Desperately seeking quinine

The malaria threat drove the Allies' WWII "Cinchona Mission".

BY VASSILIKI BETTY SMOCOVITIS

The outbreak of the Second World War saw Allied troops ill-prepared to deal with war in malarial zones. By 1942, as Java with its famous cinchona plantations—and the largest quinine factory in the world, the Banfoengsche Kininefabriek—fell to Japan, the Allies found themselves cut off from the world's largest producer of quinine. The German Army had already taken over the world's main supplier and repository of processed quinine run by the Dutch Kina Bureau, the cartel that monopolized quinine distillation, when it took over Amsterdam in 1940.

As World War II spread to the Pacific theater, more Allied troops fell to malaria than to Japanese bullets. By December 1942, more than 8500 U.S. soldiers were hospitalized with malaria. In one hospital, as many as 8 of every 10 soldiers had malaria, not war-related injuries. An Army Air Corps count of hospital admissions made between November 1942 and February 1943 made a disturbing projection: If left unabated, in just one year as many as 4 out of every 10 soldiers would be hospitalized for malaria alone.

Synthetic antimalarials such as those that would eventually be trademarked "Atabrine" were available during the war. Atabrine had originally been manufactured by the German industrial giant I. G. Farben from coal tar in the early 1930s. But Atabrine lacked the efficacy of quinine and caused horrible side effects like nausea, diarrhea, headaches, and yellow-tinged skin; if that weren't bad enough, Japanese propaganda spread the rumor that it caused impotence. U.S. troops would go to great lengths to avoid taking the bitter pill. The lack of an adequate and stable supply of a usable antimalarial agent thus became a vital national security issue. The United States had failed to stockpile adequate amounts of quinine when it should have. Secretary of Commerce Jesse Jones thought the price of quinine was too high. He refused to secure enough of the drug even though the Office of Foreign Economic Administration had ordered him to stockpile strategic military materiel, including medicines like quinine, along with rubber, nitrates, and tin. Caught largely unprepared, the United States entered the Pacific theater without an adequate amount of the best antimalarial agent available.

In the United States, significant amounts of the less desirable Atabrine became available through Winthrop Chemical Company. Winthrop had been a partner with I. G. Farben but severed its ties to the German giant through the Alien Properties Act just before the bombing of Pearl Harbor. Using intermediate chemicals imported from Germany, it was producing some 5 million tablets of Atabrine at the outbreak of war. Winthrop increased production and then licensed the production process to manufacturers without taking royalty fees. As a result, Atabrine was soon produced by other pharmaceutical companies, including Abbott, Lilly, Merck, and Frederick Stearns. Intermediates that were no longer available from Germany were supplied by chemical companies such as Harmon Color Works, Hilton Davis, the National Aniline Division of the Allied Chemical and Dye Corporation, and the Pharma Chemical Company. As a result of the concerted effort, the U.S. wartime production of Atabrine in 1944 reached 3.5 billion tablets. But the troops refused to take it.

Drastic conservation measures for quinine were adopted at home. The War Production Board restricted the use of quinine and other antimalarials to the treatment of malaria. But it was clear that such actions were not enough.

In response to the crisis, the United States began a massive effort to provide quinine to American troops. The best option appeared to be to procure species native to Andean South America and then to cultivate plantations of the highest-yielding crops. In April 1942, quinine procurement was placed under the control of the Board of Economic Warfare, a U.S. government wartime agency that had charge of the accumulation of strategic materials. Shortly thereafter, what became known as the Cinchona Mission was established under the Board of Economic Warfare with the cooperation of the Department of Agriculture and the National Arboretum. William C. Steere, a botanist from the University of Michigan, and F. Raymond Fosberg, a botanist with the Department of Agriculture, were enrolled to help organize the procurement process.

The principal cinchona-producing countries of the 19th century were approached, and "cinchona agreements" were drafted. The countries agreed to "sole buying privileges" for all cinchona bark if it had a fixed minimum total crystallizable alkaloid content, which varied from 2 to 3% minimum. The countries agreed to give technical aid in the exploration and procurement of cin-

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chona, and in return the United States was expected to establish a permanent cinchona plantation program in the host country.

The first procurement team left in the fall of 1942 for Colombia, which had been the chief provider of quinine in the 19th century. Cinchona missions were then established in Peru and Ecuador, but Bolivia, the first source of quinine-rich bark, never ratified the agreement. It had agreed to send its cinchona bark to the Dutch Kina Bureau instead. Nevertheless, the Board of Economic Warfare established agents in La Paz to arrange for the purchase of surplus quinine and quinine bark. Besides the agreements with those countries in which cinchona trees are native, agreements were made with Costa Rica and Guatemala. Cinchona plantation programs had been initiated as early as 1934 by the pharmaceutical company Merck, which had explored the cultivation of cinchona plantations in Guatemala in an attempt to gain control of the Dutch monopoly in Java. Its nurseries and laboratory became enrolled in the wartime procurement effort.

