

UNEARTHING BOTANICAL REGIMENS:  
A HISTORY OF PLANT-DERIVED PHARMACEUTICALS IN AMERICAN MEDICINE

by

Sara Robertson

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

History of Health Sciences

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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by

Sara Robertson

# UNEARTHING BOTANICAL REGIMENS: A HISTORY OF PLANT-DERIVED PHARMACEUTICALS IN AMERICAN MEDICINE

Sara Robertson

This dissertation examines the transformative presence of plants in American allopathic medicine over the last two centuries. Within this span of time, plants have dominated the pharmacopoeia, fallen out of therapeutic vogue, and now, it would appear, research interest in their therapeutic potential is on the uptick. Each chapter within this dissertation focuses on a different vantage point to analyze historical medical knowledge of plant-derived remedies. Chapter one scans the course catalogs of various American pharmaceutical colleges; pinpointing the moments when whole-plant remedies lost relevance and then lost a place within the American pharmaceutical curricula. Chapter two traces the evolving representation of plants in the *United States Pharmacopoeia*; utilizing Robert Proctor's concept of agnotology to characterize the removal of knowledge from this canon of therapeutics. A third chapter examines the use of medicinal wine, a plant-derived remedy, in allopathic medicine within the context of cultural concern and regulatory limitations over alcoholism and alcohol consumption. And the final chapter discusses how the structure of science facilitated novel research pathways to reassert plants as potentially valuable for a modern pharmacopoeia.

This dissertation offers a modern history of plants as medical objects. It traces a transformation of plant-derived therapies, from their whole-plant form as a cornerstone of pharmacy education and medical practice; to their gradual reductionism and multifaceted displacement; to their modern resurgence from an entirely different industry.

The histories in each chapter can stand alone, but their common thread makes them a cohesive representation of how significant pharmaceutical objects – drugs derived from plants – have been transformed over a span of two centuries to remain ever-present within the American medical compendium.

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## INTRODUCTION

With this dissertation, I aim to examine the shifting nature of plant-derived medicaments within the American medical compendium over the last two centuries. Within this extensive period of time, plants have dominated the pharmacopoeia, fallen out of therapeutic vogue, and now, it would appear, interest in their usefulness is on the uptick. With the exception of selectively breeding plants or genetically engineering plants to exhibit certain traits, the plants themselves have not changed. Yet, our relationship with plants in a medical context -- how we use them, which plants we consider useful -- has shifted according to a number of factors and within as many capacities.

When it comes to how plants have existed in therapeutics for the last two hundred years, a dearth exists in the historiography. Pharmaceutical histories had addressed the importance of herbal remedies for Galenic medicine, Eclecticism, and the Thomsonian practitioners. Historians of medicine have considered plants as they are used in complementary and alternative therapies, as well as in patent medicine.<sup>1</sup> But

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<sup>1</sup> For insight on herbal medicine as practiced by lay practitioners, Eclectics, and in Thomsonianism, see Paul Starr, *The Social Transformation of American Medicine: The Rise of a Sovereign Profession and the Making of a Vast Industry* (New York, NY: Basic Books, 1982) and Charles Rosenberg, "Complementary to What? Alternative to Whom?," in *Our Present Complaint: American Medicine, Then and Now* (Baltimore, MD: The Johns Hopkins University Press, 2007): 113-138. For an overview of patent and 'quackery' medicines that would have included plants in their ingredients, see Roy Porter, "Before the Fringe: 'Quackery' and the Eighteenth-Century Medical Market," in *Studies in the History of Alternative Medicine*, ed. Roger Cooter (London: The MacMillan Press Ltd., 1988); also, Joseph M. Gabriel, "Medical Science and Property Rights in the Early Republic," in *Medical Monopoly: Intellectual Property Rights and the Origins of the Modern Pharmaceutical Industry* (Chicago, IL: The University of Chicago Press, 2014): 7-41. For Galenic medicine's use of herbal remedies, see John M. Riddle, *Eve's Herbs: A History of Contraception and Abortion in the West* (Cambridge, Mass.: Harvard University Press, 1997). And for a

little work has focused on plants as they have existed for the allopath and how that existence has shifted and evolved over within American medicine specifically. Important to note, this dissertation considers only American medicine, as the cultural and regulatory contexts of American medical practice have together created a history of plant-derived drugs that would not be truly representative elsewhere. Plant-derived therapies, as pharmaceutical objects, have been transformed and have consisted in three major forms: as whole-plant materials or preparations made therefrom; as isolated compounds derived from plants, which may or may not have been synthesized; and as compounds introduced to plants for further manufacture. This dissertation explores the history of all three forms.

To be clear, this dissertation focuses solely on regular medicine. The topics selected depart from conventional analysis of plants within a context of homeopathic, folk, alternative, or any other non-orthodox medical paradigm that also include plants as therapeutic options. Instead, within these chapters, I will consider only how plants have been fashioned to fit within allopathic medicine. The chapters that follow focus on four distinct stories, but they relate analytically in that they detail the transformative presence of plants in allopathic medicine.

Chapter one analyzes how academia both reflects and reinforces shifts in medical ideologies and technologies that dictate the norms of allopathic medical practice. Overview of extant nineteenth-century medical manuscripts and documents points to a marked dependence of nineteenth-century pharmaceutical education upon

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sweeping history of herbalism in the Western world since antiquity, see Barbara Griggs, *Green Pharmacy: A History of Herbal Medicine* (New York, NY: Viking Press, 1982).

botanical studies. Universities have since eradicated this category of knowledge that once existed as a cornerstone of pharmaceutical curricula. My research aims to pinpoint this divergence of disciplines in time, but also to account for ideological shifts that reshaped pharmaceutical curricula.

Once the framing of American medicine shifted from humoral and miasmatic understandings of disease to an understanding of disease as caused by a specific microorganism or germ, botanical medicine lost its relevance. Moreover, the technology necessary to pinpoint beneficial compounds within plants did not progress concurrently with the shifting trends in medical practice. Analysis of nineteenth-century knowledge regarding botany and pharmacy, and especially botanical medicine, will indicate how the disciplines functioned relative to, and in support of, medical practice. However, as whole-plant botany lacked ideological compatibility with germ theory, pharmaceutical practice and education discarded the once-held fervor for medical botanical knowledge and instruction by the late twentieth century.

Professionalization hinged upon standardized education, and the specifics of botanical instruction will allow me to analyze the precise medical value plants offered and the popular ideologies held by nineteenth-century pharmacists. Moreover, understanding why professors in pharmacy colleges advocated for and then implemented botanical studies within curricular plans underscores why the discipline then lost its traditional relevance.

A substantial portion of this research draws on archival materials located in the Robert Day Collection at the Archives and Special Collections, Library and Center for

Knowledge Management, University of California, San Francisco. Additional research with the Ezra J. Kennedy Pharmacy Collection at the Lloyd Library and Museum in Cincinnati, Ohio, provided ample curricular materials from colleges of pharmacy situated in every corner of the United States. As such, this chapter has a west-coast focus, with supplemental nationwide perspective.

Chapter two considers the consequences of progress. Working within an agnotological framework of lost or forgotten knowledge, this chapter overviews how medical ideology gradually disregarded and then discarded plant-derived therapies. I focus on how this process took place within successive revisions of the *United States Pharmacopeia*. The agnotological framework for this chapter considers three manners of knowledge loss exhibited in the *Pharmacopeia*: editing drug monographs to remove mention of plant source and the eventual redaction of explicit association between synthetic compounds and their botanic origin; reclassifying active ingredients as excipients; entirely removing plant-derived drugs from the pages of the *United States Pharmacopeia*. As a note for this chapter, I assume a therapeutic equivalency between synthetic compounds and the natural, plant-derived compounds on which they were modeled. I am adapting Jeremy A. Greene's concept of bioequivalence as it relates to generic versus name-brand versions of drugs intended to perform the same therapeutic function. In a synthetic-versus-natural dichotomy of active drug compounds, therapeutic equivalency also applies to the intended function. Though ontologically distinct, synthetic and natural compounds are "the same in all ways that matter."<sup>2</sup>

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<sup>2</sup> Jeremy A. Greene, *Generic: The Unbranding of Modern Medicine* (Baltimore, MD: The Johns Hopkins University Press, 2014), 11.

These three agnotological pathways collectively created a dearth of medical knowledge in younger generations of medical practitioners. As once-favored remedies fell from therapeutic vogue and, thereafter, from the pages of the *United States Pharmacopeia*, knowledge of their therapeutic potential morphed into an understanding that those plant-derived remedies were simply historical, mythical, or defunct.

This chapter's research relies on the entirety of successive revisions made to the *United States Pharmacopeia*, which was originally *The Pharmacopoeia of the United States* and later the *United States Pharmacopeia - National Formulary*. I conducted archival research at the Wisconsin Historical Society in Madison, Wisconsin; working on the massive collection called United States Pharmacopeial Convention Records, 1819-2005 (bulk 1900-2005). The countless letters of correspondence between *Pharmacopeia* committee members and drug manufacturers, notes of monograph revisions, and minutes that pinpoint the precise reasoning for a drug's presence in the *Pharmacopeia* immeasurably informed this chapter's arguments. Additionally, I met with committee members at the United States Pharmacopeial Convention in Rockville, MD to gain insight regarding contemporary revision processes, the history of the Convention, and the status of plants in a modern pharmacopeia.

Chapter three considers the transformative status of wine within American medicine. Wine offers various therapeutic benefits via compounds produced by wine grapes; transferred naturally to the production process prior to fermentation. However, wine's alcohol content commits its historical trajectory within medicine to that observed with other medicinal alcohols. As such, this chapter analyzes the history of medicinal wine within the context of broader social concerns over alcoholism; from the early

nineteenth century to today. After a brief review of wine's historical uses in American medicine, this chapter considers the direct impact of pre- and post-Prohibition ideology on wine's official status as a therapy. Then this chapter discusses a constant interest of physicians and scientists, since the repeal of Prohibition and directly contrary to evolving social concerns over alcohol abuse, to determine wine's therapeutic potential with modern laboratory techniques and to advocate for its restored place in contemporary medicine.

For this chapter, I relied heavily on printed newsletters generated by the San Francisco Bay Area's Society of Medical Friends of Wine. This rich collection of newsletters, which dates from 1953-2005, is stored by the Society's secretary who generously let me borrow it for research purposes. Within the hundreds of pages of all these newsletters, I was able to pinpoint decades of research topics explored on wine and its chemical components and how social pressures have influenced the prescribing habits of physicians. But also, and significantly for this dissertation, I could trace an undercurrent of physicians who have constantly rallied for a plant-derived therapy: medicinal wine.

Chapter four explores how research from within the agricultural industry facilitated has a new pathway for pharmaceutical production; one that reimagines plants with centuries of entobotanical history as innovative sites of and sources for modern drug manufacture. The final chapter of this dissertation will explore plant-made pharmaceuticals (PMPs), as well as the interdisciplinary research that led to their development. The development of PMPs like ZMapp challenge the typical narrative of pharmaceutical production in two ways. First, the researchers who forged the field of

plant-made pharmaceuticals hail from non-medical disciplines like agriculture and plant biology. And second, plants emerged as a research subject in an entirely innovative capacity; from the cognitive integration of two unrelated industries -- agriculture and medicine. It is my argument that the discovery of a plant's capacity to manufacture medicine hinged upon two main factors: first, centuries, and sometimes millennia, of agricultural efforts to modify particular plant species. And second, the overlapping interest of two distinctive industries -- agriculture and medicine -- into the same natural sciences.

This chapter examines how an entirely new kind of medicine -- plant-made pharmaceuticals -- emerged from an unlikely source -- the laboratories of researchers with backgrounds in agricultural sciences and plant biology. In order to demonstrate how this new pathway to drug production developed, we will consider two important aspects of PMP history. First, this chapter overviews the historical modification of domesticated plants in agriculture. And then, this chapter explores early examples of concept maps, as they convey the structure of science and point to overlapping industry research into the same scientific subjects. Tracing the research that led to modern biopharmaceutical technologies, as well as overviewing the landscape of scientific knowledge, reveals how new pathways have emerged for therapeutic discovery. And since the development of PMPs manifested outside of the pharmaceutical industry, this chapter underlines the potential for broadly interdisciplinary research to develop innovative therapeutics.

The very recent development of PMPs prevents apparent archival resources for this chapter. So instead, I relied on ethnobotanical research and interdisciplinary studies

theory to frame how the development of PMP technologies could have manifested from within the agriculture industry. Additionally, I was able to procure a detailed account from Dr. Charles Artzen, a leading researcher in the development of PMPs, of the history of the field from his own perspective.

## CHAPTER 1

# DIVERGENT DISCIPLINES: THE DECLINING RELEVANCE OF BOTANICAL STUDIES IN AMERICAN PHARMACEUTICAL EDUCATION

In 1873, at the inaugural ceremony for the California College of Pharmacy, Dr. Richard Beverly Cole made the following statement —

*A physician is totally unfitted for his responsible position except he be familiar with chemistry, materia medica, botany, and pharmacy. A few days ago a patient of mine took by mistake a teaspoonful of the tincture of aconite root, enough to kill two persons. Had I possessed no knowledge of the character of the powerful root, I could have done nothing to save the life of the patient.*

*Of the pharmacist, it is expected that he will possess this knowledge and practical experience in a much higher degree not subordinately as the physician but as a specialty, through his knowledge of chemistry, materia medica, and botany he must determine error and avoid danger.<sup>3</sup>*

Overview of extant nineteenth-century lecture notes, course listings, and research materials points to a marked dependence of pharmaceutical education in the United States upon plant-based disciplines like botany and materia medica. However, American colleges of pharmacy have since eradicated these categories of knowledge from pharmaceutical curricula.

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<sup>3</sup> “Address by Dr. R.B. Cole at the Inauguration of the California College of Pharmacy, 1873,” box 1, folder 6, Robert L. Day Collection, 1878-2012, MSS 2011.23, Archives and Special Collections, Library and Center for Knowledge Management, University of California, San Francisco (hereafter cited Robert Day Collection).

Histories of medicine that concern the decline of pharmaceutical botany point to the manufacturers' shift to prefer synthetics over unprofitable drugs of vegetable origin.<sup>4</sup> But marketplace economics fail to account for the influence of a new disease theory that emerged in the nineteenth century and led to the advent of successful therapeutic approaches that gripped medicine by the middle of the twentieth century. The implications of germ theory for therapeutics particularly had major consequences for the reconceptualization of extant plant-derived remedies in the American medical compendium.

Specifically, the therapeutic revolution of the first half of the twentieth century coincided with a shift away from plant-based therapies in their traditional, crude forms. Traditionally, apothecaries, and later, pharmacists, used the entire plant or specific plant parts like roots or seeds or leaves to create tinctures, poultices, salves, and a many other various forms to administer drugs to patients. And in this whole-plant administration of medicine, pharmacists conceptualized the plant itself as the drug. For example, in a preparation made from peppermint leaves, pharmacists considered the leaves to be the drug; the entire plant part was synonymous with medicine. The whole plant helped rebalance the dis-ease affecting the whole patient.

Around the same time that illness was seen as caused by microscopic organisms, pharmacists and chemists had started to successfully isolate chemical

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<sup>4</sup> Varro E. Tyler. "Pharmaceutical Botany in the U.S., 1900-1962: Its Heyday, Decline, and Renaissance" *Pharmacy in History* 38 (1996): 21. Also see Joseph M. Gabriel, *Medical Monopoly: Intellectual Property Rights and the Origins of the Modern Pharmaceutical Industry* (Chicago IL: The University of Chicago Press, 2014), 48-49. Gabriel emphasizes that the appearance of pharmaceutical manufacturers in the late nineteenth century prompted the development of patentable medicinal compounds to gain an edge in the marketplace. Importantly, Gabriel points out that substances in their natural state could not be patented, but modifications of those substances could be.

compounds from plants in the 19th century. Friedrich Sertürner, a German pharmacist, isolated morphine from opium in 1805; Joseph Bienaimé Caventou and Pierre-Joseph Pelletier, French chemists who worked with nux vomica, isolated strychnine in 1818; then in 1820, they isolated quinine from cinchona.<sup>5</sup> But overall the isolation and study of plant constituents was very slow to gain knowledge, and even with isolation of a new compound, chemists and pharmacists still faced the inability of instrumentation to accurately measure the quantity or evaluate the purity of compounds. Moreover, isolation of plants' secondary metabolites had no immediate impact on therapeutics, as disease and therapeutic theory could not readily accommodate and implement this particular knowledge of plants until much later, in the twentieth century.

Instead of whole-plant therapeutics, the tenets of the therapies that emerged in the twentieth century increasingly harped on isolated compounds. Such compounds exist in plants as secondary metabolites. They make up the alkaloids, glycosides, flavonoids, and a host of other categories produced as the byproducts of plant metabolic processes. After the shift of therapeutics to depend upon isolated compounds, in order for therapeutic applications of plants to remain relevant within the new therapeutic framework, pharmacists increasingly focused on specific compounds, derived from either natural sources or, if possible, synthetic production. However, the instructors of disciplines like pharmacognosy and botany, dedicated to instructing pharmacy students on all matters of plant remedies, continued to organize course objectives through the traditional whole-plant approach that focused on plant structure; minimizing the significance of the compounds derived therein. Failure to sufficiently restructure the

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<sup>5</sup> Ara H. DerMarderosian, "Milestones of Pharmaceutical Botany: Pre-history to 1900" *Pharmacy in History* 38 (1996): 17.

courses according to popular therapeutic trends left plant disciplines increasingly irrelevant.

At an institutional level, academia redesigned pharmaceutical curricula to incorporate shifting theories of disease and therapeutics. The implications of those emergent therapeutic practices of the first half of the twentieth century did motivate instructors of plant studies in colleges of pharmacy to eventually redesign course objectives. However, efforts by those instructors to conform their courses to reflect broader pharmaceutical trends happened too little, too late. By the mid-1970s, colleges of pharmacy in the United States no longer offered plant-based disciplines that historically emphasized the plant itself more than the medicinal properties derived therein.

Throughout the nineteenth century and into the twentieth century, colleges of pharmacy from every corner of the United States included plant-focused courses like botany and materia medica as integral curricular components. From the California College of Pharmacy (later the University of California, San Francisco) on the west coast, to the colleges of pharmacy in Iowa, Ohio, and Illinois in the midwest; from Baylor University in Waco, Texas, to Tulane University in New Orleans and the University of Tennessee in the southeast; onward up the east coast, at Columbia University, the Philadelphia College of Pharmacy, and the Massachusetts College of Pharmacy in Boston -- every college of pharmacy surveyed for this chapter followed the same pattern: plant-focused courses were an essential component of pharmaceutical education during the late nineteenth century.

Though this trend could be found within any major American university with a program dedicated to pharmaceutical instruction, the University of California, San Francisco's School of Pharmacy serves as the primary setting to witness curricular shifts relative to plant-derived therapeutics. The exact years of curricular remodeling varied by institution, but from very early on, the college of pharmacy at San Francisco modeled its curriculum on leading, formal pharmaceutical schools and offered the same courses featured elsewhere at institutions in the United States.<sup>6</sup>

With the rise of bacteriology in the nineteenth century, scientists and medical practitioners eventually adopted an understanding of disease as caused by specific microorganisms. This new framework of disease, however, did not have an immediately successful influence on therapeutics, so physicians and pharmacists maintained usage of the usual drug remedies.<sup>7</sup> Meanwhile, traditional pharmacopoeia achieved little more than offering a patient relief from disease symptoms. Medical historian Roy Porter reminds us that, especially when medicine operated within a context of balance, therapeutics relied upon the ability of drugs to invoke physiological functions like vomiting or urination.<sup>8</sup> And plants operated beautifully as drug options within this therapeutic approach, because plants do, in fact, function as emetics and as diuretics and as various other types of drugs one might need.

This chapter first considers the establishment of American pharmaceutical colleges across the nation in the nineteenth century. Through examination of curricular

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<sup>6</sup> F.A. Beckett, Ph.G., "Inspection Report of Colleges of Pharmacy," July 11, 1895, box 1, folder 7, Robert Day Collection.

<sup>7</sup> Charles E. Rosenberg, "The Therapeutic Revolution: Medicine, Meaning, and Social Change in Nineteenth-Century America" *Perspectives in Biology and Medicine* 20 (1977): 485-506.

<sup>8</sup> Roy Porter, *The Greatest Benefit to Mankind: A Medical History of Humanity* (New York, NY: W.W. Norton & Company, 1997), 57.

expectations and the course content and resources made available to pharmacy students, knowledge of plant-focused therapies emerges as integral to pharmaceutical training. Then, as the pharmaceutical industry and medical practice shift to prefer new kinds of therapies, this chapter continues to examine how plant-focused courses evolve in content. This chapter also maps the place of plant-focused courses relevant to the rest of pharmaceutical curricula, until they are removed entirely from course offerings.

### **Establishment of American Pharmaceutical Colleges**

In 1872, members of the California Pharmaceutical Society signed a letter of incorporation establishing the California College of Pharmacy, which would later become the School of Pharmacy at the University of California, San Francisco. Through the establishment of the college, the founders sought “to promote, advance, acquire [sic], and disseminate knowledge, in Pharmaceutical sciences, to thoroughly educate all persons who may embrace it as a profession, and to develop [sic] and foster such other and kindred knowledge and acquirements in the Arts and Sciences, as may be conducive to the success of said Institution.”<sup>9</sup> These admirable objectives for pharmaceutical vocational training could be met with lecture and laboratory instruction in just four disciplines. Pharmacy students had to receive training in chemistry, pharmacy, botany, and materia medica. These few course offerings, in all of their apparent simplicity, mirrored the curricular standards of other American pharmaceutical colleges of the nineteenth century.

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<sup>9</sup> Letter of incorporation, August 7, 1872, box 1, folder 4, Robert Day Collection.

Historian of science John Parascandola reminds us that the founding of the Philadelphia College of Pharmacy in 1821 marked the beginning of formal pharmaceutical education in the United States. The Pennsylvania institution initially offered just two lecture courses, one of which was chemistry and the other was a combination of materia medica and pharmacy.<sup>10</sup> The original curriculum at the California College of Pharmacy, established fifty years later, demonstrated that minimal diversification had occurred in American pharmaceutical curricula in the interim. And as with the original curriculum designed for the Philadelphia College of Pharmacy, about half of the curricular requirements for pharmacy students at the California College of Pharmacy involved training with plants regarded as having medicinal value. Importantly, all of the training professors of botany and materia medica extended to their students regarding medicinal plants focused almost entirely on the whole plant, its structure and its history; it lent only secondary consideration, if any consideration at all, of those plant constituents that exhibited medicinal properties.

Professor Herman Behr instructed the botany course at the California College of Pharmacy beginning in its inaugural year, and the course dealt entirely with plant structure and physiology. Lectures in the junior course focused on morphology and histology, which are macro and micro anatomies of plants, respectively. In addition, botany lectures in the senior course addressed the Linnaean classification system and the natural geography of plants, as well as the influence of light, heat, air, and moisture

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<sup>10</sup> John Parascandola, "The Emergence of Pharmaceutical Science" *Pharmacy in History* 37 (1995): 69. Also, for more on the establishment of American schools of pharmacy in the nineteenth century, see Gregory J. Higby, "Chemistry and the 19<sup>th</sup> Century American Pharmacist" *Bulletin of the History of Chemistry* 28 (2003): 9-17.

on plant growth.<sup>11</sup> The course descriptions offered at pharmacy colleges across America were essentially identical.

Seldom do any of the announcements explored go into more detail of lecture topics than the announcements printed for the Iowa College of Pharmacy of Drake University in the late nineteenth century. At this particular pharmacy school, the “Materia Medica and Therapeutics” course lectures were organized around various botanical families. The course description reasons, “believing that there is general correspondence between the botanical relationship of plants, as represented in the various orders and suborders, and their medicinal properties, this method is followed as being the natural one.”<sup>12</sup> In other words, each plant family contained plant species with similar therapeutic potential. Students who took this course studied plant species and genera from precisely thirty different plant families, including species from the Rosaceae family, for example. The lecture on Rosaceae covered ten different genera, including *rosa*, *rubus*, and “*prunum*” (*sic. prunus*), which are all noted for their astringent properties.<sup>13</sup> Instructors at other pharmacy schools sometimes have opted to organize their materia medica lectures according to morphology instead of taxonomy.

Within the Department of Pharmacy at the State University of Iowa, for example, Prof. C.M. Hobby structured lectures for “The Course in Materia Medica and Botany” according to plant morphology. Drugs “from the vegetable kingdom will be divided into

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<sup>11</sup> “Address to the Board of Trustees of the California College of Pharmacy,” July 8, 1872, box 1, folder 6, Robert Day Collection.

<sup>12</sup> *The Iowa College of Pharmacy of Drake University. Announcements for 1895 and 1896. Des Moines, Iowa.* (Des Moines, IA: Iowa Printers Company, 1895), 19, box 6, folder 3, Ezra J. Kennedy Pharmacy School Collection, Collection No. 104, Lloyd Library and Museum, Cincinnati, Ohio (hereafter cited Kennedy Pharmacy Collection).

<sup>13</sup> *The Iowa College of Pharmacy of Drake University. Announcements for 1895 and 1896. Des Moines, Iowa.* (Des Moines, IA: Iowa Printers Company, 1895), 20, box 6, folder 3, Kennedy Pharmacy Collection.

classes in accordance with the part of the plant used, roots, rhizomes, tubers, bulbs, stems, barks, woods, leaves, flowers, fruits, excretions, products, etc.”<sup>14</sup> Professor S. Emory Lamphear utilized a similar method of organization for the “Materia Medica” course at the Kansas City College of Pharmacy. The junior course studied drugs derived from rhizomes, bulbs, roots, corms, flowers, and leaves, while the senior course expanded the subject to learn about drugs derived from fruits, seeds, barks, rinds, and woods, as well as flowerless plants like gymnosperms and lycophytes.<sup>15</sup> Here, botanical knowledge was depicted, not just an essential component of pharmaceutical education, but as a tool for organizing pharmaceutical information.

Consider also course examinations, as their questions illustrate the kind of knowledge considered essential for being a professional pharmacist. Scanning a handful of exams given at Cincinnati College of Pharmacy in 1890, plant-derived drugs account for sizeable portion of the exam questions. A junior examination for the microscopy course asks, “What points of difference has tea to such leaves as are used for its adulterations?”<sup>16</sup> But the general and practical pharmacy courses underline botanical knowledge as essential as well. The 1890 exam for the Theory and Practice of Pharmacy course asks, “How are Vegetable Drugs used for medicinal purposes cut? Why? Why should some be in a finer state of division than others?”<sup>17</sup> And for the junior course in Practical Pharmacy, the exam posits, “What Sulphur is used in the preparation

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<sup>14</sup> *First Annual Announcement of the Department of Pharmacy of The State University of Iowa at Iowa City, Iowa. Session of 1885-6.* (Iowa City, IA: Published by the Department, 1885), 4, box 6, folder 4, Kennedy Pharmacy Collection.

<sup>15</sup> *Fourth Annual Announcement of the Kansas City College of Pharmacy, [Pharmaceutical Department of the University of Kansas City.] 913 East Tenth Street, Kansas City, MO. 1889* (Kansas City, MO: ARGO PRINT, 1009 Main Street, 1889), 6, box 6, folder 6, Kennedy Pharmacy Collection.

