RESEARCH AS A FUNCTION OF PHARMACEUTICAL INDUSTRY: The American Formative Period

BY

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PREFACE

The epoch in which we live has been heralded as the "Age of Science" and "The Research Revolution." In America the first industrial research organized on a larger scale and with dramatic results occurred during the early 1900's. Prior to the late 1880's and the 1890's little research (except for some control work) was being conducted by American industry. While there were individuals in industry who dabbled in some scientific experimentation on their own before the 1880's, we found no traces of companies that had developed systematic research programs before this time.

While we often hear about the revolutionary advances in therapeutics, to which research efforts of the American pharmaceutical industry have been pivotal during the last twenty-five years, seldom, if ever, do we hear of the developments that led to research becoming an important function of American pharmaceutical industry. This observation was made by Glenn Sonnedecker several years ago, and I am grateful to Dr. Sonnedecker for pointing out to me that one of the gaps in pharmaceutical history is the story of how and when research actually became a function of the pharmaceutical industry in the United States. I am deeply indebted to Dr. Sonnedecker for his valuable suggestions throughout my two years of research on this subject, for

his many hours of help in locating data which may have survived from this early period, and for his keen, analytical perception of pharmaceutical history which he offered to me so freely and enthusiastically.

We have attempted to put together a representative and meaningful picture, however sketchy, of conditions and events that produced the pioneering, self-conscious research beginnings of the industrial laboratories. It is important here that we also get some understanding of the environment or social matrix surrounding the birth of such research if we are to appreciate fully and place in perspective the rapid growth which has been taking place in the research programs of American pharmaceutical companies more recently.

Since there is little information available in the literature specifically about early research in the pharmaceutical industry, it is important that an attempt be made to reconstruct this part of the history of the American pharmaceutical industry now, while a few of the early research workers are still living and the scattered records of a few early companies still remain.

Many of the records of the research work of the American pharmaceutical companies prior to 1920 have been either misplaced or discarded over the years. It should also be noted that a few of the companies, which do have some surviving records, did not find it feasible for us to examine their records.

In attempting to reconstruct the history of research work in the American pharmaceutical industry prior to 1925, an early task was to make a systematic search of the literature. We began by examining complete sets of the following bibliographies; Index-Catalogue of the Surgeon-General's Library, which is published in four A to Z series beginning, respectively, in 1880, 1896, 1918, and 1936; Current Work in History of Medicine, which began in 1954 and has been published quarterly since that time; the "Bibliography of the History of Medicine of the United States and Canada," which has been published annually since 1939 in the Bulletin of the History of Medicine; the "Critical Bibliography" which appears in Isis; Judson Gilbert's A Bibliography of Articles on the History of American Medicine compiled from "Writings on American History" 1902-1937; George Griffenhagen's Bibliography of Papers Published by the American Pharmaceutical Association that were presented before the Association's Section on Historical Pharmacy 1904-1957 (American Institute of the History of Pharmacy, Madison, 1958. 26 pp.); General Index to Volumes One to Fifty of the Proceedings of the American Pharmaceutical Association from 1852 to 1902 inclusive; Reader's Guide to the Periodical Literature, continuous since 1891; and the Industrial Arts Index, continuous since 1913. (Bibliographies and indices were examined systematically with topical categories or entries in mind such as drug, medicinal, industry, manufacturer, company, and various forms of these.)

Upon completing this phase of our literature search we began to trace down the articles that seemed relevant. We then proceeded to examine all the proceedings of the American Drug Manufacturers Association[1] and the proceedings of the American Pharmaceutical Manufacturers Association[2] to obtain clues about the research work that was being done in the early period by pharmaceutical companies belonging to these associations.

The literature search did not reveal as much information as anticipated. This circumstance underscored the importance of contacting some of the individuals who were either directly or indirectly involved for a long time in research work of the pharmaceutical industry to see if they could provide first-hand information.[3]

The final phase of this investigation involved visiting several of the older pharmaceutical companies to examine their remaining early records. Because much of the source material has become elusive or entirely lost, and

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1. This association was known as the National Association of Manufacturers of Medicinal Products from its founding in 1912 until 1917, and in 1958 it merged with the American Pharmaceutical Manufacturers Association to form the Pharmaceutical Manufacturers Association.

2. This organization was known as the American Association of Pharmaceutical Chemists from its founding in 1907 until 1921, and in 1958 it merged with the American Drug Manufacturers Association to form the Pharmaceutical Manufacturers Association.

3. We corresponded, for example, with Frank O. Taylor, George D. Beal, and Elmer B. Vliet about their experiences.

extended field trips to search industrial files are forbidding in cost, we decided to limit the present study, basically, to five companies, which we hope may be representative of the early research leaders (namely Abbott Laboratories, Eli Lilly and Company, Parke, Davis and Company, E. R. Squibb and Sons, and The Upjohn Company). Several weeks were spent in the libraries of Parke, Davis and Company, Abbott Laboratories, and E. R. Squibb and Sons. Intensive examination of early records of these companies gave additional insight into the type and extent of research work prior to 1920 in some pharmaceutical companies. I am deeply indebted to Gertrude Losie, head of the Research Libraries of Parke, Davis and Company; Walter Southern, head of Scientific Information at Abbott Laboratories; and J. E. Aurelius, head of the Library at the Squibb Institute for Medical Research, for their cooperation, advice and aid during my work at these companies. The officers of these companies likewise have our appreciation for giving free access to their early company records.

I would also like to thank Dr. Robert W. Hummel for his guidance throughout my two years of graduate study.

The Graduate Fellowship granted to me by the American Foundation for Pharmaceutical Education has gone far toward making my graduate work possible, and I shall remain grateful for it.

