influenced by the differences of race and class that separated them from their subjects, their decisions were even more determined by assumptions about malaria control generated by decades of research and experience.

Malaria Control Is Mosquito Control: The American Creed

By the 1940s, most malariologists in the United States would have scoffed at the notion that a public health campaign that targeted the parasite, and not the mosquito, could have any long-term efficacy. Even now, no drugs exist that are consistently effective against all the forms the parasite assumes in the body, and this problem is multiplied by the existence of four separate species of *Plasmodium*. Only two species were major threats in the United States, but those two—*P. vivax*

and *P. falciparum*—were challenges enough. *P. vivax* could relapse from a hidden stage (now known to be in the liver) even when a patient's blood was cleared of parasites. *P. falciparum* was (and is) the deadliest malaria species, especially so for young children and pregnant women. The two parasites were distinguishable to the trained eye under the microscope, though diagnosis was often done without blood smears in the American South of the 1930s and 1940s. Improper or incomplete treatment could suppress symptoms for a time, while allowing for a later relapse from the surviving blood-stage parasites of either parasite. Both species were transmitted by mosquitoes of the genus *Anopheles* (Humphreys 2001).

From the late 19th century, when the mosquito vector and its role in transmitting the malarial *Plasmodium* were discovered, debate raged about the most effective model for anti-malaria work. One school, championed by Ronald Ross, held that the best way to control malaria was to attack the mosquito in the larval stage with dehydration, suffocating oil, or toxic chemicals. The other school, while not doubting that the anopheles mosquito spread malaria, instead put most of its energy into finding ways of killing the parasite in the human body. Robert Koch, among others, spearheaded this work. The first drug tried was quinine; others would follow (Harrison 1978; Litsios 1997).

The strongest U.S. advocate of quinization as a public health measure was Charles C. Bass of New Orleans. He had devised the so-called "standard" quinine regimen in 1914. Free quinine dosing according to the standard regimen could effectively and economically reduce malaria incidence in highly endemic areas (Bass 1919; Bass, Leathers, and Rose 1915–16). Over time, however, it became apparent that people would not take quinine voluntarily, both because of its cost and because of its side effects. While patients saw immediate benefit from the initial high doses of quinine, the long eight weeks of follow-up therapy offered them no visible payoff. For those found loaded with parasites but not clinically ill, the recommendation was for the eight weeks of once-daily quinine alone. Patient compliance was still harder in these cases, as patients were asked to endure the side effects of quinine (nausea, tinnitus, headache) for the good of the community, not for themselves (Bass 1950). Government-issued quinine also encroached on the private sphere of the doctor-patient relationship, a problematic intrusion not welcomed by physicians and tinged with "socialism." The standard therapy might work in the experimental setting, but it was not practicable for the long term.

Instead, local authorities relied on larvicidal techniques for malaria control and left the purchase of quinine up to the individual. By the early 1930s, malariologists were pessimistic that any public health campaign based on pharmacological prophylaxis would be effective. William E. Deeks, who directed malaria control for the United Fruit Company in the Caribbean and Central America, spoke forcefully for this point of view. As he told an audience at a Southern Medical Association meeting in 1929: "Apparently no amount of quinine will prevent mosquito infection. Neither will it prevent infection in man" (Deeks

1930). While quinine could keep a man on his feet and at work, once it was stopped malaria returned. Quinine could only be relied upon for suppression, not for true (sterilizing) prophylaxis or treatment.

Perhaps the most influential work on malaria control via drugs came out of the Gorgas Memorial Laboratory in Panama. There, malariologists investigated various combinations of quinine and two new synthetic antimalarials, quinacrine (Atabrine) and plasmochin. Over 10 years, they found they could not eradicate malaria, and that interrupting chronic infection with drugs meant that when new infections then occurred they were more clinically impressive since the patients had lost acquired immunity (Clark and Komp 1941). This research appeared to settle the question. Armies on both sides of the conflict in World War II gave their troops Atabrine or quinine to keep them at fighting strength, but this was only a temporary measure while the soldiers were in malarious areas. There was no reason for malariologists in the early 1940s to be any more optimistic that a drug trial would work in Santee-Cooper, than were the Gorgas investigators in Panama.