<sup>16</sup> “Exam. Microscopy. 1890,” box 3, folder 6, Kennedy Pharmacy Collection.

<sup>17</sup> “Exam: Cincinnati College of Pharmacy. Theory and Practice of Pharmacy. Charles T.P. Fennel. Junior Class. - March 1890,” box 3, folder 9, Kennedy Pharmacy Collection.

of Compound Powder of Glycyrrhiza? Give the physical properties of the ingredients of Tully's Powder." "What two volatile oils enter into the preparation of Compound Liniment of Mustard? Does Belladonna Liniment contain the virtues of the leaf or root? Give the composition of of the liniments containing Oil of Turpentine."<sup>18</sup> Plant knowledge as it related to pharmaceutical sciences initially pervaded pharmaceutical curricula.

Even newly established colleges of pharmacy, with limited faculty and resources, incorporated plant-based therapies into the curriculum however possible. Brooklyn College of Pharmacy, for example, offered only chemistry and general pharmacy courses; when materia medica and botany was not in their course catalog in the late nineteenth century. They did, however, offer an organic chemistry course that predominantly featured lectures on plant-derived compounds. Lectures organized by type of chemical, with titles like "Tannic Acids," "The Numbing Alkaloids," and "Drugs Containing Glucosides," focused on chemicals found in plants such as aconite (wolf's bane), chestnut, tea, cinchona, dandelion, saffron, lily of the valley, and digitalis, to name only a handful.<sup>19</sup>

The Leonard School of Pharmacy at Shaw University, located in Raleigh, North Carolina, also had limited resources but still made sure to include botany and materia medica in their curriculum. Shaw's pharmacy school produced a total of eleven graduates between 1894 and 1895, and their faculty consisted of two people. Professor H.B. Battle covered medical and general chemistry, while Professor Wm. Simpson instructed on botany, materia medica, pharmacy, chemistry, compounding medicine,

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<sup>18</sup> "Exam: Cincinnati College of Pharmacy. Practical Pharmacy. Thfo. D. Wetterstroem. Junior Examination. - March 6th. 1890," box 3, folder 9, Kennedy Pharmacy Collection.

<sup>19</sup> *Prospectus of the Brooklyn College of Pharmacy, Session of 1892-1893*. (Brooklyn, NY: Eagle Book and Job Printing Department., 1892), 12, box 1, folder 8, Kennedy Pharmacy Collection.

and laboratory work.<sup>20</sup> No matter the size of institution and the resources available, American pharmacy schools included lectures on plant-derived drugs, in whatever capacity, in the curriculum.

The curricula at American pharmacy schools often required students to engage in field work. At the California College of Pharmacy, for example, Professor Behr guided pharmacy students into the countryside around San Francisco on excursions to collect and preserve plant specimens.<sup>21</sup> Behr also placed a number of those collected specimens in the school's herbarium so those plants could be available for study in the future.

Whenever a school of pharmacy had the resources, they featured descriptions of their herbariums, museums, cabinets, and green houses in their course catalogs. The Buffalo College of Pharmacy at the University of Buffalo offered numerous cabinets and an herbarium for their students, and also emphasized their hope to procure more botanic specimen:

*The Faculty desire to equip the college with complete cabinets, containing specimens illustrating the subjects of study in each department, and a beginning has already been made in this direction. Professor Kellicott has provided several hundred mounted specimens as the nucleus of an herbarium, and a small Materia Medica cabinet has been purchased. The Clinton Herbarium, one of the finest as well as one of the largest collections in the country (18,000 species), is offered to the student for purposes of study by the Academy of Natural Sciences. Upon the solicitation of Dr. D.B. Wiggins, of Buffalo, Messrs. Peek & Velsor, wholesale botanic druggists, of New York City, have kindly*

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<sup>20</sup> *Fifth Annual Catalogue of the Officers and Students of Leonard School of Pharmacy, Shaw University, for the Academic Year 1895-96.* (Raleigh, NC: printer unknown, 1895), 1; 30, box 20, folder 1, Kennedy Pharmacy Collection.

<sup>21</sup> "Address to the Board of Trustees of the California College of Pharmacy," July 8, 1872, box 1, folder 6, Robert Day Collection.

*presented the college with a complete cabinet of botanical specimens. This valuable collection of medicinal roots, barks, herbs and seeds, to be known as "The Peek & Velsor Botanical Cabinet," will always be available to the student for reference and study. It is earnestly hoped that others, and particularly manufacturing chemists and pharmacists, will aid the Faculty in providing these valuable aids to study.*<sup>22</sup>

Likewise, at the Cincinnati College of Pharmacy, "the museum contains a very complete line of drugs, chemicals, botanical specimens, and many other objects of interest to students of pharmacy."<sup>23</sup> If they had the resources available, pharmacy schools made a point to advertise having botanical specimen onsite for observation and research. Laboratories for botanical study were also a selling point.

Announcements showcased the modern and brightly lit laboratories that housed botanical specimen and instructional materials procured for training successful pharmacists. University of Buffalo had a pharmacognocal laboratory, dedicated to the study of pharmacognosy, described as "a room of very ample proportions and beautifully lighted from east and north window, which afford the most desirable light possible. This laboratory is furnished with about four hundred specimens of crude organic drugs; large, roomy, convenient tables; ample trays and drug containers;

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<sup>22</sup> *Annual Announcement of the Buffalo College of Pharmacy, Department of Pharmacy -- University of Buffalo, for the Session of 1886-87* (Buffalo, NY: Printing House of Bigelow Brothers, 1886), 15-16, box 1, folder 10, Kennedy Pharmacy Collection.

<sup>23</sup> *Fourteenth Annual Announcement of the Cincinnati College of Pharmacy, S.W. Cor. Fifth and John Sts. Session of 1884-85.* (Cincinnati, OH: Press of Knight & Co., Nos. 210 and 212 Elm Street, 1884), 14, box 3, folder 9, Kennedy Pharmacy Collection.

botanical and geographical maps; blackboards and photographic and photomicrographic illustrations of medicinal plants and drugs.”<sup>24</sup>

In the midwest, the Chicago College of Pharmacy boasted a microscopical laboratory with an herbarium of plants collected from around the world. Their 1903 announcement describes the space as follows:

*The Microscopical Laboratory is situated upon the second floor, and is adapted for classes of forty students. A compound microscope, magnifying from seventy-five to four hundred diameters, is provided for each person. The individual equipment consists of reagents and mounting media, slides, cover glasses, forceps, and other necessary apparatus. This room also contains the Materia Medica Cabinet of over three hundred samples of crude drugs, contained in half-gallon bottles, to which students have access. Here are also a collection of two hundred rare drugs, mostly from Central and South America, and another collection of 553 specimens, embracing the drugs official in the pharmacopoeias of France, Germany, Great Britain, and Scandinavia. Other features are a large number of illustrations of medicinal plants and a very extensive herbarium, the latter collected by Professor Bastin and his assistants during his connection with the botanical department of this college. It number several thousand specimens, and a sample of nearly every plant growing in this section of the country and many from the southern states and from the far west, may be found in this collection.*<sup>25</sup>

And back on the east coast, Cornell University’s School of Pharmacy built a botanical laboratory adjacent to greenhouses, “which at all seasons of the year furnish ample material for illustration and for laboratory use.”<sup>26</sup> Having resources like modern and sophisticated botany laboratories was a selling point; and so was having famous botanists on faculty.

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<sup>24</sup> *Annual Announcement of the Buffalo College of Pharmacy, Department of Pharmacy -- University of Buffalo, for the Session of 1890-91* (Elmira, NY: Advertiser Association Printers, 1890), 15, box 1, folder 10, Kennedy Pharmacy Collection.

<sup>25</sup> *Forty-Fourth Annual Announcement, Chicago College of Pharmacy, The School of Pharmacy of the University of Illinois, 465-467 State Street, Chicago, Session of 1903-1904* (Chicago, IL: Published by the University, 1903), 13, box 3, folder 7, Kennedy Pharmacy Collection.

<sup>26</sup> *Cornell University Announcement of the School of Pharmacy for the Year 1887-88* (Ithaca, NY: Published by the University, 1887), 13, box 4, folder 8, Kennedy Pharmacy Collection.

If a pharmacy school was fortunate enough, they had faculty members that were well-known botanists like Maisch, Bastin, or Rusby; all of whom had written the botany and materia medica textbooks required for many pharmacy students nationwide. Baylor University went the length of advertising their botany professor as selling point for their pharmacy school. In their first annual announcement for their College of Pharmacy, Baylor profiled their faculty botanist, M. Julien Reverchon. The page-long biographical sketch underlined that Reverchon's work in field was well-known amongst botanists. Opposite a full-page portrait of Reverchon, the announcement highlights his association with world-renowned botanist Asa Gray, with whom Reverchon co-discovered a desert annual in the Euphorbiaceae family named *Reverchonia arenaria* A. Gray.<sup>27</sup> This announcement, or any successive announcement in the next few years, featured no other faculty biographical sketches.

A famous botanist on faculty at Baylor's College of Pharmacy, as well as his substantial specimen collection, were featured in the announcement to attract the interest of potential pharmacy students. Baylor touted that "Prof. Julien Reverchon has about eight thousand species of plants -- 2600 of Texas growth collected by himself."<sup>28</sup> Reverchon invited the college's pharmacy students, in sections, to his home to see the botanical collection he had amassed in his years of fieldwork.<sup>29</sup> Having an abundance of plant materials available for the pharmacy student's observation and study elevated the sophistication and modernity of the turn-of-the-twentieth-century pharmacy school.

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<sup>27</sup> *Baylor University College of Pharmacy, Formerly Pharmacy Department of the University of Dallas, Annual Announcement, Vol. 1, No. 1, Third Session 1903-1904, 435-437 South Ervay Street, Opposite City Park, Dallas, Texas. (publisher unknown, 1903), 27, box 1, folder 6, Kennedy Pharmacy Collection.*

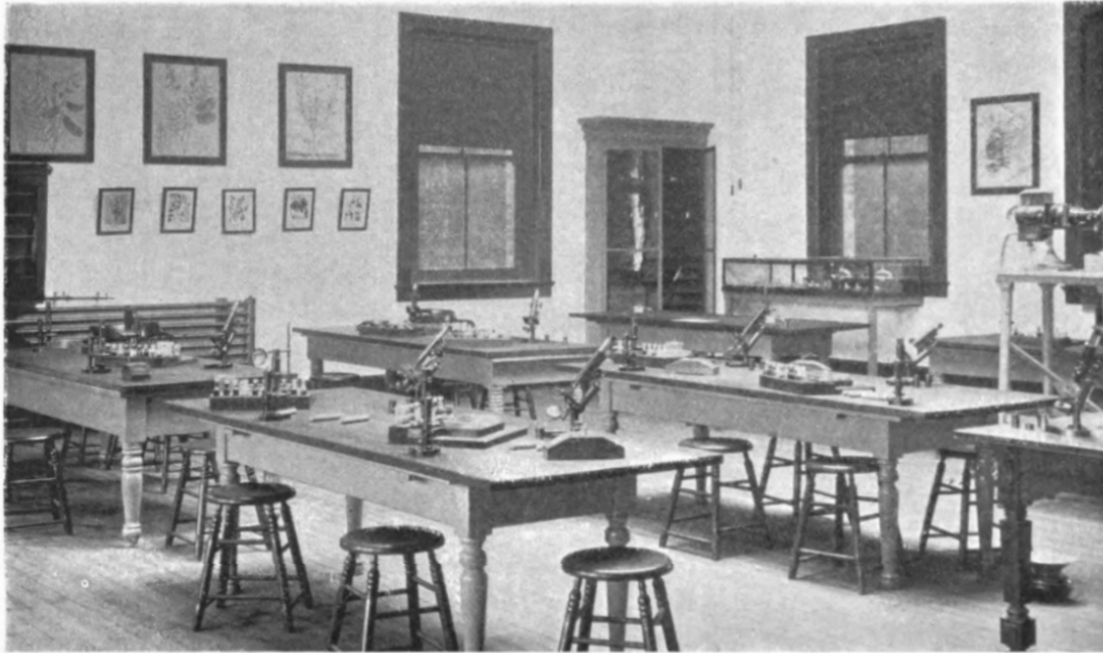
<sup>28</sup> *Ibid.*, 11-12.

<sup>29</sup> *Baylor University College of Pharmacy, Formerly Pharmacy Department of the University of Dallas, Annual Announcement, Vol. 2, No. 1, Fifth Session 1904-05, 435-437 South Ervay Street, Opposite City Park, Dallas, Texas. (publisher unknown, 1904), 12, box 1, folder 6, Kennedy Pharmacy Collection.*

Pharmacy students also had at their disposal a number of classroom instructional items to aid in their study of botany. An inspection survey of the accredited American colleges of pharmacy conducted in the last decade of the nineteenth century points to a plethora of instructional botany materials. For example, the report notes that at the College of Pharmacy of the City of New York, botany students are “assisted by having at their disposal cards in duplicate, one for each student, containing specimens of the plant in discussion [...] In addition to these, they use a number of cards with painted illustrations thereon as well as large charts.” Also, if a particular botany department had the funds and patience to upkeep them, papier-mâché models of plant parts served as aids in quizzes and private study.<sup>30</sup> In addition to these visual aid materials, students took a compulsory lab component to study internal plant structures at a microscopic level.

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<sup>30</sup> F.A. Beckett, Ph.G. “Inspection Report of Colleges of Pharmacy,” July 11, 1895, box 1, folder 7, Robert Day Collection.



MICROSCOPICAL LABORATORY. (South-west corner)

Based on photographs of laboratory spaces and the equipment featured therein, the botany lab of the late nineteenth and early twentieth centuries at colleges of pharmacy offered a rudimentary engagement with the scientific inquiry of plants. A photo of a botany laboratory at the California College of Pharmacy, taken around the turn of the century, demonstrates this point. Microscopes sit atop farm-style tables and several framed botanical illustrations hang on the walls.<sup>31</sup>

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<sup>31</sup> "U.C. Pharmacy School, San Francisco, Classroom (1898-1900)," box 34, Robert Day Collection.



An image of the botany laboratories taken a decade later at the California College of Pharmacy illustrates similar limited potential for botanical study. Men and women sit in groups of five to seven around six lab tables dispersed in a spacious, high-ceiling laboratory. Dozens of mounted botanical illustrations hang around the room; easily accessible as reference material for the students. An enormous case with glass doors sits at the front of the laboratory; full of labeled jars, though the contents of which cannot be easily discerned. The laboratory students are working with microscopes; looking into their eyepiece lenses and recording their observations in notebooks. A few empty boiling flasks and apothecary jars sit on the lab table in the foreground. An enormous chalkboard reaches the ceiling behind the instructor and indicates that the year is 1911. An enlarged chalk drawing of a microscope's viewfinder occupies the

bottom half of the chalkboard; details of the image look like vascular bundles of a stem cross-section. The top half of the chalkboard features an even larger illustration; a close-up of a stem cross-section; to indicate the types of cell bundles present from the stem's core to its epidermis.<sup>32</sup> And this scene summarizes the extent of botanical inquiry that pharmacy students experienced. The microscope and the botanical illustrations offered students microscopic and macroscopic views of plants, and satisfied the discipline's primary concern with observation of plant material in order to learn morphological and histological features. And the habit of botanical inquiry to only consider plant structure characterized the discipline's objectives in pharmaceutical colleges. Another course dealt with the actual medicinal qualities of plants - arguably a relevant aspect of plant knowledge for a pharmacist - but even then, training with those plant constituents remained limited, and sometimes optional.

Professor William Searby taught *materia medica* at the California College of Pharmacy, a discipline devoted to the medicines derived from plant and animal origin. Extant lecture notes, written by an instructor of the course who taught under Searby's guidance, indicate that drugs of vegetable origin dominated the course lectures. Within the 270 pages of his lecture notes, Otto A. Weihe described 150 individual drugs derived from plants or fungi. Drugs from insect or animal origin represent a disproportionate fifteen entries.<sup>33</sup> *Materia medica* existed as a course primarily concerned with plant remedies, but the lectures encompassed a much broader focus than just a plant's medicinal properties.

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<sup>32</sup> "Microscopical Laboratory," 1911, box 28, folder 6, Robert Day Collection.

<sup>33</sup> Otto A. Weihe, "These notes on *Materia Medica* were used by me while I was instructor in the College of Pharmacy 113 Fulton St, S.F., under Professor W.M. Searby 1892-1898," box 43, folder 2, Robert Day Collection.

Searby and Weihe placed much emphasis on pharmacy students to learn the Linnaean taxonomy and organized their lectures to describe official drugs grouped together by natural order. For example, Weihe's lecture book listed the five official drugs within natural order Ranunculaceae as Pulsatilla, hydrastis staphisagria, aconitum, cimicifuga, and delphinium. Thereafter, Weihe listed each drug's common name, if one existed, its botanical origin (Latin name), habitat, the part of the plant used, description (morphology) of parts used, constituents, medicinal properties, dose, and official preparation.<sup>34</sup>

Importantly, materia medica employed botanical traditions and grouped plants according to their natural order and morphological features, and not their medicinal qualities. Linnaean taxonomy, introduced in the first half of the eighteenth century, organized plants according to sexual characteristics expressed by the reproductive organs on flowers. Carl Linnaeus, a Swedish botanist, developed and popularized a system of organization based on the number and arrangement of stamens and pistils; respectively, the male and female sex organs that comprise the innermost whorls of flower morphology. According to the Linnaean organizational scheme set forth in *Systema Naturae* (1735), plants are first divided by the number of stamen present on each flower into *classes*. Thereafter, plants are further subdivided into *orders* according to the number of pistils typically found on a plant's flower. English botanists, as well as American botanists, increasingly implemented this sexual system of organization, and by the nineteenth century, the Linnaean system had become the standard for botanical study. The study of plants within American colleges of pharmacy also employed the

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<sup>34</sup> *Ibid.*

Linnaean sexual system of organization. Importantly, and imperative to this history, the tradition of botany shaped the pharmacist's interpretation of the drug, and in this sense, botany was the framework through which pharmacists understood plant therapies. This immense influence of traditional botanical instruction within a pharmaceutical context emphasized plant structure and plant history far more than the actual medicinal components that made any plant relevant to therapeutics.

Limitations of scientific instrumentation contributed to the narrow scope of materia medica courses. By the 1920s, the capacity of microscopes still limited observation potential. A 1924 inventory of the California College of Pharmacy's microscopes for plant-related disciplines indicates that the institution owned "111 six-inch objective lens Bausch & Lomb" microscopes for first and second year students; "6 Bausch & Lomb 1/12" objective" for third and fourth year students.<sup>35</sup> Bausch & Lomb released a microscope in 1923 with an objective lens that measured roughly six inches. The magnification varied from 60-250, depending on the lenses used with the objective. While the exact model of microscope owned by the California College of Pharmacy cannot be ascertained, based on extant microscope technology at the time of the 1924 inventory report, pharmaceutical students could observe plant morphology at up to 250 times its actual size. While this number seems large, 250 magnification can zoom into internal plant structures enough to observe vascular tissue; an activity useful for studying vegetable histology. However, such a magnification lacks the capacity to identify specific plant metabolites. Students learned of constituents through lecture and had to retain the information through notes or rote memorization. The scope of materia

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<sup>35</sup> Inventory form, 1924, box 18, folder 2, Robert Day Collection.

medica courses, further limited by simple microscopy instruments, limited the potential to study secondary metabolites.

Historically, chemists and pharmacists struggled with the isolation and measurement of pure plant constituents. Though Friedrich Sertürner isolated morphine in 1805, inaccuracy of scientific instrumentation plagued the study of plant metabolites. Today, morphine ( $C_{17}H_{19}NO_3$ ) is considered to contain 40 atoms, where nitrogen accounts for roughly five percent of the total atomic weight. However, efforts to calculate this figure in the early nineteenth century yielded several, and rather inaccurate, molecular configurations. Jean-Baptiste Dumas, for example, calculated that morphine contained 107 atoms; Justus von Liebig calculated 78 atoms. The problems faced during analysis of morphine in the nineteenth century centered upon the inadvertent mixing of atmospheric nitrogen with the molecule under study and the large number of the atoms present in the morphine molecule; whereby small uncertainties in calculation of individual atoms amounted to large inaccuracies for the molecular compound overall.<sup>36</sup> Difficulty with measuring alkaloids extended to the measurement of other plant constituents as well. And even as knowledge of secondary metabolites gained clarity, that new knowledge was not readily incorporated into the study of pharmaceutical botany. As such, materia medica placed limited emphasis on constituents and dose, and this practice became ingrained as a common oversight in the course objectives.

Materia medica and botany courses primarily emphasized observation and rote memorization of taxonomy, morphological features, and known active constituents. And

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<sup>36</sup> Alan J. Rocke, "Organizing Analysis in Comparative Perspective: Liebig, Dumas, and Berzelius, 1811-1837" in *Instruments and Experimentation in the History of Chemistry*, Frederic L. Holmes and Trevor H. Levere, eds. (Cambridge, Mass.: The MIT Press, 2000), 273-310.

initially, in addition to the evidence of curricular standards and the types instructional materials and laboratory equipment provided, colleges of pharmacy embraced this approach to studying plants by funding medicinal gardens for students and faculty. The California College of Pharmacy facilitated three efforts to plan and establish gardens within San Francisco. The College initially funded a garden project in Golden Gate Park that was open to the public. In cooperation with the park's commissioners, the College provided plants, shrubs, and trees to occupy three or four acres of park land. Established in 1904, the public park eventually hosted "about four hundred species of the more important medicinal plants and was the first of the more comprehensive gardens of its kind in the United States."<sup>37</sup>

Later efforts by the College to establish gardens limited access to students and faculty. The College planted a second garden in 1912; this one on campus. Supplied in part by the pharmaceutical firm Lilly Company, several hundred medicinal plants grew in the garden space until 1916, when the School of Dentistry needed the land for a new building.<sup>38</sup> The College started a third and final garden, established in 1936, for the especial use of teaching plant-related disciplines.<sup>39</sup> Further record and the fate of that garden could not be determined, but at least through the 1930s, the California College of Pharmacy demonstrated ample support of plant-related disciplines.

Botany and materia medica courses initially consisted of roughly half of the pharmacy students' training, but what's more, students found the therapeutic application

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<sup>37</sup> "A History of the University of California School of Pharmacy," 1964, box 18, folder 3, Robert Day Collection; "Plan Botanical Garden in Park" 1900, box 7, folder 2, Robert Day Collection.

<sup>38</sup> "History of the California College of Pharmacy, University of California," 1926, box 8, folder 1, Robert Day Collection.

<sup>39</sup> "Pharmacy Drug Garden Established By University," 1936, box 18, folder 1, Robert Day Collection.

of crude plants valuable and worth scientific exploration. The graduating class of 1886, for example, consisted of nine students. Four of their thesis subjects focused on chemical substances like bitartrate of potassium (cream of tartar more commonly), boric acid, and antipyrine. However, botany topics dominated the papers, with five of them dedicated to subjects including chlorophyll, three distinctive plant species, and tincture of the strychnine tree, nux vomica.<sup>40</sup> Chlorophyll, which is a green pigment found in cyanobacteria, was the only plant-related topic that dealt with an isolated secondary plant product. The rest of the papers, in true late-nineteenth-century form, focused on much more of the plant, or its crude plant material, than the actual medicinal property derived therein. The theses topics explored at the Philadelphia College of Pharmacy depict a similar interest with pharmaceutical botany.

Thesis titles very simply summarize a marked interest amongst pharmacy students with matters of pharmaceutical botany. In 1873, for example, the Philadelphia College of Pharmacy produced ninety-five graduates who wrote a thesis paper. A quick scan of the thesis list features titles like “Aloe Vulgaris,” “Dioscorea Villosa,” “Verbena Hastata,” and “The Advantage of the Study of Botany to Druggists.” Of the ninety-five theses listed, just over forty of the titles overtly indicate a topic pertinent to pharmaceutical botany.<sup>41</sup> Fast forward to 1921, and the dispersal of thesis topics still indicates some interest with plant-derived drugs. Of the 212 graduates in 1921 who produced a thesis paper, about thirty, or just under fifteen percent, of the paper topics clearly deal with some aspect of pharmaceutical botany. And the thesis titles are very

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<sup>40</sup> “Fourteenth Annual Commencement Exercises of the California College of Pharmacy,” November 17th, 1886, box 8, folder 5, Robert Day Collection.

<sup>41</sup> Philadelphia College of Pharmacy and Science, *The First Century of the Philadelphia College of Pharmacy, 1821-1921* (Philadelphia, PA: Philadelphia College of Pharmacy and Science, 1922), 484-487.

similar to the ones produced in the nineteenth century, named simply after a plant species or genus or alluding to the importance of plant-focused courses. Theses in 1921 included titles like “The Pine Trees and Their Products,” “The Importance of Pharmacognosy to the Chemist,” and “Gentian.”<sup>42</sup> The proportion of the paper topics devoted to plant topics decreased between the 1870s and 1920s, and that reason will be explored a bit later in the chapter. Nonetheless, pharmacy students in the early twentieth century still opted to devote their research papers to topics of pharmaceutical botany. Whole-plant therapies gripped the focus of pharmaceutical curricula and the attention of pharmacy students, but the high degree of relevance wrought by plant-related disciplines in the late 1800s would begin to lessen with the turn of the century.

### **The New Therapeutics**

The “causal organisms of malaria, anthrax, tuberculosis, cholera, plague, typhoid and many other major diseases had all been identified” by the start of the First World War.<sup>43</sup> Once scientists had determined the causes of these diseases, therapeutic approaches for treating disease then switched from targeting the symptomatology to targeting the microorganisms responsible. Likewise, where the laboratory found the microorganisms that caused disease, so too did it find the specific chemical and biological agents that could treat or prevent disease by targeting those microorganisms.<sup>44</sup>

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<sup>42</sup> *Ibid.*, 658-663.

<sup>43</sup> Mark Harrison, *Disease and the Modern World: 1500 to the Present Day* (Malden, Mass.: Polity Press, 2004), 118.

<sup>44</sup> For more on the rise of laboratory medicine in the nineteenth and twentieth centuries, see John Harley Warner, “The Fall and Rise of Professional Mystery: Epistemology, Authority, and the Emergence of

Paul Ehrlich employed this approach to therapeutics when he began to conceptualize chemotherapy in the beginning of the twentieth century. Not to be confused with contemporary linkage to cancer treatment, chemotherapeutics as it existed initially dealt solely with infectious disease. Ehrlich observed that the chemical dye methylene blue targeted and attached itself only to specific cell tissues. Ehrlich reasoned that chemical substances that behave in a similar targeted manner must exist that could attach themselves to disease agents while avoiding the host organism. Chemotherapeutic research initially concerned two types of factors — “the distributive constituents which regulated distribution” of chemicals to targeted organs or tissue; and “the pharmacophoric group which caused specific action.”<sup>45</sup> Together, these factors targeted disease-causing microorganisms; primarily acting in a bacteriostatic nature and allowing the patient’s natural antibodies to actually kill the bacteria. Only by the late 1930s did chemotherapeutic research begin to yield promising therapies, but the roughly thirty-year interim began to establish precise medicinal compounds as a major tenet of modern therapeutics.<sup>46</sup>

Not much changed in regard to plant disciplines in the first three decades of the twentieth century except for the allotted number of hours required for a particular course. Pharmacy students had to take botany and materia medica, but they increasingly had to take a number of other courses as well. By 1925, four years of

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Laboratory Medicine in Nineteenth Century America” in *The Laboratory Revolution in Medicine*, eds. Andrew Cunningham and Perry Williams (Cambridge, NY: Cambridge University Press, 1992), 110-142. Also, Jonathan Liebenau, *Medical Science and Medical Industry: The Formation of the American Pharmaceutical Industry* (London: The MacMillan Press Ltd., 1987).