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I

INTRODUCTION

Approximately 4,400,000 Americans of working age who are living today would not be alive if the nation's mortality rate had remained at the 1935 level. These lives have been saved by advances in medical care and in the standard of living in the United States. These advances have not been brought about through any one institution. Physicians, pharmacists, nurses, scientists engaged in medical and pharmaceutical research, those engaged in the production and distribution of pharmaceuticals, as well as those in governmental and voluntary health agencies have all contributed to the strides forward in medical care.[1]

"Since 1944, the death rate from influenza has dropped ninety per cent; the rate from tuberculosis, eighty-three per cent; acute rheumatic fever, eighty-three per cent; syphilis, seventy-nine per cent. Since 1940, the death rate among mothers in childbirth has declined by over ninety per cent. During the five years ending in 1960, the number of patients released from mental hospitals has increased

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1. Arthur D. Little, "A Report on the Social and Economic Benefits of the Pharmaceutical Industry in the United States," December 4, 1961, p. 4. This report was prepared for the Pharmaceutical Manufacturers Association.

fifty-one per cent. Over 200,000 more persons were released than would have been at the 1955 rate."[2]

It is difficult to quantify the contributions made by pharmaceutical research, much less determine exactly what part of the advances mentioned above can be attributed specifically to industrial pharmaceutical research. That research conducted or sponsored by the pharmaceutical industry has been significant in advancing medical care, however, is beyond doubt.

Since 1951, the expenditures of the pharmaceutical industry for research and development are reported to have increased about 276 per cent -- from over $60,000,000 in 1951, to a budgeted $227,000,000 in 1961.[3]

One expression of the yield from industrial research efforts of this magnitude comes from a study showing that in the last two decades (1941-61) individual companies originated and marketed 314 chemically distinct medicinals that are still used in pharmaceutical and medical practice. "More than 70 American firms" were credited with these discoveries, representing about 60% of such drugs introduced and still regularly available for use today.[4]

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2. "Statement of Eugene N. Beesley, Chairman of the Board, Pharmaceutical Manufacturers Association, presented before the Sub-committee on Antitrust and Monopoly, Senate Committee on the Judiciary on December 7, 1961, in Washington, D.C.," p. 2.

3. Pharmaceutical Manufacturers Association, "Pharmaceutical Manufacturers Association, "Pharmaceutical Manufacturers Association Ethical Drug Industry Survey of Research and Development Expenditures, 1960-1961," June 1961, Washington, D.C., p. 1.

About seventy per cent of the more than 500 million prescriptions dispensed in 1960 could not have been filled in 1950 because the drugs had not been discovered yet.[5]

Only during the last quarter century has pharmaceutical research so decisively transformed drug therapy. However, many years earlier, during the late 1890's and early 1900's, research in American pharmaceutical industry was finding its place and pattern, in an adolescence altogether necessary for its present maturity. While research is a well worn word in the industry today, this was not always the case.

One objective here is to show how research came to be valued so highly, who laid the foundations, and what circumstances converged to give research a new order of importance immediately following this pioneer period. Within the present context, we have not been concerned with delving into technical aspects of the early research, except to illustrate the types of research then being conducted.

During these decades most of the research conducted by the pharmaceutical industry, and indeed by industry in general, could be called "applied research." What we mean by such terms should be clarified perhaps, since we will be using them repeatedly. For our purposes we define <u>research</u> as a systematic or planned investigation looking toward new or improved pharmaceutical products, processes, and tests, toward understanding the pharmaceutical, pharmacological,

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5. Beesley, Statement Before Senate Committee, p. 3.

and physico-chemical character of medicinal substances, and indeed toward gaining any new knowledge presumably related to pharmaco-scientific developments.[6]

By industrial research we mean research which is accomplished primarily through industrial funds.[7] When we speak of the pharmaceutical industry we mean those manufacturers who are devoted to making drugs primarily for prescription use (in more or less large-scale production).

We often hear the terms "basic research" and "applied research" and the controversy over their meaning. However, for our purposes "applied research" may be considered any research which has some definite or useful goal or end product in sight when the work is initiated; while "basic

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6. Included in this concept of research are some of the points made by the Pharmaceutical Manufacturers Association: "Planned search for new knowledge, whether or not the search has reference to a specific application. Application of existing knowledge to problems involved in the creation of a new product or process, including work required to evaluate possible uses. Application of existing knowledge to problems involved in the improvement of a present product or process.

"..... The question, 'When does development end and production begin?' is often asked. If the primary objective is to make further improvements on the product or the process, then the work comes within the definition of research and development. If, on the other hand, the product or process is substantially 'set', and the primary objective is to develop markets or to do preproduction planning, or to make engineering changes in production equipment, then the work is no longer research and development. Routine quality control activities are not included .... Development of quality control methods are included." P. M. A. Survey of Research and Development Expenditures, June 1961, Washington, D. C.

7. This includes work done in universities or other institutions outside the industry, but supported by industry.

research" will be considered research conducted with no ultimate goal clearly in mind other than the advancement of knowledge. Thus, one could say that the distinction between "applied research" and "basic research" is mainly one of motive.[8]

One question about the definition of "basic research" too little recognized -- and eluding our definitions -- has been perceptively put to us by Frank O. Taylor, when he said, "We do not know what may be 'basic' until after it has been done, sometimes long after. Was Perkin's work opening up the field of color chemistry, when he was actually trying to synthesize quinine, 'basic research'? It seems to me it was what might be called 'applied research' which suddenly became 'basic' when its accidently observed meaning was realized."[9]

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8. For other definitions of research and types of research see E. R. Weidlein and W. A. Hamor, Science in Action, New York, 1920; C. C. Furnas, Research in Industry, New York, 1948; O. S. Schairer, "The Role of Research in Modern Industry," Science, 96 (October 9, 1942), p. 328; G. M. Beringer, "Pharmaceutical Research," The Journal of the American Pharmaceutical Association, 10 (1921), p. 91; C. F. Kettering, "The Functions of Research," Journal of Industrial and Engineering Chemistry, 19 (November, 1927), p. 1212.

9. Frank O. Taylor to Glenn Sonnedecker, August 16, 1961, in personal file of M. K. W.

II

THE BIRTH OF AN INDUSTRY

To understand and evaluate any industrial activity we should know something about its past history and performance. Likewise, to place in perspective the early research work of American pharmaceutical industry, it is necessary to have some understanding of the development of the industry.

