GRANVILLE PERKINS AND LEPROSY CHEMOTHERAPY IN THE PHILIPPINES

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Introduction

This article examines the career of Granville A. Perkins (1891-1985), an American organic chemist who made significant contributions to the chemical fight against leprosy in the Philippines, before returning to America to take up a career in chemical industry. Perkins also pursued research in theoretical chemistry and quantum mechanics. He came to my attention in a footnote in Russell's seminal history of the concept of valency, where the text reads (1):

> In both Lewis and Langmuir appear formulae with shared pairs that must have originated from one and the same atom, *e.g.,* in the ions of the oxy acids. Attention was drawn to this "borrowing union" by Perkins; it was termed a "semi-polar bond" by Sugden *et al.,* and a "co-ordinate link" by Sidgwick, …

The names of Lewis, Langmuir, Sugden, and Sidgwick will be familiar to anyone who has taken an interest in the twentieth century history of chemistry, but the question arises, 'who was Perkins?', since this appears to be his only contribution to the development of the valency concept and he is not remembered for other contributions to the chemical literature. In the work referred to by Russell, Perkins suggested that the coordinate bond be represented by the symbol ω, but this was not adopted. Chemists clearly preferred Sidgwick's arrow.

The Perkins paper to which Russell refers was published in the *Philippine Journal of Science* (2). This article was not the first public expression of Perkins' interest in theoretical physics and chemistry, since it had been preceded by one on the electron (3); and it was succeeded by three others, one on relativity (4), one on double bond additions (5), and one on molecular structure (6). Many years later, after he had retired from employment in the American chemical industry, Perkins returned to this interest and published a number of papers in the field of quantum mechanics that will be referred to later in this account.

Perkins' Career

Granville Akers Perkins was born in 1891 in Lin Ching, China, where his American parents were Congregational medical missionaries, his mother (née Estrella) being one of the early women medical graduates. The family returned to the United States around the turn of the century, and Perkins' baccalaureate degree was awarded by Cornell University (A.B. 1913), following which he taught at the Institute of Chemistry of the University of Puerto Rico (1913-1915). While there, he met and married Marie Waring, who was teaching in an American school there; their first daughter was born in San Juan. Perkins then spent a short time as a junior chemist in the U.S. Department of Agriculture before taking up an instructorship in chemistry at the University of Pittsburgh, from which institution he was awarded the Ph.D. degree in 1915. After a brief appointment with E. I. Du Pont de Nemours in 1917, he spent the war years as a Lieutenant in the U.S. Army Chemical Warfare Service. After World War I came the phase of his career that receives most attention in this article, for Perkins took up an appointment in the Bureau of Science of the Philippine Islands, in Manila. Following some involvement with preparation of materials for leprosy chemotherapy, he transferred in 1922 to become Chief Chemist at the leper colony on the Philipines' Culion Island, where he remained until 1927 (7).

Upon his return to America, Perkins first worked as a research chemist at the American Meat Institute Foundation in Chicago (8); but finding the climate there too different from what he had obviously enjoyed in Puerto Rico and the Philippines, he moved after two years to South Charleston, West Virginia, to undertake research in organic chemistry for the Carbide and Carbon Chemical Company, a division of Union Carbide. There a second daughter was born, and Perkins' career progressed as he became assistant director (1931-1944) and then director of research (1944-1951). Among his early work with Carbide was involvement in the development of the plastic Vinylite, a copolymer of vinyl chloride and vinyl acetate. During the years of World War II he was deferred from military service because of his work on synthetic rubbers involving butadiene, but was pleased to see his elder daughter taken into the U.S. Army as a physical therapist.

Briefly to recount the later years of his industry career, in 1951 Perkins became Vice President in the company's Carbide and Carbon Division, requiring a move to Mamaroneck, NY, where the family lived until he retired in 1956. In the mid-1960s, he and his wife then moved to Florida where he died over two decades later at age 94.

