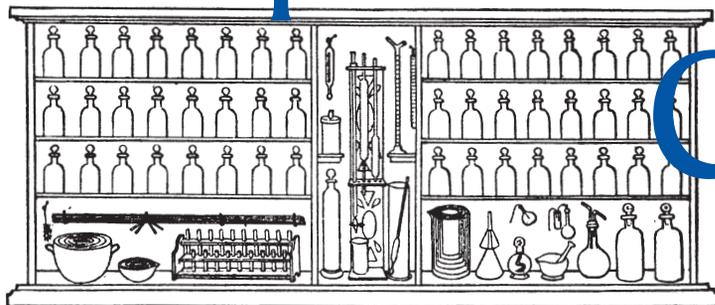


Apothecary's Cabinet



No. 9, Fall 2005

News and Notes from the American Institute of the History of Pharmacy

100 YEARS OF THE 1906 FOOD AND DRUGS ACT

The Formation and Early Work of the Drug Laboratory, USDA Bureau of Chemistry*

by John Swann**

THE institution charged with enforcement of the 1906 Food and Drugs Act, the Bureau of Chemistry, is probably best known for its efforts in regulating the food supply of the country, both when it was under the leadership of Harvey Wiley and immediately afterwards. Wiley's "overwhelming preoccupation" with foods derived from his belief that foods rather than drugs were a greater harm to the public at the time.¹ This is not to say that the govern-

ment was unmindful of adulteration and other problems associated with drugs. The 1848 drug import act charged the Treasury Department with barring adulterated drugs from entering this country. Also, from time to time beginning in the 1880s, Congress had authorized funds within the Department of Agriculture for the investigation of drugs adulterated in domestic commerce. Unfortunately, the legislative branch failed to appropriate adequate funds.²

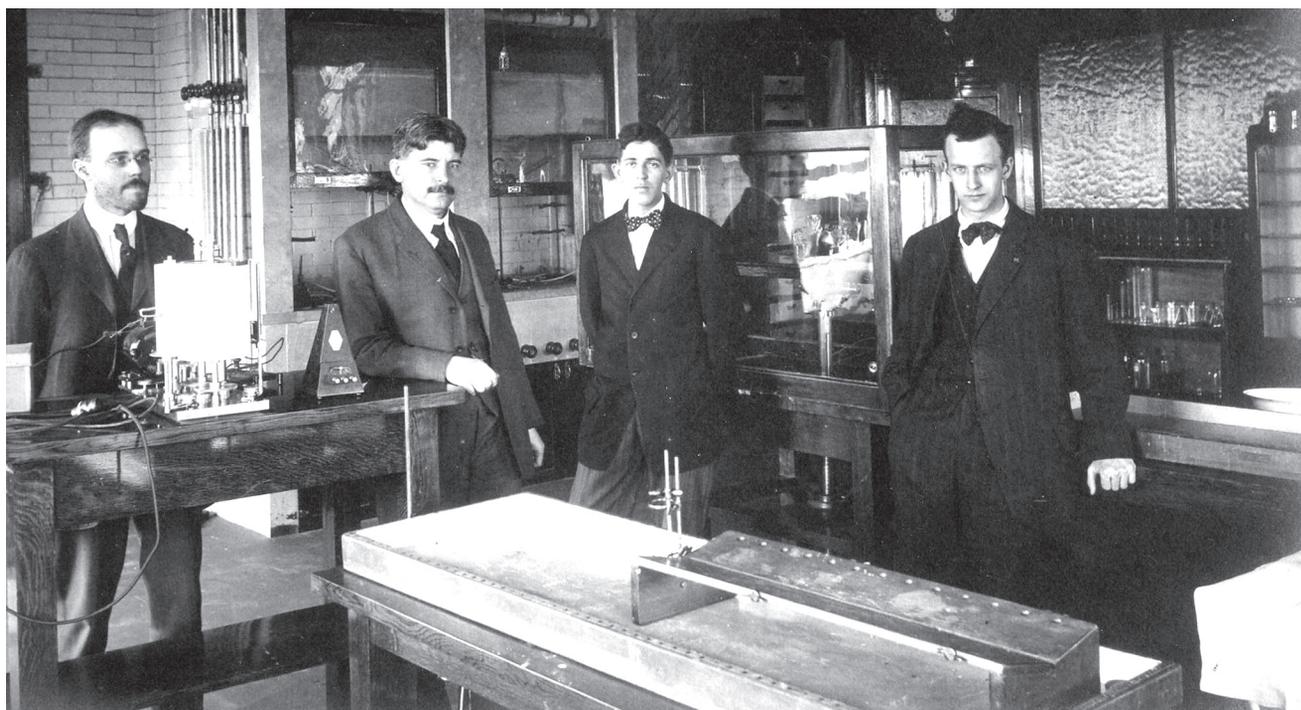
The nation's drug supply was far from safe at the turn of the century. The hundreds of brands of worthless patent medicines for self-