European Beginnings

To a certain extent the pharmaceutical industry in America was an offspring of the pharmaceutical industry in European countries, especially England, France and Germany. George Urdang wrote:

> It was about two hundred years ago, in the middle of the eighteenth century, that the beginnings of a pharmaceutical industry replacing the traditional small scale manufacturing by the retail pharmacists became obvious. Thus when about another fifty years later, in the early nineteenth century, the general conditions in the world at large offered an opportunity not only to a few industrialists gifted with special scientific or organizational talents but to an era, the new development found in pharmacy a well prepared soil....
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> Not that there had not been large scale production of certain goods in the time of Greek and Roman antiquity and in the Middle Ages. Mass production of mass goods, however, by

mechanized processes and with the tendency of creating new needs is a child not only of scientific and technical progress but of a new ideology. The industrial era is based on the recognition of the equal rights of all men not only as to heavenly goods but also to earthly ones, setting as a new goal that state of general refinement and welfare of all mankind, not only of a few privileged classes or individuals, which we call modern civilization....

The large scale production of earlier times was essentially incidental and conservative. Modern industrial mass production has been systematically planned and progressive.[1]

The first pharmaceutical industrial manufacturing aiming at replacing the preparation of compounded drugs in retail pharmacies is reported about 1600, and it is significant that it was the laboratory of a great pharmacy which became in this way an ancestor of what we call today the pharmaceutical industry. The smaller pharmacies of and around the city of Schleswig (Germany) were forced to buy the 'preparation chymica and composita' needed by them from the court pharmacy which was conducted on the Duke of Schleswig's account. The fact that this early example of pharmaceutical industry remained singular is due to the cause of its inception. This cause was not a change in general conditions but merely the egoism of one of the many German princes of this period and, therefore, the venture was restricted to the territory under the command of this prince.

It was not much later that in England a pharmaceutical industry undertaking developed from retail pharmacy. Here, however, the motive was not the enrichment of one individual representative of the fading world of autocracy, but the benefit of an entire professional group and of the public which it was to serve. The Society of the Art and Mystery of the Apothecaries of the City of London, incorporated on December 16,

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1. George Urdang, "Retail Pharmacy as the Nucleus of the Pharmaceutical Industry," in Essays in the History of Medicine, edited by Henry E. Sigerist, Baltimore, 1944, p. 325.

1617, started in 1623 with the preparation of galenicals and chemicals on a co-operative base.[2]

The breakdown of the feudal system, the improvement in means of transportation, and the concentration of capital and power in commerce instead of in estates were some important forces bringing about the development of the industrial era. In the development of the pharmaceutical industry, science and the progress of scientific techniques were particularly important.

"The fact that retail pharmacy sheltered and cultivated the young science of chemistry in the eighteenth and the early nineteenth centuries made the pharmaceutical retail stores and their laboratories in the countries concerned the birthplace not only of the pharmaceutical industry but also of a great part of applied technical chemistry."[3] In Germany, France, and England, as well as in the United States, many community pharmacies served as the nucleus for the development of a pharmaceutical industry.

One of the very first community pharmacists to make the laboratory of his community pharmacy the starting point of an important manufacturing plant on the basis of scientific knowledge and technical skill was the Frenchman Antoine Baumé (1728-1804), who not only was listed among the Parisian "Maitres d'Apothicaires" but also won a place

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2. Ibid., p. 326.

3. Ibid., p. 327.

in the roster of famous scientists of pharmaceutical origin. Joseph Pelletier and Stanislas Limousin were two other French pharmacists who enlarged their laboratories into commercial manufacturing establishments. E. Merck-Darmstadt, J. D. Riedel-Berlin, and E. Schering-Berlin were three of the German companies that developed from community pharmacies between 1814 and 1851. Both Merck and Schering later developed successful operations in the United States, which eventually became independent. Among British pharmaceutical concerns which developed in the early nineteenth century from the laboratories of community pharmacies are Allen and Hansburys, Ltd., and Howard and Sons, Ltd. (both offspring of the Plough Court Pharmacy in London); Thomas Morson and Son, Ltd.; and J. F. Marfarlan and Company.[4]

American Industrial Development

In discussing a comparable development of pharmaceutical industry in the United States, we should recall the more general framework of industrial development, and some differences from its counterpart in the "mother country" and other European nations. For example, feudalism and the guilds hampered the growth of industry in Europe, while America never developed more than the rudiments of a guild

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4. Ibid., p. 334.

system,[5] even in the environment of community pharmacy. The labor force in European countries had to be recruited from among dispossessed peasants and unemployed artisans, who were bound by tradition and loyalty to other systems of production; while in America there was no rural surplus of peasantry, and thus we had to form a labor force through the immigration of diverse peoples.

The single, stark fact that America unlike England and the other European countries was a land without traditions and without deeply entrenched classes influences pharmaceutical history as it does so much else in the American development. Conditions soon generated an 'American spirit', however, that fostered industrial development. "Confronted by a seemingly limitless frontier and unending resources, cut off from European feudalism and European tradition, Americans quickly came to value the individual over the state, the new over the old, and hard work over leisure. This spirit was expressed in and reinforced by the prevailing protestantism, which.... preached a concern with the things of this world, single-minded devotion to the task at hand, and a drive for success as a measure of God's favor. Thus American industry was nourished from the beginning by a hard-driving, self-sacrificing, individualistic, optimistic, energetic, and

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5. Victor S. Clark, History of Manufactures in the United States, Washington, D. C., 1916, Vol. 1, p. 113.

even ruthless people."[6]

Conditions in America were potentially favorable to the growth of industry, but for a long time development necessarily lagged behind that of Europe. Some potentially "favorable" factors at first posed barriers to industrial development. "The frontier, at the same time that it was helping to create the American spirit, acted as a huge drain, absorbing surplus population, making the price of labor dear.... Similarly, the vast distance from Europe, a favorable factor in one way, also meant separation from markets and from the center of technical and scientific knowledge. Internally, distance meant an unending struggle to connect scattered settlements to build roads, dig canals, and find means to cross great rivers and high mountains. Even the tranquility of American life was not an unmixed blessing, for industrial growth has always been closely connected with war. And, finally, one must not forget that for half its history America was a colonial realm, subject to the greatest industrial nation on earth, a nation which jealously guarded its own prerogatives and advantages."[7]

Even with handicaps, manufacturing in America continued to grow slowly, and at the close of the colonial period we find rudimentary industries in a number of fields, although little was yet organized on a truly factory basis.

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6. Eugene V. Schneider, Industrial Sociology, New York, 1957, pp. 51-52.