During World War II, federally sponsored research made two significant contributions to malaria therapeutics (Slater 2004). One was the development of chloroquine, which became available just as the war ended. The other took the form of new protocols for the large-scale use of Atabrine in men continually exposed to malaria. Properly administered, Atabrine appeared to be safe and effective. The drug worked well against falciparum malaria but it did not prevent relapse in vivax malaria. Thus, while Atabrine proved useful for the control of falciparum and could suppress vivax malaria, it could not clear the body of the hidden forms of vivax. At the end of the war, chloroquine's spectrum of use had yet to be fully determined, though its activity against the hidden cryptozoites of *P. vivax* seemed doubtful (McCoy 1945).

In the meantime, anti-mosquito activities surged ahead. During the 1930s, drainage received yet a further endorsement when the Works Progress Administration (WPA) set men to digging ditches to drain malarious areas. By World War II, the destruction of mosquito larvae entirely preoccupied those fighting malaria on the home front. The MCWA agency sought to contain malaria around militarily important sites, and it measured the effectiveness of its efforts not by counting cases of malaria, but by counting mosquitoes at sentinel capture stations. After the war, the MCWA's efforts were directed towards the eradication of malaria in the United States, and the agency's name was changed to the Communicable Diseases Center (CDC; Humphreys 1996). These mosquito-oriented malariologists directed the effort to control malaria around the Santee-Cooper Reservoir. The researchers were sure that medication could not eradicate malaria in poor rural communities, but they believed that DDT might break transmission effectively enough to isolate the parasite reservoirs and end endemicity. They needed to know if DDT was a sharp enough tool to do just that.

DDT

From the perspective of medical entomology, the most exciting outcome of World War II was the discovery of DDT. Although synthesized by German scientists in the 1870s, it was only in 1939 that Swiss chemist Paul Müller, then working for Geigy, found that it was useful for the problem before him: killing moths in clothing. This information filtered into the United States through Geigy's local subsidiaries, and DDT was added to the long list of chemicals tested for mosquitocidal properties during the war. This search was amplified by the urgent need to control malaria in the Pacific theater, where it was causing more casualties than the Japanese. By 1943, American scientists had demonstrated the wondrous properties of DDT. Most remarkably, it was a residual insecticide, so that it killed mosquitoes that landed on sprayed surfaces for up to three months after it was applied. It was also highly toxic to mosquito larvae. American malariologists were anxious to test the effectiveness of DDT in combating or even eradicating malaria from the American South (Dunlap 1981; Russell 2001).

When the Rockefeller Foundation asked leading malariologists in 1944 for "a well-considered plan of action" suitable for "furthering plans for a more intensive study of malaria," most responded that the field value of DDT in combating malaria was number one on the research agenda (Strode 1944). Famed Rockefeller malariologist Fred Soper (1946) announced that: "The first step . . . is to ascertain for every faunal region of the world, as quickly as possible, whether the residual DDT remaining after spraying of walls will prevent malaria transmission or not" (see also Packard and Gadelha 1994). A Rockefeller malariologist working in Trinidad and Tobago likewise chimed in: "The introduction of DDT necessitates a revision of practically our entire program of field investigations" (Shannon 1945).

DDT was anxiously awaited by the American public, too. Popular magazines told how the chemical had been used to prevent typhus among refugees at the end of World War II, and they predicted the many insect problems it would solve around the house once commercially available (Bartlett 1945; Miller 1945; Woodbury 1945). In offering the impoverished shack-dwellers of the Santee-Cooper environs an early opportunity to share in this marvel, the USPHS researchers probably saw themselves as munificent: in 1944, no other households in the United States had access to this amazing chemical, and here they were offering it for free.

