

## CHEMISTS AND NATIONAL EMERGENCY: NIH'S UNIT OF CHEMOTHERAPY DURING WORLD WAR II.

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In 2005, President George W. Bush came to the National Institutes of Health (NIH) in Bethesda, Maryland, to announce a new initiative on avian and pandemic influenza (1). This visit was part of a long tradition. In the face of national emergencies and threats to public health, the NIH has repeatedly been called upon to serve the nation. In the years leading to US entry into World War II, the NIH mobilized to confront the impending threat of malaria. In the late 1930s, malaria was in sharp decline in the US. However, war would put millions of previously unexposed soldiers, sailors, and marines into highly malarious regions, such as the Mediterranean, South East Asia, and the islands of the Pacific. Even at home, many military bases would draw inductees to areas of the South and West where mosquito vectors could readily spread the debilitating and potentially deadly disease in crowded camp conditions. NIH researchers had to prepare anew for war and disease.

In 1938, Surgeon General of the US Public Health Service (USPHS) Thomas Parran and Rolla E. Dyer, chief of the Infectious Diseases Division at NIH, planned the transfer of two drug discovery groups from the University of Virginia and the University of Michigan to NIH in Bethesda. Heading the Virginia unit was Lyndon F. Small, who had trained in chemistry with Elmer P. Kohler and James B. Conant at Harvard and with Heinrich Wieland in Munich (2). With the intention of controlling drug addiction by altering the chemistry of opiates, Small's university program had synthesized novel compounds and modified existing ones in order to

explore the chemistry and activity of morphine-related substances. The Michigan unit, which tested Small's compounds, was headed by Nathan B. Eddy, a Cornell-trained physician and pharmacologist. Parran, who had been Surgeon General since 1936, brought the two to Bethesda not to pursue analgesics, but to form the core of a new antimalarial chemotherapy laboratory (3). In January, 1939 Small and Eddy formed the nucleus of a new Unit of Chemotherapy at NIH. Both men were affiliated with the USPHS—a necessity if they were to handle narcotics—as part of their opiate work, which was funded by the Rockefeller Foundation and sponsored by the National Research Council (NRC). Their transfer to Bethesda was logical in the context of their NRC and USPHS connections.

Like many in the Federal government, Parran foresaw US involvement in World War II and knew that this would put many Americans at risk for malaria around the world. Parran's initiative became part of a larger project on antimalarial chemotherapy begun by NRC in 1939 (4). At the time only a handful of drugs was available for malaria treatment and prophylaxis. As NRC put it (5):

While quinine, plasmoquine, atabrine and a few other drugs have been quite useful, there is, in the judgment of the medical profession, a great need for something better.

The need was great for a number of reasons. Ninety percent of the world's quinine originated on the island of Java in the Netherlands East Indies, an area under threat from Japanese military expansion in Asia. Plasmoquine

and atebriane were relatively new synthetic products developed and owned by the German chemical firm Bayer. All three of these major drugs had toxicity problems. To respond to the military need for better drugs, Small had to move his people to Maryland and quickly convert his chemotherapy program from opiates to antimalarials.

With war looming, Lyndon Small established a first-rate chemical group at NIH. He brought with him from Virginia the Vienna-trained chemist Erich Mosettig. Small also recruited to NIH Everette L. May, who earned his Ph. D. at Virginia in 1939. May and Mosettig began their antimalarial efforts with materials taken directly from the opiate research program. The new antimalarial program was collecting interesting compounds from laboratories around the country for random screening. Many chemists in academic, industrial, and government laboratories contributed samples for screening in the national antimalarial program. While no one thought these opiate-related materials were necessarily promising as antimalarials, the wartime project was soliciting all potentially biologically active compounds for their large-scale screening program. Also, Small had previously sought to replace the naturally occurring alkaloid morphine with a synthetic analogue, so it made some sense to follow a similar path in looking to replace another naturally occurring alkaloid, quinine. Therefore, May and Mosettig submitted to animal testing a number of amino alcohol derivatives of phenanthrene, which they had synthesized in their opiate work. They also synthesized a series of compounds based on quinine, what they called "quinuclidine with two C-C bonds disrupted." (6) Much of May's wartime work involved various derivatives of phenanthrene. NIH chemists also synthesized other chemical series for testing. For example, when one of Eddy's S-glucosides—phenyl- $\beta$ -D-glucoside (SN-5,859)—showed slight activity against the chicken-malaria screen (*Plasmodium gallinaceum*) and relatively low toxicity in chicks, Edna M. Montgomery, Nelson K. Richtmyer, and C. S. Hudson submitted nearly forty sulfur-containing compounds of various structural types (7). Small's NIH group also included other organic chemists, such as Lewis J. Sargent, who had been a National Research Fellow at Virginia in 1938-1939. He and Small worked on the acridines, a series of compounds related to the prewar synthetic antimalarial atebriane and on developing sulfanilamide derivatives as antimalarials (8). Various sulfas, such as Parke-Davis's Promin, had shown some promise as antimalarials even before the war.