Paul Freer and Government Science in the Philippines

The Philippine Islands had long been a Spanish colony; but as the end of the nineteenth century approached, change was in the wind. There were repeated rebellions by indigenous groups during the 1890s, and these were to some extent (as in Cuba) supported by the United States. Although peace was established between the rebels and their colonial overlords in 1897, within a year the Spanish-American War had broken out, and under the Treaty of Paris that formalized its ending, the islands were ceded to the United States. Although the annexation was opposed by some in America, and certainly by many in the Philippines, the United States replaced Spain as the colonial power and within a year or two had reached agreement with the rebel groups who declared their new allegiance in April, 1901. Their struggle continued through more peaceful means over the next few decades, with Manuel L. Quezon, President of the Senate, leading repeated delegations to the United States in the 1920s seeking independence. It was finally achieved in 1946, after World War II delayed the fulfillment of President Roosevelt's promise of 1934 that it would come within ten years.

The U.S. administration moved quickly after the end of the Spanish American war to establish civil government in the Philippines, one of the initial appointees being Dean C. Worcester, a zoology professor from the University of Michigan who became Secretary of the Interior (9). In 1901 the administration founded the Bureau of Government Laboratories, and Worcester recruited his Michigan colleague, Paul Caspar Freer (1862-1912), to head it (10). Freer was a medical graduate and organic chemist with a substantial record of published research, who had taken his M.D. degree at Chicago, earned his Ph.D. degree in 1887 in Munich under von Baeyer, and also worked for a year as assistant to W. H. Perkin in Manchester. He was granted leave from his Michigan position for three years to join Worcester in the Pacific, but eventually resigned and became a permanent employee of the Philippine government.

The Government Laboratories in Manila were set up with multiple aims: to research the resources of the Philippines, to work on tropical diseases, and to provide services to government agencies responsible for customs, mining, forestry, agriculture, and health. Members of the scientific staff of the Bureau were recruited (at generous salaries) from the United States and all except directors were employed under the Civil Service Commission at Washington. Guest workers were also welcome (11). Two years after its foundation, Freer was able to report the near-completion of a laboratory and the arrival of the first staff members for branches of chemistry, bacteriology, pathology, botany, entomology, and serum production (12). Of particular note was the list of 15 reports covering botany, infectious disease, and chemistry, the latter including one on gutta percha and rubber in the Philippines (by Dr Penoyer L. Sherman) and one by Freer himself on the preparation of benzoyl acetyl peroxide and its use as an intestinal antiseptic in cholera and dysentery.

In 1905, following his resignation from the University of Michigan, Freer was designated Director of the Bureau of Science. In this position, held until his death, he argued successfully for the foundation of a medical school, which opened in 1907 with Freer as foundation Dean. Two years later the school was merged with the newly formed University of the Philippines, when Freer was also appointed to a chair of chemistry (13).

A lasting monument to Freer's work was the *Philippine Journal of Science*, which he founded a few years after taking up his appointment, in order to provide a vehicle for publication of his colleague's results. He made it a journal that would meet his exacting standards, and as editor he kept a firm hand on the nature and quality of the work published there. There was a direct correlation, of course, with the quality of men that Freer attracted to positions in Manila, and one example serves to highlight this. It is the presence on the staff of one Gilbert N. Lewis (1875-1946), who spent the year 1904 as Superintendent of Weights and Measures in the Bureau, between his appointments at Harvard and then MIT, before he moved to Berkeley where the major part of his career was spent. Like Einstein at about the same time but half a world away, Lewis did not find that his public service duties hindered his ability to contribute to science at the very highest level. Servos, in covering the history of this period notes that (14):

> While in Manila, Lewis experimentally determined the free energy of formation of water from its elements and became intrigued by the experimental challenges posed by such determinations.

In order to calculate the electrolytic potential of oxygen by an indirect method, Lewis needed to know the decomposition pressure of silver oxide at 25^o, and this he determined by extrapolation from pressures measured at higher temperatures. His result, 4.9×10^{-4} atmospheres was reported in a Bulletin of the Laboratory (No. 30) and also in the local journal (15).