One problem for those anxious to field-test DDT in the United States was that malaria had become scarce by the mid-1940s. In 1944, Louis L. Williams of the USPHS was devising a plan for its final eradication. Williams had decades of malaria control experience—indeed, he was the primary organizer of the MCWA. He knew that malaria transmission was the product of a delicate ecological balance between human carriers and mosquito vectors, and that malaria could be eliminated even in areas with substantial anopheline populations. Fur-

thermore, he believed that the "ultimate desideratum" was a reliable and safe drug or vaccine. Nevertheless, he felt that malaria in the United States could be dealt a final blow by the use of window screening and house spraying. Given the state of the disease—steep decline—he chose to promote a vector control program over medical intervention (Mountin 1944). While public health officials were aware of malaria's growing scarcity, they were also concerned that returning GIs would bring a surge of cases and new outbreaks. It was important to find out if DDT could cut these episodes short, or eliminate them altogether, but there were only a few pockets of measurable malaria left, and these suddenly became precious in the eyes of researchers.

Only one site in the United States had enough malaria cases to establish a major environmental research station. As Williams wrote to a top MCWA official in 1945: "The Santee-Cooper offers what may be the last opportunity in this country to see active malaria. I suspect that a month down there this summer . . . would be worth a great deal to you." The only alternatives for research "will be problematical small epidemics." Williams was pleased with the proposed research in South Carolina: "Your DDT study outline in South Carolina looks good and appears to be well planned. I have not made any critical analysis, for none seems to be called for."

Santee-Cooper: A Tale of Good Intentions with Bad Side Effects

The Santee-Cooper development project resembled the better known and larger Tennessee Valley Authority (TVA) in its function and funding. Its goal was to generate electrical power by damming rivers in South Carolina. Proposed in the 1930s, the project had languished for lack of funds until the prospect of U.S. entry into World War II created an urgent need for more power. Then it was rushed to completion in a wartime atmosphere, generating swarms of mosquitoes along with kilowatts. The Santee-Cooper project may have been called a "little TVA," but even so it dislocated 900 families and 42 million cubic yards of earth, stripped 171,000 acres of forest and swamp, and consumed 3 million cubic yards of concrete—all within two and a half years (Edgar 1984).

In the haste to finish the project, several important lessons from earlier hydroelectric ventures were ignored. Decades before scientists had discovered that if the site of a new reservoir was not adequately cleared before flooding, the resulting lake would be coated with debris, creating an ideal breeding locale for anopheline larvae. Initial clearing of the Santee-Cooper site was done by commercial lumber firms taking out valuable timber; WPA workers were to prepare the rest of the potential reservoir floors. But the work the Santee-Cooper's upper reservoir was never completed; the dam was ready, the power was needed, and the flooding commenced over a landscape still studded with more than a million trees, as well as brambles and not a few structures (Edgar 1984; Federal Security

Agency 1947; Hinman 1941). While malaria in the low country of South Carolina had been a severe medical and public health problem since colonial times (Wood 1974), the damming of the Santee and Cooper Rivers made a bad problem worse. Malaria erupted in the small settlements near the reservoir's shores.

Early in 1944, the Public Service Authority and South Carolina State Board of Health prepared a report summarizing the emerging malaria problem, and turned to the USPHS for assistance with disease control. The USPHS responded with an intensive malaria survey, including the epidemiological, entomological, and engineering features of the reservoirs and their immediate environs. The report showed that the lower Pinopolis Reservoir had been well cleared and produced little malaria. The Santee Reservoir, by contrast, was the focus of the malaria outbreak. The Santee Reservoir covered more than 47,000 acres of uncut forest, with dense debris on its surface. The initial sanitary report summarized the lake's condition: "Much heavy standing timber is therefore present in the central part of the reservoir. This is largely dead or dying and causes huge piles of log jams, drifting logs and small debris" (Johnson 1944). Anopheline larvae flourished in the interstices, safe from marauding fish that would otherwise feast on their ranks. There was also an abundant growth of aquatic plants such as alligator grass, whose herbaceous meshwork created further safe harbors for mosquito larvae. This vast expanse of water offered ideal reproductive conditions for the anopheline mosquito population, which exploded in the summer of 1944 (Malaria Field Studies 1944–45; Malaria Survey 1945).

