

## Alice A. Augusta Ball Young Chemist Gave Hope to Millions

By Paul Wermager and Carl Heltzel



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Imagine you are a 15-year-old returning home from school, and you are met at your front door by two officials instead of your parents. You are arrested and then told to say good-bye to your family, but hugging is not allowed. The armed officials take you to a facility for a quick physical exam. Afterward, you are sent to an isolated peninsula named Kalaupapa, bounded by vertical cliffs 2,000 feet high and surrounded by a deep ocean. Separated from your family and friends, you are banished here for the rest of your life not for what you did but for what you have: *leprosy!*

Your only escape from a lifetime sentence to this colony of exiled souls, damned by disease, rests in the hands of a young chemist named Alice Ball. She was the first to discover a chemical key that offered millions of sufferers the hope of being set free from their medical exile.

### The most cursed place on earth

Jack London called it "the most cursed place on earth" and "the pit of hell" after taking a tour of the colony. Three sides of the peninsula were ringed by jagged, razor-sharp lava rock, making landings impossible. The fourth cliff rose as a two-thousand-foot wall so sheer that wild goats tumbled from its face.

For 80 years, beginning in 1866, the Hawaiian and later the American governments forcibly removed more than 8000 men, women, and children to the remote and inaccessible Kalaupapa settlement on the Hawaiian island of Molokai. The following is an excerpt from *The Colony* by John Tayman:

*Under a law to prevent the spread of leprosy, persons suspected of having the disease were chased down, arrested, subjected to a cursory exam, and exiled. Armed guards forced them into the cattle stalls of inter-island ships and sailed them 58 nautical miles east of Honolulu, to the brutal northern coast of Molokai. There, they were dumped on an inhospitable shelf of land of the approximate size and shape of lower Manhattan, which jutted into the Pacific from the base of the tallest sea cliffs in the world. It was, as Robert Louis Stevenson would write, "a prison fortified by nature." In the early days of the colony, the government provided virtually no medical care, a bare subsistence of food, and only crude shelter. The patients were judged to be civilly dead, their spouses granted summary divorces, and their wills executed as if they were already in the grave. Soon thousands were in exile, and life within this lawless penitentiary*



Kalawao main street (on the east side of Kalaupapa) during its early years.

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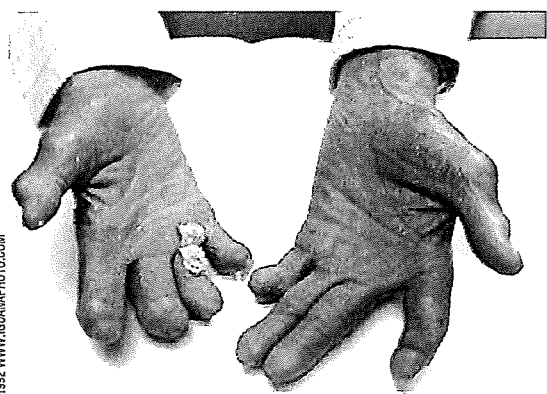
came to resemble that aboard a crowded raft in the aftermath of a shipwreck, with epic battles erupting over food, water, blankets, and women. As news of the abject misery spread, others with the disease hid in terror from the government's bounty hunters, or violently resisted exile, murdering doctors, sheriffs, and soldiers who conspired to send them away.

Some tried to escape, only to fall to their death from the cliff. Others were swept out to sea by the relentless currents.

Back on the mainland, public health and law officials rounded up thousands of people to be sent to other isolation centers across America: North Brother Island (New York City), a locked building next to San Francisco's City Pest House, Louisiana Leper Home (near New Orleans), Penikese Island in Buzzards Bay (Massachusetts), and Seattle's Diamond Point.

## Leprosy

Hansen's disease (renamed after the Norwegian physician, Gerhard Hansen, who first identified the causative bacillus, *Mycobacterium leprae*) was the scourge of mankind for centuries. Its contagious, disfig-



The disfigured hands of a patient with Hansen's disease.

uring, and seemingly incurable traits terrified people across every continent. Fear and ignorance of the disease closely paralleled the early days of the AIDS epidemic. Former U.S. Surgeon General Dr. C. Everett Koop noted in a 1989 visit to Kalaupapa, "AIDS is the modern-day leprosy." The difference between them is that AIDS is caused by a virus, and leprosy is caused by a bacterium.