medication swindled people with their egregious therapeutic claims, harmed patients with such hidden ingredients as opiates, cocaine, and alcohol, and ensured their name-recognition by blackmailing newspapers into refusing to run articles critical of the nostrums. Quacks hawked worthless cures for cancer, drug addiction, tuberculosis; the few nostrums that probably did work were opiate-laden soothing syrups to quiet infants. Muckraking periodicals exposed the extent of the abuses by the patent medicine manufacturers.³

Even the so-called ethical pharmaceuticals used in regular

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William Salant (second from the left), Chief of the Pharmacological Laboratory, poses with [J. H.] Phelps, W. H. Childress, and J. B. Rieger in 1910.

medical practice, consisting principally of drugs in their naturally-occurring form, active ingredients extracted from such crude forms, and a few synthetic remedies, were frequently adulterated and of questionable potency. Investigations by the American Pharmaceutical Association (APhA) revealed, for example, that oil of wintergreen was adulterated with synthetic oils from ten percent upwards, seventy-five percent of the samples of belladonna leaf assayed below the standard amount of atropine recommended in the USP, and samples of lithia citrate were actually fifteen percent of the labeled potency.⁴

When Congressional appropriations enabled the Division of Chemistry to become a Bureau in 1901,

Wiley promised to devote attention to the assay and composition of drugs.⁵ It should have been no surprise that he turned to the APhA for assistance in planning the scope of the drug effort in the Bureau of Chemistry. The APhA had long supported increased drug control in this country. Moreover, in the same year as the Division's elevation to Bureau status, the association established a Committee on Drug Adulterations, with which Wiley hoped the Bureau could cooperate. The Committee's chief function was to survey the quality and composition of the materia medica.⁶

Wiley appeared at the 1902 annual meeting of the APhA to announce the formation of a Drug Laboratory within the Bureau of Chemistry, which the APhA Com-

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mittee on Adulterations described rather hyperbolically as “one of the most important events that have transpired in the history of American Pharmacy.”⁷ Perhaps the committee was looking for an ally in its onerous task of surveying the quality of the *materia medica*! Wiley envisioned a drug laboratory that would help unify analytical methods to identify and standardize pharmaceuticals, and thereby instill uniformity on analytical results.⁸

He was echoing words spoken earlier at the same meeting. The chair of the scientific section of the APhA had detailed some of the shortcomings in the methodology of drug assay of the time. He complained that the variety of assay techniques for individual drugs had

the University of Michigan, he moved to the Philadelphia firm of Smith Kline and French, where he became chief chemist in 1892. He published over sixty papers during his Philadelphia years, most of them devoted to drug assay and adulteration. At Smith Kline and French, Kebler’s duties included inspection of drugs that the firm was considering for purchase. This experience familiarized Kebler with drug adulteration, and by the time of the formation of the Drug Laboratory he was a recognized expert in the field.¹¹

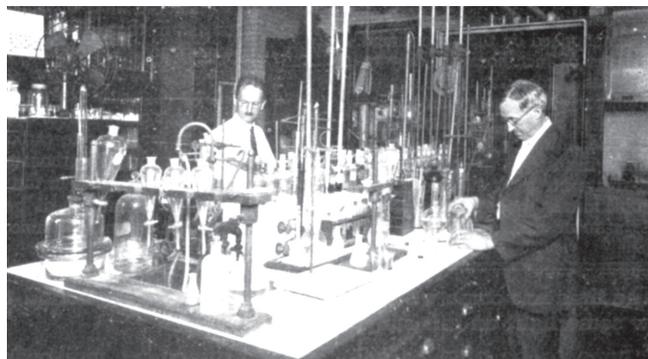
Science in major American pharmaceutical firms like Smith Kline and French at the turn of the century was quite different than the case twenty or thirty years later. New drug development or delivery, the

a different variety when they began marketing biological drugs such as diphtheria antitoxin in the 1890s.¹²