For screening compounds, Small brought G. Robert Coatney from the NIH laboratory in Columbia, South

Carolina. The Columbia laboratory had been founded in 1931 by Louis L. Williams, Jr., of NIH's Office of Malaria Investigations. He and Bruce Mayne—another eminent NIH malariologist—had sought to establish a laboratory to refine the use of malaria in the treatment of neurosyphilis and to study the biology of malaria. It was Mayne who selected the South Carolina State Hospital as the laboratory's location and served as its first chief until his death in 1941. At Columbia, Coatney learned firsthand about the use of malaria to treat syphilis: how to employ this therapeutic intervention in one disease in order to study another. The use of malaria therapy—wherein malaria's high fever spikes were believed to benefit neurosyphilitics—was first developed in Europe in the 1910s and had expanded in the US during the 1930s (9). Coatney, trained as a protozoologist, had come from Nebraska in 1938 and joined the Columbia staff to develop for research purposes a pigeon malaria he had previously isolated. With the Columbia experience behind him, Coatney was able to establish avian malaras—particularly the chicken malaria *Plasmodium gallinaceum*—for the screening of potential drugs at NIH's animal facilities in Beltsville, Maryland (10). Coatney would also develop NIH's antimalarial clinical testing programs, first at St. Elizabeths Hospital in the District of Columbia and then, in 1944, at the Federal Penitentiary in Atlanta, Georgia (11). By 1941, even before Pearl Harbor, the efforts made by NRC and Parran had been significantly augmented by the new Federal Office of Scientific Research and Development (OSRD) and its Committee on Medical Research (CMR) established by President Franklin D. Roosevelt. Before the advent of OSRD, Small ran the only comprehensive antimalarial synthesis program in the country. As a part of this much larger CMR program, Coatney and Small expanded clinical testing efforts at NIH. At St. Elizabeths, Coatney's collaborators tested antimalarial compounds in neurosyphilis patients undergoing malaria therapy. The induced malarial fever had a therapeutic effect on these patients, and the drug interventions could be made after the fever had run its course over a suitable interval. In Atlanta, the research was conducted with prisoner volunteers, again with malaria induced either by the injection of infected blood or by the bite of infected mosquitoes raised for this purpose. These programs tested potential drugs produced not just in Small's laboratory, but by other collaborators in OSRD's expanding antimalarial program.

The wartime antimalarial program was a large-scale cooperative project, spread across scores of laboratories in government, academe, industry, and nonprofit orga-

nizations. So it is not surprising to find that the NIH worked with industrial collaborators, such as G. Carsch, Melvin A. Goldberg, E. P. Ordas, and J. Schultz from Lady Esther, Ltd., of Chicago, who expanded the phenanthrene series in new directions. After the war, these industrial chemists pursued careers at a number of firms including Velsicol Corporation, Lever Brothers Company, and New York Quinine and Chemical Works, which was one of Small's industrial collaborators on his opiate work (12). Additional academic collaborators, funded with OSRD money, were also essential to the work. Key compounds in the phenanthrene series were scaled up for testing by Ralph L. Shriner and his group at Indiana University and Charles C. Price's team at the University of Illinois.

During the war, several amino alcohol derivatives of phenanthrene showed activity similar to that of quinine, but often with some toxic effects. The phenanthrene series did eventually have one postwar chemical cousin with some clinical success, halofantrine, which emerged from clinical trials in the late 1980s. It retained the amino alcohol moiety but added a more modern trifluoromethyl substituent to the ring system (13). In the fall of 1944, however, adverse reactions in this series led Small and Mosettig to the conclusion (14):

..that the phenanthrene series appeared to be exhausted with the exception of the lot of drudgery to be done in the hope that some derivative other than those already under examination would turn up with a higher antimalarial activity.