7. Ibid.

Although the growth of manufacturing was hampered by the Jacksonian regime, investment in industry after 1820 doubled in each decade until the Civil War.[8]

The factory loomed larger on the American scene than ever before; and with it grew the power of the manufacturer, although he tended to be outweighed in the Federal government by the Southern planter.

The Civil War ushered in changes favorable to the tremendous growth in American industry during several following decades. When the Civil War broke out and the Southern states seceded from the Union, the control of the government came to be dominated by a coalition of Northeastern manufacturers and independent Middle Western farmers, which quickly enacted legislation to protect American industry. This new political program provided a favorable climate for an explosive expansion of industry between 1860 and 1890, which included the first major development of large-scale pharmaceutical industry. The products produced by American factories in 1860 were valued at over 1,800 million dollars, making America the world's fourth most important industrial power. By 1870 this figure had doubled; by 1880 it was three times as large; and by 1890 it was five times as large.[9] "Sulfuric acid manufacture,

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8. Schneider, Industrial Sociology, New York, 1957, pp. 53 and 55.

9. Arthur Meier Schlesinger, Political and Social History of the United States, 1829-1925, New York, 1925, pp. 280-281.

which some authorities consider as a chemical index, grew from what has been estimated to be 100,000 short tons in 1880 to 487,377 short tons by 1900. This then increased to nearly 2,300,000 short tons by 1914, /but/, still less than a sixth of what is manufactured today. Many other chemicals showed similar growth curves."[10]

With these outlines of the industrial development in mind, let us look more specifically at the birth and growth of pharmaceutical-chemical industry.

Early Pharmaceutical Beginnings in the United States

The early North American colonies were not able to develop a pharmaceutical or chemical industry, because of deficiencies that included two foundations upon which every industry is built: demands for its products and its peculiar techniques of production.[11] The American colonies were sparsely populated and there was no need or demand for large quantities of drugs or chemicals. Moreover, the colonists did not have the technical knowledge and resources to develop a pharmaceutical or chemical industry that would produce drugs of the European quality. Moreover, industry of whatever kind was hampered by poor transportation and the

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10. H. M. Corley, ed., Successful Commercial Chemical Development, New York, 1954, p. 15.

11. Williams Haynes, American Chemical Industry, New York, 1939, Vol. I, p. 49.

fact that it was not in the best interest of England to foster or even to allow industrial development in the colonies. Because of these conditions large-scale industrial production of pharmaceutical chemicals in the United States did not begin until the end of the Revolutionary War.

The pharmaceutical industry can be called justifiably "the Child of Wars." "It was born during the Revolutionary War (1775-1783). It took the decisive step from childhood to manhood after and in consequences of the Civil War (1861-1865) and it became independent from Europe and dominant on the world market after World War I (1914-1918). World War II (1941-1945) made this dominance a generally accepted fact."[12]

Let us now look briefly at some of the reasons why these conflicts stimulated the birth and growth of the drug industry. First, there was a great increase in the demand for drugs during each war. Moreover, even the normal flow of imported drugs was reduced, and in some instances almost completely halted. Thus the industry had to increase its production of drugs to meet wartime demands.

Prior to the Revolutionary War the United States was heavily dependent on England not only for drugs but for many other manufactured goods. "Drugs and medicines were two items which the Earl of Sheffield believed the emancipated colonists would continue to import, and by preference from Great Britain. This was largely true until the War of 1812

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12. Edward Kremers and George Urdang, History of Pharmacy, 2nd ed., Philadelphia, 1951, p. 427.

cut off these essentials."[13] At this time some pharmacists were making various fine chemicals themselves, such as ammonium and iron acetates, potassium arsenate, bismuth subnitrate, iron and zinc oxides, tartar emetic, Rochelle salt, and sodium phosphate.

To the drug industry World War I seemed an even greater challenge than did the Revolutionary War, because meanwhile the United States had become dependent upon Germany for many drugs, especially valuable synthetic organic compounds. World War I cut off this supply and the United States was forced to manufacture its own. This pressure, reinforced by German pharmaceutical knowledge gained as war booty, catalyzed an advance that eventually transformed American pharmaceutical industry.

It is possible to see this line of development of the pharmaceutical and chemical industry in terms of three life stages: the formative period lasted until about 1870; the adolescence took place between 1870 and 1914; and a third period beginning about the time of World War I that still seems characteristic of current developments.

During most of what we term the formative period the United States was primarily an agrarian nation. While very small amounts of certain chemicals -- such as potash, sulfur, and saltpeter -- were made for local use occasionally in the early part of this period, it was not until the end of the Revolutionary War that commercial large-scale production of

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13. Williams Haynes, American Chemical Industry, Vol. I, New York, 1954, p. 212.

drugs was undertaken.

One of the earliest such ventures of record came in 1786 when the Philadelphia firm of Christopher, Jr. and Charles Marshall, community pharmacists and wholesale druggists, began making muriate of ammonia and Glauber's salt.[14] It should be noted that non-commercial production of pharmaceutical chemicals on a large scale was undertaken still earlier when "In 1778 the apothecary general, Andrew Craigie, initiated and later on managed 'a general laboratory' in which medicines for the needs of the military hospitals and fighting army were prepared."[15]

Not until around 1850 did such activities begin to take visible form as an industry. This embryo or core developed, during the second period after 1870, into the skeletal structure of the pharmaceutical industry of today.

Prior to the Civil War, Philadelphia dominated the field of pharmaceutical manufacturing. John Farr established a manufacturing plant at Philadelphia in 1818. Four years later Rosengarten and Sons, a Philadelphia company that played a role in the development of pharmaceutical chemistry in this country, was founded (1822). Smith, Kline and French Laboratories got its start in Philadelphia in

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14. S. P. Sadtler, "Influence of Pharmacists on the Development and Advance of Modern Chemistry," American Journal of Pharmacy, 93 (1921), p. 200.

15. Kremers and Urdang, History of Pharmacy, p. 427.

1841.[16] In 1862 John Wyeth decided to enlarge the laboratory of his community pharmacy in Philadelphia into a pharmaceutical plant for producing fluidextracts, wines, syrups and elixirs.

In 1866, William R. Warner, another Philadelphia pharmacist decided to expand his community pharmacy and wholesale drug business to include the manufacturing of pharmaceuticals. William R. Warner and Company (now Warner-Lambert Pharmaceutical Company) became well known for its successful manufacturing of sugar coated pills.