Although he received his appointment to head the new Drug Laboratory in November 1902, Kebler’s responsibilities at Smith Kline and French prevented him from assuming his position in the Bureau of Chemistry until the following March. Prior to the Federal Food and Drugs Act, the Drug Laboratory worked on a variety of topics—not all directly relevant to drugs. One of the first projects that Kebler initiated was a study of the Bureau’s own stock of reagents, primarily because this was a long-standing problem that was obviously relevant to any laboratory that relied on analytical procedures.

The Drug Laboratory exam-

Lyman Kebler (r.) and W. O. Emery are shown working in the government laboratory. This image was used to illustrate Kebler’s series, “The Mail-Order Medical Game,” published by The Druggists Circular, 1928-29.



a deleterious impact on consistent analyses. The field needed organization, he argued, someone or some institution to promote consistent methodologies for drug assays and standardization.⁹ Keep in mind that, even though some states recognized the USP as the standard compendium of drug identity, this was still prior to federal recognition of the USP as an official compendium of drug standards. Only two months earlier John Uri Lloyd—at Wiley’s invitation—had nominated this section chairman, Lyman Frederic Kebler, to head the Drug Laboratory of the Bureau of Chemistry, the institution that would play an important role in unifying these crucial elements of pharmaceutical science.¹⁰

Kebler was a likely candidate for the job. After receiving his education in pharmacy and chemistry from

hallmark of scientific research in the modern drug industry, in general was a phenomenon pertinent to the industry only after World War One. Key supporting sciences such as pharmacology and medicinal chemistry were still at a nascent stage in American universities at the time, much less in American companies. Some firms manifested a commitment to science in the form of drug standardization, a part of quality control. Parke-Davis hired chemist Albert Lyons in 1880 to standardize drugs, and within three years the company had introduced twenty chemically assayed fluidextracts. Other firms, including Eli Lilly and Company, G. D. Searle, and H. K. Mulford, also utilized science in this way. It is also worth mentioning that a few companies, led by Mulford and Parke-Davis, made use of science of

ined over 700 chemicals within two years. This effort—and the problems Kebler discovered in his survey—led the Association of Official Agricultural Chemists (AOAC) to formalize its own concern about the quality of chemical reagents as an issue of national concern. The AOAC created the Committee on the Testing of Chemical Reagents, with Kebler as head, to investigate the quality of these chemicals.¹³ A common problem Kebler observed was the labeling of a reagent as chemically pure when it was of medicinal quality, or worse. Eventually, reports of this committee became *de facto* reports of the quality of reagents at the Bureau of Chemistry, since few if any chemists outside of the Bureau were willing to assist the Committee in its work.¹⁴ In any case, the Drug Laboratory early on assumed a central role in organiz-

ing efforts to improve pharmaceutical analysis—in keeping with Wiley's original vision for the laboratory. Kebler remained in charge of chemical reagent testing for the AOAC until the 1920s.

Another cooperative venture between the Drug Laboratory and the AOAC was more directly related to drugs. In its 1903 report, the APhA Committee on Drug Adulterations questioned its ability to promote uniformity in drug standards without greater involvement by chemists. The available assay techniques resulted in significant discrepancies even when experienced chemists analyzed the same drug.

So, the Committee looked to the Drug Laboratory for help in developing analytical methods to identify drugs with results consistent among a group of chemists. At the same time, the Committee urged the AOAC to appoint a referee on medicinal plants and chemicals. Later that year, the AOAC appointed Kebler as the referee on this subject. Kebler explained why the involvement of the AOAC at this point would be helpful:

The idea of suggesting a referee in connection with the American Association of Official Agricultural Chemists is, that we take up the work on the same lines along which they have been working for a number of years, and thereby bring about uniformity of methods and results. The object is, to have the co-operation of a number of men throughout the country, . . . to bring the analytical methods that are being used by the port chemists before the public, so that we will know exactly what they are doing and thus obtain an exact guide to ascertain whether they are the best, or whether they can be improved upon.¹⁵