While the *Journal* carried many articles about natural resources of the Philippines, including their chemistry, the chemists also published the results of what today we would call 'curiosity led' research that continued the interests they had developed before coming to the Philippines. Three important contributors were H. D. Gibbs (1872-1934), H. C. Brill (1881-1968), and D. S. Pratt (1885-1920) (16), physical organic chemists who in the years 1913-1916 published on absorption spectra, rates of hydrolysis of esters, and the photochemistry of methanol. Harry Drake Gibbs (Ph.D. Stanford University) spent the period 1907-1914 in the Bureau, for the last three years of which he was also Associate Professor of Chemistry at the University of the Philippines. His subsequent career included periods in the U.S. Department of Agriculture and the U.S. Public Health Service (17), but in between these he was a research chemist with the Du Pont company where he discovered the vanadium oxide-catalyzed vapor-phase air oxidation of naphthalene to phthalic anhydride (18). Harvey Clayton Brill, another Michigan graduate (Ph.D. in organic chemistry, 1911), served in the Philippines during 1913-1916 while on leave from his *alma mater*, Miami University in Oxford, Ohio, to which he returned to continue a long career in teaching and research (19). Brill achieved emeritus status at age 71 in 1952 but remained active for many years and was accorded the honor, by the American Chemical Society, of being chemist of the year for the Cincinnati Section in 1959.

The careers of Lewis, Gibbs, Brill, and no doubt others who spent some of their early career years in the Philippines further testify to the quality of staff recruited by Worcester and Freer. None of the chemists stayed for long, perhaps seeing a stint in the Philippines as a contribution to international development, since their later careers developed in directions other than those they had pursued in Manila. Perkins, while he was in the Bureau Laboratory, would presumably have done his share of routine analytical work, but like Lewis (although without the latter's impact) he also conducted research on chemical physics in his own time.

The chemical impetus given to the new institution by Freer survived his early death in 1912, at age 50, which was noted in the *Journal of the American Association for the Advancement of Science* (20). The AAAS also published the resolution expressing admiration and regret, drawn up by his colleagues in Manila (21). This resolution also headed a supplement to the July, 1912 issue of the *Philippine Journal of Science*, which carried a number of articles concerning Freer's life and work, as chemist and administrator.

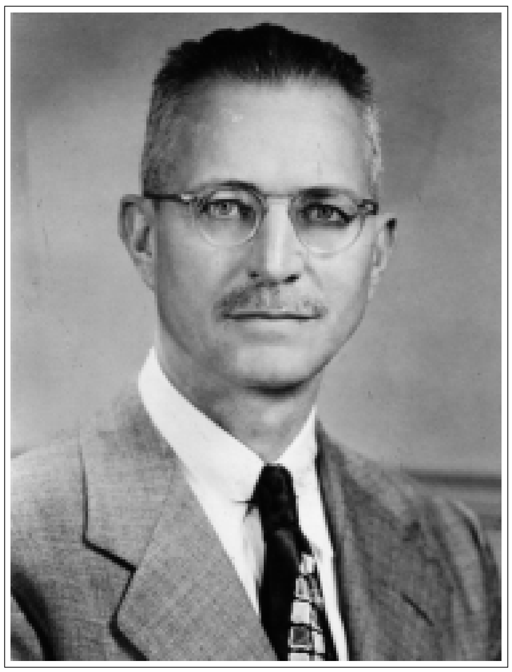
Leprosy Chemotherapy and Ghaulmoogra

In the days before effective chemotherapy for leprosy, it was common to isolate infected people from society in leprosaria, from which few returned (22). It is little wonder that the Philippine establishment at Culion (discussed below) attracted the epithet 'island of the dead.' Although many substances including arsenic were touted as treatments for leprosy, the only medication available to infected persons that seemed to do any good was chaulmoogra oil, derived from the seeds of a tree of the *Hydnocarpus* genus. Administered orally it produced nausea as a side effect, and by injection it caused considerable irritation. Variants on the chaulmoogra theme were explored without notable success by a number of groups, including the scientists and doctors in the Philippines; but it was not until the advent of diphenyl sulfones in the early 1940s that effective chemotherapy became available (23).