The compounds had mostly been tested in human subjects at Alf Alving's University of Chicago program, which employed prisoner volunteers at the state prison in Joliet. None of these compounds showed sufficient antimalarial activity at the time to justify further pursuit (15), so they were dropped from the program. After the war with the need for secrecy over, the NIH laboratory

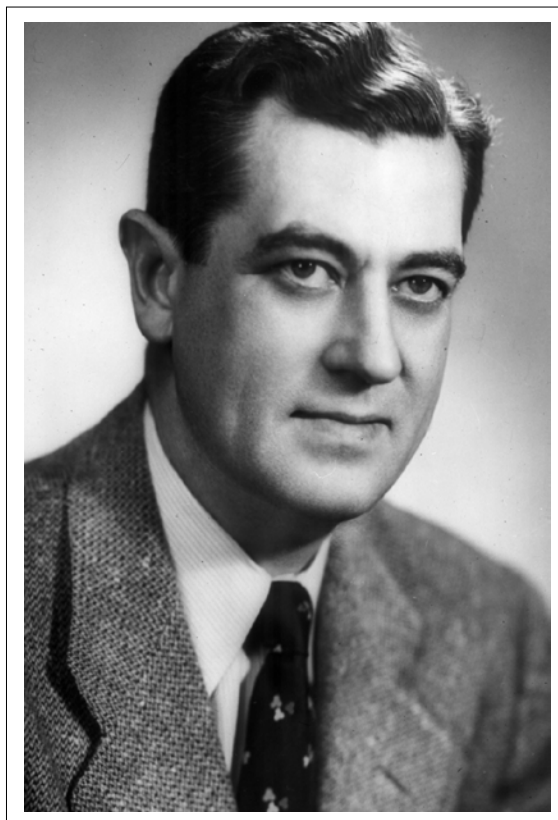
and its collaborators published dozens of papers on their work, including more than 20 in a series entitled "Attempts to Find New Antimalarials," which appeared in the *Journal of Organic Chemistry* in 1946 and 1947. In the postwar years, the NIH chemists and their government colleagues for the most part returned to their

prewar pursuits. Small and Eddy resumed their work on analgesics, while Coatney and his colleagues, malariologists before the war, continued in this field.

The CMR antimalarial program, of which Small's group was a part, did much more than successfully reappraise chloroquine, the postwar antimalarial of choice. It developed safe and effective protocols for the use of atebriane during the war and tested more than 14,000 compounds for antimalarial activity, many of which were new substances synthesized expressly for the program. Some 80 compounds—including a number of NIH's phenanthrene derivatives—were clinically tested in human subjects, primarily neurosyphilitics, prisoner volunteers, and servicemen (16). This clinical testing, international in its

scope, was overseen by James A. Shannon, trained as a physician and physiologist, whom Rolla Dyer would bring to the NIH in the years immediately following the war (17). Reporting as chairman of the Clinical Panel to the CMR Board for the Coordination of Malaria Studies in March of 1944, Shannon characterized the program's first years (18):

The direction of the early work (1942-1943) was conditioned largely by the early loss to the United Nations of their normal sources of supply of quinine, by the lack of adequate stock-pile of quinine, and by the lack of information which would permit the intelligent use of [atebriane]. Those who were intimately concerned with the malarial problem during the first year of the war may recall the gravity of the situation.



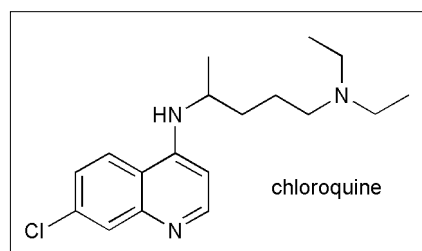
James A. Shannon

Shannon added that concern about the adequacy of atebriane compounded the worries about quinine. Shannon was an M.D.-Ph.D. at New York University working at New York's Goldwater Memorial Hospital. Early reports from the field suggested that atebriane was not adequate to the military's needs with regard to *falciparum* or *vivax* malaria. As atebriane was the drug available, the antimalarial program conducted clinical and toxicological investigations of atebriane, with the goal of optimizing its prophylactic use. Shannon, as chief of clinical research for the antimalarial program, oversaw the development of protocols for the safe and effective use of atebriane. The synthesis of new compounds and the screening of old and new ones had continued, even as work on atebriane proceeded.

