A Brief History Quinine and Quinidine Production in the Americas

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Summary. Quinine, oldest of the anti-malarials still in use, and quinidine, an anti-arrhythmic, have been extracted from *Cinchona* bark since about 1823. Exploitation of natural stands of *Cinchona* in the Andes led to several attempts at plantation production. Of these, the most successful were in Netherlands Indonesia (Java). Just before World War II, a cooperative effort to develop technologies for successful cultivation of *Cinchona* in the western hemisphere was undertaken by the governments of the United States and Guatemala, a major pharmaceutical firm, and four Guatemalan coffee planters. Cultural requirements of this cloud-forest genus were ascertained, and selection of clones for superior yield and disease resistance was achieved. Guatemalan plantings continue production despite the excessively cyclic nature of the market.

Long before the Spaniards conquered Andean America, the indigens knew about the antimalarial properties of *Cinchona* bark. For 300 years following the conquest, tropical residents around the globe consumed dried and powdered bark to treat "fevers." Quinine, the active principle, was isolated first by Pelletier and

Caventou in 1820. Shortly thereafter, industrial-scale extraction and distribution of the alkaloid began on both sides of the Atlantic Ocean. In 1898, J.W. England wrote a report to the Philadelphia College of Pharmacy entitled "The American Manufacture of Quinine Sulphate." According to this report, the industry began in Philadelphia with Farr & Kunzi, followed by George Rosengarten and, eventually, by Powers & Weightman—all destined later to be absorbed by Merck & Co., of Rahway, N. J.

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Figure 1. *Cinchona* stands in upslope sequence: last-harvested and now coppicing trees; old seed trees; earlier-harvested stand; trees in flower just below cinder cone of volcano.

In Philadelphia, the industry reached its peak in 1897, when 320 tons of dry bark were imported from South America. Evidently, this did not suffice to meet demand, for 6.5 tons of quinine sulphate were brought in during the same year. By 1897, imports of bark had fallen to 127 tons, but those of quinine sulphate had soared to 85 tons. Nearly all the latter came from a vigorous extraction industry that had grown up in Germany. J.W. England's lament of 1898 over the loss of American industry to foreign competitors is curiously similar to those heard today.

During the 19th century, the market for quinine was driven by needs of European colonials, who were expanding into humid tropical regions where malarial parasites were endemic. Eventually, supplies of wild bark diminished as natural forests of *Cinchona* in Peru, Bolivia, Ecuador, and Colombia were exploited. Tropical planters everywhere, always alert for alternatives to cane, cotton, and cattle, considered planting *Cinchona* on marginally profitable hill lands. The first such attempts suffered from lack of prior technology; but eventually colonial governments in eastern Africa, Indonesia, Ceylon, India, and the Philippines achieved varying degrees of success. Margaret Kreig has described some of these efforts in her book "Green Medicine." The more successful were the under-

takings in eastern Africa, which supplied German extraction facilities, and eventually those in Indonesia, which supplied Netherlands interests. At the end of World War I, Germany lost its African holdings. The Netherlands held its plantations in Java until Japan invaded the region in World War II. Following that war, German and Dutch firms established virtually a complete monopoly of production, pricing, and sales of quinine, as well as *Cinchona* bark. Principal players were Boehringer of Mannheim, Buchler GmbH of Braunschweig, and Amsterdamische Chinin Fabrik (A.C.F.).

Just prior to World War II, the Dutch monopoly became the target of considerable public and official resentment in the United States. To offset somewhat the unfavorable public image, the Netherlands interests established a quinine research foundation in New York with Norman Taylor, a well-known horticulturist who was director of the Brooklyn Botanic Gardens. Taylor's task was to provide information aimed at increasing the medical uses of quinine and, in the process, to support research projects at medical schools on the same subject. At the close of World War II, the Netherlands interests expected to regain their former plantations in Java and to reestablish the earlier position of trade leadership. Wartime neglect of the plantations on Java

and the rise of unfriendly nationalism there prevented this reestablishment. The foundation was terminated, and Taylor retired with a memorable Indonesian-style dinner and speeches at the Netherlands Building in Rockefeller Center. A similar fate befell at least temporarily, the *Cinchona* plantations in eastern Africa and India as these regions shook off the colonial ties to European government.