Elsewhere in the country, a number of other successful drug companies developed during this formative period, and many of them were offspring of community pharmacies. Thus arose William S. Merrell Company, for example, founded in Cincinnati in 1828. Merrell utilized indigenous plants as the basis of its manufacturing.[17] Frederick Stearns and Company (now merged into Winthrop) started in the back room of the community pharmacy that Frederick Stearns had opened at Detroit in 1855. A. P. Sharp, who owned a small pharmacy in Baltimore, took his clerk, Louis Dohme, into partnership in 1860 and began manufacturing pharmaceuticals as the Sharp and Dohme Company.

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16. The original name was George K. Smith and Company; and then after several changes in name was finally incorporated in 1891 under its present name. Ibid., p. 428.

17. Kremers and Urdang, History of Pharmacy, p. 429.

Parke, Davis and Company also had a community pharmacy as its birthplace. Samuel P. Duffield was a pharmacist as well as a physician and held a Doctor of Philosophy Degree in Chemistry from the University at Giessen. Duffield was determined to put his education to work and began producing pharmaceutical chemicals in the laboratory of his pharmacy in 1862. However, because of a lack of capital, Duffield had difficulty expanding his laboratory and purchasing equipment. Success for this firm did not come until the early 1870's when Hervey C. Parke and George S. Davis took over the company.[18]

Prompted by his medical friends and his desire for purer and better drugs, E. R. Squibb established his laboratory in 1858, at Brooklyn, New York.

Two companies now prominent were not established until what we have called the "adolescent period." Eli Lilly and Company was founded at Indianapolis in 1876 by Eli Lilly, a pharmacist and Civil War colonel. Eli Lilly owned community pharmacies at Greencastle, Indiana, and Paris, Illinois. Twelve years after the founding of Lilly, a physician, Wallace Calvin Abbott, began manufacturing "dosimetric granules" in Chicago (1888), and thus began the life of The Abbott Alkaloidal Company, which later became Abbott

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18. Tom Mahoney, The Merchants of Life, New York, 1959, pp. 69-71.

Laboratories.[19]

Thus generous evidence may be shown to illustrate the metamorphosis that George Urdang discussed in terms of "retail pharmacy as the nucleus of pharmaceutical industry." Superficially, this seems only one expression of the steam-power industries arising on the ashes of home industry and artisanry. Yet, what happened in pharmacy seems more than a transfer or concentration of function, more than meeting an old need in a more efficient way. For the old community pharmacy, in its highest development, often included a small back-room laboratory in the hands of personnel with both the business experience and technical knowledge to guide it into larger-scale production and wider scope of operation. For the most competent in pharmacy, therefore a new industrialism could mean not so much being supplanted as a larger and challenging opportunity.

As these pharmacists prepared many of the drugs they

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19. Some other firms that were established during the "formative period" are playing an important role in the industry today. For example, in 1849 two German chemists, Charles Pfizer and Charles F. Erhart formed a partnership and began manufacturing fine chemicals in a one-story wooden building in Brooklyn, New York. A number of other firms which are important in the industry today were not established until after 1870. Among this group were such companies as Merck, Upjohn, Schering, Lederle, and Hynson, Westcott and Dunning. Although a number of other firms were established during the latter part of the 19th century, it is not our purpose here to trace the founding of all such firms, but rather to demonstrate the structuring of a clearly discernible industry.

dispensed in bulk in their small early laboratories, they naturally encountered ideas for improved products or processes, leading to modest experiments during slack hours, as the pages of the American Journal of Pharmacy testify during the 19th century. This echoed a West European tradition -- at a lower level of American development -- in which the best practicing pharmacists had pursued research yielding such important results as the discovery of elements, new types of compounds, analytical procedures and other chemical knowledge significant, beyond the immediate needs of pharmacy, to the science of chemistry at large.

The chemist and historian, Ernst von Meyer says:

> The interest which chemistry and pharmacy had in common resulted in their exercising a beneficial action upon one another. A large number of famous investigators owed to the practice of pharmacy their stimulus to the study of purely chemical phenomena; of these we may mention Kunkel, the Lemerys (father and son), Geoffroy, Rouelle, Neumann, Marggraf and Scheele. While they themselves and others contributed a wealth of the most valuable observations, indeed of fundamental discoveries, to chemistry pharmacy was at the same time materially advanced, not only by those discoveries, but also by special pharmaceutical researches. The chief gain for pharmacy lay in its intimate fusion with pure chemistry. On the other hand, the work required in apothecaries' shops proved itself the best preparatory training for future chemist, for at that time [pre-19th century] there were no laboratories in which systematic instruction was given.[20]

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20. Ernst von Meyer, A History of Chemistry, George McGowan, trans., London, 1906, p. 161. For a summary of some of the important discoveries through research by pharmacists from the 17th through the 19th century, see the topical chapters in George Urdang, Pharmacy's Part in Society, 3rd ed., Madison, 1959.

Some of these research successes fostered industrial growth, both here and abroad, and at least set early examples for the close association between laboratory research and laboratory production that became characteristic of progressive pharmaceutical development. Even so, the meager resources and utilitarian bent of pharmaceutical industry in the 19th century left it dependent upon the more mature science of Europe until, as W. A. Noyes concluded, "The exclusion of chemicals imported from Germany during the /First world/ war lead to a very rapid development of the chemical industries in America, especially in the direction of dyes and pharmaceutical chemicals."[21]

The end of the war found American pharmaceutical industry expanded and strengthened, not only productive but now also creative, and beyond its adolescence. The subsequent strength of the industry has been so much nourished by this creative or research function that a closer examination of how it was drawn upon, and then was imbedded as an integral part of leading laboratories, should hold more than ordinary significance for this segment of the history of American industry and applied science.

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21. W. A. Noyes, "Potent Influences in Chemical Progress," Drug and Chemical Markets, 9 (1921), p. 512.