<sup>45</sup> “Chemotherapy,” *The Lancet* 168 (Oct. 6, 1906): 945.

<sup>46</sup> For more on the rise of chemotherapy, see John E. Lesch, *The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine* (Oxford: Oxford University Press, 2007). And John E. Lesch, “Chemistry and Biomedicine in an Industrial Setting: The Invention of the Sulfa Drugs,” in *Chemical Sciences in the Modern World*, ed. S.H. Mauskopf (Philadelphia, PA: University of Pennsylvania Press, 1994), 158-215.

instruction included 24 unique subjects, from basic sciences like physics, chemistry, and biology; to practical courses on bookkeeping, drawing, and pharmaceutical calculations; to more innovative courses focused on bacteriology and industrial poisons.<sup>47</sup> Then, in the 1930s, the California College of Pharmacy started to tweak its course offerings in regard to plant disciplines.

After 1935, materia medica no longer appeared in course announcements. The pharmaceutical college instead offered a pharmacognosy course. Roy Porter claims that “the study of materia medica developed during the nineteenth century into laboratory-based pharmacology,”<sup>48</sup> but pharmacy students continued to study materia medica well after the development of pharmacology. Pharmacology deals with the physiological action of isolated chemical compounds, whether from animal, mineral, or vegetable origin. The discipline would ultimately forge forth as the relevant methodology for studying plant-derived drugs.<sup>49</sup> However, pharmaceutical study of the entire plant and its structure lasted far after the emergence of pharmacology. Pharmacognosy replaced materia medica, but only in title, as the course material remained mostly identical.

In suit with departmental restructuring in 1933 and impending affiliation with the University of California, the Curriculum Committee convened a meeting in January of that year to consider new elective courses to offer. Faculty members voted and approved the addition of an elective course dedicated to the study of powdered

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<sup>47</sup> Transcript of courses, Feb 1925- Aug 1933, box 2, folder 2, Robert Day Collection.

<sup>48</sup> Roy Porter, *The Greatest Benefit to Mankind: A Medical History of Humanity* (New York, NY: W.W. Norton & Company, 1997), 333; 448.

<sup>49</sup> For more on the emergence of pharmacology as a pharmaceutical science and its relationship to materia medica, see John Parascandola, *The Development of American Pharmacology: John J. Abel and the Shaping of a Discipline* (Baltimore, MD: The Johns Hopkins University Press, 1992). Also, John Parascandola and John Swann, “Development of Pharmacology in American Schools of Pharmacy” *Pharmacy in History* 25 (1983): 95-115.

vegetables and spices.<sup>50</sup> The addition of this particular course came at a relatively late moment in pharmaceutical study of plant-based drugs. In fact, textbooks on powdered vegetables circulated at least as early as 1893.<sup>51</sup> Though, the subject matter typically comprised one of the objectives of the materia medica or pharmacognosy laboratory courses.

Studying powdered vegetables and spices enabled a pharmacist to discern the physical characteristics of crude drugs at a microscopic level so that they could determine whether or not a particular drug sample contained adulterants or contaminants. Textbooks on powdered drug anatomy, which also served as reference works for laboratory use, contained detailed illustrations of the microscopic physical components one would expect to see during an examination of a powdered plant sample. If a pharmacist needed to check the purity of a powdered belladonna root sample or a powdered cinchona bark sample or even discern one from the other, as they appear fairly similar macroscopically, a simple examination with a microscope would suffice. At a microscopic level, the physical components of powdered, crude vegetable material differentiated powdered drugs from each other. The objective of the subject matter most certainly shifted away from consideration of the whole plant, as it only concerned the anatomy of the plant in a powdered form. However, even microscopic study of crude plant material failed to reach the level of precision that characterized new therapeutics. Dr. Robertson Pratt, an instructor at the pharmaceutical school now referred to as the School of Pharmacy at the University of California, San

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<sup>50</sup> "Faculty Meeting," January 24, 1933, box 2, folder 2, Robert Day Collection.

<sup>51</sup> Henry George Greenish and Eugene Collin, *An Anatomical Atlas of Vegetable Powders Designed as an Aid to the Microscopic Analysis of Powdered Foods and Drugs* (London: J. & A. Churchill, 1904), 4.

Francisco, offered the powdered drugs course as an elective until his retirement in 1975. And for four decades, pharmacy students at the University of California had the option to study powdered drugs. But as we will see later, the powdered vegetables course, as well as pharmacognosy, eventually only existed as remnants of earlier pharmaceutical culture.

Following the development of Prontosil Albumin in 1935, chemotherapeutic drugs flourished in the early twentieth century. The first of many sulphanilamide drugs, Prontosil Albumin proved efficacious in treating streptococcal and staphylococcal infections.<sup>52</sup> As of the 1940s, conceptualization surrounding chemotherapy remained tied to infectious diseases. A survey of medical journals from the first few decades of the twentieth century returns articles linking chemotherapeutic treatments to osteomyelitis, gonorrhea, and among many others, infections in compound fractures.<sup>53</sup> Still, the immediate popularity of chemotherapeutic drugs and the exponential increase in chemotherapeutic research that began in the 1930s did little to influence plant-based disciplines that traditionally disregarded specific chemical compounds.

In 1942, the National Pharmaceutical Syllabus Committee published the fifth edition of its nationwide syllabus. Since its first edition in 1910, the curriculum outlined in this national syllabus was designed as a framework for pharmaceutical instruction at all accredited colleges of pharmacy in the United States; where multiple professionals from all of the pharmaceutical disciplines collaborated and submitted course outlines which

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<sup>52</sup> William H. Brock, *The Chemical Tree: A History of Chemistry* (New York, NY: W.W. Norton & Company, Inc., 2000), 624.

<sup>53</sup> M.L. Crossley, "Recent Advances in Chemotherapy" *Science* 91 (April 19, 1940): 373; Robert W. Johnson, "Chemotherapy in the Prevention of Infection in Compound Fractures" *The American Journal of Surgery* 49 (1940): 195-200.

featured those topics considered most important and beneficial for their respective disciplines. Heber W. Youngken, Jr., alongside B.V. Christensen and E.H. Wirth, contributed the pharmacognosy outline for the 1942 edition, and they borrowed much of their summarization of the course material from the fourth edition, printed a decade earlier in 1932.

Youngken, Christensen, and Wirth defined pharmacognosy as a science that emphasized “the history, source, cultivation, collection, preparation, distribution, commerce, identification, composition, purity, and preservation of drugs of vegetable and animal origin.”<sup>54</sup> This description harked back decades; to the course’s initial emergence from the study of *materia medica*; even to the description typically reserved for *materia medica* itself. But the scope and characteristics of the pharmacognosy course, as set forth by Youngken, Christensen, and Wirth in the 1942 edition, illustrated minimal innovation with the course material; instead, demonstrating marked dependence upon those topics of instruction pharmacognosy instructors traditionally implemented. The authors even lifted the scope of the course, verbatim, from the fourth edition of *The Pharmaceutical Syllabus*. Insisting “that it would be impossible as well as impracticable to study in detail every crude drug that the pharmacist might be called upon to sell or dispense,” the *Syllabus* offered a primary list and a secondary list of crude vegetable drugs. And the lists printed in the 1942 edition varied only slightly from the 1932 edition.<sup>55</sup> As of the early 1940s, with less than a decade of promising research

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<sup>54</sup> *The Pharmaceutical Syllabus* (Baltimore, MD: The National Pharmaceutical Syllabus Committee, 1942), 112.

<sup>55</sup> *The Pharmaceutical Syllabus* (Baltimore, MD: The National Pharmaceutical Syllabus Committee, 1932), 119-123; *The Pharmaceutical Syllabus* (Baltimore, MD: The National Pharmaceutical Syllabus Committee, 1942), 112-116.

with and discovery of chemotherapeutics, colleges of pharmacy continued to require students to study the same courses dedicated to crude plant-derived drugs that had long existed as standard pharmaceutical curricular features. However, continued burgeoning success with new therapeutics would begin to shift curricular focus away from crude vegetable drugs.

Interpreting the course catalogs and announcements independently of all external factors, from the sheer diversification of pharmaceutical curricula from the three or four core subjects of the nineteenth century to the dozens of course offerings of the mid-twentieth century, plant-rich courses declined simply proportionally. Dwarfed by technological advances and epistemological divergences that facilitated new frontiers in pharmacology, bacteriology, vaccinology, and many other burgeoning fields in pharmaceutical sciences. But declined proportion does not account for what happened next: absence. By the mid-1970s, American pharmacy schools stopped offering courses that dealt with plants altogether.

### **The Final Years of Plant-Focused Disciplines**

Once Howard Florey and Ernst Chain discovered the medical application of penicillin, the efficacy of isolated chemical and biological agents with treating disease solidified the focus of modern therapeutics on precise compounds. Crude plant drugs no longer fit into therapeutics in any relevant manner, and pharmaceutical colleges addressed this disconnect in the following decades; first by redesigning the objectives of plant-based disciplines; finally by removing the courses altogether.

In the spring of 1946, a collaborative effort between the National Association of Boards of Pharmacy, the American Association of Colleges of Pharmacy, and the American Pharmaceutical Association initiated a nationwide pharmaceutical survey that covered, in addition to other topics, American pharmaceutical education. The study aimed to gather information pertaining to the state of pharmaceutical education and to thereafter recommend improvements where deemed necessary, for the benefit of both the profession and the public more broadly.<sup>56</sup>

Some of the survey results materialized in a 1952 report prepared for the American Association of Colleges of Pharmacy's Committee on Curriculum. The report, entitled *The Pharmaceutical Curriculum*, overviewed various courses typical of American pharmaceutical curricula. Two authors, Lloyd E. Blauch and George L. Webster, wrote the majority of the report, but they also sought input from members of a consultative committee. Blauch and Webster consulted five men for the report's section on pharmacognosy. J. Hampton Hoch, Arthur E. Schwarting, Ralph F. Voigt, as well as Heber W. Youngken, Jr. and Robertson Pratt, all with doctorates and all teachers of pharmacognosy at colleges of pharmacy, served as the report's pharmacognosy consultants. Instructors hailing from institutions in South Carolina, Connecticut, Illinois, Washington, and California, these men contributed nothing like the other sections featured in the report. Rather than the typical, short summaries of required hours for lecture and laboratory instruction, course objectives, and suggestions for future course listings, the pharmacognosy consultants issued a fourteen-page plea for the continued inclusion of the discipline, a list of reasons why pharmacy students would benefit from

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<sup>56</sup> Lloyd E. Blauch and George L. Webster, *The Pharmaceutical Curriculum* (Washington, D.C.: American Council on Education, 1952), vii.

the course, and a proposal for a thoroughly detailed outline for a completely revamped syllabus. The five pharmacognosy instructors perceived the declining relevance of their field, and they not only proposed to combat the possibility of removing pharmacognosy from pharmaceutical curricula; but collaborated to overhaul and remodel the discipline in an effort to ensure its future presence in colleges of pharmacy.

The traditional objectives addressed by pharmacognosy courses had, by 1952, raised concerns of curricular relevance and “been the subject of controversy” in designing pharmaceutical curricula.<sup>57</sup> Pharmacognosy instructors acknowledged the shortcomings of their discipline in light of modern developments in pharmacy, as well as in science more broadly. Drs. Hoch et al argued that because of the “trend toward the use of isolated constituents, there [had] been a decrease in the number of crude drugs handled by the pharmacist.”<sup>58</sup> Crude drugs were a thing of the past, and pharmacists were less and less likely to handle them. Naturally, then, the knowledge of crude drugs traditionally extended by plant-based courses no longer needed to be imparted to younger generations of pharmacy students.

Instructors of pharmacognosy, however, strove to avoid this notion, and instead endeavored to redesign the course objectives to conform to modern therapeutic tenets. The pharmacognosy consultants for the pharmaceutical curriculum report listed, among a handful of other aspects that needed attention, the traditional organization of course material as outdated and impractical. When pharmacists handled crude drugs regularly, pharmacognosy inherited from *materia medica* the practice to employ the same

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<sup>57</sup> *The Pharmaceutical Curriculum*, 103.

<sup>58</sup> *The Pharmaceutical Curriculum*, 109.

taxonomic organizational scheme implemented by botany. Even though the study of plants in colleges of pharmacy had different utility than pure botanical study, in both circumstances, instructors taught the study of plants in an essentially identical manner. So when twentieth-century therapeutics emerged to focus on those plant constituents that caused physiological action in the body rather than the whole plant or plant part, organization of knowledge according to traditional botany taxonomy or morphological features no longer made sense. Drs. Hoch et al addressed this concern, then, by reorganizing the course material according to plant constituents. Their proposed outline of course content divided subject matter into sections dedicated to carbohydrates, glycosides, alkaloids, vitamins, resins, hormones, proteins, and a number of other categories of isolated secondary metabolites.

The proposal for the pharmacognosy course objectives turned the historical focus of the discipline upside down. Drs. Hoch et al suggested that “limitations should be placed upon the study of the origin and anatomy of drug plants. [...] In a basic undergraduate course in pharmacognosy emphasis should be placed upon the study of pharmaceutically significant drugs and chemical constituents of drugs.” The five instructors went on to suggest that, in the future, only graduate research in pharmacognosy should incorporate substantial inquiry with plant morphology.<sup>59</sup> Some of the pharmacognosy instructors even went beyond the syllabus proposal to publish articles that set forth a similar agenda.

Heber W. Youngken, Jr. especially endeavored to retain the presence of pharmacognosy courses in pharmaceutical curricula. In addition to his work with the

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<sup>59</sup> *The Pharmaceutical Curriculum*, 109.

nationwide syllabus report, Youngken published articles to promulgate the new objectives of pharmacognosy instruction. In an article published in the *American Journal of Botany* in 1956, Youngken operated under the guise of supposed nationwide renovation regarding the plant-rich course. He claimed that the discipline “[had] now begun to deal with [...] aspects of experimental botany [like plant chemistry, biochemistry, and physiology] as they can be related to medicinal plants. This change [had] also been greatly reflected in the teaching of pharmacognosy in pharmacy schools and it [could] be observed in the publications and textbooks of more modern pharmacognosists.”<sup>60</sup>

Youngken was a prominent individual in the subfield of pharmacognosy. Starting in the 1920s, he published multiple pharmacognosy textbooks that experienced as many printings and editions. In 1951, Youngken collaborated with Dr. Robertson Pratt to publish the first edition of *Pharmacognosy: The Study of Natural Drug Substances and Certain Allied Products*. This textbook, unlike former pharmacognosy textbooks, included emphasis on plant constituents. But, even though a text may be printed on a subfield discipline, and even if that text maybe be printed in numerous editions thereafter, the accumulation of those texts does not necessarily represent the field as a whole. And so with the case of pharmacognosy, Youngken’s and Pratt’s efforts to publish pharmacognosy textbooks post-mid-century most certainly failed to influence or demonstrate the trends in pharmaceutical research at a broader level.

Lack of esteem for whole-plant disciplines could also be witnessed by the general dearth of quality instructors in colleges of pharmacy. A 1951 report based on a

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<sup>60</sup> Heber W. Youngken, Jr., “Botany and Medicine” *American Journal of Botany* 43 (Dec. 1956): 863.

study conducted by the American Council on Pharmaceutical Education indicated that of the 71 accredited colleges of pharmacy surveyed, only 25 colleges offered pharmacognosy courses that were taught by professional pharmacognosists. Richard A. Deno, the author of the report, defined professional pharmacognosists as any person whose “graduate study, memberships in scientific societies, and research publications have been in this field; or if one or more of the proceeding is or has been true, and the other criteria appear likely to be fulfilled.”<sup>61</sup> Even with a lenient definition of professional, Deno found only 25 professional pharmacognosists nationwide. More often, colleges of pharmacy delegated pharmacognosy instruction to amateurs and “the last man to be added to the staff.”<sup>62</sup> Younger generations of pharmacy students, overall, were not seeking careers as pharmacognosy instructors, and colleges of pharmacy hired minimally qualified course instructors to teach the subject. Still, some pharmacognosy instructors, like Robertson Pratt at University of California, strove to overcome the doubts stacked against the discipline; even as their institutions moved away from plant-based courses.

As of 1953, and as part of a massive overhaul in curriculum design, pharmacy students at the College of Pharmacy at University of California, San Francisco no longer had to take botany as part of the new four-year program. Instead, the botany requirement moved to a new “pre-pharmacy” curriculum that applicants had to complete prior to entry into the College of Pharmacy.<sup>63</sup>

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<sup>61</sup> *The Pharmaceutical Curriculum*, 116.

<sup>62</sup> *The Pharmaceutical Curriculum*, 116.

<sup>63</sup> “Minutes of the Faculty of California College of Pharmacy,” June 1952 to June 1954, box 3, folder 2, Robert Day Collection; *Announcement of the School of Pharmacy, 1953-1954* (San Francisco, CA: University of California, San Francisco, 1953), 23.

Also in 1953, Dr. Alex Shrift joined Dr. Robertson Pratt on the faculty as an Instructor in Pharmacognosy and Plant Physiology. Earlier that year, Shrift had completed his doctorate at Columbia University, where he focused his dissertation on the anti-metabolic effects of selenate and selenomethionine on the growth of the green algae *Chlorella vulgaris*. Basically, Shrift's topic demonstrated the impetus of chemotherapeutic research within a microbiological context. He took two specific chemical compounds -- a sulfate and a plant-derived amino acid -- and studied their influence on an organism at a microscopic level. The potential of Shrift's methodology for pharmacognostical research immediately resonated at the University of California's College of Pharmacy, and especially with Robertson Pratt, as the fresh innovation that could revive pharmacognosy courses.

Pratt and Shrift rewrote the 1953 description of the introductory pharmacognosy course to shift emphasis away from the traditional plant-history lessons toward a "major emphasis [...] on the cell as a biosynthesizing structure, and its products. The physiologic properties of these products and the basis for the therapeutic, prophylactic, and other uses [were] stressed."<sup>64</sup> The following year's announcement made the newfound emphasis on plant metabolites even more explicit by stressing the physico-chemical properties of plant products.<sup>65</sup> Shrift left the University of California after three years of instruction, but Pratt continued to release pharmacognosy announcements according to the 1954 description until the mid-1960s.

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<sup>64</sup> *Announcement of the School of Pharmacy, 1953-1954* (San Francisco, CA: University of California, San Francisco, 1953), 34.

<sup>65</sup> *Announcement of the School of Pharmacy, 1954-1955* (San Francisco, CA: University of California, San Francisco, 1954), 30.

However, Shrift's and Pratt's efforts to redesign pharmacognosy course objectives were done in vain. Varro E. Tyler, a professor of pharmacognosy, sums up the noticeably declining interest of pharmacognosy courses. By the 1950s, Tyler explains, "pharmacy students had already begun to describe the old-fashioned courses to which they were subjected by the pejorative appellation 'weeds and seeds.'"<sup>66</sup> And while institutions like the College of Pharmacy at San Francisco did not immediately adjust curriculum requirements to reflect lack of interest toward plant-based disciplines, pharmaceutical instruction did begin to slowly disregard the traditional botany courses and the attention given to plant structure until finally removing plant-related courses altogether. Moreover, the instructional spaces — both lecture halls and laboratories — of the pharmaceutical college no longer appeared to emphasize botanical study.

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<sup>66</sup> Varro E. Tyler, "Pharmaceutical Botany in the U.S., 1900-1962: Its Heyday, Decline, and Renaissance" *Pharmacy in History* 38 (1996): 22.



Photos of the College of Pharmacy laboratories at the University of California taken in the late 1950s do not depict anything like the atmosphere of earlier decades that promoted the study of the entire plant. One now could find glass jars with the contents labeled “Digitalis” or “white pine syrup compound” or “wild cherry syrup (*Prunus virginiana*),” with Latin names sometimes in parentheses, but botanical illustrations no longer hung on laboratory walls.<sup>67</sup> Pharmacy students studied plant constituents in pharmacy lab courses, but the actual plant was not featured in the course objectives. Pharmacy labs now stocked only prepared remedies and isolated chemicals for laboratory instruction. Then, in 1962 and in accord with the lessening

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<sup>67</sup> “Foreground - Robert M. Childers - Class of 1958, Biopharmaceutical Lab,” 1958, box 28, folder 14, Robert Day Collection; “8th Floor Compounding Lab,” undated, box 28, folder 14, Robert Day Collection; Misc. photographs, undated, box 36, Robert Day Collection.

relevance of crude plant drugs and their structures in pharmaceutical education, the pre-pharmacy curriculum no longer listed botany as a requirement for entry into the College of Pharmacy.<sup>68</sup>

In 1966, Pratt opted to remove plant history from the pharmacognosy course and instead only focused the class on the physico-chemical products of plant and animal origin.<sup>69</sup> This last-ditch effort to retain interest in pharmacognosy failed, however, and in 1971, the College of Pharmacy at San Francisco no longer required pharmacy students to take pharmacognosy. The course did retain its presence in the annual announcement of courses, but only as an elective.<sup>70</sup> The 1974 announcement featured the last listing of the pharmacognosy and powdered vegetable courses.<sup>71</sup> Pratt retired the following year, and, as no instructor replaced him, no one was left at the institution to champion for the relevance of plant-focused disciplines.

Botany and plant-focused courses like pharmacognosy lacked ideological compatibility with germ theory and the therapeutics and pharmaceutical sciences embraced thereafter. Emphasis upon whole-plant structure stagnated the disciplines and their methodologies eventually failed to garner enough support or attention from students and faculty to retain pharmaceutical botany courses. The therapeutic revolution of the twentieth century took place at an institutional level, as colleges of pharmacy redesigned the objectives of plant-based courses and restructured curricula to

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<sup>68</sup> *Announcement of the School of Pharmacy, 1962-1963* (San Francisco, CA: University of California, San Francisco, 1962), 16.

<sup>69</sup> *Announcement of the School of Pharmacy, 1966-1967* (San Francisco, CA: University of California, San Francisco, 1966), 33.

<sup>70</sup> *Announcement of the School of Pharmacy, 1971-1972* (San Francisco, CA: University of California, San Francisco, 1971), 28.

<sup>71</sup> *Announcement of the School of Pharmacy, 1974-1975* (San Francisco, CA: University of California, San Francisco, 1974), 24.

deemphasize training in plant disciplines. But ultimately, as modern therapeutics embraced isolated medicinal compounds, institutions in the United States dedicated to pharmaceutical education discarded the once-held fervor for botanical knowledge and the whole-plant approach that had historically characterized the study of pharmaceutical botany.

Professional medical institutions likewise started to reconsider the presence of crude plants and plant-derived drugs. The next chapter examines the transformative representation of these therapies within a major canon of American therapeutics, the *United States Pharmacopeia*.

## CHAPTER 2

# PHARMACOPEIA IN FLUX: REVISING ‘THE ART OF PREPARING’ PLANT-DERIVED DRUGS

Skim the pages of the first edition of *The Pharmacopoeia of the United States of America* and you will find well over a hundred plants and plant parts listed as medicines. Much has changed with the *Pharmacopoeia* since its inaugural printing in 1820. The name, for instance, has undergone two changes; first to the *United States Pharmacopoeia* and then to the *United States Pharmacopoeia-National Formulary*.

The publication started as an effort to consolidate and standardize the well-known drugs found in the many herbals and pharmacopoeia printed during the early nineteenth century; all of which were printed without professional consensus or discussion.<sup>72</sup> When compiling the first *Pharmacopoeia* in 1820, its contributors aimed to create national standards of strength, purity, and nomenclature for drugs in usage at the time. Up until that point, pharmaceutical knowledge of this kind was essentially disparate. So the *USP* created a national cohesion in allopathic medical practice for how to dose, prepare, and name pharmaceuticals. Professionalization of medicine was

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<sup>72</sup> Joseph M. Gabriel, *Medical Monopoly: Intellectual Property Rights and the Origins of the Modern Pharmaceutical Industry* (Chicago IL: The University of Chicago Press, 2014), 40. For a thorough look at the organizing the first printing of the *Pharmacopoeia*, see Glenn Sonnedecker's three-article series that details the influence of European pharmacopoeias on generating interest for an American pharmacopoeia; how elite medical doctors managed to organize an American pharmacopoeial project; the meeting procedures for generating the first edition of the *Pharmacopoeia*. Glenn Sonnedecker, "The Founding Period of the U.S. Pharmacopoeia: I. European Antecedents" *Pharmacy in History* 35, no. 4 (1993): 151-162. Glenn Sonnedecker, "The Founding Period of the U.S. Pharmacopoeia: II. A National Movement Emerges" *Pharmacy in History* 36, no. 1 (1994): 3-25. Glenn Sonnedecker, "The Founding Period of the U.S. Pharmacopoeia: III. The First Edition" *Pharmacy in History* 36, no. 3 (1994): 103-122.

another goal in compiling the *USP*.<sup>73</sup> So its founders emphasized scientific criteria when designing the language and content for each drug. The book reflected medical practice and it was meant to only be intellectually accessible by those formally trained in allopathic medicine.

Today the *USP* functions in much the same manner; as a reference for quality, purity, and identity of those drugs considered essential for contemporary medical practice; as determined by scientists, physicians, and other medical practitioners who use them. The one major change since 1820 is that as of 1906, with the Pure Food and Drug Act of 1906, the federal government began to recognize the *Pharmacopeia* as the “official” and legal record of modern drugs.

Likely the most noticeable of all its changes over the last two centuries, the *Pharmacopeia*’s content has dramatically evolved; from simple lists of common names accompanied by short descriptions in Latin; to lengthy monographs of precise chemical formulas and assays, lists of known impurities, as well as detailed specifications on quality, storage, and dosages. Monographs are the organizational equivalent of an encyclopedic ‘entry.’ Each monograph contains a set of information dedicated to one specific drug. The quantity of monographs has increased substantially since 1820, from 219 to almost 5,000 monographs. And new drugs are suggested for addition with each new revision and supplemental printing.

The *USP-NF* undergoes constant revision. Since its first printing, volunteer (and later, paid) scientists and medical practitioners have endlessly endeavored to tweak

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<sup>73</sup> Jan McTavich, *Pain and Profits: The History of the Headache and Its Remedies in America* (New Brunswick, NJ: Rutgers University Press, 2004), 86-89.

preparations and fine-tune dosages; to rename and reorganize; to vote in new drugs and vote out ones no longer considered relevant. These revision activities take place within subcommittees dedicated to certain aspects of the *USP-NF*. For example, nomenclature and labeling, statistics, monographs of chemical medicines, or botanical dietary supplements and herbal medicines each have a dedicated subcommittee.. And while the exact landscape of subcommittees has changed over time, each of these expert committees reports their findings to the Committee of Revision, which is responsible for then compiling all the updated drug information into a final version for print. Up until 1942, the United States Pharmacopeial Convention printed each *USP* as a decennial revision; then a quinquennial revision; and by the early twenty-first century, the *USP-NF* had a new revision printed annually.