As part of the survey project, the USPHS researchers took blood from every willing person living within 1.5 miles of the reservoirs. They sought out people working in the cotton fields, resting at home, or attending school, making thick blood smears from them all. Fixed and stained, these were sent on to the USPHS laboratory in Memphis, where the results were subsequently coded into IBM punch cards, ultimately recording nearly 4,000 names (Reider 1944). The survey revealed a substantial *P. falciparum* penetrance around the Santee Reservoir. On the north shore, 39% of the population had *P. falciparum* parasites in their blood, and it was not unusual for everyone in the household to be infected, with some houses lodging a dozen people. In another area just below the dam, 15% of those surveyed showed positive smears, while in areas adjacent to these, some 8% of those tested were infected. Elsewhere in the survey zone, especially around the lower reservoir, the inhabitants showed significant but lower rates. Mosquito surveys proceeded alongside the human ones, with thousands of mosquitoes caught and dissected under microscopes to determine the insects' infection rates (Malaria Field Studies 1944–45, 1945–46; Malaria Survey of the Santee-Cooper Impoundment 1945).

In June 1945, a MCWA publication announced the beginning of a trial, in cooperation with the South Carolina Board of Health, "to test the basic assumption that DDT controls malaria as a result of the residual house spray killing mosquitoes which transmit the disease." To track this effect, every effort was

"made to obtain a complete picture of malaria in the test areas before, during, and after treatment with DDT." Two areas in the study would be sprayed with DDT; two others would be watched as controls. Altogether, 1,807 people lived in the sprayed houses and 2,307 in the control areas (Malaria Field Studies 1944–45; Malaria Survey of the Santee-Cooper Impoundment 1945). Aside from issues of possible DDT toxicity, which were more relevant to workers' health than to that of the householders, the spraying appears to have been beneficial for the people involved (Daniel 2005). Although their permission was required before spraying the houses, most were enthusiastic in their cooperation.

One year on, the USPHS published the first results of the Santee-Cooper DDT study. Researchers reported on two principal endpoints: mosquito infection as demonstrated by dissections, and human infection as evident on blood smears. A expected, they found that there were more infected mosquitoes in the DDT-free areas than in those receiving the insecticide. The findings in humans were a bit more ambiguous: "The parasitemia prevalence [in humans] during the post-spraying period [of 1945] was higher in the unsprayed area than in the sprayed area." In November, this amounted to a difference of a little more than 2%, but by January 1946 the curves were converging, with a difference of less than 1% (Figure 1). Complicating the data was the fact that the highest human parasite rate noted in 1945 was no more than 4.5%, a far cry from the 39% prevalence with which the peak area was cursed in 1944, or even the 20% "average" parasitemia that was also used as a starting point (Malaria Field Studies 1944–45).

Because of this sharp but unexplained decline of malaria prevalence in treated and untreated areas alike, it was difficult to show a significant gradient between the sprayed and unsprayed areas. Notably, the first report made no claim for the formal statistical significance of this data. A 1947 paper, using the same data set, did claim the differences were significant, and took the data regarding children who were under 10 years of age as particularly illustrative of significant difference. Indeed, the difference in December smears was dramatic: the lines are almost three percentage points apart (2.6 vs. 5.3), but in January 1946 the lines cross, with the sprayed area actually having a higher rate (5.4%) than the untreated area (4.6%) (Figure 1). The report's author quickly passed over these data to more convincing work being done in Puerto Rico (Link 1947b). In a subsequent article, the same author admitted that the rapid fall in malaria rates over the course of the study limited the value of the information obtained (Link 1947a).

In 1946, the percentage of positive smears became tiny, in some months zero and in others less than 1% (Frohne et al. 1950). Justin Andrews (1946), the leading malariologist of the CDC, reported that the study was "being carried on primarily to determine the effect on malaria prevalence of DDT residual spraying of houses and latrines as was practiced by MCWA and CDC." Without assigning credit for the reasons, he admitted that "During the last two years the Santee-Cooper area has been the only one in the country with notable prevalence of malaria, and even here it has declined markedly." With malaria disappearing