III

MILIEU OF RESEARCH BEGINNINGS IN THE UNITED STATES

The creative or research function, on a systematic basis, did not spring up over night in the pharmaceutical or chemical industries. It was many years from the time some of the early American pharmacists began their modest experiments in back-room laboratories of their community pharmacies until systematic research programs became a generally accepted function of the pharmaceutical industry. Probably it was almost 1920 before systematic research seemed indispensable to most firms that aspired to be among the industry's leaders. Nevertheless, there were a number of pharmaceutical companies with earlier systematic research programs.[1]

It was during the "adolescent" life-stage of the pharmaceutical-chemical industry, the period 1870 to 1914, that technologic capital was built up for the manufacture of pharmaceuticals and chemicals and it was in this period that organized industrial research was started. Irving Langmuir, Ph. D., Associate Director of the General Electric

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1. Unless otherwise mentioned throughout, the discussion of research developments refers to American pharmaco-industrial research.

Company's Research Laboratory notes that, "about 1870 or 1880, the industrialists of this country began to realize how much they could profit by applying scientific knowledge to manufacturing processes and to the discovery of new products and processes."[2]

Ernst von Meyer points out that,

> The immense development of large chemical industries and, in fact, of all the branches of chemical technology during the nineteenth century is the natural consequence of the great advances in chemical knowledge and the rational application of these to technical processes. The light of scientific research has thus been shed upon the latter, and new branches of industry have been grounded upon exact investigations. ....The great advances which have been made in chemical technology only became possible with the development of analytical chemistry, [whose gravimetric basis was laid down in the second half of the 18th century and was systematized by the mid-19th century] which allowed of a clear insight into the composition of the original intermediate and final products of technical processes. Since the beginning of the nineteenth century, methods of research have gradually became more perfect, methods which more and more meet the requirements of the technical chemist, and which have constituted and still constitute the most important aids to the development of chemical industry.[3]

In many respects the early American chemical manufacturers echoed the development of some of their contemporaries abroad, especially an English bent toward wedding the principles of chemistry with trial-and-error methods to

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2. Irving Langmuir, "The Unpredictable Results of Research," in Lilly Research Laboratories: Dedication, Indianapolis, 1934, p. 7.

3. Ernst von Meyer, A History of Chemistry, George McGowan, trans., London, 1906, p. 597.

produce bulk chemicals. American industry also utilized this principle at first -- a semiscientific empiricism.

Beginning in the 1870's and 1880's isolated segments of the American chemical and pharmaceutical industries began to apply scientific principles more meaningfully to their manufacturing. Here, it might be due to the efforts of an entrepreneur interested in science; there, to the work of one or two of the supervisory staff who had some training in science. Initially such efforts occasionally resulted in improvements in apparatus, or improvements in some of the products produced. These rather incidental innovations were followed by more systematic attempts to produce standardized or uniform drug and chemical products.

"Something like research, as we know it, supplanted trial and error experiment, and the chemical industry, abroad and here, became the first to make a definite task of deliberately seeking scientific facts as a means to making its products better or cheaper. New products and new uses were uncovered, first by chance or as a side issue, later with conscious intent, and so during these years [1865-1910] this new tool was adopted and perfected.... It is significant therefore that we began to harvest them [the fruits of applied research] in a haphazard way by appropriating scientific knowledge and using it to industrial ends long before we carried on anything like conscious research."[4]

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4. William Haynes, American Chemical Industry, New York, 1954, Vol. 1, p. 393.

Even after pharmaceutical manufacturers developed a self-conscious research endeavor of their own, this naturally remained geared primarily to the prospect of economic success. Hence, the practice of "appropriating scientific knowledge" of a more basic kind to improve the lot of mankind in an applied way, changed only in degree over the years. This free exchange and cumulation that are characteristic scientific knowledge internationally makes it difficult to assess and express the extent to which discoveries are "industrial" or "non-industrial," which in any event is not our present purpose.

It can be said, however, that throughout most of the American "formative period" here discussed, pharmaceutical progress depended heavily upon European scientific centers with the men, facilities, and maturity to yield basic materials.

The evolving patterns of pharmaceutical research and discovery tend to merge into one another, in long-time waves of transition. Yet we need not hesitate to distinguish times of transition and changing emphases in industrial research efforts if in doing so we remain aware of the extent of overlap.[5]

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5. Periodization is suggested by Frank O. Taylor's statement that "the history of Manufacturing Pharmacy as a whole and of Parke, Davis and Co., may be divided into four periods characterized by the most important activity of the time.... These periods are as follows:
   1. Formative Period -- 1867 to 1874
   2. Botanical Research Period -- 1875 to 1882
   3. Standardization Period - 1882 to 1894
   4. Biological Period -- 1895 to present time [1915]."

Much of the earliest pharmaco-industrial research here showed the influence of a pharmacognosy that had outgrown the old herbalist tradition and reflected the strength of its full scientific maturity. Since the second quarter of the 19th century pharmacognosy paired with phytochemistry had led to the isolation of large numbers of physiologically active plant constituents. Thus pharmaco-botanical work found renewed respect; and through the medium of chemistry it produced both the potent preparations and the methodologic tools that led to a research emphasis upon drug assay and standardization, particularly notable during the last quarter of the century.

In the closing years of the 1890's, research interests were shifting to exciting biological products discovered in Europe, based on fundamental work by giants such as Robert Koch and Louis Pasteur, and finding a pharmaceutical culmination in the antitoxins of Emil von Behring in Germany and Emile Roux in France.[6] Organic chemistry had put forward, since the 1880's, the vanguard of an army of new synthetic drug products; but American industry was to remain heavily dependent upon Europe in this field until World War I.

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5. (Cont.) Frank O. Taylor, "Forty-five Years of Manufacturing Pharmacy," The Journal of the American Pharmaceutical Association, 4 (April, 1915), p. 469.

6. Diphtheria antitoxin had come into clinical use by 1892; and in 1894 at the International Congress of Hygiene (Budapest, 1894) Roux read a paper announcing the clinical effectiveness of diphtheria antitoxin.

By the end of the first decade of the present century, the whole world knew that Paul Ehrlich and his co-workers, with a new concept and systematic method, had made a synthetic chemotherapeutic agent that was an effective specific against syphilis. Ehrlich's influence was to transform the whole outlook of pharmaceutical research, both in and out of industry. The methods of chemotherapeutic research, when coupled with the new touchstone of experimental pharmacology for evaluating drug usefulness, gave a potential and prospect to American pharmaco-industrial research that brought to a close its "formative period."