Each revision of the *USP*, from 1820 to today, offers a static moment of insight into a body of knowledge otherwise characterized by constant learning, innovation, and change. When comparing each successive edition of the *Pharmacopeia*, with a focus specifically on crude plants and their derivatives, a pattern of representation emerges that speaks volumes about the reputation of those drugs in American medicine over the course of two centuries. Plant-derived drugs very much faded from their once-held prominence to a point where they are hardly recognizable. Though they are definitely still there, the representation of crude plant drugs and their derivatives has become minimal.

Robert N. Proctor's concept of agnotology proves useful in characterizing the overall transformative representation of plant-derived drugs in the *Pharmacopeia*. Agnotology, a term that Proctor promulgates for the cultural production of ignorance,

includes three variants of ignorance. The first variant of agnotology is ignorance as native state. This is the ignorance that everyone is born with, and Proctor describes it as a condition that you move away from as you engage with the world around you. The second variant of agnotology, ignorance as lost realm or selective choice (or passive construct), describes the missed opportunities of knowledge and lost knowledge. For example, by persuing one avenue of inquiry, a researcher by default ignore another avenue. Or, the second variant could account for forgotten knowledge as a by-product of new knowledge. The third variant of agnotology is ignorance as active construct. In this variant, a person or an institution actively either withholds knowledge or releases incorrect knowledge as truthful; as a mean to keep factual knowledge from the intended person(s).<sup>74</sup>

The second variant, ignorance as lost realm, characterizes the manner by which the *Pharmacopeia* featured less and less plant-derived medicines over time; but also, to the resulting lost knowledge of those plant-derived medicines. By removing printed medical knowledge from a standardized medical record, over time those items removed are forgotten and create a realm of lost knowledge.

I argue that the shift of modern Western medicine from preferring crude drugs to preferring their chemical derivatives inadvertently made knowledge of herbal medicines unknown within the realm of allopathic therapies. No single, explicit decision prompted an agnotological dearth regarding the therapeutic potential of plants in allopathic medicine. But patterns of representation emerge throughout successive revisions of the

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<sup>74</sup> Robert N. Proctor, "Agnotology: A Missing Term to Describe the Cultural Production of Ignorance (and Its Study)" in *Agnotology: The Making and Unmaking of Ignorance*, Robert N. Proctor and Londa Schiebinger, eds. (Stanford, CA: Stanford University Press, 2008), 6-8.

*United States Pharmacopoeia* to disassociate chemical compounds from their botanical origins, to reclassify plant-derived drugs as inactive, and to remove the monographs of plant-derived drugs altogether.

The Pharmacopeial Convention committees collectively consider many kinds of edits for each *USP* revision, but this chapter focuses on three specific manners of revision. We will explore historical revision of content within a monograph. We will look at reclassifying an entry's drug category or function. And finally, we will consider the removal of monograph entries voted out. Important to remember, all three of these manners of revision have agnotological implications for the knowledge of plant-derived medicines.

## **Revision of Monograph Content**

During the nineteenth century, plant-derived drugs existed as a mainstay in American medicine, but a new industry took over the manufacture of these remedies used by the allopathic practitioner. The production of galenicals increasingly shifted away from the duty of the pharmacy shop keeper, instead becoming a primary manufacturing focus of the burgeoning pharmaceutical industry. Historian David L. Cowen offers that in order for that shift to have taken place, drug manufacturing

companies had to produce medicaments of a quality and efficacy high enough to wedge their products into the marketplace as a reliable and equivalent replacement.<sup>75</sup>

Initially, the pharmaceutical industry produced two major types of plant-derived drugs: fluidextracts and vegetable alkaloids. Fluidextracts come from a generally simple preparation where crude plant materials are soaked in alcohol for a given length of time to make a concentrated solution. While soaking, the plant matter releases into the alcohol its water-soluble components, very much aligned with the process of making a tea, except using alcohol as the solvent. Remove the plant material once it has soaked long enough, and the resulting solution is a fluidextract.

Fluidextracts were inherently imprecise in content, as any and all water-soluble lipids could escape the plant material to the ethanol solution. In fact, they were designed to be liquid substitutes of the whole-plant drug. The 1919 edition of *The Pharmacopoeia of the United States* defined fluidextracts as “bearing a uniform relation to the drug used so that *one mil* of the fluidextract closely represents the activity of *one gramme* of the air-dried and powdered drug of standard quality.”<sup>76</sup> Named simply after the plant from which they are derived -- Fluidextract of Cascara Sagrada, Fluidextract of Aconite, and Fluidextract of Ergot, for example -- fluidextracts contained all the secondary plant metabolites of their plant source; not simply the target active ingredient that would have produced a particular desired effect.

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<sup>75</sup> David L. Cowan, “The Role of the Pharmaceutical Industry” in *Safeguarding the Public: Historical Aspects of Medical Drug Control*, John B. Blake, ed. (Baltimore, MD: The Johns Hopkins Press, 1970), 72.

<sup>76</sup> The United States Pharmacopoeial Convention, *The Pharmacopoeia of the United States of America, Ninth Decennial Revision* (Philadelphia, PA: P. Blakiston’s Son & Company, 1916), 173.

Vegetable alkaloids, on the other hand, are isolated and purified chemical compounds, either derived from plant material or synthetically manufactured in the likeness of the natural compound. Morphine, strychnine, and atropine, for example, are vegetable alkaloids. They are named, as the pattern indicates, with an -ine suffix.

The shift of modern Western medicine from preferring crude drugs to preferring their chemical derivatives inadvertently made knowledge of herbal medicines disappear from the realm of allopathic therapies. Though no explicit decision disassociated chemical compounds from their botanical origins, patterns of representation emerge throughout revisions of the *United States Pharmacopoeia* indicating less interest in and relevance of that origin.

To clarify an important point for this chapter, phytochemicals include both those compounds produced naturally by living plant material and those compounds created synthetically in a laboratory which are modeled on their natural counterpart. Inspiration to create the latter would not exist without knowledge of the former. Therefore, discussion of plant-derived chemical compounds and their USP monographs do not take into account whether or not a particular compound would be natural or synthetic. The focus here is instead on the precise content of USP monographs; whether the derivatives of phytochemicals were represented as such or if the association with their botanical origin was omitted.

Before the United States Pharmacopoeial Convention acquired the *National Formulary* and combined the two publications into the *USP-NF* in 1980, each item listed in the *USP*, regardless of its therapeutic function as an active or inactive ingredient, had its own monograph. Monographs in the *USP* have a history of their own, as the content

evolved from the simple recipes of early editions to the increasingly thorough descriptions and precisely measured preparations of more contemporary revisions. Monographs of chemical compounds produced early on in *USP* revisions made explicit mention of their botanical sources. In the mid-twentieth century, monographs of newer chemical compounds which had been derived from phytochemicals began to exclude that association to botanical origin. Though the precise motivations or reasoning for removal of botanical origin is unclear, it is possible that this shift in content reflected a shift toward modernity, which will be discussed further in the third section of this chapter.

Mentioning botanical origin within the description of any and all plant-derived compounds had been a matter of tradition. Around the 1930s, some voices from within the pharmaceutical industry started to question the necessity of that practice. In a letter sent to the Committee of Revision in 1934, a representative of Merck & Co. Inc. challenged listing the botanical origin for ephedrine and ephedrine sulphate:

*Definition of source.- Is it necessary to give the source of the alkaloid? The synthetic alkaloid is excluded by its being optically inactive and also by its somewhat different melting point. In my opinion the source should not be give (sic). The Swiss Pharmacopieia (sic) doesn't give it, and the structural formula will show what it is.  
[...]*

*Ephedrine Sulphate*

*My comments about the definition of the source, made under Ephedrine, apply to this salt too.<sup>77</sup>*

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<sup>77</sup> Letter to Dr. George D. Beal from Joseph Rosin, dated July 30, 1934. Box 105, Folder 22, United States Pharmacopeial Convention Records, 1819-2005 (bulk 1900-2005), Wisconsin Historical Society, Madison, WI (hereafter cited USPCR).

By the mid-twentieth century, monographs of newly developed derivatives started to omit the former explicit association to its botanical origin. Ergotamine maleate and ergotamine tartrate, both derivatives of ergot added to the *USP* in 1942, lacked any mention of their botanical origin in the 1950 revision. In its first appearance in the *USP*, also in 1950, cocaine hydrochloride was described as “colorless crystals, or as a white, crystalline powder.”<sup>78</sup> No explicit link was made to either its plant or alkaloid source.

Some monographs of derivatives of plant-derived compounds even started to omit any association to their alkaloidal source. In the 1926 revision, ethylmorphine hydrochloride’s monograph described the drug as “a synthetic alkaloid prepared from morphine by ethylation.”<sup>79</sup> By the 1940s, drafts for the drug circulated around the Revision of Committee that lacked mention of morphine as its source.<sup>80</sup>

With regard to those monographs dedicated to crude plant drugs, the content changed very little. But the monographs dedicated to the derivatives of crude plant drugs offer more insight as revisions progress throughout the twentieth century. As derivatives increased in complexity throughout the twentieth century, moving away from tinctures and oils of medicinal plants and their isolated alkaloids, toward salts and hydrochlorides and more modern preparations, monograph revisions placed less and less emphasis on any association to a plant source or origin.

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<sup>78</sup> The United States Pharmacopeial Convention, Inc., *Pharmacopeia of the United States of America, Fourteenth Revision (USP XIV) and the First USP XIV Supplement* (Easton, PA: Mack Printing Company, 1950), 146.

<sup>79</sup> The United States Pharmacopeial Convention, *The Pharmacopeia of the United States of America, Tenth Decennial Revision (USP X)* (Philadelphia, PA: J.B. Lippincott Company, 1926), 37.

<sup>80</sup> “Ethylmorphine Hydrochloride,” Box 98, Folder 11, USPCR.

Analysis of the evolving pharmaceutical compendia that comprise the many revisions of the United States Pharmacopoeia reveals a mixed representation of crude drugs and their derivatives. Sometimes the text establishes a very clear relationship between crude drug, its target alkaloid, and the chemical derivatives existent thereafter. Sometimes this clear relationship erodes in later revisions. In some cases, particular monographs of chemical derivatives never establish any relationship to the crude plant material from which the chemical derivative was isolated or obtained. The chemical derivatives of plant-derived alkaloids progressed further from their botanical origin, the representation of that once-apparent association between drug and natural origin dwindled. As derivatives increased in complexity, moving away from tinctures and oils of medicinal plants and their isolated alkaloids, and toward salts and hydrochlorides and more modern preparations, monograph revisions placed less and less emphasis on any association to a plant source or botanical origin. And this lost association created a loss of knowledge.

### **Revision of Drug Classification; Active to Inactive**

Historically, a single medicinal plant could have been utilized for multiple therapeutic functions. Balsam of Tolu, for instance, functioned as a stimulant, expectorant, vulnerary, and flavoring.<sup>81</sup> Gelsemium functioned as a nervine, antispasmodic, and sedative.<sup>82</sup> Cinnamon, in both its Ceylon and Saigon varieties,

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<sup>81</sup> John S. Wright, Francis A. Federer, and Harry W. Tuft. *A Guide to the Organic Drugs of the Ninth Revision of the United States Pharmacopoeia 1916, The Third Revision of the National Formulary, and a Few of the More Commonly Used Unofficial Drugs* (Indianapolis, IN: Eli Lilly & Company, 1917), 21-22.

<sup>82</sup> *Ibid.*, 64.

functioned as a carminative, astringent, stimulant, and flavoring.<sup>83</sup> But if a new drug performed a therapeutic function better than a crude plant drug, and then replaced that plant as the preferred therapy in medical practice, the plant may have remained in the *Pharmacopeia* because it continued to be useful for its other functions.

A handful of crude plant drugs that still remain in the *USP-NF* today are listed as active ingredients. Opium and digitalis, for example, for reasons unknown to myself, have yet to meet a revision committee that found these lacking therapeutic value. So these and a handful of other crude plant drugs remain in the *USP-NF*, even if now only their derivatives are used in contemporary medical practice. But the vast majority of crude plant drugs that once existed as active ingredients in the *Pharmacopeia* were re-categorized in the 1980 *USF-NF* as excipients, or inactive ingredients. This section overviews the transitional processes that centered around medicinal plants many times throughout the twentieth century; as medical knowledge shifted to reconsider and then forget the active therapeutic potential of many crude plant drugs.

The perceived value of drugs in the *Pharmacopoeia* exists along a constantly progressive pathway of pharmaceutical innovation and discovery. As preference for a particular therapy shifts away from a crude drug and toward its modern counterpart, that shift creates two circumstances. First, lost interest in a once-useful drug creates an agnotological potential to lose knowledge of the plant's historical therapeutic value. Second, that shift also created generational medical knowledge where standardized medical knowledge and medical practice did not necessarily align. The *USP* dealt with

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<sup>83</sup> John S. Wright and Arthur L. Walters. *A Guide to the Organic Drugs of the United States Pharmacopoeia 1900 and a Few of the More Commonly Used Unofficial Drugs*, Second Revision, with Appendix (Indianapolis, IN: Eli Lilly & Company, 1906), 32-33.

this latter circumstance, and its inherent confusion, by revising the *USP-NF* to specifically signify a drug's intended purpose.

Prior to the consolidation of the *USP and NF* in 1980, the *USP* listed all therapeutic ingredients, both active and inactive, without a formal protocol for distinguishing between the two. This imprecision in drug category, paired with generational knowledge of medicine, caused some confusion regarding the intended utility of certain drugs listed in the *Pharmacopeia*.

During the early 1940s, Dr. Heber W. Youngken chaired the *USP's* Subcommittee on Botany and Pharmacognosy, also referred to as Subcommittee No. 5. This subcommittee of the Committee of Revision focused all of their efforts on the monograph content for the medicinal plants listed in the *Pharmacopeia*, as well as the preparations derived therefrom. While Chairman of Subcommittee No. 5, Dr. Youngken kept ample correspondence with Dr. E. Fullerton Cook, the chairman of the Committee of Revision.

A letter between Drs. Cook and Youngken underlines the kind of confusion made possible by not making intended therapeutic function explicit:

*Dear Doctor Youngken:*

*Thank you for calling my attention to the Oil of Cinnamon listing in the Pharmacopoeia. I do not think this need give you any concern, for after all we are thinking primarily of the Cinnamon flavor.*

*The doctors did not consider it desirable to give a dose for Cinnamon, for I do not believe they would ever think of using it, excepting for its flavor, at least from the viewpoint of modern medical practice. Would not the oil have the same value as the bark from the therapeutic standpoint. The list of titles is in the U.S.P. largely as a medical guide related to basic drugs and preparations.*

Sincerely yours,  
E. Fullerton Cook<sup>84</sup>

Youngken was a foremost authoritative figure in the study of pharmaceutical botany. His textbooks were nationally recognized in pharmaceutical education as a standard for the discipline. And he had seasoned knowledge of cinnamon's therapeutic potential, as his own textbook listed the bark of both the Ceylon and Saigon species.<sup>85</sup> So when Youngken noticed that the cinnamon monograph omitted a safe dosage and presumed this drug must indeed need to include one, he likely did not imagine that this former multi-tasker had been reduced to perform a single intended function: flavoring.

Cinnamon, like many crude plant drugs in the twentieth century, existed for some time in an epistemological limbo; between the knowledge of what it could once do and the knowledge of what it could do moving forward. Until the generational knowledge gap caught up, cinnamon was simultaneously only a flavoring and also a carminative, astringent, and stimulant.

The *Pharmacopeia* reclassified some plant-derived titles before its major push for reorganization in 1980. Tannic acid, for example, was categorized as a reagent officially for the first time in 1950 edition of the *Pharmacopeia*; described as “yellowish to light brown, glistening scales, or an amorphous powder. It is odorless or has a faint, characteristic odor”; followed by a list of solubility in various kinds of liquids.<sup>86</sup> The newly reclassified ingredient now had no mention of its botanical origin. With the 1980

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<sup>84</sup> Letter dated September 10, 1942, Box 87, Folder 16, USPCR.

<sup>85</sup> Heber W. Youngken, *Pharmaceutical Botany* (Philadelphia, PA: P. Blakiston's Son & Company, 1914), 74.

<sup>86</sup> The United States Pharmacopeial Convention, Inc., *Pharmacopeia of the United States of America, Fourteenth Revision (USP XIV) and the First USP XIV Supplement* (Easton, PA: Mack Printing Company, 1950), 922.

revision, the Committee of Revision made a concerted effort to clearly differentiate active from inactive pharmaceutical ingredients.

Combining the *United States Pharmacopeia* and the *National Formulary* into the *USP-NF* involved a massive undertaking to consolidate and reclassify all of the items listed in both publications. The Convention overviewed its new organizational scheme for the *USP-NF*, noting that “the scope of both USP and NF has been changed, the *Pharmacopeia* now being limited to drug substances and dosage forms, and the *National Formulary* now being limited to pharmaceutical ingredients.”<sup>87</sup> Pharmaceutical ingredients, or excipients, include all of the therapeutically inactive ingredients, like reagents, buffers, dyes, and flavorings, used in the manufacture of medicines. Though excipients are essential for successful delivery of the active ingredient to patients, the *USP-NF* emphasized in its first printing that excipients have no therapeutic function and should be labeled as such. In regard to reagents, for example, the *USP-NF* specified that “listing of these reagents, including the indicators and solutions employed as reagents, in no way implies that they have therapeutics utility; furthermore, any reference to *USP* in their labeling shall include also the term “reagent” or “reagent grade.”<sup>88</sup>

Many plant-derived drugs that formerly existed in categorical ambiguity, co-mingling amongst active ingredients and inactive ingredients without distinction, were relegated to the pages of the *National Formulary*. Gum arabic and agar, cocoa and wild

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<sup>87</sup> United States Pharmacopeial Convention, *The United States Pharmacopeia - National Formulary, Twentieth Revision (USP XX-NF XV)* (Rockville, MD: United States Pharmacopeial Convention, Inc., 1980), 1199.

<sup>88</sup> United States Pharmacopeial Convention, *The United States Pharmacopeia - National Formulary, Twentieth Revision (USP XX-NF XV)* (Rockville, MD: United States Pharmacopeial Convention, Inc., 1980), 3.

cherry, were now labeled explicitly as excipients. A few titles like cardamom seed and caraway, which had been removed from the *Pharmacopeia* in the fifteenth revision, reappeared in the *USP-NF*; now as excipients. With the massive reorganization and reclassification effort on the 1980 *USF-NF*, many of the plant-derived titles that formerly functioned as therapeutic multi-taskers were now reclassified as inactive pharmaceutical ingredients. If any question remained as to their therapeutic value, their new label as an excipient made them officially and categorically incapable of functioning otherwise. Moreover, this kind of reclassification erased medical knowledge of former therapeutic function.

### **Revision of Entries; Both Added and Removed**

Tracing the presence of crude plant drugs and their derivatives in concurrent revisions of the *USP* clearly indicates that plant-derived drugs appeared less frequently with each revision. Long had the Committee of Revision focused its sights on the place of crude drugs and officinal preparations in the *USP*. Logically, since crude drugs originally accounted for such a large percentage of the entries, they would be under a considerable amount of scrutiny for any sort of revision. But as early as 1880, *USP* committees questioned the appropriateness of having crude plants listed in the *Pharmacopoeia* when physicians used their derivatives far more often than the crude plant material itself. This question of appropriateness, which hinged on frequency of use, prompted the Committee of Revision to start tabulating, as precisely as possible, just how frequently physicians prescribed crude plant drugs and their official

preparations. In a call to action entitled, “Alphabetical List of Pharmaceutical Titles,” the Committee of Revision hoped to gather three to six months of prescribing data, to be reported by any medical person willing to keep a systematic record; then collated and summarized as a statistical reference for the next revision of the *USP*.

In making their call to action in 1880, the Committee of Revision underlined two major lines of thought regarding plant-derived medicines:

*There are many titles in the list which will never, or but rarely, be met with prescriptions, for instance, crude drugs, such as Allium, Geranium, etc., etc. Yet, if it is found that the officinal preparations derived from such substances (Syrupus Allii, Extractum Geranii Fluidum, etc., etc.) are sufficiently used to warrant their retention in the pharmacopoeia, the corresponding crude drugs will probably, in all cases, have to be retained also.*<sup>89</sup>

By the late nineteenth century physicians rarely, if ever, prescribed crude plant drugs and instead preferred their derivatives and preparations.<sup>90</sup> But the above excerpt expressly concluded that featuring medicines derived from crude plants necessitated featuring the crude plants themselves in the pharmacopeia. And therein the passage points to a habit of linking a derivative to its botanical origin, regardless of whether the

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<sup>89</sup> “Alphabetical List of Pharmacopoeial Titles. From the U.S. Pharmacopoeia of 1880,” Box 33; Folder 14, USPCR.

<sup>90</sup> For an overview of the new therapies that garnered much attention of physicians around the 1860s and 1870s, see Joseph M. Gabriel, *Medical Monopoly: Intellectual Property Rights and the Origins of the Modern Pharmaceutical Industry* (Chicago, IL: The University of Chicago Press, 2014), 86-93. For insight on emergent medical perspectives on therapeutics in the 1870s, see John Harley Warner, *The Therapeutic Perspective: Medical Practice, Knowledge, and Identity in America, 1820-1885* (Princeton, NJ: Princeton University Press, 1997), 7.

crude plant material itself still had a presence in medical practice. Listing one begot listing the other; as a matter of fact.<sup>91</sup>

Into the twentieth century, as skepticism sharpened regarding the effectiveness of some crude plant drugs, some physicians readily criticized the fact that the *USP* continued to list particular medicinal herbs as having any therapeutic value. In a review of a proposed ninth revision of the *USP*, which would be printed in 1920, a professor of therapeutics at Yale University explained why not all the plants featured in the *USP* necessarily belong there:

*Placing lemon-peel in a legal position equal to that held by digitalis is like inviting the boy who takes your hat to a seat at the guest table with the president of a country; or like giving the laborer who digs the grave a seat in the chancel with the minister who reads the burial service; it is absurd. Shall drugs which are therapeutically valueless and whose activities are mythical and historical (such as marigold, saffron, condurango, etc.) appear in this supposedly scientific book of drugs found valuable in the year 1913?*<sup>92</sup>

Worth by association to its derivatives and worth by former glory no longer held up as sufficient reason to list a crude plant drug in the pharmacopeia. Voices from within medical practice now adamantly wanted only to see drugs listed that they *knew* had therapeutic value. They wanted to see only the drugs that they used; not

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<sup>91</sup> For more on the scientific notion of fact, see Barbara J. Shapiro, *A Culture of Fact: England 1550-1720* (Ithaca, NY: Cornell University Press, 2000). For insight on different types of knowledge as contributors of scientific fact, see D. Graham Burnett, *Trying Leviathan: The Nineteenth-Century New York Case That Put the Whale on Trial and Challenged the Order of Nature* (Princeton, NJ: Princeton University Press, 2007). As discussed by Shapiro and Burnett, fact has in no way remained a stagnant concept. Instead, a culture of fact constantly evolves to redefine what can constitute knowledge and who can contribute to knowledge. In matters of natural knowledge, or more specifically, medical knowledge of those natural objects utilized for medical practice, similar tensions manifest over fact as matter of tradition and fact as changing knowledge of therapeutic objects.

<sup>92</sup> Oliver T. Osborne, M.D. "The Absurdities and the Commercialism of the Proposed Ninth Decennial Revision of the of United States Pharmacopeia" *Journal of the American Medical Association* 60, no. 26 (June 28, 1913): 2039.

the drugs of generations prior. In the next few revisions of the *USP* throughout the mid-twentieth century, the Committee of Revision implemented a new standard for revising the American pharmacopeia: modernity as defined by therapeutic value.

On February 24 and 25 of 1947, the Subcommittee on Scope of the United States Pharmacopoeia met in Atlantic City, New Jersey to decide which drugs should remain, which drugs should be considered for inclusion, and which drugs should be removed from the fourteenth revision of the *USP*. The subcommittee carried out five sessions over their two-day stay at Haddon Hall, and their meeting's method featured somewhat of a departure from the historical collaborative synthesis of only *USP*-appointed members.

The fourteenth revision of the *Pharmacopeia* aimed to expand the usual process by including a mail-in questionnaire to be completed by physicians at medical schools as well as three hundred private physicians. These physicians all recorded their opinions on 1326 drugs; rating each as either essential, of high value, or questionable. And the USP Subcommittee on Scope took these opinions into consideration at their meeting in Atlantic City.

A news article that covered the revision meeting reached out to Dr. E. Fullerton Cook, chairman of the General Committee on Revision of the USP, for insight on the newly implemented survey system. The article summarized Cook's belief that the hundreds of mail-in questionnaires culminated "the most truly scientific effort in

pharmaceutical history to evaluate essential medicines of the world in terms of therapeutic effectiveness.”<sup>93</sup>

The transcribed proceedings of the two-day revision meeting in Atlantic City repeatedly showcased how the mailed-in surveys influenced the discussions and voting over the fourteenth revision. When discussing any particular drug, one of the attending physicians, Dr. Eggleston, would provide voting results from the mailed-in questionnaires. “On cinchophen, I call your attention to 4 considering it essential, 11 of high value, and 24 questionable.”<sup>94</sup> Note that the physicians who submitted a mail-in questionnaire did not vote on every single one of the 1326 drugs listed for review. They would have focused instead on those drugs with which they had experience and knowledge.

The experience and knowledge of each participating member of the General Committee on Revision informed conversations on which drugs should remain in the pharmacopeia and which new drugs should be considered for addition. Throughout the transcribed proceedings, the members posited one question repeatedly to keep them focused on their mission of revision -- Does this drug have therapeutic value? At no point in the transcribed proceedings did anyone at the revision meeting explicitly define the meaning of therapeutic value, but contextual implications reveal much about how to measure value. Consider, for example, the following discussion on eucalyptol, which purportedly had a value in dentistry and as an ingredient for cold treatments:

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<sup>93</sup> “Opinions Of 300 Experts Guide Scope Committee For USP XIV,” 1947, Box 236, Folder 12, USPCR.

<sup>94</sup> “Proceedings: Subcommittee on Scope of the United States Pharmacopoeia” February 24-25, 1947, Haddon Hall, Atlantic City, New Jersey (The Master Reporting Company), 30, Box 236, Folder 12, USPCR.

*DR. SMITH: How is eucalyptol used, Dr. Hill?*

*DR. HILL: It is used in some of the treatments of pulpless teeth and it is also used as an ingredient in mixing up root canal filling materials.*

*DR. SMITH: As an antibacterial agent?*

*DR. HILL: Yes.*

*DR. SMITH: Has it any real value, do you think?*

*DR. HILL: I think so. I think it has some value. We don't use it in our particular clinic, but I think it has a value, yes. I think it should be included.*

*CHAIRMAN BASTEDO: It would be just too bad if all these men who make the nasal sprays and drops couldn't use eucalyptol, wouldn't it?*

*DR. SMITH: And cough drops.<sup>95</sup>*

Therapeutic value equated to usefulness rather than to efficacy. Dr. Smith proceeds with the assumption of efficacy when he inquires about its purpose, and Dr. Hill answers that eucalyptol functions as an antibacterial agent. After they've established the drug's purpose, Dr. Smith continues to ask if the drug has any real value; meaning, is it useful beyond simply performing its intended function? Does anyone actually still use it? Dr. Hill's response that it has value even though *he* doesn't use it drives the point home. A drug has a place in the *USP* if it has therapeutic value -- determined by whether medical practitioners continue to use it -- regardless of whether the drug performs its intended therapeutic function.