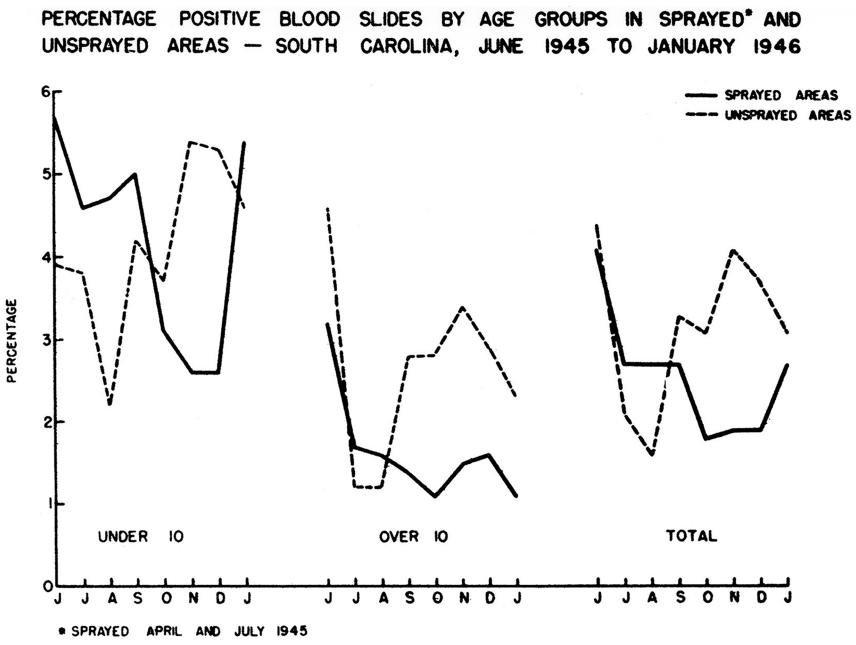

FIGURE 1

Santee-Cooper Project DDT spraying results.

SOURCE: LINK (1947A).

throughout the area, the research project was unlikely to show a significant impact from DDT spraying.

The USPHS faced a new ethical and compliance problem in 1947. Not only were test areas around the reservoir being sprayed, but all over the Southern states the CDC was spraying houses for malaria control. The local inhabitants in the control group were no longer willing to be left out. The CDC report on the study noted ruefully at the end of 1947: "This year it was found impossible to continue to withhold spraying from the unsprayed area because of the great clamor from the people involved, who were entirely surrounded by areas in which houses had been sprayed." The researchers therefore decided to spray the complete study area and to compare the areas with one year's spraying to that with two consecutive years of intervention (Malaria Field Investigations 1946–47).

Throughout the year the parasitemia prevalence remained close to zero, which stymied efforts to draw conclusions about the effect of DDT. The USPHS researchers were pleased to note that "there was very little reported use of antimalarial drugs." The report concluded that the spraying probably lowered the carrier rate but noted that "it is to be remembered, however, that there had been a steady decrease in malaria prevalence from October 1944 (20 percent) to the present time." Rather than taking credit for the decline, the researchers felt impelled to point out that: "This trend began to manifest itself rapidly even prior

to spraying in the spring of 1945." Although there was one spike in malaria cases in a small focus in 1947, the rate overall remained low. The USPHS researchers continued to find parasites in the mosquitoes, though, raising the possibility that what they had been calling human malaria in mosquitoes was evidence of the presence of other species of *Plasmodium* parasites that favored birds or other animals. Overall, very little could be learned from the data of the Santee-Cooper study (Malaria Field Investigations, 1946–47).

The Treatment Decision

With this background, we turn to the discussion of medicating the Santee-Cooper population that occurred in early 1946. The discussants were all malariologists, convinced that drug treatment would not work as a control measure, and excited about proving the efficacy of DDT. In fact, the CDC had already committed itself to DDT spraying regionwide—before having proven that this method would work to prevent malaria. Positive results from the Santee-Cooper study were urgently needed. The letters in which the treatment option was discussed reveal more, though, about the mindsets of these men: the letters show that these malariologists were so focused on killing mosquitoes that the needs of malaria's victims faded into the background.

The conversation began in January 1946, with a suggestion from Justin Andrews that all of the people from the study with positive smears be treated with atabrine, which was known to cure cases of falciparum malaria. He reasoned that this would help distinguish flares of persistent cases from newly acquired infections. This proposal was communicated to the South Carolina State Board of Health physicians working on the Santee-Cooper malaria project, and it was also circulated among CDC officials to get their reactions. In February, George Bradley, the CDC's preeminent entomologist, shot back his disapproval: "I am against using atabrine on Santee-Cooper this year. Am afraid it might interfere too much with anoph [mosquito] infection and we will not learn what DDT will do. Let's try atabrine elsewhere" (Bradley 1946).