As we look more closely for the American industrial beginnings of this development, we find a number of experimenters in back-room laboratories of community pharmacies and wholesale drug houses, following a tradition established by eminent practitioners among European pharmacists by the 18th century. Under American conditions noteworthy attempts of this kind awaited such 19th-century figures as Charles Marshall, Samuel P. Wetherill, Robert Shoemaker, William S. Merrell, John Uri Lloyd, Samuel P. Duffield, John Wyeth, and Frederick Stearns.

Some of these practitioners were among the founders of American pharmaceutical industry itself, as we have noted; and indeed their initial experiments often were concerned with applying chemical principles and pharmaceutical art to the development of methods for producing various drugs on more or less a large scale.

Much of the scattered experimentation in the period of botanical emphasis dealt with projects such as improving the pharmaceutical characteristics of currently available products and developing better methods of preparing fluid extracts by maceration or percolation. Some work was being done on glandular specialties or digestive enzyme preparations. It is reported that John Carnrick, a New York chemist and founder of Reed and Carnrick, became interested in the work of the French physiologist, Claude Bernard, as early as 1853. The first glandular product introduced by Reed and Carnrick "was the result of experimentation which he began in 1861. He obtained some crude pepsin from a Dr. Corvisart of Paris, purified it, added pancreatin and other glandular extracts, and offered it as a prescription digestive aid under the name of Peptenzyme. The product, now used largely to mask the unpleasant taste of other medicines, is still in the Reed and Carnrick line."[7]

Parke, Davis and Company also began research on digestive enzymes about this time, stimulated by the European probing of the nature of enzyme action, especially

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7. "A Century of Pharmacy," Medical Times, Vol. 88, No. 1 (January, 1960), p. 125. The author refers to a problem characteristic of our present study, with regard to various pharmaceutical companies, when he says, "Present glimpses of Reed and Carnrick's early years tend to be more tantilizing than revealing, because of the failure to preserve corporate records. In that period the company moved several times, with each move unfortunately also bringing a cleanout of company files; for in those blessed days before the income tax there were fewer compelling reasons than now for making and keeping detailed records." (p. 123)

after the revealing work on diastase reported in 1833 (Payen and Persoz), and the German discovery of pepsin three years later (by Theodor Schwann). "In 1874 they introduced a saccharated pepsin of such strength that 5 grains would digest 60 grains of albumin, this being of 1:12 strength Today [1927] that would be considered so weak as to be absolutely useless. In 1881 appeared a product dignified by the name 'concentrated' of 1:100 strength, but in 1883 this was displaced by a 1:500 pepsin... by 1893 strengths of 1:3000 and 1:4000 were regularly supplied, while up to 1:15,000 could be made... [and by 1927] in the research laboratory as high as 1:42,000 strength has been obtained."[8]

Some of the earliest research conducted by pharmaceutical companies sought new products, which in an important way (especially before the turn of the century) was thought of as a search for plants or herbs containing therapeutically active principles.

As early as 1874 Parke, Davis and Company began such efforts to discover botanical drugs. At first the company investigated plants suggested by physicians or by papers appearing in journals of botany and pharmacognosy. If these drugs showed promise, the company made preparations of the drug and sent them to physicians to try on patients.

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8. Frank O. Taylor, "Parke, Davis and Company," Industrial and Engineering Chemistry, Vol. 19, No. 10 (October, 1927), pp. 1206-1207.

Several years later Parke-Davis began to take the initiative in the search for valuable plant drugs by sending representatives of the company to explore the northwestern United States, British Columbia, Mexico, and a number of the South American countries. For example, in 1880 Count Hansen, the explorer, was sent to the Fiji Islands to obtain shipments of tonga, a newly discovered drug.[9]

In 1885, Parke, Davis and Company sent the distinguished botanist, Henry H. Rusby on an extensive trip to South America to investigate the native drugs and to purchase large supplies of coca.[10] Eventually the company played an instrumental role in introducing to the American medical profession nearly fifty different fluidextracts, according to Taylor. Many of these drugs resulted from the expeditions which they sponsored.[11]

Today young practitioners find it hard to conceive of physicians administering potent drugs without knowing precisely how much active ingredient the patient receives

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9. Parke, Davis and Company, The Saga of Parke, Davis and Company, Detroit, 1942, p. 17 (an anniversary booklet by the company). In the jungle Count Hansen broke his leg, and only after a courageous and melodramatic episode was he able to keep a tryst with natives and bring back the tonga to Detroit.

10. On his experiences, see his book, Jungle Memories, New York, 1933.

11. Taylor, "Forty-Five Years of Manufacturing Pharmacy," The Journal of the American Pharmaceutical Association, 4 (April, 1915), p. 471.

in each dose. Yet, this remained true of complex drugs of natural origin until 1879, when Parke, Davis and Company introduced a preparation of ergot (Liquor Ergotae Purifactus) that was standardized by a chemical assay.

In speaking of this development, which had European beginnings in the 1860's,[12] Frank O. Taylor,[13] the Company's chief chemist, considered it,

> ... the most important advance in pharmacy that has occurred in modern times, viz., the application of the principle of standardization, or uniformity in production of preparations of drugs [of natural origin]. With no flourish of trumpets and little realization of what is heralded, in September, 1879, there appeared a preparation known as Liquor Ergotae Purificatus, which was a fluid preparation of ergot, standardized by a simple form of assay so that each different lot was of uniform character. The assay appears to us, at this day, as very crude and inefficient, but we must remember that this was simply the beginning, and any kind of attempt to give uniformity of strength was an advance upon untraveled ground.
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> According to the best researches of the time, the activity of the ergot was supposed to be chiefly in the sclerotic acid, and a crude estimation of this was made by the precipitation of the organic acid with lead acetate. The standard was this: "Ten cc. of the normal liquid require for complete precipitation, 100 cc. of a solution containing 1% of crystalized lead acetate."

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12. Edward Kremers and George Urdang, History of Pharmacy, 2nd ed., 1951, p. 405.

13. Frank O. Taylor is a graduate of the Cincinnati College of Pharmacy (1899) and was awarded a D. Sc. (h.c.) at Wayne University in 1944. He joined the staff of Parke-Davis in 1902, at the age of 23, as an analyst and rose to the position of chief chemist (1924-1945). Since his retirement in 1945 he has served as a Technical Consultant for Parke-Davis. Taylor has been active in both chemical and pharmaceutical associations.