Kebler wanted to involve workers from many different types of institutions—pharmacy schools, universities, manufacturers, boards of health, and boards of pharmacy. Indeed, he was able to recruit assistance from an array of institutions for the early work of this AOAC committee. For the first two to three years, Kebler and his colleagues worked exclusively on assays of opium for morphine, largely because of the therapeutic importance of this drug and inconsistencies with some of the analytical methods. Kebler and ten other chemists analyzed similar samples of powdered opium

with several different methods, either pharmacopoeial assays, modifications thereof, or independent techniques. They compared similarity of results for each method, and concluded that the most recent USP assay provided the most consistent results.¹⁶

In 1905, the joint work of the Drug Laboratory and AOAC began to include other crude drugs. They compared different assays of cinchona, ipecac, and nux vomica for the principal alkaloids of each. The following year they extended the comparative analyses to include aconite, belladonna, and coca. While USP assays yielded more uniform results with some drugs, other methods had more consistent results for other drugs. For example, a group of analysts using the aconite analysis recommended by the USP experienced a fifty-one percent variation from the average for similar samples, whereas the use of another established method produced only a ten percent variation.¹⁷

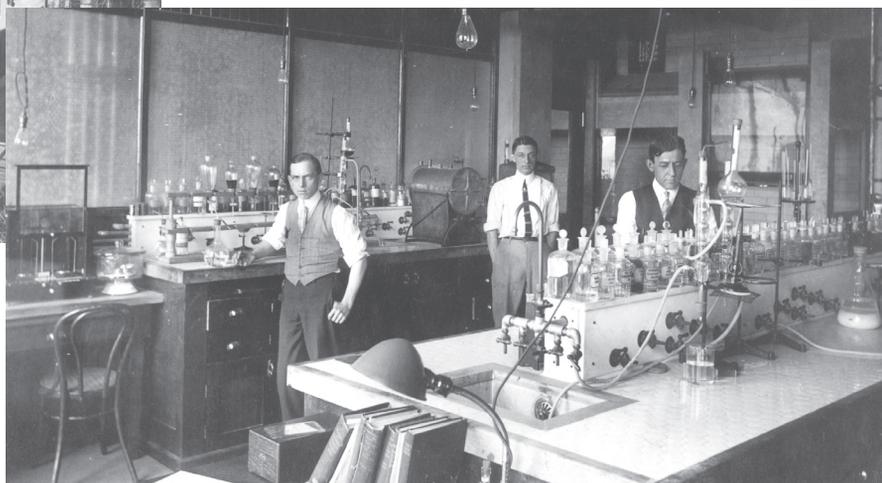
These were detailed, extremely laborious, and necessary procedures.



Researchers inside the Synthetic Products Laboratory of the Bureau of Chemistry include (l. to r.) Rex Shiveley, L. B. Mears, and W. O. Emery.



The Bureau of Chemistry laboratory building (left) and the Drug Inspection Laboratory inside (below).



From a therapeutic standpoint, a practitioner had to know how much active ingredient was in a crude drug. If a manufacturer were unknowingly using an unreliable assay method, how predictable could dosage be in such a case? From a legal standpoint, the 1906 act gave official status at the federal level to USP and National Formulary standards of identity. The Bureau of Chemistry thus had a tool for bringing actions against products whose strength, quality, or purity varied from the official standards for that drug. A loophole in the law, known as the variation clause, had some bearing here, since it permitted manufacturers to market substandard drugs as long as the variations were plainly stated on the label.¹⁸

Nevertheless, how well could

a procedure that produced erratic results hold up in a court? Official procedures had to produce results as uniform as possible. Toward this end, the Drug Laboratory tried to determine where analytical procedures were flawed. Perhaps there was a problem in the length of the maceration (steeping) period called for in a particular method for analyzing cinchona for quinine, or maybe the amount of morphine to be extracted from opium depended on the degree of agitation required for shaking out morphine during that analysis.¹⁹

The above efforts mirrored Wiley's desire that the laboratory organize analysts around the country to improve specific problems of pharmaceutical analysis and address

concerns with chemical reagents. However, the early work of the Drug Laboratory was not entirely devoted to such rigorous and technical work. Kebler publicized problems with the drug supply in a popular vein, much in the same spirit that characterized his supervisor.