The CDC and State Board of Health researchers on site in South Carolina were similarly opposed to treatment. As researcher Wayne Yeager (1946) said of another's opposition: "The main thing that concerns him is the effect such a program would have on the results of dissections of [mosquito] glands. Of course, the parasite reservoir in the human host is a vital part of the dissection program, and if we should reduce the number of parasite carriers too much by such a measure, it might seriously affect the results of the dissections." In other words, the point of the research was to evaluate the effect of DDT on the number of infected mosquitoes (identified by salivary gland dissection); people entered into this analysis only as "parasite reservoirs."

It is possible that these men did not see their trial in South Carolina as human subjects research at all. The intervention targeted mosquitoes; the measured vari-

able was the rate of infection in mosquitoes. Human suffering did not enter into their deliberations, as is evident from the next paragraph of Yeager's letter: "I would suggest that in order to get around the danger of upsetting our parasitemia reservoir too much and possibly ruining our dissection results, we treat those *P. falciparum* carriers between the ages of 10 and above." In other words, if children under 10 remained untreated, the reservoir of parasites would remain sufficient. Nothing in this letter, nor elsewhere in the discussion, indicates a concern for these children with malaria, children who might well die of the disease. And certainly if the drug was given to everyone, as another letter from South Carolina argued, "it would make the mosquito dissection program superfluous" (McDaniel 1946).

In 1948, Justin Andrews got his way, and all people with positive smears identified within the previous two years began to be treated with chloroquine, the new malaria drug. Andrews had first mentioned this course of action with chloroquine as early as September 1945, even suggesting that all the residents within the high prevalence areas be treated. If done in wintertime such treatments would eliminate recurrent or persistent infections so that a truer measure of new transmission might be made (Malaria Morbidity Observations 1945). *P. falciparum* could not "relapse" in the same sense that *P. vivax* could. But *P. falciparum* could well have relapsed from low asymptomatic levels in the springtime—the season of pellagra and malnutrition—particularly among chronic falciparum malaria carriers. Whatever the true infection states, drug intervention was not done to test the efficacy of controlling or eradicating malaria with chemotherapy. Rather, the point was "to determine whether the few positive cases being diagnosed now represent relapses or new infections" (Goodwin 1948a). Although Andrews was rebuffed in 1945, by 1949, the researchers were treating all people who had shown positive smears since 1944 with chloroquine to wipe malaria out completely (Center Director Files 1949). The last positive smear was detected and the infected person treated in February of 1949. During 1950, researchers surveyed 85% of the population in the study area with blood smears, but found no parasites. Malaria was gone from its last endemic focus in the United States (Goodwin 1948b).

A 1949 summary of the Santee-Cooper project, published by George Bradley and M. H. Goodwin Jr., who had been intimately involved in the work, made no claims about the effectiveness of DDT to reduce parasite rates. Instead, they stressed the value of the station as a surveillance post for recurrent infection. A graph demonstrated the sharp decline in cases, but Bradley and Goodwin made no comment about the source of the decline, or about the sprayed versus the unsprayed areas. Similarly, they did not mention the early decision not to treat with drugs, although they did note that residents with positive smears received medication later. Ultimately, the reader is left hanging: just when one expects the conclusions, the article closes with a statement that the station continues to monitor malaria prevalence in areas once heavily diseased. Curiously, Bradley did

not mention the Santee-Cooper project at all in his later review of the history of malaria in the United States (Bradley 1966).

Discussion

The fact that the USPHS researchers referred to human children as "parasitemia reservoirs," whose place in the study was to supply a necessary factor in DDT/mosquito research, has prompted cringes among epidemiologists learning about this study. Such language violates universal ethical codes that call for treating individuals with dignity, respect, and accord for their rights (Bayer et al. 2007; Macklin 1999; Public Health Leadership Society 2002). The inadequate informed consent at the core of the study protocol has also prompted concern. We know that the researchers explained to each householder that DDT would kill the mosquitoes that spread malaria, and that they received consent to enter the house. However, we do not have evidence that the researchers discussed treatment with the study participants, or that they actively prevented them from seeking it. Still, if their primary goal had been the subjects' best interests, the researchers obviously could have done more to help the people in the study. But even Andrews, who promoted the treatment option, did so only to clarify the impact of DDT, not directly to benefit the study population.