In the end, Small's extensive work on phenanthrene and acridine derivatives at NIH expanded the structure-activity profiles of these promising drug series; and atebriane filled the military's needs, but all were eclipsed by the success of the 4-aminoquinolines, especially chloroquine. However, chloroquine, the wartime program's major contribution to the pharmacopoeia, was not a new compound. It had first been made and tested by Bayer in Germany during the 1930s, but the company's clinical collaborators had erroneously found the drug to be toxic. The discovery of a closely related 4-aminoquinoline, sontochin, in the possession of prisoners of war in North Africa, caused the Americans to revisit this series and rediscover chloroquine as a highly effective, low-toxicity drug for the treatment and prevention of malaria.

By August 1944, chloroquine was sufficiently promising to be extended beyond animals, and it was tested for toxicity on conscientious objectors at the Massachusetts General Hospital. No adverse toxic symptoms were observed in these preliminary trials. Further trials in malaria therapy at the Boston Psychopathic Hospital soon followed (19). The tests in Boston were just a few of many. Initial animal research expanded into testing in mental patients, prisoners, and servicemen. Testing for efficacy in humans progressed as well. Alf Alving and his group at the University of Chicago tested chloroquine and related compounds at the Stateville penitentiary. The Army expressed interest in moving ahead with "a fairly large-scale field study" of the suppressive capability of chloroquine as soon as the positive results in prisoner volunteers became available (20). The next big milestone would be tests conducted on Australian soldier-volunteers, supervised by Neil Hamilton Fairley. Fairley and his group had previously conducted advanced clinical testing on atebriane and sontochin (21). CMR

soon sent the Australian Army 2,500 chloroquine tablets with which to begin its chloroquine trial. Over time this large-scale test grew larger still: the US program arranged for 500 pounds of chloroquine to be delivered to the Australians (22). As with atebriane earlier in the war, this Australian clinical work was definitive for chloroquine progress. For the Australians, separated from the Japanese advance into South East Asia by the island of New Guinea, malaria had been a major concern and a serious problem. Fairley's unit had been called upon to determine effective protocols for quinine, atebriane, and plasmoquine. The Australians ran numerous series of tests on healthy military volunteers in Australia and New Guinea. These included heavy exercise and high altitude, to determine the effectiveness of drugs under the stress of simulated combat. Eventually, the Australian program tested not just the prewar drugs (quinine, plasmoquine, and atebriane), but sulfas, biguanides, sontochin, paludrine—the novel British antimalarial developed during the war—and chloroquine. Coatney, Shannon, and others had helped raise chloroquine from obscurity and in so doing created one of the wonder drugs of the postwar period (23).



With the malaria project behind him, Shannon had a vision of what federal biomedicine, properly mobilized and funded, could accomplish. He was one substantial connection between the wartime regime and subsequent organizations, but he was not alone. Shannon, the wartime malaria researcher who oversaw the program's clinical investigations, went on to become an influential Director of NIH. He first came to work in Bethesda in 1948, at the National Heart Institute. He became Associate Director of NIH from 1952 to 1955 and Director from 1955 to 1968. Shannon, speaking about his initial NIH recruitment by Rolla Dyer (Director 1942-1950) and Norman H. Topping (Associate Director, 1948-1952), mentioned that Dyer was director of NIH by war's end, and "more importantly" that Dyer was a member CMR, which had been responsible for "the management of American Science for the military during World War II." Shannon later recalled that Dyer and Topping "knew that the wartime enterprises had been outstandingly successful, despite the complexity and breadth of the program. They felt that the

Goldwater [where Shannon had conducted his malaria work] enterprises, which were sprung up and developed in a very short period of time, [were] precisely the thing they wanted done at the new NIH—the post-war NIH.” (24) Dyer, too, was well placed to appreciate Shannon’s malaria work and the significance of the wider wartime program. In his previous post he had been head of the Division of Infectious Diseases at NIH, a division that included the Malaria Office. With malaria fading as a domestic threat to public health and the war over, the Federal health officials turned more to chronic illnesses, such as cardiovascular disease, establishing the Heart Institute at NIH in 1948 and bringing Shannon in as its associate director to oversee the new research program. During Shannon’s time at NIH its annual appropriations grew from tens of millions to more than a billion dollars (25). In the postwar decades that followed, Shannon—NIH Director from 1955-1968—and his NIH chemists would transform and expand medical research in the United States, and the growing organization would be called upon again and again to meet health emergencies.

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