The head of the Drug Laboratory drew on his experience as an analyst for Smith Kline and French when he wrote of tricks in the trade to supply spurious oils for rheumatism, phthisis, or other diseases. As long as demands existed for bat oil, mermaid's oil, rabbit oil, porcupine oil, and other such concoctions, a supplier would give the patient something, whether or not it was the genuine article. Such oils were of dubious composition as well as dubious value.²⁰

Early in his tenure as head of the Drug Laboratory, Kebler also began exposing proprietary medicines such as hair restorers, consumption cures, cures for lost manhood, and obesity cures.²¹ We will learn later that the Bureau was accused of not paying nearly enough attention to the patent medicine industry.

The character of the Drug Laboratory's work did not change immediately after passage of the 1906 act. The laboratory continued to investigate drug adulteration, perfect analytical methods, examine chemical reagents, and analyze patent medicines. Of course, after 1906 the Bureau could actually do something about adulterated or misbranded drugs. One significant change in the Drug Laboratory before and after the act concerned its organization. In 1908 it became one of two divisions within the Bureau, with four laboratories to handle different functions more efficiently. Notable as well after the Food and Drugs Act was the laboratory's concerted effort to work with several government agencies and outside organizations.

Each of the Drug Division's four laboratories had its own head. Kebler remained in charge of the Division, and in fact had risen to the number three position in the Bureau of Chemistry by this time.²² The Drug Inspection Laboratory, under George Hoover, was the laboratory most concerned with enforcement within the Division. This laboratory examined drugs seized as adulterated or misbranded under the 1906 act. Investigations of drug establishments were much more abbreviated in this early period, due to the limits of the law. Inspectors tried to obtain information about the product's formula, how it was manufactured, how it was labeled, and its distribution. From 1909 to 1910 alone, this laboratory examined over 900 drug samples from interstate commerce, over 1200 from imports, and recommended 115 samples for prosecution; comparatively few of these actually went to court. The sort of violations seen in imports was similar to that found with articles of domestic commerce, i. e., false representations on

the packaging or accompanying literature, and to a lesser extent, adulteration.²³

The Synthetic Products Laboratory was under the direction of W. O. Emery, who had investigated food and drug adulteration in Germany for several years before coming to the Bureau of Chemistry. This laboratory was responsible for examining chemical drugs and active ingredients from crude *materia medica*, and it focused on headache remedies and other preparations with habit-forming ingredients. Many of these remedies actually were mixtures of several drugs with rather different therapeutic actions, such as phenacetin, caffeine, heroin, acetanilid, antipyrine, and other compounds.

This laboratory's major research project early on was the development of techniques for quantitative determination of each of the ingredients involved. From 1907 to 1910, the laboratory was able to apply its procedures to about half of the estimated 800 brands of headache, cold, and grippe cures. Later on, Emery and his coworkers worked with other analysts through the AOAC, who confirmed that these methods produced uniform results for the amount of each ingredient in the mixtures.²⁴

The Essential Oils Laboratory focused on this group of compounds that were used therapeutically or in the manufacture of other therapeutic agents. Like Kebler, E. K. Nelson, who headed this laboratory, had worked in industry prior to coming to the Bureau. The quality of certain essential oils was especially problematical, so this laboratory developed analyses to detect adulterations in such products. Analyses required good, authentic samples of oils. For example, the synthetic product methyl salicylate often was used as an adulterant of oil of wintergreen and oil of sweet birch, because it was a fraction of the cost of these essential oils. Inspector John McManus described an interesting visit to the mountains of North Carolina around 1912 to collect some authentic oil of sweet birch for reference analytical use back in Washington:

A chemist and I went up to North Carolina and arranged with one of these distillers to make several pounds of Oil of Sweet Birch. . . . I recall the chemist was kind of nervous about the mountain people. He had heard stories about them so he brought an old pistol with him and put it under his pillow. In the morning, we were awakened by a pistol shot. One of the distillers had come in, seen the handle of the pistol, pulled it out from the guy's pillow, and shot it off to wake us up.²⁵