In mitigation, it should be noted that the Santee-Cooper study was undertaken in an era when textbooks of epidemiology and public health said little about research ethics, and when a general utilitarian viewpoint sustained public health research and practice (Coughlin and Beauchamp 1996). And the study took place at a time when overt racism was a visible presence throughout U.S. society. Certainly the behavior of USPHS colleagues in the Tuskegee syphilis study attests to the pervasiveness of such attitudes among public health researchers (Reverby 2000; but see also Benedek and Erlen 1999). If all the inhabitants around the Santee-Cooper Reservoir had been white, perhaps the researchers would have been less likely to refer to children as "parasitemia reservoirs" or to be so cavalier about denying them treatment and risking their lives. We have little to go on beyond the obvious disparities between scientists and subjects, but the objectification of persons evident in the "parasitemia reservoir" phrase makes it hard to conclude that they saw the Santee-Cooper residents as citizens with the same rights as themselves and their own families. Even if standards of informed consent and human experimentation were much looser in the 1940s than today, one still doubts that the researchers would have wanted their own children treated this way.

The specific characteristics of malaria's epidemiology had much to do with the choices researchers made in this case. By the 1940s, American malariologists had become, by and large, mosquito-focused people. Once the researchers had decided on a plan that involved environmental manipulation, the human population involved went from *being* the study population to becoming one aspect of

the landscape that influenced the actual study population, which was made up of infected mosquitoes. Particularly during World War II, military imagery was invoked to characterize the fight between insect and man. The mosquito was "Public Enemy No. 1"—people actually suffering with malaria took second place. Private Snafu fenced with Anopheles Mike (the cartoon's creators ignored the sex of the infected mosquito), the Seven Dwarfs battled the mosquito in a widely distributed cartoon about malaria prevention, and mosquitoes attacking aircraft was a common wartime cartoon trope (see *Complete Uncensored Private Snafu* 1943; *Winged Scourge* 1943). Visible, annoying mosquitoes made for more concrete enemies than either the invisible plasmodium or the bodies it occupied.

The fact that this was a public health research project, and not a therapeutic study, likewise shaped the course of events. As the bioethicist G. Rose (1985) has noted: "The central ethos of medicine is seen as an acceptance of responsibility for sick individuals." This is not true for the physician working in public health, however. "In public health," explain Beauchamp and Steinbock (1999), "the 'patient' is the whole community or population. The goal of public health is to reduce disease and early death in populations." The public health researchers in South Carolina had no contractual obligation with the study subjects as patients, as they were not the subjects' personal physicians. Instead their goal was to improve the health of the population as a whole, both directly in the sprayed area and remotely by demonstrating that this new technique could indeed eradicate malaria. Rose (1985) has referred to this tension as the "prevention paradox," pointing out that "A preventive measure that brings much benefit to the population offers little to each participating individual."

Public health's focus on the population builds on the utilitarian philosophy of promoting the greatest good for the greatest number, and malaria research, so often focused on the environment rather than individuals, is particularly well matched to utilitarian thinking. Historians have identified this gulf between malariologist and persons with malaria at other places and times. Frank Snowden (2006) described the choices facing Italian malariologist Alberto Missiroli in the mid-1940s, when he, too, chose not to treat a study population with malaria because "this would have disturbed the experiment with DDT." Randall M. Packard (1997), in his critique of the World Health Organization's malaria eradication program in the 1950s and 1960s, found local people reduced to "subjects of study rather than as social beings." And Margaret Humphreys (2003) notes that in the worst case—malaria research programs that abused prisoners during World War II—a Nazi researcher justified the work by saying "I admit that people had to suffer because of each experiment. . . .Yet, the scientific interest to protect millions of people from this disease and to save them was predominant." The principle critique of utilitarianism is that it must be balanced with respect for individual human rights, but the peculiar features of malaria and its vector may tend to push human needs into the background.