A key element in the Javan success story was the persistent and systematic development of plantation technologies adapted to *Cinchona* cultivation by Dutch agriculturists (Taylor, 1945). Eventually, however overproduction arose to plague the main producers. Following discovery of the mosquito vector of malaria, improvements in public sanitation did much to reduce dependency on quinine. Prices fell, and efforts to maintain a profitable industry became even more stringent. For consumers, the inelasticity of supply and price that resulted was felt most keenly when threat of military conflict justified stockpiling. Thus, Japan's conquest of Indonesia in 1942 shut off 95% of the world supply of quinine and quinidine. The Western allies were confronted with a severe emergency.

Frederic Rosengarten, Jr., (1944) wrote the "History of the *Cinchona* Project of Merck

& Co., Inc., 1934-1943." The project took the form of a first serious reconnaissance of the possibilities for growing *Cinchona* in the hemisphere to which it is native. As early as 1932, the U.S. government had become uneasy over the virtually complete dependence upon sources far removed from North America and vulnerability to arbitrary control of supply and price on the one hand and to military conquest on the other. Noting that Merck's predecessors had pioneered quinine production in the United States, the government urged Merck to take the lead role.

From the outset, emphasis was on the generation of plantation production technology. Extraction and purification of quinine and quinidine held the status of ancient arts-the problem was to produce the bark in required amounts and with a sufficiently high quinine and/or quinidine content to make extraction profitable. In 1933 Merck purchased select seed from growers in Java and chose Guatemala as a principal site for experimentation. Wilson Popenoe well-known tropical horticulturist, and then director of field research for the United Fruit Company, assisted Merck in organizing and planning the new undertaking. The result was a well-conceived, cooperative venture involving the government of Guatemala the State and Agriculture departments of the

Figure 2. *Cinchona* stand in downslope view: regenerating and coppicing trees showing some foliage characteristics; Pacific coastal plain at base of volcano.

Figure 3. *Drying bark is pulled into rainsheds at night.*

United States, Merck, and a group of accomplished coffee growers—Gordon and Owen Smith, Lind Pettersen, Walter Lind, and Percy Davies. An experimental program was devised that focused on the selection and clonal propagation of vigorously growing, high-assay trees as well as on cultural technologies. To the best of my knowledge, none of the group had attempted before to grow cloud-forest species on a plantation scale. Hence, little or nothing was known of the physiological and environmental requirements of the plant. A sequence of specialists on aspects of plant ecology, propagation, pathology, hybridization, and general physiology was brought in to solve unitary problems. However, there was needed someone at the head who had the ability to analyze problems, perhaps intuitively, as they arose and thus to choose the most suitable and effective visiting specialists as rapidly as possible. For this position they chose Boris Alexander Krukoff, forester and field botanist, a one-time member of the Czar's army, and a driven individual. His life has been summarized by Landrum (1986) for the New York Botanical Garden. I met Krukoff in 1944, and carried on a voluminous correspondence with him over the next 30 years, much of which related to technical problems of *Cinchona* cultivation.

One of Krukoff's early efforts was to obtain from Japanese-occupied Java, by means never revealed, a complete set of the periodical titled CINCHONA. With characteristic presumption, he passed the pile on to me with "orders" to translate all relevant papers from Dutch into English for use by his project. I spend one summer at home in Princeton learning to read Dutch and accomplishing the task assigned to me. The information so gleaned was summarized in the *Annual Review of Biochemistry* in 1948. Thus began my apprenticeship in tropical horticulture.

Shortly thereafter, Norman Taylor's foundation provided funds for hiring a research assistant, and I began to experiment with the physiological requirements of *Cinchona*, first at Princeton and subsequently at Columbia. Although the *Cinchona* tree was a refractory experimental object, at least in my hands, some interesting conclusions were drawn. First, unlike most conventional crops of the temperate zone, *Cinchona* elevates water and mineral nutrients from soil to foliage by a substantial hydrostatic pressure generated in the root system. By hindsight, this would seem a most natural mechanism for plants adapted to essentially water-saturated atmospheres. Second, this hydrostatic pressure appeared to be dependent on a continuing supply of soil-borne magnesium and or-