Leprosy is a chronic disease that affects the skin, peripheral nerves, mucus mem-

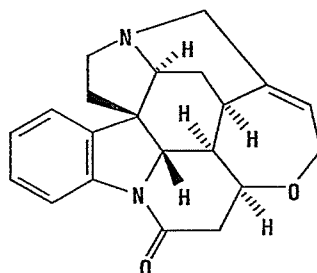
branes in the respiratory tract, and eyes. It is known to affect people of all ages from newborns to the elderly. It is most common in warm, wet areas in the tropics and subtropics.

Although the disease is known to be contagious, the exact mechanism of transmission of leprosy is unknown. It was thought that direct contact between someone with the disease and a healthy person was the only way the disease spread. Some believe that it may be spread via the respiratory route. *M. leprae* was the first bacterium that was discovered to cause disease in humans. Its size and shape resembles *tubercle bacillus*, the pathogen responsible for tuberculosis.

Though rare in the United States, the disease still surfaces in parts of Texas and Louisiana. Worldwide, there are about 600,000 new cases of leprosy reported each year.

## Early treatments

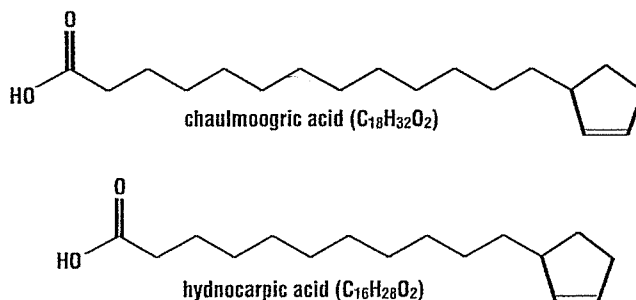
Down through the ages, desperate physicians and researchers had tried numerous treatments to combat the horrible disease, including surgery, diet, X-rays, mercury, arsenic, antimony, copper, dyes, strychnine,



strychnine

and other esoteric concoctions administered as ointments or injections. All failed to cure the disease.

Only one natural substance seemed to offer relief and improvement to some patients suffering from Hansen's disease.



## Chaulmoogra oil

Since the 14th century in China and even earlier in India, chaulmoogra oil was used with moderate and inconsistent success to lessen the effects of Hansen's disease.

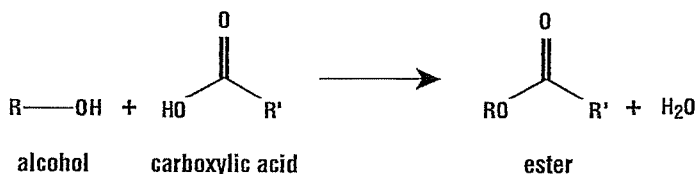
Obtained from the seeds of the chaulmoogra tree, or *Taraktogenos kurzii*, healers administered chaulmoogra oil orally or applied it as an ointment. One reason for the limited effectiveness of early chaulmoogra treatments resulted from a botanical mix-up.

Taraktogenos is from a Greek word meaning "confused" and refers to the earlier confusion between it (the true chaulmoogra) and two other genera, *Hydnocarpus* or *Gynocardia*, (both false chaulmoogras). The false chaulmoogra oil lacked several of the essential chemicals found in the true oil. Because most of the commercial chaulmoogra on the market before 1900 was false chaulmoogra, unsuspecting physicians and patients often experienced varying and disappointing results from chaulmoogra.

Chaulmoogra oil was first introduced to Hawaii in 1879 but failed to gain widespread use because of its unreliable therapeutic effects. Physicians and researchers continued to be frustrated but were also intrigued by the mystery of why some patients showed remarkable improvements with chaulmoogra oil, while others did not. Originally, the oil was applied topically to leprosy areas but external application had only limited value in treating the disease. An oral remedy was more effective but had an extremely nauseating effect on the patient. Furthermore, plain chaulmoogra had a bitter, disagreeable taste thus patients were very reluctant to take it long term.

Scientists around the world searched diligently for an effective way to administer chaulmoogra oil as an injection. Early attempts with injectable forms of chaulmoogra failed because the oily drug was virtually insoluble in water, and so it was painful when injected and created abscesses (lumps). We now know the active con-

stituents of chaulmoogra oil are chaulmoogric acid and hydnocarpic acid. These drugs are solids in their purified state and their relatively long, nonpolar hydrocarbon chains render them water insoluble.



Forming an ester from an alcohol and a carboxylic acid. R and R' represent two different hydrocarbon groups.