As conversations continued in Atlantic City, members of the Convention posited the question of therapeutic value over and over. Even if a more modern therapy existed for certain purposes, if a crude plant drug, for example, still had ample interest amongst physicians, it found support for remaining in the *USP*:

*CHAIRMAN BASTEDO: [...] Peruvian balsam! That is apparently of great value.*

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<sup>95</sup> "Proceedings: Subcommittee on Scope of the United States Pharmacopoeia" February 24-25, 1947, Haddon Hall, Atlantic City, New Jersey (The Master Reporting Company), 76-77, Box 236, Folder 12, USPCR.

*DR. KRANTZ: For what?*

*DR. EGGLESTON: It is used on the skin very extensively.*

*CHAIRMAN BASTEDO: For bed sores and things of that kind.*

*DR. EGGLESTON: There are better methods of treating them.*

*CHAIRMAN BASTEDO: That may be, but that is why it is used a very great deal. I have seen marvelous changes when you got a little Peruvian balsam on a wound.<sup>96</sup>*

If a plant-derived drug had unquestioned value, it garnered a proportionate amount of discussion. When Chairman Bastedo announced salicylic acid for debate, not a single person had any comment to make, and the meeting moved along to the next drug on their debate list.<sup>97</sup> *Aspidium* and *aspidium oleoresin*, a species of male fern and its derivative with repute for the treatment of worms, also prompted very little conversation:

*DR. DOOLEY: It is the best thing for tapeworms, isn't it?*

*CHAIRMAN BASTEDO: It is a good thing for tapeworms.<sup>98</sup>*

But when it came time for the revision committee to discuss a drug with questionable value, where once-ample interest had waned, the committee members found ample points to consider in determining present-day therapeutic value:

*CHAIRMAN BASTEDO: Black mustard and mustard plaster--do they go in the Pharmacopoeia? What do you think, Dr. Brown?*

*DR. BROWN: I don't see much use for them, but I guess somebody does.*

*CHAIRMAN BASTEDO: This is what we would all say, I think. Mustard has its uses maybe. We possibly prefer Musterole or some combination*

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<sup>96</sup> "Proceedings: Subcommittee on Scope of the United States Pharmacopoeia" February 24-25, 1947, Haddon Hall, Atlantic City, New Jersey (The Master Reporting Company), 86-87, Box 236, Folder 12, USPCR.

<sup>97</sup> "Proceedings: Subcommittee on Scope of the United States Pharmacopoeia" February 24-25, 1947, Haddon Hall, Atlantic City, New Jersey (The Master Reporting Company), 92, Box 236, Folder 12, USPCR.

<sup>98</sup> "Proceedings: Subcommittee on Scope of the United States Pharmacopoeia" February 24-25, 1947, Haddon Hall, Atlantic City, New Jersey (The Master Reporting Company), 129-130, Box 236, Folder 12, USPCR.

*that isn't quite so potent a medicine. Dr. Smith would be offended if we did that.*

*DR. EGGLESTON: I think mustard plaster is still---*

*CHAIRMAN BASTEDO: The question would be black mustard. It comes in solely in relation to mustard plaster, doesn't it? Very well, do we want mustard plaster?*

*DR. SMITH: The dermatologists in Philadelphia at that meeting didn't feel mustard plasters were one kind of plaster that could or should be used. They recommended only one, and I have forgotten what that is.*

*CHAIRMAN BASTEDO: The dermatologists are pretty difficult to deal with. They are putting the kibosh on everything that has been good in the past because they get a reaction once in a while.*

*DR. BROWN: Am I wrong in thinking the dermatologists would have much use for a mustard plaster if they used it as a counterirritant to relieve pain or pleurisy or whatnot? The dermatologist doesn't get that close to disease.*

*DR. NICHOLS: That only came up because the subcommittee is one that covers related conditions and---*

*DR. SMITH: Isn't a good sedative or analgesic better to relieve pain in pleurisy than mustard plaster?*

*DR. EGGLESTON: There are some time when you don't want to use them.*

*DR. SMITH: Do without them.*

*DR. BROWN: It depends on whether you have the pain or not.*

*DR. EGGLESTON: The patient doesn't like that. I think a mustard plaster has a limited field of usefulness.*

*CHAIRMAN BASTEDO: You know, I am an old-fashioned doctor, too, and so I use a mustard plaster once in a while.*

*DR. EGGLESTON: Even Dr. Gold does.*

*CHAIRMAN BASTEDO: Well, that doesn't say that it ranks as a Pharmacopoeial preparation, does it, and that is what we have to decide now. Will you vote on it, gentlemen?<sup>99</sup>*

Black mustard and mustard plaster did not get voted into the fourteenth revision of the *United States Pharmacopoeia*. Eucalyptol, Peruvian balsam, salicylic acid, and aspidium did. Reviews of the fourteenth revision simply painted the removal of obsolete

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<sup>99</sup> "Proceedings: Subcommittee on Scope of the United States Pharmacopoeia" February 24-25, 1947, Haddon Hall, Atlantic City, New Jersey (The Master Reporting Company), 202-204, Box 236, Folder 12, USPCR.

drugs with a shade of modernity. A review in the *Journal of the American Medical Association* summarized the 1950 pharmaceutical compendium as follows:

*Although more than 100 drugs that appeared in the preceding edition have been deleted, the present edition is significantly larger than any of its predecessors. Alum, arsenic trioxide, calomel, mustard plaster, rhubarb, strychnine sulfate and other articles that certainly have a questionable place in modern day therapy have been rightfully replaced by such drugs as the antibiotics (aureomycin, chloramphenicol and streptomycin), the antihistaminics and the new antimalarial agents. Thus, the inevitable trend toward more rational therapeutics is evident and well recognized.*<sup>100</sup>

Crude plant drugs like rhubarb, once utilized for its purgative quality, and mustard plaster, once utilized as a remedy for chest congestion, no longer had a place in a modern pharmacopoeia. And with the removal of their monographs from the *Pharmacopoeia*, modern knowledge of therapeutic standards forgot about these and other plant-derived therapies.

Over the course of its almost two hundred years in print, the *USP* contributors have altogether removed many plant-derived drugs from its pages. Other plant-derived drugs faced a reclassification; from active to inactive ingredient, with knowledge of their historical therapeutic potential lost. And the derivatives that remain, they largely have lost explicit association to their botanical origin. Each of these instances of revision represents a shift to forget. Recalling again Proctor's concept of agnotology, where ignorance can be a product of knowledge lost, to quote Robert Proctor verbatim: "It may

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<sup>100</sup> "Review of *The Pharmacopoeia of the United States of America (The United States Pharmacopoeia). Fourteenth Revision (U. S. P. XIV) and First U. S. P. XIV Supplement*, By Authority of United States Pharmacopoeial Convention, Inc.," *Journal of the American Medical Association* 145, no. 7 (February 17, 1951): 529.

well be that no *decision* was ever made to ignore or destroy such knowledge.”<sup>101</sup> But as this chapter has examined, the successive revisions of the *United States Pharmacopeia* clearly indicate a marked agnotological loss of knowledge regarding plant-derived therapies.

In the early twentieth century, a drug’s worth was measured by whether or not medical practitioners still used it. Therapeutic value was defined as a measure of present interest.<sup>102</sup> And as interest faded, especially with regard to particular crude plant drugs, so too did their therapeutic value; and thereafter, so did knowledge of their therapeutic potential; until they were categorically reconceptualized as inactive, historical, mythical, or defunct.

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<sup>101</sup> Robert N. Proctor, “Agnotology: A Missing Term to Describe the Cultural Production of Ignorance (and Its Study)” in *Agnotology: The Making and Unmaking of Ignorance*, Robert N. Proctor and Londa Schiebinger, eds. (Stanford, CA: Stanford University Press, 2008), 8.

<sup>102</sup> For more insight on how therapeutic value has historically been defined, see Harry M. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990*. (Cambridge, UK: Cambridge University Press, 1997). Marks’ monograph traces the impact of regulation on perceptions of what constitutes an acceptable drug throughout the twentieth century. Though usefulness was an acceptable marker for therapeutic value up through the mid-twentieth century, new federal regulations redefined that marker later. Specifically, the FDA’s new requirement in 1970 for “adequate and well-controlled investigations” that implemented statistical evidence in order to determine drug safety and efficacy before entering the medical marketplace ushered in the statistical era of medicine.

## CHAPTER 3

### ‘VINE AND SCALPEL’: THE HISTORY OF WINE IN AMERICAN MEDICINE

*“Now that we are again committing ourselves to our substantial purposes, after taking stock of our twenty-five years of pleasant effort together, let us resolve together:*

- a) To use wines wisely, moderately, and cheerfully ourselves, and encourage others to do likewise;*
- b) To do our best professionally to spread sound knowledge among our people of the health values of wine; and*
- c) To encourage our vinters to keep the art with care, so that the wines we drink may honestly be as healthy for us as we ever hope them to be.”*

*-- Dr. Chauncey D. Leake,*

1964<sup>103</sup>

Historians of medicine and historians of wine have thoroughly explored the history of wine as a therapy. Historians of wine Salvatore Lucia, P.A. Norrie, and Harry Paul, in particular, have collectively traced therapeutic practices surrounding wine from antiquity to the ‘French paradox’ in the 1980s.<sup>104</sup> This chapter brings the history of wine as therapy to a contemporary moment and explores the presence of wine in allopathic

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<sup>103</sup> Chauncey D. Leake, PhD, “The Record of Twenty-Five Years” (address, 64th Quarterly Dinner Meeting of the Society of Medical Friends of Wine, San Francisco, CA, January 9, 1964). In *Bulletin of the Society of Medical Friends of Wine* 6, no. 1 (February 1964): 6.

<sup>104</sup> See P.A. Norrie, “The History of Wine as a Medicine,” in *Wine: A Scientific Exploration*, eds. Merton Sandler and Roger Pinder (New York, NY: Taylor + Francis Group, 2003) for a sweeping overview of wine’s global therapeutic applications since the start of viticulture around 7000 BC.; including a list of contemporary clinical and laboratory research on wine’s therapeutic potential. For a more thorough history of wine in medicine, from antiquity to its eclipse in the early twentieth century, see Salvatore P. Lucia, M.D., *A History of Wine as Therapy* (Philadelphia, PA: J.B. Lippincott Company, 1963). For European-centric applications and research since the nineteenth century, see Harry W. Paul, *Bacchic Medicine: Wine and Alcohol Therapies from Napoleon to the French Paradox* (New York, NY: Editions Rodopi B.V., Amsterdam, 2001). The ‘French Paradox’ refers to epidemiological research conducted in the late 1980s that revealed low instances of coronary heart disease in French populations despite their cultural inclination to divulge in habits typically thought to cause coronary heart disease; ie, consuming large amounts of foods high in saturated fats. The paradox led to many hypotheses, one of which being that wine consumption possibly mitigates damage to coronary heart health.

medicine within the context of broader and evolving social concerns over alcoholism since the late eighteenth century.

Wine as a plant-derived therapy has roots in antiquity. And though its medical application today is far from official, modern medical ideology continues to consider its therapeutic potential. Who, for example, has not heard that a glass of wine is likely beneficial to cardiac health.

Professors of epidemiology and public health, Martin Bobak and Michael Marmot, have gone so far as to claim, “the notion that wine is protective against heart disease has become part of conventional wisdom.”<sup>105</sup> And yet, wine eludes official recognition as a therapeutic option in the modern American medical compendium. This chapter examines the historical context that has facilitated that modern disconnect between conventional wisdom and medical knowledge.

When it comes to medical advice, the therapeutic potential of fermented grapes and grape skins hides in plain sight. And wine remains one of the few plant-derived medicaments to still exist today; unchanged in form throughout its historical usage. However, and as with medicinal brandy and medicinal whiskey, social concerns surrounding alcohol abuse have drastically shaped the place of medicinal wine in modern American medicine.

Wine, hops, brandy, and whiskey each have had tenure in the *United States Pharmacopoeia*. And while none of them today remain the *United States Pharmacopoeia-National Formulary*, each has had a unique history in American

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<sup>105</sup> M. Bobak and M. Marmot, “Wine and Heart Disease: A Statistical Approach,” in *Wine: A Scientific Exploration*, Merton Sandler and Roger Pinder, eds. (New York, NY: Taylor + Francis Group, 2003), 92.

allopathic medicine. This chapter will focus on wine primarily. However, since wine contains alcohol, its place in medicine has followed a largely similar trajectory as other alcohol-containing therapies.

Wine's trajectory in the *United States Pharmacopoeia* is also similar to most other plant-derived therapies -- it was present initially, then later it wasn't. But wine specifically differs from most other plant-derived therapies, as well as from other ethanol-containing therapies. Even after its removal from the *Pharmacopoeia*, and ever since the repeal of Prohibition, an undercurrent of physicians and scientists have facilitated ongoing studies on the therapeutic potential of wine and those components found therein which are derived directly from wine grapes.

In particular, a Bay Area group called The Society of Medical Friends of Wine formed just after the repeal of Prohibition to fund and promote research on medicinal wine. Important to note, this wine society is an exception. Relative to the sum of American medical practitioners, the society represents a small tangent of interest in wine grapes that persevered in their mission to discover, with modern laboratory science, what made wine therapeutically adept. And often times, as this chapter will show, their mission operated in direct opposition to broader cultural and legal circumstances that keep wine, and alcohol in general, outside of the accepted allopathic pharmaceutical compendium and the supported scientific competence.<sup>106</sup>

This chapter will start with a review of alcohol-containing drugs in American medicine and their therapeutic applications. Thereafter, the chapter's scope broadens to

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<sup>106</sup> For a critique along these lines of scientific competence, see Pierre Bourdieu, "The Specificity of the Scientific Field and the Social Conditions of the Progress of Reason," *Sociology of Science* 14 (December 1, 1975): 19-47.

consider the impact of Temperance ideology on wine's official status as a medicament. And finally, this chapter considers the aspect of wine which makes its medicinal history unique: constant research since the 1930s that utilized modern laboratory and clinical techniques to explain the potential health benefits for which wine had been consumed since antiquity.

## **Alcohol and Wine in Orthodox Medicine**

Within the United States, all of your basic alcoholic beverages or their key ingredients found a spot in the *Pharmacopoeia of the United States* or its immediate predecessors in the early nineteenth century. Hops, for example, appeared in *American Medical Botany*, Jacob Bigelow's three-volume collection on native medicinal plants. Bigelow, a regular physician and botanist, practiced both disciplines after a formal education at Harvard University and the Perelman School of Medicine at the University of Pennsylvania. Bigelow offers that many physicians utilized hops, that critical ingredient for beer making, for its sedative properties. A possibly common practice held that "a pillow of hops [was] thought instrumental in procuring sleep."<sup>107</sup>

In 1850, sherry (*Vinum Xericum*), port (*Vinum Portense*), whiskey (*Spiritus Frumenti*), and brandy all had their own monographs added to the *United States Pharmacopeia*. And by 1883, the *Pharmacopeia* added a series of wines, or vini, to its

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<sup>107</sup> Jacob Bigelow, M.D., *American Medical Botany, Being a Collection of the Native Medicinal Plants of the United States, Containing Their Botanical History and Chemical Analysis, and Properties and Uses, in Medicine, Diet and the Arts, with Coloured Engravings, Vol. III* (Boston, Mass.: Published by Cummings and Hilliard, At the Boston Bookstore, No. 1, Cornhill. University Press....Hilliard and Metcalf., 1820), 171.

pages as well. In addition to its place as a standard for everyday orthodox medicine, alcohol has had an ever-present history within American military medicine.

During the nineteenth century, whiskey especially found its way into the portable, medical supply panniers and instrument bags of army doctors as an aid for battlefield pain management. Doctors in military hospitals treated soldiers and infants alike with dosages of sherry wine, port wine, champagne, and brandy; all of which were utilized for their inherent stimulating effect.<sup>108</sup>

Historian Anton Sohn notes that alcohol was a popular ingredient for home remedies on the Western frontier in the mid-nineteenth century. Different kinds of alcohol especially served in the making of bitters and elixirs, both homemade and commercially prepared. Hostetter's Bitters, for example, contained 32 percent alcohol and an assortment of herbs.<sup>109</sup> And some bitters utilized wine as their solvent, as with Bininger's Wine Bitters and Mercado & Seully's California Wine Bitters.<sup>110</sup>

Both red and white wines could be employed as solvents for roughly a dozen or so medicinal preparations. Some of the *Vinum Medicata*, or medicated wines, consisted of wine mixed with various other pharmacopeia drugs like opium or fluidextract ergot;

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<sup>108</sup> Anton P. Sohn, *A Saw, Pocket Instruments, and Two Ounces of Whiskey: Frontier Military Medicine in the Great Basin* (Spokane, WA: The Arthur H. Clark Company, 1998), 92-93.

<sup>109</sup> Anton P. Sohn, *A Saw, Pocket Instruments, and Two Ounces of Whiskey: Frontier Military Medicine in the Great Basin* (Spokane, WA: The Arthur H. Clark Company, 1998), 93.

<sup>110</sup> Though these are typically categorized as patent medicines, historian Joseph Gabriel reminds us that the herbal ingredients found in patent medicines often were identical to those used in the preparation of orthodox medicine. Of course, wine would be no different. Joseph M. Gabriel *Medical Monopoly: Intellectual Property Rights and the Origins of the Modern Pharmaceutical Industry* (Chicago, IL: University of Chicago Press, 2014), 265.

other preparations called for wine with extract of beef or tincture of iron. Wine was primarily utilized in these preparations for its stimulating property.<sup>111</sup>

**WINE, RED—*Vinum Rubrum*.**

An alcoholic liquid made by fermenting the juice of fresh colored grapes, the fruit of *Vitis vinifera* Linné (nat. ord. *Vitaceæ*), in the presence of their skins.

*Constituents*—Alcohol, water, sugar, tannin, potassium bitartrate, calcium tartrate, acids, coloring matter, etc.

*Use*—Chiefly as a sti.

1—*Vitis vinifera* Linné—A climbing woody shrub.

*Range*—Asia; cultivated throughout the world in the temperate zone.

**WINE, WHITE—*Vinum Album*.**

An alcoholic liquid made by fermenting the juice of fresh grapes, the fruit of *Vitis vinifera* Linné (nat. ord. *Vitaceæ*), free from seeds, stems, and skins.

*Constituents*—Alcohol, sugar, water, acids, tannin in small quantities, etc.

*Use*—Chiefly as a sti.

[See Wine, Red.]

Excerpt from *A Guide to the Organic Drugs of the United States Pharmacopoeia 1890*. Both red and white wine are listed as therapeutic ingredients, with their uses narrowed to “chiefly as a sti.,” or stimulant.<sup>112</sup>

Wine has had a distinct history as a therapy within the American medical compendium. But despite the therapeutic benefits that stem from its plant-derived

<sup>111</sup> *A Guide to the Organic Drugs of the United States Pharmacopoeia 1890*, John S. Wright, ed. (Indianapolis, IN: Press of Eli Lilly & Company, 1895), 88.

<sup>112</sup> *A Guide to the Organic Drugs of the United States Pharmacopoeia 1890*, John S. Wright, ed. (Indianapolis, IN: Press of Eli Lilly & Company, 1895), 88.

components -- the polyphenols, anthocyanin pigments, and propionaldehyde from the wine grapes, for example -- the alcohol in wine determined wine's trajectory to follow that of other alcohol-containing therapies. Progressive-era social and cultural opinions regarding alcohol consumption, and well as legal restrictions put in place during Prohibition, degraded the status of wine as a therapeutic option.

### **Alcohol as America's Evolving Drug Problem**

Historian Harry Gene Levine offers that the perception of alcoholism as a disease and an understanding of the addictiveness associated with consuming alcohol dates to the eighteenth century.<sup>113</sup> The difference between perceptions of alcoholism during the Temperance Movement and during the post-Prohibition era deals with whom or what is thought to be responsible for it. Leading up to Prohibition, popular understanding held that alcohol itself was inherently addictive; hence the wet-dry axis of controversy. Belief held that if alcohol was consumed, the user was likely facing an impending battle with alcoholism. So best to not partake in its consumption.

By the late eighteenth and early nineteenth centuries, social concern over rampant alcohol consumption emanated from the urban centers on the east coast to the frontier settlements and military camps scattered toward the west. Historian Anton Sohn notes that alcoholism was rife throughout frontier military posts as soldiers battled the

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<sup>113</sup> Harry Gene Levine, "The Discovery of Addiction: Changing Conceptions of Habitual Drunkenness in America" *Journal of Studies on Alcohol* 39 (1978): 143-174.

boredom, loneliness, and anxiety that manifested from their unsettled surroundings.<sup>114</sup>

But in burgeoning east-coast cities like Philadelphia, populations saturated with alcohol abuse, observed in closer proximity by concerned social elite, inspired medical practitioners to take up the alcohol problem themselves.

American physicians have long played an integral role in shaping social and cultural understanding of alcohol consumption; especially in regard to defining compulsive consumption and its debilitating physiological effects.<sup>115</sup> Beginning in the late eighteenth century, concerns of the elite over the social decay of poverty-stricken citizens and their high rates of alcohol consumption, garnered the attention of the medical practitioners. And by the early nineteenth century, this social response to the rampant alcohol abuse in the early Republic prompted Philadelphia physicians to study and define delirium tremens.<sup>116</sup>

Author Eric Burns claims that “the term ‘delirium tremens,’ if not the actual condition, seems to have made its American debut at about the same time that the first Temperance groups were warning people about the horrible consequences of alcohol.”<sup>117</sup> Articles printed in the *Scientific Temperance Journal* claimed that alcohol contributed to the onset of tuberculosis and that large amounts of alcohol [temporarily]

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<sup>114</sup> Anton P. Sohn, *A Saw, Pocket Instruments, and Two Ounces of Whiskey: Frontier Military Medicine in the Great Basin* (Spokane, WA: The Arthur H. Clark Company, 1998), 134-135.

<sup>115</sup> Sarah W. Tracy, *Alcoholism in America: From Reconstruction to Prohibition* (Baltimore, MD: The Johns Hopkins University Press, 2005), especially chapter one, entitled “Disease Concept(s) of Inebriety.”

<sup>116</sup> For a history of how American physicians in the eighteenth and nineteenth century defined delirium tremens and influenced the temperance movement, see Matthew Warner Osborn, *Rum Maniacs: Alcohol Insanity in the Early American Republic* (Chicago, IL: The Chicago University Press, 2014).

<sup>117</sup> Eric Burns, *The Spirits of America: A Social History of Alcohol* (Philadelphia, PA: Temple University Press, 2004), 64.

injured the eyes' ability to distinguish shades of green and red.<sup>118</sup> And all the while, the fact remained that, alcoholic beverages had been part of the American medical compendium since its colonial settlement.<sup>119</sup> Toward the end of the Progressive Era, the controversy over alcohol consumption started to displace wine's status in the American pharmacopoeia.

The early twentieth century hosted an entangled understanding of alcohol's place in medicine and of how it affected the body. While some physicians would prescribe wine as a treatment for anything, the Temperance movement readily linked alcohol to degenerative disorders and an increased likelihood of developing certain diseases. Wine historian and physician Phillip Norrie offers that, within the United States, the Temperance movement had eroded wine's position as a trusted medicine.<sup>120</sup> The ninth revision of the *United States Pharmacopeia* removed all preparations of medicated wines from its contents, instead recommending that simply ethanol be employed instead:

*The class of preparations known as "Wines" has not been included in this revision. Wine as a menstruum or solvent can with advantage be replaced*

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<sup>118</sup> "The Connection Between Alcoholism and Tuberculosis" *Scientific Temperance Journal* 28 (Spring 1919): 44. And Hugo Schulz, "The Effect of Alcohol Upon Ability to Distinguish Colors" *Scientific Temperance Journal* 28 (Autumn 1919): 123-125. It should be noted that the scientific rigor of the *Scientific Temperance Journal* could absolutely be scrutinized. The journal was published by the Scientific Temperance Foundation, which had Christian-centric undertones in their journal articles. And though the publishers may not have had formal training in medical sciences, they did tend to cite those who did. But their citations of medical journals like *The Lancet* and of researchers at the Yale Psychological Laboratory, for example, introduced a message of alcohol abstinence that may or may not have always been present in the original research. That said, journals like the *Scientific Temperance Journal* garnered momentum for the Temperance movement; regardless of their scientific rigor.

<sup>119</sup> Eric Burns overviews the many colonial applications of various wines, liquors, and beers for ailments like scurvy, colic, cholera, the shakes, headaches, sore muscles, and snake bites; but also, its presence in childbirth 'to keep up [the mother's] spirits through the long ordeal.' Eric Burns, *The Spirits of America: A Social History of Alcohol* (Philadelphia, PA: Temple University Press, 2004), 30-33.

<sup>120</sup> P.A. Norrie, "The History of Wine as a Medicine" in *Wine: A Scientific Exploration*, Merton Sandler and Roger Pinder, eds. (New York, NY: Taylor + Francis Group, 2003), 46.

*by alcohol of various strengths, and the uncertainties, due to the variability in quality and alcoholic content of the wines of commerce, are avoided.*<sup>121</sup>

Even though wine was removed from the *United States Pharmacopoeia*, its use as a medicine continued throughout Prohibition. But Prohibition-era legislation required that wine and other medicinal alcohols could only be manufactured and prescribed under formal monitoring constraints. The California wine industry continued to grow grapes, but each harvest, the grapes were slated for bottles of medicinal wine and sacramental wine.

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<sup>121</sup> *The Pharmacopoeia of the United States of America, Ninth Decennial Revision* (Philadelphia, PA: P. Blakiston's Son & Company, 1916), xxxvi.



Loading "gondola" R.R. cars to haul grapes to winery to make sacramental and medicinal wines, Guasti, Calif., 1923.<sup>122</sup>

The Volstead Act made exceptions for medicinal wine to be obtained by two legal means: under the supervision of a physician or by prescription written by a licensed physician, dentist, or veterinarian and then filled at a pharmacy. The former option would have been technically restricted to in-office use, where the patient would

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<sup>122</sup> Philip Brigandi. Loading "gondola" R.R. cars to haul grapes to winery to make sacramental and medicinal wines, Guasti, Calif. 1923. Library of Congress Prints and Photographs Division, Washington, D.C. [www.loc.gov](http://www.loc.gov).

consume it only under the direct observation of the prescribing doctor. Though, Lucia offers that in-office use may not have always happened in practice, as physicians prescribed wine “more often for festive than for therapeutic purposes.”<sup>123</sup> J.M. Doran, the Commissioner of Prohibition, described the alcohol-acquirement process for permit-carrying medical practitioners during Prohibition:

*“Applications, Form 1410, for medicinal whiskey or alcohol for office use may be executed by doctors, dentists, and veterinarians holding “J”, permits at any time now, and may be delivered to the vendors named therein and held by them...”*<sup>124</sup>

Of course there was also the other option of procuring a prescription and having a pharmacist fill it. Author Daniel Okrent offers that, though “there were many regional differences [in price and availability], the tab was generally \$3 to purchase the prescription from a physician and another \$3 to \$4 to have it filled.”<sup>125</sup> And regulation limited a physician to prescribing one pint of alcohol, regardless of strength, to each patient every ten days.