The work of the cinchona missions involved hunting for the quinine-rich strains first found in the Andes. The survey teams consisted of a botanist, a forester, and local Latin assistants who were to be trained in the collection of cinchona. At their peak, the cinchona missions involved as many as 30 American botanists. For more than two years, beginning in 1942, these teams traversed known cinchona regions of the Andes, finding, in addition, several previously unknown bark areas.

Botanists on the team were expected to identify and collect cinchona. They also collected related *Rubiaceous* genera that might prove useful in breeding programs. The task of the foresters was procurement, estimation of bark volume, and determination of best harvesting procedure. Once procured, the bark was transported back to one of the field laboratories in Bogotá, Colombia; Quito, Ecuador; Lima, Peru; or La Paz, Bolivia. The work was arduous. Indian packmen or bark-cutters called cascarilleros were hired to transport 40–80 lb of the bark on their backs along narrow trails. Occasionally, mules were used to transport bark to the nearest rivers for further transport. Landing strips were sometimes built so that the bark could be airlifted. Detailed reports were produced, which included geographical data of the cinchona areas where plantation development was desirable and feasible, and other commercial information valuable in addressing the immediate problem of harvesting and transportation.

Collection was more difficult than anyone had realized. Cinchona frequently hybridized with diverse strains and with numerous varieties that contained varying amounts of alkaloids. Chemical tests soon determined that there were variations in type and amount of the alkaloid in individual plants based on their location. Barks were classified into good bark and bad bark, depending on their usefulness, but quick and easy tests based on color or taste quickly proved unreliable. Many of the botanists, too, had never seen tropical plants in situ, let alone been trained to quickly identify such a complex genus. The American foresters were equally baffled; they could easily recognize their own native trees but initially had a hard time recognizing and working with cinchona. Nor could the local people easily recognize the plants. Despite some residual harvesting of bark in Colombia and Ecuador before the wartime need, the local people lacked special skills at stripping or shipping the bark. To prepare the botanists, foresters, and local collectors and to help train a permanent staff, Department of Agriculture botanist Fosberg wrote *The Cinchona Manual* and translated it into Spanish.

Cinchona, the source of quinine and other antimalarial alkaloids, is an evergreen tree (genus *Cinchona*) native to mountainous areas of South and Central America. The tree was named for the Spanish Countess of Chinchón, said to have been cured of a fever in 1638 by a preparation of the bark.

Other problems ensued. The survey teams encountered hostile local peoples. Rivalries soon broke out among the local collectors, the landowners, and government collecting agencies. Easily accessible trees were soon harvested, and botanists had to survey more and more remote areas. The botanists experienced altitude sickness at collecting sites as high as 11,000 ft and suffered from the high humidity, which rotted their clothes and damaged their instruments. They also suffered from malnutrition, amoebic dysentery, and even malarial fevers. One botanist, Arthur Feathersonhaugh, died of a heart attack induced by the high altitude. His body was carried on a stretcher in a dangerous trek down a precipitous slope.

The botanists hunted for two years. Then, in 1944, synthetic quinine (in a nonstereoselective mixture) was synthesized from precursors by two American scientists, William E. Doering of Columbia University and Robert B. Woodward of Harvard University. Although it was not made available for commercial purposes, it eventually led to more synthetic drugs that, although lacking the ability to cure malaria, were able to control various stages of the disease. As a result of the improvement of such synthetic antimalarial agents, the U.S. cinchona missions returned home at the end of 1944, after having shipped back some 12.5 million lb of cinchona bark. In November 1945, all agreements with the South American governments for the collection of bark were terminated. Overall, the cinchona missions met with mixed success. They provided a significant quantity of cinchona for the Allied war effort, but they were never able to locate the high-quinine-yield species *Cinchona ledgeriana*.

Editors' note: Gilbert Stork and co-workers completed the first total stereoselective synthesis of quinine in 2001.

Sources

Hodge, W. H. *Econ. Bot.* **1947,** *1–2,* 229–257.
Howard, R. A. *Bot. Rev.* **1994,** *69,* April–June, 197–257.
Rosengarten, F. *History of the Cinchona Project of Merck and Co., Inc. and Experimental Plantations, 1934–1949;* Merck: Rahway, NJ, 1944.
Worthen, D. B. *Pharmacy in History* **1996,** *38,* 143–147.

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