William Salant, a founding member of the American Society of Pharmacology and Experimental Therapeutics, was in charge of the Pharmacological Laboratory. This laboratory investigated the physiological effects of drugs and drug mixtures on animals. For example, this group performed exhaustive pharmacological examinations of caffeine and alcohol—both common ingredients in proprietary medicines.²⁶ In addition to drugs, Salant and his colleagues studied the physiological action of bleached, unbleached, and over-bleached flour, a matter of considerable concern in food regulation.²⁷

The Pharmacological Laboratory also engaged in some work on drug standardization. Chemical assays were the most common means of standardizing drugs at this time, but they were not the only way, and in fact were useless for certain products. Pharmacologists had been using biological assays in a systematic way to standardize ergot and other drugs since the 1890s. The USP requested assistance from the Bureau of Chemistry in providing to manufacturers reference standards for biologically-assayed drugs, and Wiley fully supported this idea. But the Secretary of Agriculture in 1910 refused to permit the Bureau to take on this responsibility; he argued that it was beyond the scope of the Bureau's functions under the law.²⁸ However, by the early 1920s the Bureau had reached an agreement with the Committee of Revision of the USP to supply companies with specimens of drugs assayed biologically according to USP guidelines.²⁹

Harvey Wiley strongly believed in the importance of collaborative work, with other federal agencies and with outside institutions and organi-

zations.³⁰ By 1911 the federal government employed fewer than 300 chemists, seventy percent of whom worked in the Department of Agriculture.³¹ It is not surprising then that other agencies would turn to this department—and to the Bureau in particular—for assistance with chemical analyses. The Drug Division, with experienced analysts such as Kebler, Emery, Nelson, and others, carried out much work in association with outsiders. For example, the importance of ties between the AOAC and the division with respect to analytical work has already been mentioned.

The division analyzed the composition and any therapeutic effect of many quack pharmaceuticals for the Post Office Department: alleged cures for tuberculosis, cancer, drug addiction, epilepsy, syphilis, and other nostrums. One such cure that the division investigated was Radol, an aqueous solution supposedly irradiated with radium so it would cure cancer. Division analysts revealed that it was neither radioactive nor effective against cancer. In this case the Post Office Department issued a fraud order against the business, leading to its termination. Also, the Bureau brought a successful criminal action against the firm under the 1906 act.³²

Early in 1910 George McCabe, Solicitor of the Department of Agriculture with whom Wiley occasionally had clashed,³³ accused Wiley and Kebler of failing to devote enough effort to prosecuting patent medicine manufacturers. McCabe mentioned forty-one recently purchased nostrums, all with likely fraudulent claims on their labels. But Wiley was able to show that the Bureau had under investigation, or had recommended prosecution of, all but ten of the examples cited by McCabe.³⁴

The Drug Division investigated cod liver oils for the Bureau of Fisheries, part of the Department of Commerce and Labor. From time to time in this early period of the division, chemists also handled requests for analyses from the Interior Department, Congress, and the Bureau of Printing and Engraving. Kebler

described the event when Wiley assigned him the task of analyzing different samples of glue for the latter Bureau:

[I] told ["the Big Chief"] that [I] had never tested glue and did not know anything about the subject. In reply the Boss said, "You know as much about testing glue as anyone in the Bureau." I further protested that glue was not a drug. He retorted, "Glue is certainly a drug around here and it is your job." He had shopped, without success, around the Bureau for someone to do the work, and the Drug Chief was a newcomer and the logical victim. . . . Some of my fellow chemists considered it a good joke.³⁵

The Drug Division cooperated with several components of the Department of Agriculture. For example, at the request of the Bureau of Plant Industry, they analyzed samples of hops for arsenic contamination, and they determined if the levels of barium in animal feed could account for a disease known as "loco" found in cattle. Conversely, the division sent analytical work to Plant Industry that drew upon the expertise of chemists in that Bureau.³⁶

The Drug Division worked with the Bureau of Entomology on beeswax, analyzing physicochemical properties of this substance as a function of the kind of bees involved and the location of the production. Dealers often maintained, quite incorrectly according to the Drug Division, that these factors made a difference in the quality of the product. In the process, the division improved upon pharmacopoeial tests for beeswax.³⁷ The division's work for the food commissioner of the State of Texas, on cocaine-containing soft drinks, eventually revealed that many of the brands on the market were entirely free of cocaine, yet this was present in many other samples, ranging from a trace to five-hundredths of a grain per ounce of beverage. The division consequently recommended thirteen cases for prosecution under the 1906 act.³⁸