The use of chaulmoogra oil is believed to have originated in Burmese medicine some centuries ago, and to have been carried into Indian, Chinese, and other south- and east-Asian cultures. As the twentieth century wore on, it became clear that, although showing *in vitro* activity, neither the oil nor its derivatives (see below) were the hoped-for specific cure for leprosy (infection with *Mycobacterium leprae*), but the thought that it might have certain more general therapeutic properties has maintained it as a material for continued study (24). It is difficult to find definitive evidence, but a recent judgment was that (25):

> Chaulmoogra oil seems to have made a significant contribution to the management of leprosy for many years, giving some hope where there had been none.

The principal ingredients of chaulmoogra oil are the glycerides of chaulmoogric and hydnocarpic acids. The molecular formulas and tentative molecular structures for these acids were established early in the twentieth century (26). Chaulmoogric acid, $C_{18}H_{32}O_2$, an isomer of linoleic acid, contains only one double bond (linoleic having two) and is moreover optically active (signifying the presence of molecular dissymmetry). Barrowcliff and Power postulated that its structure must contain a ring, and they formulated it with a cyclopentene or cyclohexene ring incorporated into a long paraffinic chain. Hydnocarpic acid is a homolog with similar core structure but with three fewer carbons in the chain and was regarded as less active pharmacologically.



Granville Perkins in middle age when he was a research director with Union Carbide (photograph kindly provided by Perkins' daughter, Mrs. Barbara P. Clark)

The correctness of one of these proposed structures was proven by Shriner and Adams (27); Noller and Adams also completed syntheses of the achiral dihydro acids in 1926 (28). In that and the following year, Perkins published the results of his research in the Philippines that culminated in a synthesis of the racemic mixture of the isomers of chaulmoogric acid (29). Synthesis of the fully optically active acid, involving the resolution of an intermediate with brucine, was achieved many years later (30).

Some applications of the oil in the early part of the twentieth century included its co-administration with adjuvants such as camphorated oil or creosote, while others relied on derivatization to yield mixtures of sodium salts or ethyl esters. The latter product, known as Antileprol and marketed by the Bayer Company, was claimed in the years before World War I to be effective against leprosy (31), and Granville Perkins was involved with it and similar esters in the Philippines where extensive investigations into their efficacy were conducted.

Perkins and the Culion Leper Colony

The welfare of sufferers from leprosy in the Philippines under the Spanish regime and in the early years of American administration was in the hands of Catholic priests of the Franciscan Order, but no medical care was provided apart from basic hygiene. Following an executive order by the Philippines administration in 1904, it was decided to establish a leprosy colony (later Sanitarium) on Culion Island, approximately 350 km SSE of Manila. The first group of 370 patients arrived in May 1906, to be cared for by the medical officer in charge of the colony, assisted by a Jesuit Father and four Sisters of St. Paul de Chartres, who acted as nurses (32).

Over the next fifty years, the colony was home to approximately 30,000 people, some 3,000 of whom were born there. The population grew steadily to a peak of 7,000 in 1935, but thereafter declined under the influence of three factors: many patients were declared 'negative' following treatment with chaulmoogra ester; the advent of sulfone medication offered real cures; and government restrictions on sufferers' living in the community were relaxed. (Until then sufferers were banished to leprosaria.)

A driving force in the administration of the Colony was Herbert Windsor Wade (1886-1968), an American scientist who earned an M.D. from Tulane University in 1912 (33). After working for several years in New Orleans, Wade married and he and his bride moved to Manila, where he had been appointed pathologist and bacteriologist in the Bureau of Science. He served in that position 1916-1918 and then as professor of pathology and bacteriology at the University of the Philippines, before joining the Culion Leper Colony as chief pathologist in 1922. In that year Granville Perkins also transferred from the Bureau to Culion, and together they launched a chemical assault on *Mycobacterium leprae*. Although Wade remained in Manila, he was appointed in 1931 medical director of the Washington-based Leonard Wood Memorial for the Eradication of Leprosy. Wood (1860-1927), a U.S. Army officer who was governor of Moro Province in the Philippines in 1903-1910, took a great interest in the development of the country under American administration. After a stint in Washington as Chief of Staff of the U.S. Army, Wood returned to the islands as governor from 1921to1927 (34). Wade spent more than 20 years in the Philippines and was interned there in 1941-1945 when Japanese forces occupied the islands. Early in his directorship Wade founded the *International Journal of Leprosy*, which he edited almost until the time of his death. He had long served as a consultant to Culion. Upon his resignation from the Leonard Wood Memorial in 1948, he rejoined the Colony as pathologist and associate medical director until 1959, when he accepted the status of Pathologist Emeritus (35).