Prohibition and its restrictive access to medicinal alcohols shifted medical interest in utilizing these controversial therapies; even after their renewed legalization. After passage of the twenty-first amendment in 1933, Dr. Morris Fishbein, who would later become the editor of the *Journal of the American Medical Association*, “circulated a questionnaire to all of the doctors in the United States trying to figure out if alcohol was necessary in the practice of medicine.” Fishbein reported a 51-49 split favoring the

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<sup>123</sup> Salvatore P. Lucia, M.D., *A History of Wine as Therapy* (Philadelphia, PA: J.B. Lippincott Company, 1963), 150.

<sup>124</sup> J.M. Doran “Circular Letter No. 24” November 4, 1930.

<sup>125</sup> Daniel Okrent, *Last Call: The Rise and Fall of Prohibition* (New York, NY: Scribner, 2010), 193.

inclusion of alcohol in medical practice and cited Prohibition-era mob mentality for the disapproving 49 percent.<sup>126</sup> Without saying for certain precisely why wine continued to decline in status as a therapeutic option, in 1937, the *US Dispensatory* deleted all wines from its pages.

Post-Prohibition thought shifted away from the innate strictness of the wet-dry controversy. During the twentieth century, modern understanding of alcoholism as a disease pinned ownership on the individual body. Within this framework of alcoholism, exposing two different persons' bodies to alcohol yields entirely different likelihoods of each body developing any degree of alcohol addiction.<sup>127</sup> Onward into the twentieth century, physicians continued to study alcohol abuse; defining our modern understanding of "alcoholism," now as a disease seated in the individual rather than alcohol itself. And in this new understanding of alcoholism as disease, hospitals introduced wine to their corridors in a new capacity.

In the early 1960's, although the pharmacopoeia officially did not recognize wine as a treatment for any disease, some physicians still insisted that its inherent stimulating effect would be useful for patients in their care. As such, some hospitals around the United States served wine to their patients. Mount Zion Hospital in San Francisco included 3 1/2 -ounce glasses of wine on the hospital menu. Patients wanting wine could simply order it with their evening meal. Mount Sinai Hospital in Chicago, as well as the Memorial Center for Cancer and Allied Diseases in New York also featured wine

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<sup>126</sup> Dr. Morris Fishbein, "A Doctor Looks At Wine" (address, 47th Quarterly Dinner meeting of the Society of Medical Friends of Wine, San Francisco, CA November 18, 1959). In *Bulletin of The Society of Medical Friends of Wine* 2, no. 1 (February 1960): 4.

<sup>127</sup> Harry Gene Levine, "The Discovery of Addiction: Changing Conceptions of Habitual Drunkenness in America" *Journal of Studies on Alcohol* 39 (1978): 144.

on their hospital menus.<sup>128</sup> St. Louis Hospital in Missouri offered sauterne and burgundy to patients with lunch and dinner, and a reported 45 percent of the patients imbibed with their meals.<sup>129</sup> Maternity patients imbibed as well. “At the St. Rose Hospital in Hayward, California, where patients on a general diet are offered a glass of wine with dinner, it is noted that patients in the maternity ward order wine three times as often as other patients.”<sup>130</sup> I’m not aware of any hospitals that today still offer wine to patients admitted for their physicians’ care. As concerns over alcohol consumption evolved in the twentieth century, so too did perceptions of alcohol being in close proximity to medical care. As the next section demonstrates, even if some medical practitioners avidly supported the use of medicinal wine for their patients, they had to temper that support in the face of cultural concerns and stigmas surrounding alcoholism and alcohol consumption.

### **Post-Repeal Research Into Potential Wine Therapies**

As outlined above, by the end of Prohibition in 1933, wine’s status in the American medical compendium had overall suffered. Government-recognized lists of official drug preparations, like the *United States Pharmacopeia* and the *US Dispensatory*, had removed all mention of wine from their pages. And roughly half of American physicians believed medical practice could do entirely without medicinal alcohols, including wine. Within this environment of increasingly doubtful medical

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<sup>128</sup> *Bulletin of the Society of Medical Friends of Wine* 4, no. 1 (March 1962): 6.

<sup>129</sup> *Bulletin of the Society of Medical Friends of Wine* 6, no. 2 (September 1964): 7.

<sup>130</sup> *Bulletin of the Society of Medical Friends of Wine* 7, no. 1 (February 1965): 7.

opinion, The Society of Medical Friends of Wine organized in California's Bay Area to scientifically pin down any and all evidence of wine's therapeutic potential.

The Society established itself to focus predominantly on the medicinal benefits of wine, though they did consider other alcoholic beverages. Time and again, though, the research that the Society showcased, pointed to wine's superior therapeutic benefit in comparison to other alcoholic beverages; and pointed also to the non-ethanol components found in wine, like tannins, vitamins, and pigments, as wine-exclusive therapeutic agents. In other words, published studies on the medicinal benefits of wine primarily indicated that therapeutic benefits stemmed from the wine grapes used to make the wine. But the results of these studies, published and promulgated by the Society since their inauguration in the 1930s, did little to bolster either the broader cultural concerns over alcoholism or standard medical opinion concerning alcohol's place in medical practice. Despite the support of research findings that would seemingly validate the use of medicinal wine in contemporary medical practice, medical practitioners like those in the Society of Medical Friends of Wine found their personal interests at odds with professional expectations.

The Society of Medical Friends of Wine was established in 1938. The members, all doctors in northern California, found common interest in evaluating and furthering scientific evidence of the therapeutic potential of wine, touring regional vineyards and wineries, and hosting meals with carefully selected wine pairings and with guest speakers whose topics focused on their special interests.<sup>131</sup> Supplemental to their

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<sup>131</sup> Initially, all members of the Society held a degree as a medical doctor. Though, they did accept a doctor of veterinary medicine in 1960 as an associate member. Eventually, membership opened to accept medical professionals beyond doctors specifically.

annual meeting, and starting in 1956, the Society published a quarterly bulletin that showcased published monographs and research that focused in some capacity on the therapeutic benefits of drinking wine. And the list of published research identified by the Society was not short.

Some research supported the contemporary understanding that wine is beneficial to heart health. “Pharmacologists at the University [of California] reported that propionaldehyde, isolated earlier from Zinfandel, possesses marked stimulating action on blood pressure and is otherwise pharmacologically similar to arterenol.”<sup>132</sup> And Carlo Romano published a study in 1954 demonstrating that isolated compounds from Zinfandel behave in a pharmacologically similar manner as norepinephrine and arterenol to lower blood pressure.<sup>133</sup>

Some research found evidence of wine’s known stimulating effect. Chemists at the University of California completed assays of various wines and “found significant quantities of folic acid in certain red wines, which may provide objective support of the age-old belief of their value in treatment of anemia.”<sup>134</sup> Other research focused on wine’s ability to relieve stress. Professor Greenberg at Yale University had conducted this research under the pretense of discovering why wine might have been common amongst so many cultures for millennia and with the hypothesis that wine protects us from stress. At an address to the Society at their quarterly dinner in 1960, Dr. Milton Silverman summarized Greenberg’s findings, stating:

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<sup>132</sup> *Bulletin of the Society of Medical Friends of Wine* 1, no. 1 (January, 1956): 2.

<sup>133</sup> Dr. Salvatore Lucia, “Physiologic Activity of the Pharmacodynamic Constituents of Wine” (address, 63rd Quarterly Dinner of the Society of Medical Friends of Wine, San Francisco, CA, November 20, 1963). In *Bulletin of the Society of Medical Friends of Wine* 6, no. 1 (February 1964): 4.

<sup>134</sup> *Bulletin of the Society of Medical Friends of Wine* 1, no. 1 (January, 1956): 2.

*“A slight but distinct drop in the [Emotional Tension] index can be produced by as little as 80 or 90 ccs of a California burgundy - roughly the equivalent of 1 ½ wine glasses. Plain alcohol or plain whiskey in equivalent small amounts -- a little less than a highball -- works a little better and a little faster, which is just about what you’d expect, since alcohol from whiskey or an aqueous solution is absorbed more rapidly, giving the familiar quick lift, the high peak of alcohol in the blood, and then the quick let-down. [...] As one wag put it by paraphrasing Dorothy Parker, “Wine is fine, but lickin’s quicker [sic].”<sup>135</sup>*

But some of the research supported by the Society focused on lesser-known and unexpected therapeutic applications of wine. Research by T. L. Althausen at the Gastrointestinal Clinic of the Department of Medicine, University of California School of Medicine found that gastrectomized patients absorb Vitamin A at double the rate following ingestion of dry white wine; whereas in normal patients, absorption decreases after consuming wine.<sup>136</sup> Another study focused on the bactericidal activity of the anthocyanin pigments of wine. John J. Powers and his team found that “certain anthocyanin fractions extracted from Pinot Noir wine, when tested apart from alcohol, definitely inhibited the growth of *E. coli*, *S. aureus*, and *L. casei*.”<sup>137</sup>

This short list of research identified or supported by the Society between 1956-1962 does little to represent the sum of research identified in the decades that followed. By 2005, the Society had cited countless journal articles and hosted nearly as many lectures at their quarterly dinners; dining to addresses with titles like “Wine: Health and

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<sup>135</sup> Dr. Milton Silverman, “Wine and Stress” (address, 48th Quarterly Dinner of the Society of Medical Friends of Wine, San Francisco, CA, January 13, 1960). In *Bulletin of the Society of Medical Friends of Wine* 2, no. 1 (February 1960): 6.

<sup>136</sup> *Bulletin of the Society of Medical Friends of Wine* 2, no. 2 (September 1960): 8.

<sup>137</sup> *Bulletin of the Society of Medical Friends of Wine* 4, no. 1 (March 1962): 4.

Pleasure Across the Ages,”<sup>138</sup> “Wine in the New Era of Medicine,”<sup>139</sup> and “Wine vs. Alcohol in Nutrition.”<sup>140</sup>

And the Society worked to re-publish studies on wine into categories of relevance based of respective medical fields. The Society’s Wine Advisory Board published and distributed its own monograph, “Uses of Wine in Medical Practice -- A Summary.” Their inaugural bulletin describes the 42-page monograph as “contain[ing] ten sections which summarize the chemical constituents of various wines and their uses in nutrition, gastroenterology, cardiology, urology, neurology and psychiatry, geriatrics, convalescence, diabetes, the control of infections, and in pharmacy. The bibliography contains 141 references.”<sup>141</sup>

In 1939, a year after its inauguration, the Society’s Wine Advisory Board initiated sponsorship of research in the United States and abroad “to determine with modern analytical techniques the physiologically active constituents of wine and its values in prevention and treatment of disease.”<sup>142</sup> They initially cited research coming from Yale, the University of California, and the University of Rome. Dr. Milton Silverman expanded on the research mission of the Society’s Wine Advisory Board in 1960:

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<sup>138</sup> Jan I. Shrem, “Wine: Health and Pleasure Across the Ages” (address, 176th Quarterly Dinner of the Society of Medical Friends of Wine, San Francisco, CA, January 8, 1992). In *Bulletin of the Society of Medical Friends of Wine* 34, no. 1 (March 1992): 7.

<sup>139</sup> Cortez F. Enloe, Jr., M.D., “Wine in the New Era of Medicine” (address, 88th Quarterly Dinner of the Society of Medical Friends of Wine, San Francisco, CA, January 7, 1970). In *Bulletin of the Society of Medical Friends of Wine* 12, no. 1 (February 1970): 5.

<sup>140</sup> Janet T. McDonald, PhD, “Wine vs. Alcohol in Nutrition” (address, 109th Quarterly Dinner of the Society of Medical Friends of Wine, March 5, 1975). In *Bulletin of the Society of Medical Friends of Wine* 17, no. 2 (September 1975): 3.

<sup>141</sup> *Bulletin of the Society of Medical Friends of Wine* 1, no. 1 (January, 1956): 1.

<sup>142</sup> *Bulletin of the Society of Medical Friends of Wine* 1, no. 1 (January, 1956): 2.

*We want to find all we can about the chemicals which are contained in wine, and the physiological and pharmacological effects of these compounds in living tissue. We want to find where wine can be most effectively applied in the prevention or treatment of disease, and where it should not be applied. And then we want to take our findings, whatever they may be, and turn them over to the medical profession for whatever use you may wish to make of them.*<sup>143</sup>

In the 1980s, research into the therapeutic potential of wine increased noticeably following the ‘French paradox,’ which spurred the initial hypothesis that wine has some kind of protective effect on cardiac health.<sup>144</sup> Historian Harry W. Paul gave little credit to the piqued interest of medical research in the 1980s and 1990s that focused on the medical potential of wine-specific compounds; describing the summation as “a depressing experience for the believer in the beneficial effects of wine” that reported very little and then not much to do with medicinal benefit. The research facilitated by the Society, as well as by the many research teams around the globe since the 1930s, have had minimal impact overall on the prescribing habits of physicians in American medical practice. Despite the constant undercurrent of research into the therapeutic potential of wine, broader concerns over alcohol abuse have overall tempered wine’s status in medicine all along.

Almost as soon as concern over alcohol abuse manifested in the public consciousness and as soon as physicians constructed an understanding of alcohol

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<sup>143</sup> Dr. Milton Silverman, “Wine and Stress” (address, 48th Quarterly Dinner of the Society of Medical Friends of Wine, San Francisco, CA, January 13, 1960). In *Bulletin of the Society of Medical Friends of Wine* 2, no. 1 (February 1960): 5.

<sup>144</sup> For a synopsis of ‘the French paradox,’ see M. Bobak and M. Marmot, “Wine and Heart Disease: A Statistical Approach” in *Wine: A Scientific Exploration*, Merton Sandler and Roger Pinder, eds. (New York, NY: Taylor + Francis Group, 2003), 101. For an early epidemiological study pointing to wine’s uniquely negative correlation to heart disease related deaths, especially in the context of national per capita consumption rates, see Ronald E. LaPorte, James L. Cresanta, and Lewis H. Kuller, “The Relationship of Alcohol Consumption to Atherosclerotic Heart Disease” *Preventative Medicine* 9 (January 1980): 22-40.

abuse, American physicians have overall tread a cautious balance between advocating alcoholic beverages as therapeutic while not encouraging alcohol abuse. The reality of compulsive alcohol consumption being truly compulsive has historically discouraged physicians from trusting patients to consume medicinal alcohol responsibly. Historian Simon Finger notes that Benjamin Rush, the famous Philadelphia physician who upheld the republic-era value of American citizens having the capacity and ability to self-medicate, did not trust those same “citizens to make their own decisions about alcohol.”<sup>145</sup> Though Finger does not specify which types of medicinal alcohol Rush would have been hesitant to leave to the citizen’s care, alcohol used for medicinal applications would have been similarly defined by the popular understanding of alcohol as inherently addictive.

Onward into the twentieth century, concerns over alcohol abuse continued to shade the affiliation of wine with medicine. From their very outset, the Society underlined the distinction between drinking wine as food or for its health benefits and drinking too much wine. In a 1956 bulletin, the Society showcased statistical studies coming out of Yale. These studies, “made on hundreds of normal subjects and more than a thousand known alcoholics, indicated that early exposure to wine as food, routine use of wine as a food with meals, and cultural distaste toward drunkenness, all serve as preventatives of alcoholism and excessive alcohol use; and that while alcoholics may turn to wine largely for economic reasons, wine drinkers relatively rarely become alcoholics.” Twenty-four years after the ratification of the twenty-first amendment, the doctors in a medicinal wine society felt it prudent to negotiate the morality of their work;

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<sup>145</sup> Simon Finger, *The Contagious City: The Politics of Public Health in Early Philadelphia* (Ithaca, NY: Cornell University Press, 2012), 118.

explicitly underscoring that consuming wine in a very particular context was neither linked to or likely to cause alcoholism.

And following this need for balancing want of therapy with ongoing social concerns, physicians who wanted to include wine in their patients' regimen couched their prescribing habits well outside of officially recognized drug treatment. In an address to the Society in 1980, for example, Dr. Paul Scholten explained:

*"I have been prescribing and recommending wine to my patients as a healthful food, appetite stimulant, and mild natural tranquilizer for almost thirty years. These values are soundly documented and have been known to physicians for centuries."*<sup>146</sup>

Despite years of research pointing to evidence of wine's many therapeutic potentials, Scholten found himself limited to recommending wine much in the fashion one might expect: have a glass of wine with dinner for its seemingly beneficial stimuli on appetite and its vague dietary contribution. Scholten did not recommend wine for specific medical treatment. By the late 1980s, a new concern over alcohol consumption would further mitigate the place of wine in medical practice.

Starting in late 1989, as a result of a mandated warning issued by the U.S. Surgeon General to be printed on every bottle of alcohol distributed in the United States, the public grew increasingly aware of fetal alcohol syndrome and the effects of alcohol exposure in the uterus.<sup>147</sup> And by the early 1990s, concern over the ideal mother and fetal alcohol syndrome had started to weigh on the prescribing habits of

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<sup>146</sup> Paul Scholten, M.D., "Why the Doctor Prescribes Wine" (address, 130th Quarterly Dinner Meeting of the Society of Medical Friends of Wine, San Francisco, CA, June 4, 1980). In *Bulletin of the Society of Medical Friends of Wine* 22, no. 2 (September 1980): 3.

<sup>147</sup> For a history of fetal alcohol syndrome and how medicine came to recognize and define this syndrome, see Janet Golden, *Message in a Bottle: The Making of Fetal Alcohol Syndrome* (Cambridge, Mass.: Harvard University Press, 2005).

physicians who upheld the therapeutic potential of wine. Dr. Wells Shoemaker explains that concerns over FAS essentially stripped physicians of their casual wine suggestion and left them out of sorts with new absolutist expectations:

*“Adopting the conveniently absolutist posture keeps us docs comfortably safe from malpractice lawyers...but does it reach any patient truly at risk?”*

*The zero tolerance paradigm doesn’t really fit with our own medical and personal observations over the years and around the world. [...] What do we tell the mom who feels a huge guilt pang when she discovers she’s pregnant after having a glass of wine on Thanksgiving? How do we cope with the 20% of pregnant women who still drink, albeit at a median consumption level of only four drinks a month? It would be nice to have some facts.”*

Shoemaker goes on to sum up what he described as an ethical Catch-22 posited by absolutists: “We say it’s bad; you can’t prove it isn’t; lives are at stake; so it’s morally imperative for you to take our view.”<sup>148</sup> Echoing the post-Repeal understanding of alcoholism as seated in the individual, physicians like Shoemaker interpreted zero-tolerance in motherhood as the new Dry.

Laboratory and clinical research into the medicinal benefits of wine, and alcohol more broadly, continues to take place. In 2002, The New York Academy of Sciences published an entire volume of their *Annals of The New York Academy of Sciences* to over three dozen overviews and studies of wine and alcohol in relation to specific diseases and specific chemical interactions within animal and human bodies.<sup>149</sup>

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<sup>148</sup> Wells Shoemaker, M.D., “Wine and Mothers” (address, 175th Quarterly Dinner Meeting of the Society of Medical Friends of Wine, San Francisco, CA, November 13, 1991). In *Bulletin of the Society of Medical Friends of Wine* 34, no. 1 (March 1992): 4.

<sup>149</sup> *Annals of The New York Academy of Sciences* 957, Dipak K. Das and Fulvio Ursini, eds. (New York, New York: The New York Academy of Sciences, 2002).

Scientific and medical opinions lean in several directions with regard to wine's therapeutic efficacy and the source of any therapeutic significance. Bobak and Marmot, cited earlier for insisting that wine's therapeutic influence on cardiac health is conventional wisdom, also deny that the phytochemicals within wine grapes contribute to that wisdom's reasoning. They insist that the "much publicized beneficial biological effects of substances in red wine (polyphenols, antioxidants, etc.) found in cross-sectional studies [...] do not provide definite evidence that wine is more beneficial than other types of alcohol."<sup>150</sup> Ethanol has therapeutic applications as well, some of which were described early on in this chapter, but to this chemical only do Bobak and Marmot credit the known cardiac benefits of drinking wine.

Contrary to Bobak and Marmot, M.E. Weisse and R.S. Moore found that the antimicrobial properties of wine come from its phenols, stilbenes, and flavonoids; compounds that appear to perform antimicrobial functions independently of other antimicrobial factors of wine, like the presence of ethanol and its inherently low pH.<sup>151</sup> Some research has concluded that ethanol in combination with wine-specific compounds produces prophylactic benefit. In the case of stroke, for example, research known more commonly as the Copenhagen study indicated that wine provides more protective effect against possible stroke than beer or spirits; suggesting something about wine in particular provides benefit.<sup>152</sup>

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<sup>150</sup> M. Bobak and M. Marmot, "Wine and Heart Disease: A Statistical Approach" in *Wine: A Scientific Exploration*, Merton Sandler and Roger Pinder, eds. (New York, NY: Taylor + Francis Group, 2003), 103-104.

<sup>151</sup> M.E. Weisse and R.S. Moore "Antimicrobial Effects of Wine" in *Wine: A Scientific Exploration*, Merton Sandler and Roger Pinder, eds. (New York, NY: Taylor + Francis Group, 2003), 309-310.

<sup>152</sup> Thomas Truelsen, MD, Morten Grønbaek, MD, PhD, *et al.*, "Intake of Beer, Wine, and Spirits and Risk of Stroke: The Copenhagen City Heart Study" *Stroke* 29 (December 1998): 2467-72.

And some medical opinions hark to a familiar history for plant-derived compounds. D.M. Goldberg and G.J. Soleas, biochemists who worked on resveratrol, concluded that wine-derived resveratrol does indeed have potential for aiding in disease prevention. However, the levels of resveratrol needed to see those benefits would not be achieved by simple consumption of red wine on its own. Goldberg and Soleas suggested that synthetic resveratrol, which could provide greater concentration and potency, may be the solution.<sup>153</sup> The advent of which would put wine square on to the well-known trajectory of other plant-derived drugs.

Twentieth-century and twenty-first century research has tackled many various aspects of whether wine is therapeutic and which specific components of wine (tannin, polyphenols, etc.) affect the progress of disease or create beneficial chemical reactions in the animal body. But wine is, of course, an alcoholic beverage. So the almost century of medical research conducted on wine since the repeal of the eighteenth amendment has been all along tempered by concurrent social concern over alcohol abuse and alcoholism. And so wine remains the one plant-derived medicine that dates to antiquity and has never been transformed to fit into contemporary allopathic medicine. But wine's potential as a therapy evades official recognition; existing instead in a balance between the collective understanding of its health benefits and its concurrent social expectation for moderate consumption.

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<sup>153</sup> D.M. Goldberg and G.J. Soleas "Resveratrol: Biochemistry, Cell Biology, and the Potential Role in Disease Prevention" in *Wine: A Scientific Exploration*, Merton Sandler and Roger Pinder, eds. (New York, NY: Taylor + Francis Group, 2003), 183-185.

## HARVESTING PHARMACEUTICALS: CROPS AS MANUFACTURING SITES OF MODERN MEDICINE

Follow the Moa River upstream, and it winds along the borders of Guinea and Sierra Leone; then the borders of Guinea and Liberia; until finally it reaches the Guéckédou Province in southeast Guinea. A small farming village, called Meliandou, sits roughly 8 miles northeast from the Moa River in Guéckédou, and within this village, in 2013, lived a toddler named Emile Ouamouno. On December 2, 2013, Emile fell ill with fever, black stool, and vomiting. And four days later, the two-year-old died. By the new year, Emile's three-year-old sister, mother, and grandmother had all succumbed to the same virus. This family's home, in their rainforest village in Guinea, is believed to be ground zero for the 2014 West Africa Ebola outbreak.<sup>154</sup>

The World Health Organization released its first situation report to include Ebola cases on March 25, 2014. By that time, 86 Guinea citizens had contracted the disease and 59 of those people had succumbed to the virus. Two days later, a handful of cases, with almost as many deaths, had been reported in both Sierra Leone and Liberia.<sup>155</sup> Over the next two years, a total of 28,646 people contracted the virus and 11,323 of

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<sup>154</sup> Sylvain Baize, et al., "Emergence of Zaire Ebola Virus Disease in Guinea," *The New England Journal of Medicine* 371 (15): 1422. And Holly Yan and Esprit Smith, "Ebola: Who is Patient Zero? Disease Traced Back to 2-Year-Old in Guinea," *CNN*, January 21, 2015. <http://edition.cnn.com/2014/10/28/health/ebola-patient-zero/index.html> (accessed: October 1, 2015).

<sup>155</sup> Centers for Disease Control and Prevention, *Graph 1: Total suspected, probable, and confirmed cases of Ebola virus disease in Guinea, Liberia, and Sierra Leone, March 25, 2014 – February 14, 2016, by date of WHO Situation Report, n=28603* (Atlanta, GA, February 17, 2016), <https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/cumulative-cases-graphs.html> (accessed June 10, 2016).

those died.<sup>156</sup> Infographics published by the Center for Disease Control touted this outbreak as the largest Ebola outbreak in history, where two out of every five people who contracted the disease died thereafter.<sup>157</sup>

At the start of the 2014 outbreak, Ebola had no vaccines or curative pharmaceuticals with proven efficacy. Ebola is a zoonotic disease, meaning the pathogen that causes Ebola in humans can be transmitted from an animal host. Scientists have no definitive understanding of which animal species act as a reservoir for Ebola. Spillover events, when a pathogen crosses from one type of host to another kind of host, that cause Ebola outbreaks in human populations could happen from eating infected chimpanzee or ape meat. However, author David Quammen offers that ample evidence exists that chimps and gorillas are just as highly susceptible to the Ebola virus as humans<sup>158</sup>, so these species would unlikely be able to serve as an Ebola reservoir. Bats are the more suspected contender.<sup>159</sup> But to date, very little is proven concerning where Ebola hides in nature when it is not causing flare ups in outbreaks amongst human populations. And what's more, very little has been proven concerning how to successfully treat or cure the disease once contracted.

However, in the fall of 2014, amongst daily news updates covering the Ebola outbreak, news reports began surfacing that suggested one cure for the virus may had

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<sup>156</sup> World Health Organization, *Ebola Situation Report - 30 March 2016* (Geneva, Switzerland, March 30, 2016), <http://apps.who.int/ebola/ebola-situation-reports> (accessed June 10, 2016).

<sup>157</sup> Centers for Disease Control and Prevention, *West Africa Outbreak Infographic*, CS250531-K (Atlanta, GA, 2016), <https://www.cdc.gov/vhf/ebola/pdf/west-africa-outbreak-infographic.pdf> (accessed June 10, 2016).

<sup>158</sup> David Quammen, *Ebola: The Natural History and Human History of a Deadly Virus* (New York: W.W. Norton & Company, 2014), 8.

<sup>159</sup> N. Allocati, et al. "Bat–Man Disease Transmission: Zoonotic Pathogens from Wildlife Reservoirs to Human Population," *Cell Death Discovery* 2 (2016): 2.

been developed. Articles claimed that two Americans infected with Ebola had received a newly developed drug and later went home infection-free. Kent Brantly and Nancy Writebol had ventured to West Africa to assist with treating Ebola patients and had contracted the disease while doing so. After returning to the United States, and after a few weeks of hospitalized treatment that included doses of a new mysterious antidote, Brantly and Writebol both survived the Ebola virus and appeared to be cured of the disease.<sup>160</sup>

While possible cure for a virus that has plagued humans for centuries would have been notable in its own right, the source of the new Ebola drug remained all the more intriguing. The drug, called ZMapp, had been manufactured in the leaves of *Nicotiana benthamiana*, a close relative of commercial tobacco plants. ZMapp is an example of an entirely novel kind of drug -- a plant-made pharmaceutical (or PMP). In chapters one and two of this dissertation we explored the diminished presence of plants in pharmaceutical education, and therein, in medical practice throughout the twentieth century. Plant-made pharmaceuticals stem from a history of science largely exterior to the history of medicine and pharmacy. They were made possible by the synthesis of an immunological technology, hybridoma, with plant specimens to create transgenic plants capable of producing large amounts of antibodies; just as a hybridoma would function in its usual host, a lab mouse.