Previous writings on public health ethics offer few analogies for this sort of

research protocol, where human beings are but one component of an environmental intervention. One exception is the literature surrounding a lawsuit in Maryland, brought against the Kennedy Krieger Institute (KKI), a Johns Hopkins University affiliate. Recognizing the serious problem of lead paint ingestion by slum children in Baltimore, KKI sought to demonstrate whether cost-effective methods of partial lead abatement might significantly reduce lead levels in children. In a 1993 to 1995 study, three groups received three different modes of lead paint reduction, while they chose as controls children living in houses without a lead paint hazard. One media estimate claimed that 95% of community housing contained lead paint, so the children in the study were to be exposed to conditions better than the status quo for others in their community. Lead levels were measured in the children at intervals over two years after the intervention. Almost all children in the intervention groups had a drop in lead levels; in a few, the levels rose. Two families of such children brought suit against KKI (Buchanan and Miller 2006; Mastroianni and Kahn 2002).

In 2001, the Maryland Supreme Court reversed a lower court ruling that dismissed the case. The Supreme Court opinion assailed KKI for treating the children as "canaries in a mine" or "guinea pigs," and recalled the horrors of the Tuskegee syphilis study and Nazi war crimes. This view carried considerable weight in the popular media and has found its way into one historical account of medical experimentation on African Americans (Washington 2007). But others have taken a more moderate approach to the case and provide analysis that offers insight into the Santee-Cooper case. Buchanan and Miller (2006) argue that "A clear distinction needs to be make between applications of the principle of justice in macrolevel distributions of social resources and the principle of fairness in the microlevel conduct of research." By macrolevel they refer to issues of justice on the societal level, the morality of allowing children to live in poverty and want, and responsibility of society as a whole to alleviate that inequality. The KKI researchers did not cause the poverty of the Baltimore slums and were no more responsible than other members of society for its alleviation. They did not create the exposure to lead and were not responsible for moving the children to safer housing. On the microlevel of the study, on the other hand, they were responsible for treating the study subjects fairly. They used appropriate informed consent and offered each family in the lead paint housing a direct benefit by reducing lead paint exposure. As Buchanan and Miller conclude: "the ethically relevant question is not how an alleged therapeutic obligation can be fulfilled but how the participants can be protected from harm and exploitation." They believe that the KKI researchers fulfilled the latter obligation.

A similar rubric can be applied to the Santee-Cooper situation. If one can step away from the language of "parasitemia reservoirs" to look at what the researchers actually did, the study appears in a somewhat less negative light. As in the KKI case, the researchers did not create the unhealthy situation they sought to ameliorate. The public health researchers did not have a therapeutic relation-

ship with their subjects, and they thus did not have an ethical obligation to provide them with care. While a social justice perspective might well decry the lack of universal health care in the United States, this situation was not created by the Santee-Cooper investigators. They may have been pleased that their subjects did not receive treatment for malaria, but the researchers neither blocked that care nor were responsible for it. From the standpoint of assessing beneficence, they did not increase the risk to the study participants by denying them care, since the status quo before the study was the absence of care. And the act of DDT spraying offered an expected benefit to the study participants. In fact, the only reported community resistance was from those households denied DDT, rather than from any concern over medication.

Historical cases of malfeasance have long been useful tools in teaching the fundamentals of bioethics (Coughlin and Beauchamp 1996). Historians frequently judge the behavior of prior actors, overtly or covertly, as they sift evidence and read the past (U.S. Advisory Committee 1996). Such case studies allow students to consider the pros and cons of actual events and to discuss appropriate behavior. When Duke University briefly lost its NIH funding in 1999 due to perceived inattention to informed consent (among other factors), part of the remedy was for every doctor to attend a medical ethics lecture that reviewed past research horrors as morality tales to guide present attitudes and actions. (MH, personal experience; Campbell 1999). The Santee-Cooper malaria story can serve a similar function, alerting public health researchers to the dangers to human subjects when animal vectors and environmental interventions preoccupy the research gaze. It also demonstrates the extra care that should be taken when vulnerable populations—the poor, the young, those with minority status—become surveillance points in public health research.

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