It is reported that Dr. Eliodoro Mercado (1866-1933) pioneered parenteral (that is, not by ingestion) treatment of leprosy patients with chaulmoogra oil at the San Lazaro Hospital, where he became a specialist leprologist (36). He presented the results of his work at the Second Regional Assembly of Physicians and Pharmacists of the Philippines, in Manila in 1914, but he seems to have had no connection with the chemists at the Bureau or the staff at Culion. The first evidence of work being undertaken on chaulmoogra in the government laboratories comes from two of Brill's papers (37), in the second of which the authors noted the lack of effect obtained with commercial Antileprol or the crude chaulmoogra oil itself and expressed surprise that this should be the case. The experiments, involving several batches of oil from different sources, were carried out at the Culion Colony. A subsequent issue of the journal carried an article by the Chief of the Culion Leper Colony, illustrated with photographs to show the different types of external lesions found in the patients there (38).

Perkins was involved in the investigation of chaulmoogra even before he left the Bureau of Science in Manila (39), and that probably explains why he was chosen (or chose) to transfer to the Culion Colony. He began his first publication on chaulmoogra by recounting the history of its use. He noted that oral or external administration was giving way to intramuscular and intravenous injection, and that the efficacy of the sodium salts of the acids pointed to the acid structures, rather than those of the glycerides or associated impurities such as glycosides, as the therapeutic units. In his paper Perkins refers to Mercado and his work at the San Lazaro Hospital and offers some support for the theory of action advanced by Rogers (40), and also acknowledges Power's work with ethyl esters of the acids and the existence of subsequent patent coverage. Mercado was most successful with intramuscular injection of a mixture of chaulmoogra oil, camphorated oil, resorcine (the antiseptic phenol resorcinol) and ether (41). Irritation persisted when crude chaulmoogra oil was used, but this was found to be due to the presence of free acids in the oil, which could be removed by a purification process. Perkins also experimented with the mixed ethyl esters formed from chaulmoogra oil by transesterification with ethyl alcohol, and found that concentrated sulfuric acid was a superior catalyst to the dry HCl that had been used by earlier experimenters. His paper provides detailed instructions for the preparation of this ester in quantities up to 50 liters and its purification by distillation at reduced pressure. Some 200 liters were produced each month in Manila for use in intramuscular therapy at Culion. Following earlier work that had shown promise, the ester was injected together with 2% iodine, and clinical trials were also conducted with the 'soaps'—sodium salts of the chaulmoogra acids—that Rogers had pioneered. Perkins also noted Walker's theory that the acid-fast bacilli incorporate the unsaturated chaulmoogric acids into their 'fatty capsules' (cell walls), with fatal consequences, but that this property was not possessed by other unsaturated acids such as those of cod-liver oil (42).

Walker and Sweeney's work was followed up by one by Perkins' colleagues Otto Schöbl, of the Serum Laboratory at the Bureau of Science, who conducted *in vitro* trials of Perkins' materials with the acid-fast or-

A 1996 photograph of the laboratory at Culion, where Perkins worked in the 1920s. The bronze plaque at the entrance commemorates the work of H. W. Wade (photograph kindly provided by Mr. Harold Nou of Culion, whose mother was the Perkins' babysitter)

ganism *Bacillus tuberculosis* (43). Growth was inhibited on a two- to four-week time scale by

- chaulmoogra oil from India or Japan, but not by cod-liver or olive oil
- the oils of various closely related species, but not G*ynocardia odorata*
- sodium gynocardate but only to a minor degree by sodium chaulmoograte.