This chapter will explore plant-made pharmaceuticals, as well as the interdisciplinary research that led to their development, because the development of

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<sup>160</sup> Maggie Fox, "What Cured Ebola Patients Kent Brantly and Nancy Writebol?" *NBC News*, August 21, 2014. <http://www.nbcnews.com/storyline/ebola-virus-outbreak/what-cured-ebola-patients-kent-brantly-nancy-writebol-n186131> (accessed October 1, 2015).

PMPs like ZMapp challenge the typical narrative of pharmaceutical production in two ways. First, the researchers who forged the field of plant-made pharmaceuticals hail from non-medical disciplines like agriculture and plant biology. And second, plants emerged as a research subject in an entirely innovative capacity; from the cognitive integration of two unrelated industries -- agriculture and medicine. It is my argument that the discovery of a plant's capacity to manufacture medicine hinged upon two main factors: first, centuries, and sometimes millennia, of agricultural efforts to modify particular plant species. And second, the overlapping interest of two distinctive industries -- agriculture and medicine -- into the same natural sciences.

This chapter will examine how an entirely new kind of medicine -- plant-made pharmaceuticals -- emerged from an unlikely source: the laboratories of researchers with backgrounds in agricultural sciences and plant biology. In order to demonstrate how this new pathway to drug production developed, we will consider two important aspects of PMP history. This chapter overviews the historical modification of domesticated plants in agriculture; focusing primarily on the long history of manipulating tobacco. And then, this chapter explores early examples of concept maps, as they convey the interdisciplinary structure of science and point to overlapping industry research into the same scientific subjects. But first, as the field of plant-made pharmaceuticals has a rather recent and unfamiliar history, this chapter will first overview the field's history, its aims and achievements, and the technology that makes PMPs possible.

Plant-made pharmaceuticals are not at all similar to traditional plant-derived therapeutics, or phytopharmaceuticals. The use of plants as manufacturing sites for, or

as tools for the production of, modern medicines is a significant departure from the narrative of plants in medicine up to this point. Traditionally, and this holds true for every known medical system, medical practitioners who use plants as curative agents for diseases use whole-plant parts or specific compounds, or secondary metabolites, derived from plants in order to treat illnesses. Medicines that utilize either whole-plant parts or active ingredients with plant origins collectively fall under the category phytopharmaceuticals. Even if a drug utilizes a synthetic version of a plant-derived compound, as with acetyl salicylic acid, those synthetic active ingredients are largely modeled on compounds originally isolated from plants.

Plant-made pharmaceuticals represent an entirely novel type of drug in the pharmaceutical marketplace. The active ingredients of PMPs are manufactured in transgenic plants, and then later extracted, but the active ingredients are not natural to the plants -- they are always introduced. Researchers who create plant-made pharmaceuticals introduce foreign material, usually antigens, into plants, allow the plant time to manufacture antibodies, and then extract that antibody material later for purification and use as a medicine.

Ask a biochemist to trace the research on plant-made pharmaceuticals back to its origins, and they would likely point to Andrew Hiatt's 1989 article that proved the leaves of transgenic tobacco plants could produce antibodies.<sup>161</sup> Hiatt was a molecular biologist working at the Research Institute of Scripps Clinic, but his precise goal in utilizing hybridoma technology to create transgenic tobacco is unclear.

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<sup>161</sup> Andrew Hiatt, et al., "Production of Antibodies in Transgenic Plants," *Nature* 342 (1989): 76-78. Also Edward P. Rybicki, "Plant-Made Vaccines for Humans and Animals," *Plant Biotechnology Journal* 8 (2010): 623. Rybicki points to Hiatt's article as the "first proof of concept for production of a vaccine-relevant protein in plants"; a proof of concept which therein forge a new field of research.

PMP researchers do not randomly select particular plants as their research subjects. Hiatt chose tobacco leaves as his research subject because so much information about the genetics of tobacco readily exists. Molecular biologist Edward Rybicki notes that, when Hiatt's team opted to use cultivated tobacco as their research subject, cultivated tobacco was "generally seen as [...] useful proof of principle plants."<sup>162</sup> In other words, plant biologists and biochemists liked to utilize tobacco plants, which are broad-leafed and high-bulk,<sup>163</sup> because they were the traditional go-to plant, so much work had already been done on them, and there was a standing precedent to reach for tobacco when working on a new theory or concept. We will delve into the history of tobacco finding its way onto lab benches when we explore further the ethnobotany of crop plants leading up to PMP research. But note that tobacco did not have a continuous presence in PMP research.

After Hiatt's proof of concept, the impetus for PMP research was a needleless vaccine that could be stored without refrigeration and thereby travel to remote areas of the world with minimal production, shipping, and storage costs. Broader interest with research into the potential of genetically modified plants to function as manufacturing sites for vaccines spurred from a call from the World Health Organization for the creation of a needleless delivery system of vaccines.<sup>164</sup> Currently, liquid vaccines must be kept at a cool temperature, which is difficult and expensive to maintain when vaccines travel the globe and to remote populations. Parents, in addition, are hesitant or

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<sup>162</sup> Rybicki, "Plant-Made Vaccines for Humans and Animals," *Plant Biotechnology Journal* 8 (2010): 623.

<sup>163</sup> Kathleen Laura Hefferon, *Biopharmaceuticals in Plants: Toward the Next Century of Medicine* (New York: CRC Press, 2010), 119. Hefferon summarizes the advantages of tobacco for PMP research; offering that the plant is "easy to manipulate, [with a] large and rapid harvest."

<sup>164</sup> Hefferon, *Biopharmaceuticals in Plants: Toward the Next Century of Medicine*, 3.

sometimes unwilling to submit their children to the fear and pain of having a needle stuck in them. And once a needle is used, medical practitioners run the risk of inadvertent disease transmission because the device is so sharp. These problems with vaccine delivery sparked the WHO to encourage research into possible needleless vaccine delivery systems in 1992 with their Children's Vaccine Initiative.<sup>165</sup> This call, in turn, prompted an increased interest with and research effort for effective mucosal vaccines that could be stable at room temperature and delivered without the use of a needle.

In order to meet the end goal of a needleless vaccine delivery system, biochemists building off of Hiatt's discovery chose to work with plants commonly found in agriculture for food production. They planned to make an edible, mucosal vaccine system, where the ingested vaccine material could be absorbed through intestinal lining. These researchers were working with common food crops: alfalfa, carrots, potatoes, and corn, for example. The main idea being, if those food crops were modified to manufacture antibody material, eating them would deliver a vaccine; no needles or refrigeration needed.

In the simplest terms, researchers aimed to determine whether PMP technology could grow vaccines in food, specifically vegetables. Plants already travel the globe along trade routes of international agricultural commerce. Some vegetables can sit in crates, stored without refrigeration, for up to weeks at a time before their quality degrades. If PMP researchers could grow a mucosal vaccine in potatoes, for example,

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<sup>165</sup> Glynis Giddings, et al., "Transgenic Plants as Factories for Pharmaceuticals," *Nature Biotechnology* 18 (2000): 1153.

then those potatoes could hypothetically be eaten and orally administer the vaccine within it. This was the initial idea behind the efforts of PMP research, and this is why researchers in that field always chose crop plants as their research subjects -- plenty of genetic data was already available because crop plants were already well-researched for agriculture, and crop plants were common in food production, which was essential when the end product would be edible. However, the biochemists who strove for developing edible vaccines overlooked an integral aspect of pharmaceutical production found in every contemporary vaccine development process.

When a patient receives a vaccine from a health practitioner today, the drug will be one of five types of vaccines -- attenuated (live), inactivated (killed), toxoid (inactivated toxin), subunit (also called conjugate), and recombinant. While the vaccine is most likely injected via a shot, attenuated vaccines can also be administered by nasal spray.<sup>166</sup>

Attenuated vaccines and inactivated vaccines both involve presenting a live virus to a series of cell cultures or animal cells. This process can be achieved a few different ways, but one of the more common methods involves chicken eggs. With the flu vaccine, for example, a live virus strain is injected into a chick embryo, then reintroduced to another embryo, and so on. As the virus incubates inside the egg, it replicates itself and adjusts or mutates to fit the cellular environment of the egg host. Once the incubation has completed, the final version of the live virus has replicated into a mutated state that is no longer capable of successful replication in a human host.

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<sup>166</sup> The Center for Disease Control is presently reconsidering the effectiveness of this drug-delivery method. Carolyn Beams, "Bad News for Kids Who Don't Like Flu Shots," *National Public Radio*, June 23, 2016. <http://www.npr.org/sections/health-shots/2016/06/23/483239744/bad-news-for-kids-who-dont-like-flu-shots> (accessed June 23, 2016).

Large machines then slice off the top of each egg, inverting the eggs to release the egg white, which is now brimming with live virus material. The next step in the process is dependent on whether the vaccine is destined to be a shot or a nasal spray.

If the drug will be an inactivated vaccine, chemicals kill the virus and the egg whites are then cut into pieces; purifying the virus antigen. In the case of flu vaccines, one virus strain is then mixed with the mutated strains of two other flu varieties. The three flu strains are present in the final flu shot, to hopefully ward off multiple strains of the flu. If the drug will be an attenuated vaccine, the virus in the egg whites is weakened and then the final product contains a total of four virus strains. In both delivery systems, the human body can still recognize the viruses in the vaccine as invasive and produce an immunological response to further protect itself from future exposure, but the scale of the infection will usually not be large enough to produce illness, as the virus can no longer replicate well, if at all.

Private sector vaccine manufacturers have utilized the egg-vaccine method for just over seventy years, and while effective, the method has its drawbacks. Procuring attenuated and inactivated vaccines from chicken eggs requires roughly six months, from injecting the virus into a fertilized egg to finally harvesting the mutated virus, chemically treating it, and introducing all the stabilizers that make it a shelf-stable, viable vaccine.

The FDA approved a quicker egg-based method in 2012 that produces cell-based flu vaccines. With this method, viruses grown in eggs are then incubated in mammalian cells. The harvesting process is slightly different, because the virus material

is now outside of an egg, but the final vaccine is still purified antigen. Because the flu virus grows more quickly in mammalian cells, this method's production process takes less time than the traditional egg-based method. Time factors as a drawback for the egg-based method, but so do limited resources in egg supply.

Pharmaceutical companies go through many millions of eggs each year in order to produce enough doses of flu vaccines to meet demand. Over the last ten years, annual total distribution has increased from 81.2 million doses in 2005 to 147.8 million doses in the 2015-2016 flu season. The CDC estimates that doses needed for the 2016-2017 flu season numbered closer to 170 million.<sup>167</sup> The amount of eggs needed for this production method is significant, because one chicken egg yields roughly one dose of flu vaccine. To give a vivid idea of how many eggs the vaccine industry needs each year for flu vaccines alone, 170 million eggs would occupy the space of just over seven Olympic-sized swimming pools. Or, if laid end to end, 170 million eggs could span the width of the United States more than twice.<sup>168</sup>

Since 2013, private sector vaccine manufacturers have had FDA approval to utilize recombinant technology to produce flu vaccines. And this method does not make use of any eggs. For this method, the HA (hemagglutinin) protein is removed from a virus sample and then introduced to another virus that replicates in insect cells. The mixed virus material then replicates inside those insect cells; then harvested and purified to only contain the necessary HA protein. The final product has the HA protein,

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<sup>167</sup> Center for Disease Control and Prevention, *Seasonal Influenza Vaccine & Total Doses Distributed* (Atlanta, GA, March 15, 2016), <http://www.cdc.gov/flu/professionals/vaccination/vaccinesupply.htm> (accessed August 1, 2016).

<sup>168</sup> Calculations are based on 36 eggs fitting into a gallon-sized container, where the standard size of an Olympic pool is 660,430 gallons. Assuming a roughly average length of 2.2 inches for a chicken egg, 170 million eggs could cover 5902.7 miles. The horizontal width of the United States is 2680 miles.

which the human body will recognize and react to by making antibodies. However, the rest of the virus material that was used in the replication process is left out of the final dose. The production time for this method is much shorter than that required for the egg-vaccine method, but currently only one vaccine in the US market is made using recombinant technology.<sup>169</sup>

The key feature of each of these methods for vaccine production lies in one of the final steps of the processes -- purification. No matter how a manufacturer opts to produce their vaccine doses, purifying the actual vaccine material from everything else involved in its production process is always one of the final steps. Egg-produced antigens are purified from the egg whites in which they incubated. Recombinant vaccines contain only the HA protein, though it had relied on insect virus for replication. The antigens are the singular piece of a vaccine that make it effective, and vaccine technologies hinge upon isolating and purifying those necessary proteins. All other viral materials, though vital for the production process, are removed as a final step; reducing the vaccine to its active or active-passive ingredients -- the antigens.

When biochemists envisioned plants as an edible delivery system for vaccines in the early 1990s, they did not model their final products according to long-established regulatory requirements enforced by the Food and Drug Administration. Initial research on PMPs that aimed to utilize food crops as a delivery system for vaccines overlooked FDA regulations in place to test safety and efficacy. In order for the FDA to approve a new drug, the active ingredient of that drug must be tested in clinical trials to ensure that

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<sup>169</sup> "Why Flublok," *Protein Sciences Corporation*, 2015, <http://www.flublok.com/about-flublok/why-flublok/>. FluBlok Seasonal Influenza Vaccine was the first FDA-approved recombinant vaccine. The quadrivalent vaccine boasts an effectiveness rate of 31-45% higher than the egg-produced quadrivalent (nasal spray) vaccine. However, FluBlok has a much shorter shelf life, expiring six months from its production date.

the drug works as intended and that the drug does not cause more harm or side effects than are considered reasonable. In order to carry out a clinical trial, and this is the significant aspect of FDA testing that made edible vaccines unrealistic, drugs have to be measurable.

Vegetables are inherently irregular when it comes to growth and mass. No two ears of corn are pollinated the same, meaning each ear potentially has a different number of kernels. And if each and every flower on an ear of corn is not pollinated, kernels have room to grow to different sizes with different mass. And for vegetables that grow as tubers, regardless of how completely the plant pollinates, there's still the matter of even distribution of a drug within the vegetable during its development. Assuming you could hypothetically produce vegetables with equal mass, the difficulty in ensuring even and equal distribution of medicine throughout each vegetable would be infeasible. Because drug efficacy and safety hinges on administering a particular dosage, edible vaccines did not make sense with modern drug regulatory standards.

Charles Arntzen, a contributor to the research that developed ZMapp, admits that he initially overlooked the need for drug purification in order to go to market. In coining the term “edible vaccine” and designing their development without a purification process, Arntzen claims he was “ignoring the rigorous regulatory requirements that government agencies and the vaccine industry follow to give us today’s highly effective and wonderfully safe vaccines.”<sup>170</sup> Arntzen and his colleagues initially approached pharmaceutical research and development from the perspective of researchers working

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<sup>170</sup> Charles Arntzen, “Plant-made Pharmaceuticals: From ‘Edible Vaccines’ to Ebola Therapeutics,” *Plant Biotechnology Journal* 13 (2015): 1015. In this article, Arntzen elaborates on his academic and professional background, as well as on his research and the collaboration between Arizona State University and Mapp Biopharmaceutical, Inc. that led to the development of ZMapp.

in a non-medical industry -- without active cognizance concerning the implication of FDA approval regulations on pharmaceutical production.<sup>171</sup>

However, biochemists working on PMPs eventually adjusted their aims and modeled their research to hit particular standards expected of FDA-approved vaccines. Contemporary development of plant-made pharmaceuticals does include a purification process, and, as of 2016, the field has gotten one drug through FDA and into the pharmaceutical market. In 2012, an enzyme for treating type 1 Gaucher's disease, produced in transgenic carrot cells, entered the United States medical market as the first plant-made pharmaceutical approved by the FDA.

Contemporary PMP researchers engineer transgenic plants so that they contain the genes necessary to produce specific proteins. In the case of vaccine production, once PMP researchers produce a transgenic plant, it is then propagated into even more identical transgenic plants. The plants grow in greenhouse facilities and are carefully monitored until they grow large enough to function as manufacturing sites. Then the plants begin the production process. An *Agrobacterium* suspension will be introduced to the plants, and the *Agrobacterium* contains the specific protein or VLP that the plants will be replicating. The plants are immersed in the *Agrobacterium* and then placed in a vacuum chamber, so that the *Agrobacterium* is pulled into each leaf. The plants then typically grow for another three to four months while manufacturing their target proteins. The proteins are then extracted, purified, and introduced to a standard medium for vaccine delivery. So far, transgenic plants have been utilized to manufacture

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<sup>171</sup> Charles Arntzen earned his BS and MS in plant physiology and his PhD in cell physiology. He has since led research laboratories in American universities and in private research institutes focused on botany, agricultural sciences, and plant biotech.

monoclonal antibodies, antigens, virus-like particles (or VLPs), enzymes, and blood proteins.

PMP research has taken aim at a number of diseases, ranging from Crohn's disease to HIV to iron deficiency to Hepatitis C; though, no PMP treatments for these specific diseases have yet come to market. A quick scan of the last twenty years of PMP research reveals a veritable cornucopia of common crop plants that have been research subjects in the development of new PMPs. Researchers working on PMPs have utilized species of potatoes, barley, corn, carrots, alfalfa, tobacco, and rice in an effort to produce therapeutic proteins for an array of illnesses. How these crop plants found their way onto the benches of PMP labs brings us to a main point -- concerted agricultural efforts to develop and modify each of these species of crop plants has been an ongoing process that has lasted centuries, and sometimes millennia. Ethnobotanists have elaborated on the many methods humans have developed in order to modify these domesticated plants. In exploring that long history, one can begin to scratch the surface of how well-studied domesticated plants had to be for researchers within the agriculture industry to fathom their potential as pharmaceutical manufacturing sites.

### **Ethnobotany + The Many Ways We Manipulate Plants**

Humans have domesticated and cultivated plant species for what ethnobotanists estimate as at least 10,000 years. That leaves room for lots of experimentation with growing conditions, countless attempts at trial and error with selective breeding, and tons of knowledge accumulated along the way. Also consider the multi-faceted and

varied qualities of plants that humans utilize for a host of applications. Plants are used as food and medicine, but they also are essential for the manufacture of shelter, textiles, and tools. We know a great deal concerning the many ways plants can be manipulated and utilized for economic purposes.

When we tally those plants that find their way onto the benches of PMP labs, a marked similarity emerges -- each plant has been a major ethnobotanical subject, capitalized for various human uses, for at least thousands of years. Let's consider tobacco specifically, which has a particularly well-documented history as a domesticated plant.

Tobacco's "role in medical opinion has shifted from hero to villain."<sup>172</sup> Long and very researched histories of tobacco's association with cancer cases, efforts of the tobacco industry to deny adverse health effects linked to tobacco usage, and the many legislative measures to prevent tobacco usage and generate public health warnings inform contemporary notions that tobacco kills. However, tobacco plants have had, as underlined by ethnobotanists and historians of horticulture, a significant stint as a viable therapeutic in many worldwide cultures. After Christopher Columbus introduced tobacco to Europe in 1492, and at least as early as the sixteenth century, medical texts written in Spain, and later, reprints of those texts in England, claimed as many as 36 medical conditions could be cured by tobacco; including toothache, halitosis, and lockjaw.<sup>173</sup>

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<sup>172</sup> Toby and Will Musgrave, *An Empire of Plants: People and Plants that Changed the World* (New York: Cassell & Co., 2000), 15.

<sup>173</sup> Musgrave, *An Empire of Plants*, 19-20. Monarde's *Materia Medica*, printed in 1571 in Seville, listed a total of 36 illnesses curable by tobacco, and Toby and Will Musgrave point to this specific text as an influential factor that encouraged European physicians to adopt tobacco as a therapeutic. In 1577, Monarde's text was translated to English and reprinted in England under the title 'Joyfull News out of the New Founde Worlde.'

Three hundred years later, tobacco still appeared in the pharmacopoeia of medical practitioners. *Merck's 1896 Index, An Encyclopedia for the Physician and the Pharmacist* listed a handful of conditions treatable with extract of *Nicotiana tabacum*. Internal usage could treat whooping cough and chronic asthma, while external application treated toothache, hemorrhoids, and tinea capitis, or ringworm of the scalp.<sup>174</sup> Importantly, tobacco found its way into medicine as a worthy therapeutic because of its beneficial alkaloids, a quality common to many other species within its plant family.

Tobacco species all belong to the *Nicotiana* genus, which is categorized within the Solanaceae family. This family includes common food crops like tomatoes, peppers, eggplants, and potatoes, the latter of which we will explore later. These food crops make the Solanaceae family economically significant, but this plant family also includes plant species with historically and contemporarily important pharmacological uses.

*Solanum dulcamara*, also called “the woody nightshade plant,” lends this plant family its name. This species appears in *Materia Medica* and pharmaceutical reference books up until the early twentieth century as a remedy for dermatological conditions like psoriasis and pityriasis.<sup>175</sup> And not to be overlooked, the nightshade family includes the infamous, highly toxic, and hallucinogenic deadly nightshade plant, *Atropa belladonna*. Belladonna, meaning ‘beautiful woman’ in Italian, was named for its cosmetic application during the Renaissance period. When introduced to the eyes via eye drops, the anticholinergic compound atropine in belladonna dilates the pupils. Roman women

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<sup>174</sup> Merck & Co., *Merck's 1896 Index, An Encyclopedia for the Physician and the Pharmacist* (New York: Merck & Co., 1895), 115.

<sup>175</sup> Samuel O.L. Potter, *Materia Medica, Pharmacy, and Therapeutics, Tenth Edition* (Philadelphia: P. Blakiston's Son & Co. 1012 Walnut Street, 1906), 268.

harnessed this side effect as a cosmetic aid for seduction, as dilated pupils can indicate sexual arousal. In addition to this historical cosmetic application, atropine has multiple uses within a medical context. Contemporary allopathic therapies utilize atropine for some types of irregular heart rhythms, and the compound is also useful in surgeries as a way to decrease saliva production. Since its initial publication in 1977, the World Health Organization has featured atropine in its biennial *Model List of Essential Medicines* as beneficial in multiple therapeutic capacities.<sup>176</sup> The plant species in the nightshade family have contributed significant compounds to medicine, but the ethnobotanical uses of Solanaceae plants extend well beyond medical applications and are sometimes solely the product of human endeavor to domesticate plants.

*Nicotiana tabacum*, for example, is presently the most commonly used tobacco species, and the plant is only found in cultivation. This species has dozens of varieties that make up the many blends of tobacco products found in worldwide markets. From ‘White Burley,’ a tobacco discovered in the 1860s by an Ohio farmer that later became a staple in American blends;<sup>177</sup> to the brightleaf variety, or ‘Virginia tobacco,’ originally cultivated and developed by John Rolfe in 1612;<sup>178</sup> to the Viñales, criollo, and corajo tobaccos used for manufacturing Cuban cigars,<sup>179</sup> *N. tabacum* cultivars make up the most widely known tobacco species to anyone cognizant of tobacco products. Another species of tobacco, *Nicotiana glauca*, the precise cultivar used for the production of ZMapp, has a relatively recent history in agriculture. *Nicotiana glauca*

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<sup>176</sup> World Health Organization, *Model List of Essential Medicines* (Geneva, Switzerland, 1977), 21 and 26.

<sup>177</sup> Musgrave, *An Empire of Plants*, 34.

<sup>178</sup> Iain Gately, *Tobacco: A Cultural History of How an Exotic Plant Seduced Civilization* (New York: Grove Press, 2001), 70-72.

<sup>179</sup> Thomas A. Wikle, “Tobacco Farming, Cigar Production and Cuba’s Viñales Valley,” *Focus on Geography* 58, no. 4 (2015): 156.

originated in Australia, and it was incorporated into Linnaean taxonomy after James Cook and Joseph Banks encountered it during the HMS *Endeavor* voyage in the late eighteenth century.<sup>180</sup> Over several millennia of growing various tobacco species for habitual consumption of its leaves, either by chewing or smoking them, or for its benefits as a medical therapy, agriculturalists accumulated a considerable weight of information concerning how to effectively and successfully manipulate, cultivate, and harvest different species of tobacco plants.

During the nineteenth century, both Charles Darwin and Alphonse de Candolle dedicated much of their efforts to examining how human intervention modified plant species; specifically within the context of domesticated plants. Importantly for our topic at hand, both Darwin and de Candolle noted that the part most valuable to man is the plant part most manipulated. Manipulation of domesticated plants is best understood when observing cultivars of the same plant species.

Take for instance the modifications that took place on the Brassicaceae family, commonly referred to as the cabbage family. Ethnobotanists regard wild cabbage as the common ancestor to all species within the cabbage family. After a few thousand years of cultivating wild cabbage, with preference for leaves or with preference for the inflorescence or with preference to any other part of the plant, the resultant plant will in no way resemble the original species.<sup>181</sup> Wild cabbage is believed to be the original

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<sup>180</sup> Gately, *Tobacco*, 130.

<sup>181</sup> Jack R. Harlan, *Crops and Man*, second edition. (Madison, WI: American Society of Agronomy, Inc., 1992), 43. Botanist Jack Harlan characterizes the origins of agriculture with the term diffuse origins, meaning that every crop plant begins as its wild form and is then modified at distinct global locations, repeatedly and sometimes enormously, so that the end products are nothing like the original form or each other.

species of many cultivars, including cabbage, both green and red; cone cabbage and savory cabbage; broccoli and broccolini; cauliflower and collard greens; the many varieties of kale; kohlrabi and brussel sprouts; as well as romanesco broccoli.

The particularly elaborate modification of the Brassicaceae family occurred via selective breeding. Each cultivar's specific history is varied, as particular plants fade in and out of use, experiencing periods of modification and then natural variation once returned to a wild state. But our very precise understanding of these crop plants, as with any crop plant, stemmed from our prolonged use of these plants as valuable commodities. The cabbage family included valuable foodstuffs, so a concerted effort to cultivate its species produced a significantly modified collection of cultivars. After thousands of years of manipulating a plant species, the people who steered that cultivation came to understand a great deal about their plant subjects. As agricultural knowledge and technology expanded, plant researchers developed new ways of manipulating both crop plants and their growing environments.

Our fundamental understanding of the consequences of people's dominion over plants is expressed early on in Charles Darwin's *The Variation of Animals and Plants Under Domestication* (1896). Ethnobotanist Charles B. Heiser claims that Darwin's work on this topic enriched the potential of ethnobotany by exposing the extent of manipulation that man performs on nature via agriculture.<sup>182</sup> From Darwin we learned that "although man did not cause variability and cannot even prevent it, he can select, preserve, and accumulate the variations given to him by the hand of nature almost in

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<sup>182</sup> Charles B. Heiser, "The Ethnobotany of Domesticated Plants" in *Ethnobotany: Evolution of a Discipline*, eds. Richard Evans Schultes and Siri von Reis (Portland, OR: Dioscorides Press, 1995), 200.

any way which he chooses; and thus he can certainly produce a great result.”<sup>183</sup>

Through centuries of actively studying and selecting plants for preferred variability, agrarian efforts and agricultural sciences amassed a wealth of knowledge concerning how to grow crops with more yield, how to grow plants that are more drought tolerant and pest resistant, and how to manipulate a plant at a genetic level to reach those ends.