Both Wiley and Kebler were charter members of the Council on Pharmacy and Chemistry of the American Medical Association. The AMA established this council in

1905 to evaluate patent and ethical drugs from a variety of standpoints, including composition, therapeutic claims, and advertising. Council approval or disapproval of a product determined whether or not manufacturers could advertise them in much of the professional medical literature.³⁹ Kebler's group investigated dozens of drugs for the council, especially with respect to false, misleading, and exaggerated therapeutic claims.⁴⁰ The American Pharmaceutical Association was involved with the Drug Division since Wiley's announcement at the 1902 APhA meeting. Kebler and his colleagues assisted the APhA's Committee on Drug Adulterations and the Committee on the Drug Market in the evaluation of essential oils, crude drugs, and the general nature of drug adulteration in America.⁴¹

Notwithstanding the Hygienic Laboratory of the U. S. Public Health Service, which the law charged with overseeing biological medicines marketed in the U. S., the Drug Laboratory of the Bureau of Chemistry was responsible for controlling the vast majority of the nation's supply of drugs for self-medication and prescription use. The laboratory failed to keep pace with problems in the drug supply,⁴² for many reasons, including: shortcomings in the 1906 act (which became only more pronounced with the Sherley Amendment of 1912), Wiley's preferential attention to food problems, insufficient staff in the Drug Laboratory and Drug Division, and the need of Kebler and his group to revise pharmaceutical analyses for many of the products before they could be regulated. But during this first decade of its existence, Kebler and his colleagues appeared to organize the Drug Laboratory and marshal outside assistance in as effective a manner as possible under the scientific, legal, economic, and personal constraints of the day.

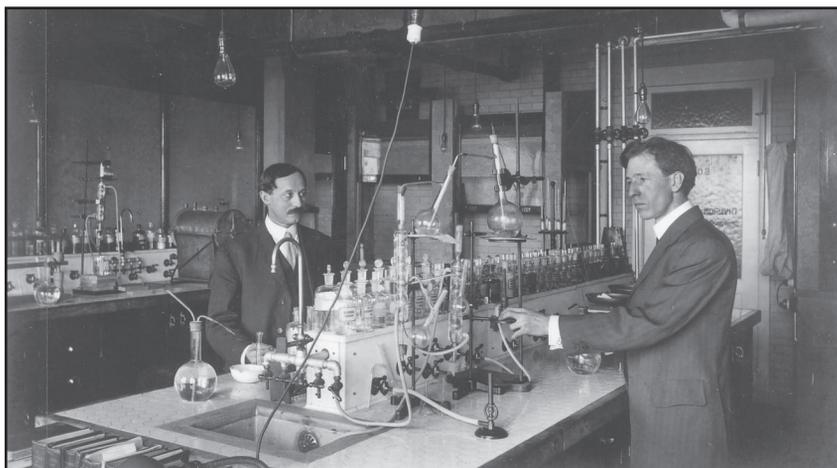
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35. Kebler, "Division of Drugs (n. 23)," 3-4, 10; "Bureau of Chemistry: Division of Drugs (n. 32), 13-14; and Kebler, "Establishment of the Drug Laboratory (n. 2)," 382-383 (quotation).
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41. Edgar L. Patch et al., "Report of Committee on Drug Adulteration (n. 15)," 155-157; Kebler, "Opium Assaying (n. 15)," 369-375; Lyman F. Kebler, "Inferior Drugs and Insidious Methods of Deception," *Proc. APHA* 51 (1903): 332-343 (cf. *idem*, *Adulterated Drugs and Chemicals* (n. 14), 7-22); and untitled 54-page typescript, c. 1910 (n. 23), [51].
42. On problems with official drugs, see Sonnedecker, "Drug Standards Become Official (n. 18)," 37; For 9000 samples of six USP drugs collected in 1911, about forty-five percent were not in compliance with official standards.



The Essential Oils Laboratory dealt with the rather broad problem in the marketplace of adulterated essential oils, such as oil of wintergreen.

Lyman Kebler, the first person to head the drugs function in the Bureau of Chemistry, published widely on drug assay and the problem of drug adulteration before he came to the agency.