## Enter Alice

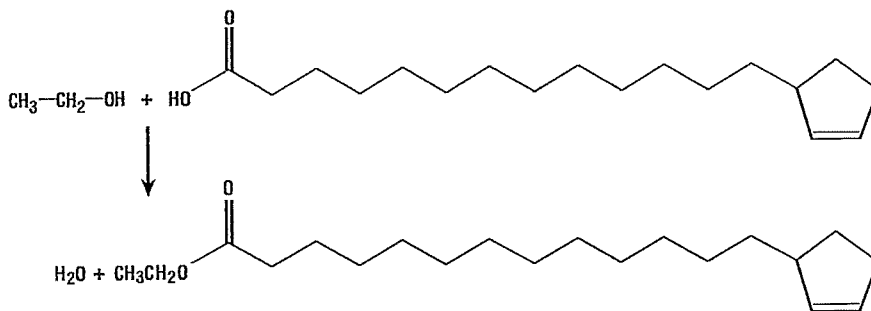
Dr. Harry T. Hollmann was the catalyst who brought the chaulmoogra problem to its chemical solution by enlisting the right problem solver: Alice Ball. As Assistant Surgeon at Kalihi Hospital in Hawaii where new Hansen's disease patients were sent, Dr. Hollmann had refused to give up on chaulmoogra's promise. He'd been a physician at the federally funded Leprosy Investigation Station when it opened at Kalaupapa in 1909. In his 1922 medical article, he explained how it all began:

*"I interested Miss Alice Ball, M.S., an instructress in chemistry at the College of Hawaii in the chemical problem of obtaining for me the active agents in the oil of chaulmoogra. After a great amount of experimental work, Miss Ball solved the problem for me by making the ethyl esters of the fatty acids found in the chaulmoogra oil, employing the technique herewith described."*

Alice's solution to the problem involved preparing the ethyl esters of the fatty acids present in the oil. An ester can be prepared from a carboxylic acid by reacting it with an alcohol, usually in the presence of another acid as a catalyst. An alcohol has an -OH functional group, and a carboxylic acid functional group has the general formula -COOH, or -CO<sub>2</sub>H. The ethyl ester of an acid is formed using ethanol as the alcohol.

The straight, untreated oil consists of a variety of different esters with very high molecular weights and are highly viscous. Viscosity is a measure of a substance's resistance to flow. A thick liquid like honey is highly viscous, whereas gasoline is not. Patients described the injections of chaulmoogra oil as burning like fire, and the viscous oil moved visibly through the skin like a snake slithering under a sheet. Alice's ethyl esters reduced the viscosity of the bioactive compounds in the oil. The active acids themselves are solids, and as mentioned previ-

ously, are not water soluble. When formulating a drug, water solubility is a highly desirable property for the obvious reason that, if soluble, a drug can make its way through the body (which is mostly water). Many of today's drugs are in their salt form. You can prepare the salt of a carboxylic acid by treating it with a base such as sodium hydroxide.



Forming the ethyl ester of chaulmoogric acid

The sodium salts of chaulmoogric and hydnicarpic acids would be water soluble. But because of their size, they would act like soaps and could cause the undesirable side effect of hemolysis (breakdown of red blood cells) when injected.

It often takes a hero to rescue us from desperate times and desperate situations. In this case, our heroine was a remarkable young female chemist. Alice Augusta Ball accomplished what many researchers, chemists, and

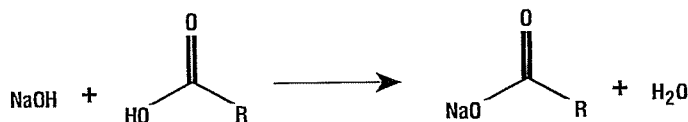
pharmacologists working in some of the world's most sophisticated and well-equipped laboratories had been unable to do. At the age of 24, Alice discovered the first preparation of a water-soluble, injectable form of chaulmoogra oil for the treatment of leprosy.

## Her early years

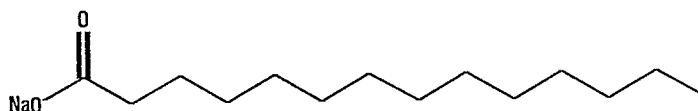
Alice Ball was born on July 24, 1892, in Seattle, WA, to African-American parents. Alice grew up around chemicals. Her grandfather, J. P. Ball, Sr., was a famous photographer and one of the first African Americans in the United States to learn the art of daguerreotype (early photographic images were developed on silver coated glass or copper plates). She probably helped out in the family photo gallery, mixing fresh developers and preparing

photographic plates. Her father, mother, and aunt were also photographers.