Millennia of manipulating crop plants culminated in much more than simple selection. With the passing of the Land-Grant College Act of 1862, also called the Morrill Act, new land-grant colleges began elevating agriculture to a scientific level of inquiry. The development of agriculture to our modern period has expanded considerably to facilitate advances in biotechnology relevant to plant pathologies, soil science, parasitology, and genetic engineering. Plant biologists and biochemists working in the agriculture industry can manipulate both plants and their growing conditions in countless ways. But importantly, many of the natural sciences that have been studied by plant researchers within the context of improving our knowledge of crop plants overlap with those natural sciences that are also relevant within the context of medical research. And this brings us to the second aspect of PMP history that we will consider today: overlapping industry research on the same scientific concepts.

### **PMPs from Interdisciplinary Scientific Research**

Overlapping interests of separate industries into the same natural sciences has facilitated the emergence of an entirely new pathway to pharmaceutical development.

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<sup>183</sup> Charles Darwin, *The Variation of Animals and Plants Under Domestication*, Vol. 1. (London: John Murray, Albemarle Street, 1868), 3.

Traditionally, plant biologists deal with pathogens as they relate to plants while medical researchers deal with pathogens as they relate to humans. Basic scientific concepts like viruses and genes -- concepts that exist distinctly in both medical sciences and agricultural sciences -- facilitated a convergence point for PMP research to emerge and link the two fields in a novel pathway to find new pharmaceutical products.

Plants and humans respond differently to pathogens. However, they have similar first lines of defense. Human skin and plant cuticle exist for the same reason: to keep the bad stuff out. When those barriers fail, allowing pathogens to enter the human body or plant structure, immunological responses between humans and plants are then noticeably different.

Plants produce secondary metabolites, which are the same compounds that have made plants historically useful in human therapies. But secondary metabolites are also believed to serve, in addition to a number of other purposes, immunological purposes in plants. The variety of secondary metabolites that can exist in one plant specimen can number in the thousands. Plant biology holds that some of those compounds, which vary immensely in type between plant species, have evolved with plants and their environments to aid against bacterial, viral, and fungal pathogens. Though plant immunology is not entirely understood, recent work on how plants fight pathogens points to a multi-pronged defense system.<sup>184</sup>

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<sup>184</sup> Steven H. Spoel and Xinnian Dong, "How Do Plants Achieve Immunity? Defence Without Specialized Immune Cells," *Nature Reviews Immunology* 12 (Feb. 2012): 89-100. This article overviews recent developments on plant immunology research that demonstrates an innate immune system in plants. This innate system includes pattern-triggered self-surveillance, systemic signalling between cells once a pathogen is detected, and responsive synthesis of pathogenesis-related proteins (secondary metabolites).

Humans, like all vertebrates, have an adaptive immune system. Rather than having immunological compounds built into us from birth, humans have the amazing capacity to produce antibodies as needed for each specific pathogen that finds its way into the body. Plants do not have antibodies, nor do they normally produce antibodies. Yet, Hiatt's team had enough conceptual knowledge of plant and animal immunology to hypothesize the potential for tobacco plants to produce antibodies if those plants were genetically modified to facilitate antibody production. Their hypothesis, and therein their research, linked two unrelated fields of inquiry -- plant science and medical science. Hiatt's team was able to bridge this disciplinary divide because their research subjects, namely genes and virus material, exist universally in nature and in despite of the narrow disciplinary purviews dedicated to them by specific fields of inquiry.

Historian of science Scott Weingart echoes this point precisely when he offers that "the division of concepts and bodies of studies have no natural kind."<sup>185</sup> Though natural philosophers, and much later, scientists, have devised classification systems and denigrated nature into tidy fields of inquiry based on similarities in structure and commonalities of function or feature, nature itself does not recognize or abide those divisions. And moreover, scientific fields of inquiry to study nature often overlap on research topics, creating a mass of knowledge that spans across disciplines.

In the beginning of the twentieth century, scientists began what later became a concerted effort to map our knowledge of the sciences. This effort of concept mapping,

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<sup>185</sup> Scott B. Weingart, "From Trees to Webs: Uprooting Knowledge through Visualization" (pre-print of the paper presented at the annual meeting for the Universal Decimal Classification entitled "Classification & Visualization: Interfaces to Knowledge," Koninklijke Bibliotheek, The Hague, Netherlands, October 24-25, 2013): 53.)

which is now considered bibliometrics or scientometrics<sup>186</sup>, aims to visually convey how distinctive areas of scientific inquiry actually interact with each other through their overlapping inquiry of the same scientific concepts. Two of the earliest examples of concept mapping came from John D. Bernal in 1939 and Harold J.T. Ellingham almost a decade later in 1948.

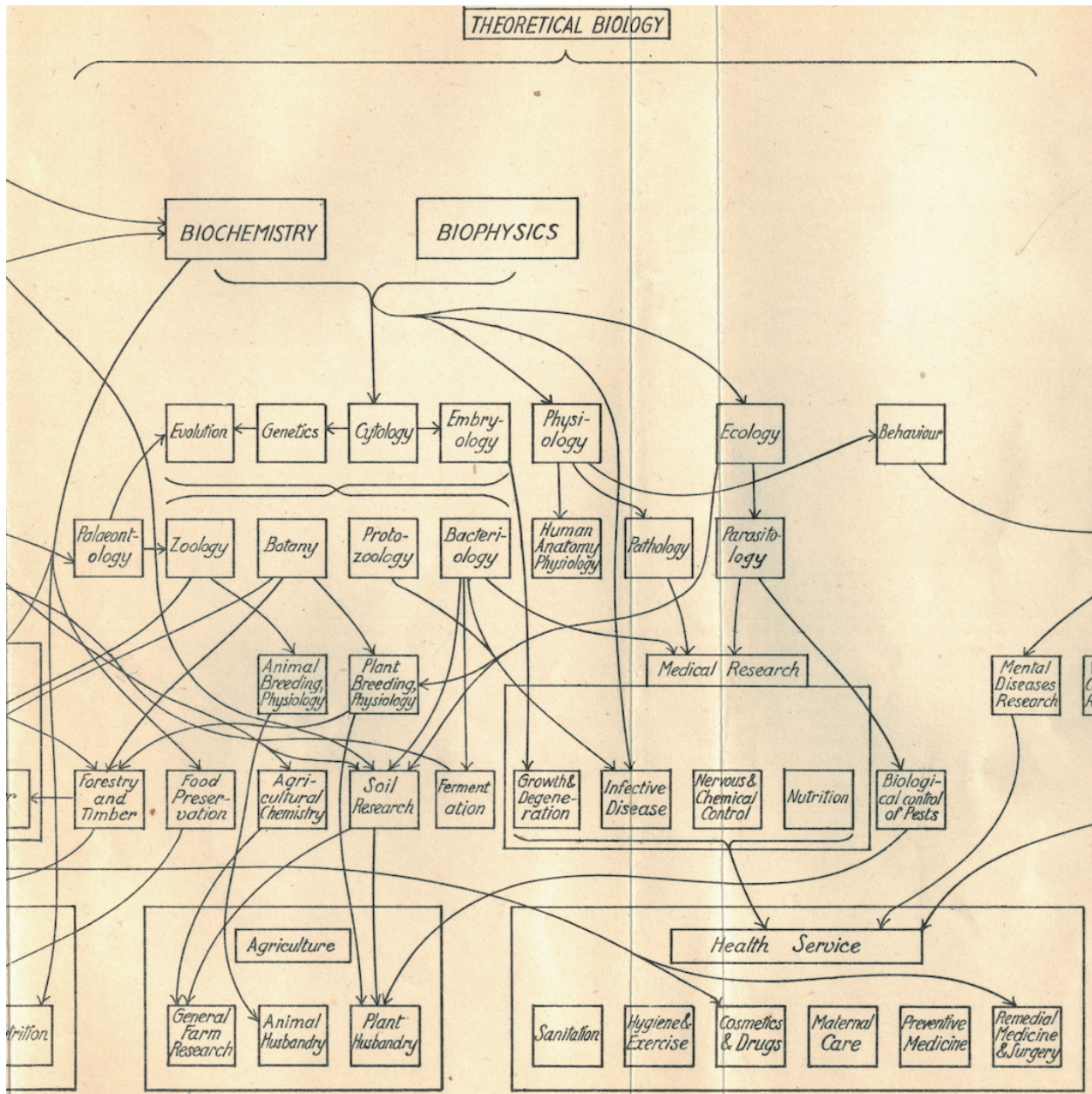
Historical accounts of concept mapping cite Bernal's map as the first map of this kind.<sup>187</sup> Bernal was a physicist and a sociologist of science. In his 1939 *The Social Function of Science*, he included a hand-drawn map of the scientific disciplines as they related to each other.<sup>188</sup>

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<sup>186</sup> Katy Börner, et al., "Visualizing Knowledge Domains" (pre-print of article in *Annual Review of Information Science & Technology* 37 (2003): 179-225.) Börner et al. overview the emergence of bibliometrics and scientometrics as as a systematic mapping of citations; distinguished from their hand-drawn predecessors. Their article also details the techniques and theories of the field. Katy Börner is a Professor of Engineering and Information Science. Her work in bibliometrics and scientometrics aims to visualize the many paths that facilitate the development of knowledge. Bibliometrics, for instance, accomplishes this end by tabulating and analyzing the citations in published scientific articles; to trace and thereafter map the previous research on which new research relies.

<sup>187</sup> Katy Börner, *Atlas of Science: Visualizing What We Know* (Cambridge, Mass.: MIT Press, 2010), 11. Also see Peter A. Hook, "Domain Maps: History, Parallels with Cartography, and Application," *Conference Proceedings of 11th Annual Information Visualization International Conference* 4 (2007): 443.

<sup>188</sup> John D. Bernal, "Chart 1" in *The Social Function of Science* (London: George Routledge & Sons Ltd., Broadway House: 68-74 Carter Lane, E.C.4, 1939), 280.



Importantly, though Bernal's map situated the sciences in the traditional hierarchical orientation,<sup>189</sup> he also drew arrows across the map, connecting fields of scientific

<sup>189</sup> Weingart, "From Trees to Webs": 54-61. Weingart explores the ancient tradition of ordering nature in a hierarchy, whether with the classic tree metaphor or with circle diagrams. Weingart claims this format of mapping nature continued until a new trend of webbed mapping emerged in the early twentieth century.

inquiry laterally. Bernal's map represents a departure from understanding nature as hierarchical and instead, understanding nature as interwoven.

This emergent thought trend of interconnectedness found in Bernal's map influenced Harold Ellingham almost a decade later. Ellingham was a physical chemist and in 1948 he completed his own hand-drawn concept map.<sup>190</sup> Ellingham produced a map based on the distance-similarity metaphor, which means that the proximity of concepts or topics on the map indicates how closely those topics relate to each other in practice.<sup>191</sup> Peter Hook offers that Ellingham's two-dimensional map was meant to be wrapped around a cylinder to convey the continued connectedness of disciplines and topics on either margin of the map; claiming also that Ellingham "wished it were possible to 'allow for the chart to be spread over the surface of a sphere and this would have the advantage of avoiding the need to select a particular science for the center.'"<sup>192</sup> As it is, the chart displays physical chemistry as the center of scientific knowledge.

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<sup>190</sup> Ellingham, H.J.T. 1948. *A Chart Illustrating Some of the Relations Between the Branches of Natural Science and Technology*. Courtesy of The Royal Society. In "7th Iteration (2011): Science Maps as Visual Interfaces to Digital Libraries," *Places & Spaces: Mapping Science*, edited by Katy Börner and Michael J. Stamper. <http://scimaps.org>.

<sup>191</sup> Sara Irina Fabrikant, et al., "The Distance-Similarity Metaphor in Network-Display Spatializations," *Cartography and Geographic Information Science* 31 (2004): 237.

<sup>192</sup> Hook, "Domain Maps": 443.



OVERLAY 1

## ABSTRACTS OR GROUPS OF ABSTRACTS COVERING A VERY WIDE FIELD (OVERLAY 1)

1. **Science Abstracts (Joint Board of the Institution of Electrical Engineers and the Physical Society).**
    - A. Physics Abstracts.
    - B. Electrical Engineering Abstracts.
  2. **British Abstracts (The Bureau of Abstracts representing the Chemical Society, the Society of Chemical Industry, the Physiological Society, the Biochemical Society, the Anatomical Society of Great Britain and the Institution of Chemical Engineers).**
    - A. I. General, Physical and Inorganic Chemistry.
    - A. II. Organic Chemistry.
    - A. III. Physiology, Biochemistry, Anatomy.
    - B. I. Chemical Engineering and Industrial Inorganic Chemistry, including Metallurgy.
    - B. II. Industrial Organic Chemistry.
    - B. III. Agriculture, Food and Sanitation.
    - C. Analysis and Apparatus.
  3. **Commonwealth Agricultural Bureaux Abstracts (Separate Bureaux for the individual sets of Abstracts—details shown on Overlay 2).**
    - (1) Soils and Fertilisers (Commonwealth Bureau of Soil Science).
    - (2) Plant Breeding Abstracts (Commonwealth Bureau of Plant Breeding and Genetics).
    - (3) Horticultural Abstracts (Commonwealth Bureau of Horticulture and Plantation Crops).
    - (4) Herbage Abstracts (Commonwealth Bureau of Pastures and Forage Crops).
    - (5) Forestry Abstracts, Silviculture and Utilization (Commonwealth Forestry Bureau).
    - (6) Dairy Science Abstracts (Commonwealth Bureau of Dairy Science).
    - (7) Review of Applied Mycology (Commonwealth Mycological Institute).
  4. **Engineering Abstracts (Institution of Civil Engineers with the co-operation of other engineering societies in Great Britain and the Dominions).**
    - (1) Engineering Construction (in abeyance since 1939-40).
    - (2) Mechanical Engineering (in abeyance since 1939-40).
    - (3) Shipbuilding and Marine Engineering (Institute of Marine Engineers in co-operation with the Institution of Naval Architects).
    - (4) Mining Engineering (in abeyance since 1939-40).

Once Ellingham had mapped the proximity of the natural sciences, he then traced the topics indexed in a collection of journal abstracts. So, for example, in "Overlay 1," the space within the green lines represents the topics covered by twelve specific agricultural journals. The article abstracts in those journals list topics within the natural sciences like crop sciences, virology, genetics, pathology, and nutrition.



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OVERLAY 2

#### OTHER SETS OF ABSTRACTS (OVERLAY 2)

5. Rheology Abstracts (in Bulletin of the British Rheologists' Club).
6. "The Analyst" (Society of Public Analysts and other Analytical Chemists).
7. Macromolecular Abstracts (in Macromolecular Magazine and Journal of the Macromolecular Society).
8. Journal of Glaciology (British Glaciological Society).
9. Recent Ornithological Publications (in "The Ibis," British Ornithologists' Union).
10. Abstracts of World Medicine (British Medical Association).
11. Bulletin of Hygiene (Tropical Diseases Bureau).
12. Tropical Diseases Bulletin (Tropical Diseases Bureau).
13. Quarterly Journal of Pharmacy and Pharmacology (Pharmaceutical Society of Great Britain).
14. Wireless Engineer (Hill & Sons, Ltd.).
15. Issue of Abstracts, Motor Industry Research Association.
16. Railway Engineering Abstracts (Institution of Civil Engineers).
17. Water Pollution Research (D.S.I.R., Water Pollution Research Board).
18. Monthly Review of Current Literature in "Water and Water Engineering" (Institution of Water Engineers).
19. Journal of the British Shipbuilding Research Association.
20. Index, Aeronautics (Technical Information Bureau, Ministry of Supply).
21. Aeronautics Abstracts (D.S.I.R., Road Research Laboratory—issued in collaboration with the Air Ministry).
22. Fuel Abstracts (D.S.I.R., Fuel Research Board).
23. Monthly Bulletin, British Coal Utilisation Research Association. [Deals more briefly with papers in part of the field of 23].
24. Bulletin, Coke Oven Managers' Association.
25. Journal of the Institute of Petroleum.
26. Sugar Industry Abstracts (Tate & Lyle, Ltd., for the Sugar Refiners' Association and the British Sugar Corporation).
27. Journal of the Institute of Brewing.
28. Abstracts from British and Foreign Journals and Patents, Society of Dyers and Colourists.
29. Transactions of the British Ceramic Society.
30. Review of Current Literature relating to the Paint, Colour, Varnish and Allied Industries (Research Association of British Paint, Colour and Varnish Manufacturers).
31. Journal of the Society of Leather Trades' Chemists.
32. Journal of the Textile Institute.
33. Summary of Current Literature, British Cotton Industry Research Association. [Deals with the field of 32 in relation to cotton.]
34. Empire Cotton Growing Review (Empire Cotton Growing Corporation). [Deals with parts of the fields of 3 and 32 in relation to cotton.]
35. Summary of Current Literature, Research Association of British Rubber Manufacturers.
36. Abstracts, British Plastics Federation.
37. Building Science Abstracts (D.S.I.R., Building Research Board).
38. Bulletin of the British Scientific Instruments Research Association.
39. Photographic Abstracts (Royal Photographic Society).
40. Kodak Bulletin of Current Information (Kodak Research Laboratories). [Covers a similar field to 39.]
41. Metallurgical Abstracts (Institute of Metals).
42. Survey of Current Literature, Bulletin Iron and Steel Institute.
43. Bulletin British Non-Ferrous Metals Research Association. [Deals more briefly with papers in the field of 41.]
44. "Nickel Bulletin" (Mond Nickel Company).
45. "Z.D.A. Abstracts" (Zinc Development Association).
46. "Light Metals Research" (British Aluminium Company).
47. "Light Metals Review" (British Aluminium Company).
48. "Magnesium Review and Abstracts" (Magnesium Elektron, Ltd.).
49. Road Abstracts (D.S.I.R. and Ministry of Transport).
50. Journal of the Society of Glass Technology.
51. Abstracts of World Surgery (British Medical Association).

\* Deals with papers in the field of 41 in relation to the specified metals.

Meanwhile, “Overlay 2” illustrates, among other journals, the scientific topics covered by a sample of four medical journals; marked by numbers 10 through 13. They cover topics like pathology, nutrition, virology, and pharmacy.

Unrelated fields of natural inquiry are in close proximity on Ellingham’s map because they deal with the same scientific concepts; just in different contexts. Plant geneticists working from within the agriculture industry focus on genes as they relate to plants. Human geneticists working within the medical industry focus on genes as they relate to humans. But genes, as a basic scientific concept that exists independently of specific fields of inquiry, allow for points of convergence amongst those fields and amongst those industries.

The resulting topography in Ellingham’s map illustrates approximately which natural sciences were relevant to particular fields of industry. But also, and more importantly for the purposes of this lecture, the resulting topography illustrates where those fields not at all relevant to each other still had interest in the same natural sciences and scientific concepts.

So in 1948, the sample of agricultural journals chosen by Ellingham had no interest in explicitly medical topics. And likewise, his sample of medical journals had no interest in explicitly agricultural topics. But agriculture and medicine independently had common interest in natural sciences like pathology, virology, parasitology, and so on. Though this map does not indicate a shared interest in genetics, I would underscore that Ellingham only mapped the indexes of four medical journals and that 1948 was very early in the development of medical genetics. So while this chart is in no way

representative of the entire body of medical and agricultural journals extant in 1948, it would be fair to say that both the medical and agricultural industries were working on overlapping topics within the natural sciences. Furthermore, this pattern of overlapping topographies of industry research into the natural sciences continued well onward to the present day and has facilitated the development of plant-made pharmaceuticals as an interdisciplinary field of research.

The development of plant-made pharmaceuticals as a field of inquiry required the integration of knowledge from agricultural and medical sciences. When a new field of scientific inquiry emerges from the cognitive integration of two well-established disciplines, where the resulting data represents a “common understanding of a complex issue,”<sup>193</sup> the new field is considered interdisciplinary scientific research. PMP research integrated agricultural and medical sciences in this exact manner.

Plant-made pharmaceuticals represent a point of convergence, where the research of one industry can now readily contribute to the technology and knowledge of another industry; utilizing the natural knowledge found in those sciences that are relevant to both. Genetics, for example, readily applies to both human and plant subjects because both are biological and all things biological have genes. Immunology also readily applies to both plants and human subjects. Even though plants and humans do not suffer the same pathologies, the language and knowledge of disease translates fluently between plant and human pathology. Agricultural research that focuses on combating plant diseases creates a pronounced overlap with research efforts to fight

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<sup>193</sup> Caroline S. Wagner, et al., “Approaches to Understanding and Measuring Interdisciplinary Scientific Research: A Review of the Literature,” *Journal of Infometrics* 165 (2011): 16.

human diseases, because all life sciences (regardless of plant, animal, or human subject) rely on the same fundamental concepts. Cells, antigens and viruses, genes and proteins all exist within the contexts of both human and plant subjects. The industries devoted to either research subject may not have historically overlapped to influence the technology used in the other, but plant-made pharmaceuticals demonstrate a viable and novel pathway to influence human therapeutics.

Today, researchers working on plant-made pharmaceuticals continue to face regulatory challenges as they submit new drugs to the FDA for approval. For this reason, voices from within the PMP industry foresee their drugs as having a more immediate application in veterinary medicine. However, many PMP researchers also believe that PMP drugs still offer an optimal solution for manufacturing vaccines in emergency-response scenarios. These PMP advocates and visionaries hope that, in desperate times, like that experienced during the 2014 West Africa Ebola epidemic, PMPs will be considered as a tenable therapeutic, at least until the well-established animal models for drug manufacture have had time to create an adequate drug supply.

No matter what the future has in store for plant-made pharmaceuticals, we can be certain that the path to their discovery was altogether innovative. Plant-made pharmaceuticals continue to challenge well-established notions of which industries drugs come from and how they can be made. But they also challenge notions of who is capable of making therapies for a modern pharmacopoeia, as plant-made pharmaceuticals illustrate the possibility for an interdisciplinary development of medical and pharmaceutical knowledge from fields typically exterior to medicine and pharmacy.

Plants re-emerged as viable research subjects for pharmaceutical development because the researchers working on plant biotechnology hailed from non-medical backgrounds that had not marginalized plants as useful for therapeutics. In previous chapters, we have explored the diminished presence of plants in pharmaceutical education, where American colleges of pharmacy had removed botany, materia medica, and pharmacognosy from their course catalogs by the 1970s. We have also considered the declining interest of medical practitioners and the pharmaceutical industry regarding plant-derived compounds with therapeutic potential. Without any substantial interest toward plant-derived remedies coming from the medical industry, the development of plant-made pharmaceuticals and the plant biotech that made them possible came from non-medical sources: the lab benches of plant biologists and agriculturalists.

When it comes to finding new technologies and processes for pharmaceutical development, researchers are putting plants back on their lab benches. Plant biotechnology has reached a point of sophistication and innovation that they now present themselves as viable sites for drug manufacture. So the advancements made by PMP research in the last few decades, as well as forthcoming research based on plant chemical reactions, forces us to re-examine the full scope of an ancient question: How do plants treat and cure disease?

## CONCLUSION

The previous four chapters each consider a distinct aspect of plants and their derivative components as they have existed within American allopathic medicine since the early nineteenth century. These histories depart from the conventional analysis of plant-derived therapies which typically focus on plants as they related to medical paradigms like folk medicine, eclecticism, Thomsonianism, homeopathy, Ayurvedism, complementary and alternative therapies, and, of course, Galenism and other ancient medical practices. Instead, the chapters within this dissertation contribute to the knowledge of pharmaceutical history through their sole consideration of plants within orthodox medicine.

This dissertation traces a transformation of plant-derived therapies; from their whole-plant form as a cornerstone of pharmacy education and medical practice; to their gradual and multi-faceted displacement in multiple contexts; to their modern resurgence from an entirely different industry. The histories in each chapter can stand alone, but their common thread of plant-derived remedies makes them a cohesive representation of how a significant pharmaceutical object – drugs derived from plants – have been transformed over a span of two centuries to remain ever-present within the American medical compendium.

In chapter one, I traced the place of botany and other plant-focused courses like *materia medica* and pharmacognosy within the curricula of American colleges of pharmacy. In the nineteenth and early twentieth centuries, pharmaceutical curricula at

every American college required studying plants and plant-derived drugs. These subjects were considered essential for successful pharmaceutical practice. As the pharmaceutical industry and medical practice shifted to prefer isolated chemical compounds and their synthetic counterparts, the courses that focused on whole-plant therapies gradually lost relevance and their place within American pharmaceutical curricula.

Chapter two focused on the monograph revisions of plant-derived pharmaceuticals within the *United States Pharmacopeia*; depicting an agnotological development regarding knowledge of plants in allopathic medicine. Furthermore, by redacting the once-explicit link between synthetic compounds and their botanic origin, those plant-derived pharmaceuticals that remain in the *Pharmacopeia* no longer appear in any way botanical. These revisions collectively created a modern generation of medical practitioners whose general understanding of drug efficacy overlooks the therapeutic potential of plants.

The third chapter considered the place of wine within American medicine within the context of social concerns regarding alcohol abuse. Ever-tempered by legal, professional, and moral pushback surrounding alcohol consumption, physicians who advocated for the use of medicinal wine have modified their prescribing habits without ever abandoning their belief in the therapeutic potential of wine.

And the final chapter analyzed how research from within the agriculture industry came to focus on allopathic medicine and create pharmaceuticals within plants that are appropriate for a modern pharmacopeia. Where the medical industry had long forgotten

or otherwise lost avid interest in plant-derived pharmaceuticals, agriculture's long history of manipulating crop plants and its overlapping study of subjects like pathology and facilitated a new pathway to vaccine production. But it also reinserted whole-plant materials into the development of modern drugs; except now in an entirely innovative manner.

Plants are still utilized in orthodox medicine today, but in almost no way like they would have existed two hundred years ago. Though the plants themselves have not evolved, allopathic medicine has in various capacities transformed plant-derived therapies to fit into a modern pharmacopeia.

Future research should consider other ways in which biochemical research utilizes plant processes as inspiration for new pathways to pharmaceutical production. PMPs are not the only example of plant biotechnology making novel contributions to pharmaceutical development. For example, in early 2017, Danish researchers announced ongoing work to develop an artificial leaf structure capable of producing drugs via photosynthesis. In addition, more work could consider recent drug developments from within the pharmaceutical industry that have resulted from research on plants as sources for new drugs. In 2017, the United States Pharmacopeial Convention voted in favor of including green tea extract (*Camellia sinensis*) as an active ingredient for the treatment of genital warts. Also, new antibiotics derived from fungi are undergoing clinical trials for FDA approval. These would be utilized for the treatment of bacterial infections on the skin and bacterial pneumonia. Between plant biotechnology and renewed interest in plants as a source for new therapies, the history of plants in allopathic medicine continues to garner need for closer consideration.

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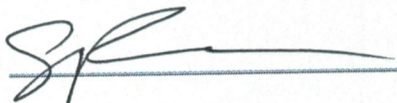
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