In a subsequent paper, Schöbl reported *in vitro* experiments with *Bacillus tuberculosis* and *Bacillus typhosus* and the acid-fast bacteria *Vibrio Choleræ* and a *Staphylococcus sp* (44). Only the chaulmoogra-derived substances suppressed growth of *B. tuberculosis*, and no other combinations produced suppression of any species except some essential oils, which were known to possess antiseptic properties.

Perkins' next paper summarized the physical properties and the chemical compositions of chaulmoogra and related oils from the literature and added extensively to the data collection as the result of his own experimental work (45). A subsequent paper giving practical details for the preparation referred back to this data compilation as 'Part I' and reported that oil of *Hydnocarpus wightiana* was the preferred source for obtaining the free acid (46). Perkins concluded his series of practical papers, revealing his command of experimental chemistry undertaken under what must have been difficult circumstances at Culion, with detailed instructions for the preparation of a number of esters of the mixed acids from chaulmoogra oil (47). Perkins acknowledged H. W. Wade's suggestions concerning these esters, each of which was prepared by transesterification of the oil with the appropriate alcohol, and the paper includes reaction curves showing yields of various mixtures that were stirred with sulfuric acid for up to 60 days at room temperature. Equilibrium was, however, reached more rapidly by boiling the mixtures. Each ester was purified by steam distillation and characterized by refractive index, specific gravity, acidity, and optical rotation.

Perkins' contribution to the work at Culion was vital to the attack on leprosy being undertaken there by Wade and his medical staff. As chemist, Perkins was responsible for characterizing the oils and related materials and producing large quantities of designated substances. With the encouragement of his superiors—all of his papers were published with the permission of the Director of Health and the approval of the Philippine Leprosy Research Board—he published detailed experimental methods and physical and chemical data on his products that would enable other researchers to follow in his footsteps. With this phase of the work complete and with a growing family, Perkins was anxious to develop his career further. In 1927 he returned to the United States to take up a position in chemical industry. In his early years there, he continued in the laboratory but later moved into management.

Quantum Mechanics

Reference has already been made to several theoretical articles published by Perkins while he was in the Philippines, but later publications show that he retained his interest in this field and after a long break resumed active interest in it after his retirement from Union Carbide. While this is remarkable in itself—quantum mechanics being an unlikely hobby even for a trained scientist—he continued to publish until he was well into his tenth decade. His papers contain few references to original literature later than the 1930s, however. In the first of these papers he gave his New York address and acknowledged that part of the work "was completed while the author was associated with Union Carbide Corporation" (48), revealing that even while in senior management he was still 'moonlighting;' but thereafter his addresses were in Florida and no institutional affiliation was given (49). A candid assessment is that these papers reported sound but not groundbreaking work, which was seldom cited by contemporary authors. They represented a 'tidying up' of matters that had remained unresolved while the main field of research moved on.

Conclusion

Granville Perkins was one of a number of young American scientists who worked in the Philippines in the first few decades of the twentieth century before returning to the United States to continue their careers along more traditional paths in industry and academe. A number of them became well known during those times, but by-and-large their contributions to the development of science, and particularly chemistry, in the service of the Philippine government have been lost to sight.

Perkins' contributions were unique, because his chemistry underpinned a serious assault on leprosy that was devised and carried out on that remote Culion Island. His detailed recipes for the assessment and purification of raw materials, and for the preparation of derivatives of the natural products that make up chaulmoogra oil, added substantially to the repertoire available to other researchers who followed the fruitless trail of a leprosy cure through administration of chaulmoogra and chaulmoogra-derived materials. Subsequent drug discovery and application of the sulfones has changed the face of leprosy chemotherapy, leaving only a few experimenters to continue the exploration of the properties of the unusual fatty acids contained in that ancient remedy.

Alongside his contributions to leprosy chemotherapy and later the polymer industry, Perkins applied his chemistry to university teaching, to agriculture, meat science, and to war materials. His interest in quantum mechanics and chemical physics resides uncomfortably and unexpectedly alongside this working life in organic chemistry, but it was a personal interest that spanned 60 years of publishing and would have to be rated as something more than a hobby.

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