Alice first came to Hawaii in 1903. She accompanied her family, including her grandfather, who was suffering from arthritis and seeking comfort in Hawaii's warm climate. In 1904, her grandfather died in Honolulu, and she moved back to Seattle with her family. She attended Seattle High School and earned excellent grades, especially in the sciences. In her four years at the University of Washing-



Forming the sodium salt of a carboxylic acid.



Structure of a typical soap.

ton, Alice earned two degrees: pharmaceutical chemistry (in 1912) and pharmacy (in 1914). Before departing to Hawaii for graduate school, Alice copublished with her pharmacy instructor a 10-page article "Benzoylations in Ether Solution" in the prestigious *Journal of the American Chemical Society*.

After one year of graduate study, Alice Ball graduated on June 1, 1915, with her master's degree in chemistry from the College of Hawaii (later renamed the University of Hawaii). Her master's thesis involved the identification of the active constituents of kava root. She was the first woman and the first African American to graduate with a master's degree from the college. Alice was also the first Black female instructor in the college's chemistry department from 1915 to 1916.



Young girls during the early years at Kalaupapa.

## Triumph of spirit

Reflecting on the tremendous obstacles and oppressive discrimination that Alice—and all African Americans—faced during this period of history, makes her achievements even more outstanding. Following the Civil War, the corrosive Jim Crow laws and the inhumane attitudes they engendered made life humiliating and treacherous for Blacks.

We don't know the setbacks or disappointments that Alice experienced in her research because no record of her daily work exists. We do know that she taught chemistry classes and chemistry labs during the day so she probably conducted the chaulmoogra experiments in her free time. Because she solved the chaulmoogra puzzle rather quickly—between 1915 and early 1916—we can presume she possessed a brilliant insight and persistent work ethic.

At the height of her accomplishment, but before she could publish her research, Alice tragically became ill. She returned home to Seattle and died on the last day of December 1916, at the age of 24. The cause of her early

demise remains unknown because her death certificate was altered.

A 1917 newspaper article in the Honolulu *Pacific Commercial Advertiser* may offer a clue: "While instructing her class in September 1916, Miss Ball suffered from chlorine poisoning." During this time, ventilation hoods were not a mandatory safety feature in laboratories.

After her untimely death, Dr. Arthur L. Dean, a chemist and President of the College of Hawaii, carried on Alice's pioneering work. A laboratory at the College began producing large quantities of the new injectable chaulmoogra to supply the numerous requests for their preparations from all over the world.

Sadly, Alice never lived to witness the results of her discovery. In 1918, a Hawaii physician reported in the *Journal of the American Medical Association (JAMA)* that 78 patients of Kalihi Hospital were released by board of health examiners after being treated by chaulmoogra injections. During the four years between 1919 and 1923, no new patients were exiled to Kalaupapa. As late as 1936, the *Philippine Journal of Science* noted that Hansen's disease patients treated with chaulmoogra continued to be paroled from that country's Culion Leper Colony.

But like the ebb and flow of life, joy gave way to sadness as patients began relapsing and ships once again returned to Kalaupapa with their human cargo. It appeared that the devious bacterium had developed a resistance to Ball's chaulmoogra. Some speculated that patients who returned to their old homes were reinfected by dormant spores in their environment. Whatever the cause, the disease began to reclaim old patients and destroy new lives, but with nothing better to offer patients, chaulmoogra remained the standard of care until the sulfones (Sulfa antibiotics) were developed in the 1940s.

The injectable form of chaulmoogra oil developed by Alice Ball gave hope to the hopeless for almost two decades that one day they would be reunited with their loved ones. Some say it also offered a new form of hope to the world. Governments and researchers don't like to waste their time and money on hopeless causes. Ball's chaulmoogra showed that Hansen's disease was no longer hopeless. Increased funding for research resulted



Kalaupapa National Historical Park was established in 1980. Kalaupapa is still home for many surviving Hansen's disease patients.

in the development of the sulfones and other effective treatments for Hansen's disease.

The Governor of Hawaii issued a proclamation on February 29, 2000, declaring it "Alice Ball Day." On the same day, the University of Hawaii honored its first woman graduate and pioneering chemist with a bronze plaque mounted at the base of the lone chaulmoogra tree on campus. In December 2006, the Board of Regents of the University of Hawaii honored Alice's work and memory with its Regent Medal of Distinction (posthumously conferred).

Hopefully, the world will not forget Alice Augusta Ball and how this young African-American chemist, researcher, and instructor overcame impossible odds and racial and gender discrimination to give hope to the millions of banished and forgotten victims of Hansen's disease. ▲

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