> This truly appears to us with the retrospect of forty-five years of experience, as almost laughable, but it was the best that the knowledge of the times afforded and was a step toward the dreams of the future which were beginning to take form in actuality. With this there began a systematic investigation of the possibility of rendering uniform, fluid preparations of many drugs with the result that in February, 1883, there was publicly announced a list of twenty normal liquids which were actually fluidextracts standardized by some form of assay, in most cases an estimation of the alkaloids which they contained. The man responsible for the beginning of these assayed fluidextracts and who established the analytical methods for their control is Dr. A. B. Lyons, to whom in this, as in many other things, pharmacy owes much.[14]

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14. Taylor, "Forty-Five Years of Manufacturing Pharmacy," The Journal of the American Pharmaceutical Association, 4 (April, 1915), pp. 473-474; on the remarkable Lyons, see The Journal of the American Pharmaceutical Association, 15 (1926), p. 411. It should be noted that Lyons probably did not personally develop all of the processes that he used to standardize drugs. He implies this in the preface of his book, Pharmaceutical Assaying, when he says, "To the labors of Prof. Dragendorff [a Russian chemist], especially, I find myself indebted for many of the processes that I shall offer, and I must acknowledge a like indebtedness to that indefatigable and enthusiastic American worker, Dr. Squibb, and to others whose contribution in this field have been less numerous. Many of the processes, however, which I shall describe have this measure of originality, that they have grown up under the exacting demands of the laboratory work in which I have for several years been engaged. From hints that have been gathered from various sources, these methods have developed into their present form, and every year's added experience will no doubt find still something in them to change and improve. They are offered for what they are worth, in the belief that to those at least who do not read German they will be of material service, and that from this small beginning there will arise before many years a literature in our own tongue of a subject of such growing importance." (A. B. Lyons, Pharmaceutical Assaying, Detroit, 1886, p. iv.)

The possibilities of precise standardization, so particularly important in medication, had been achieved earlier of course in the field of inorganic drugs. Discussing chemical analysis, at the beginning of the present century, as a source of methods for "testing and investigating used in industrial chemistry," the historian-chemist Ernst von Meyer said:

> Since these have for their aim the attainment of a fair degree of accuracy within the shortest possible time, volumetric processes [" developed within the last seventy years or so "] are the ones most frequently employed. The rapidity with which acids and alkalies, chlorine, many metals in their compounds, and other substances can be determined quantitatively by volumetric methods, has rendered it possible to exercise a continuous control over manufacturing processes, -- with what benefit need not be said.
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> ... For technical chemists, and in an equal degree for medical officers of health, the development of the analysis of articles of food and drink has been of the first importance; the pharmacist, too, frequently finds it needful to apply the methods which have approved themselves in such cases. By their aid the analyst is able to decide whether the products are what they pretend to be, or, if they should be adulterated, the nature of such adulteration.[15]

Before precise methods of assay were developed or adapted to industrial needs, standardization and accuracy of procedure was a foremost technical concern of conscientious drug manufacturers. It is in this area of "process standardization" that the remarkable Dr. E. R. Squibb labored so earnestly in order to have his firm's products of uniform strength. In discussing these early

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15. von Meyer, History of Chemistry, London, 1906, p. 415.

attempts at producing uniform products George D. Beal says,

> Standardization is one of the greatest contributions of the manufacturers who became active during the last half of the nineteenth century. Since the majority of their operations were initiated, supervised and carried out by pharmacists, they were done as far as possible in accordance with the art of the apothecary. Standardization of procedure thus preceded standardization of product. The private journal of Edward R. Squibb, the founder of E. R. Squibb and Sons, shows that at that time his interests were largely in process standardization. (Volume 9, began in 1869; earlier volumes were lost in a fire.) He records among many others, data on ether and the density of alcohol (the Squibb pycnometer is widely used today); menstrua for drug extractions and data on thirty or more vegetable drugs, including such important ones as cinchona, senna, aconite, cascara, and belladonna; the assay of opium; and data on chloral, cocaine, chloroform, bismuth salts, amyl nitrite, ethyl iodide and atropine.[16]

A few years after the first chemically standardized botanical product appeared on the American market, Josiah Kirby Lilly, Sr., immediately after graduating from the Philadelphia College of Pharmacy, joined Eli Lilly and Company (1882) as plant superintendent. "He was interested in research and began working on standards for the more important fluidextracts and tinctures then manufactured by Eli Lilly and Company. In 1884 circulars were issued announcing standards on certain fluidextracts. They were

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16. George D. Beal, "The American Way in Pharmacy," The Journal of Industrial and Engineering Chemistry, 31 (May, 1939), p. 534.

then introduced in the Price List of 1885."[17]

That development and application of drug assays had awaited the initiative of such progressive manufacturing laboratories may be largely explained, first, by the lack of a national food and drug law (leaving the Pharmacopeia optional except for certain state laws) and, secondly, by the circumstance that the practicing pharmacist assumed a responsibility for drug quality that, in the case of closely standardized drugs, he recognized should be admired in principle, but that he scarcely had the possibility of fulfilling in his own practice.

This dilemma is clearly reflected in an Era editorial, whose co-editor was A. B. Lyons[18] of Detroit, himself a

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17. Archives of Eli Lilly and Company to M. Keith Weikel, March 1, 1962. While Lilly might be considered as following the lead of Parke-Davis in developing product standards, nevertheless J. K. Lilly, and other manufacturers, must have faced considerable developmental work, since the details of the assays that Parke-Davis developed were not published. While the United States Pharmacopoeia published in 1883 gave a new expression to the era of assayed and standardized drugs, the extensive addition of quantitative standards applied mainly to chemical drugs. "Whenever any substance is capable of being assayed (provided the assay or valuation is of practical utility, a process is added." (p. xxviii)

18. Albert B. Lyons received an M. D. from the University of Michigan in 1868 and immediately accepted a position as Professor of Chemistry at Detroit Medical College. In 1880, at the age of 39, he joined the staff of Parke-Davis as a consulting chemist. In 1888 he accepted a position as a professor of chemistry at Ohau College. Lyons was responsible for developing the chemical assays used by Parke-Davis during the 1880's.

"founder of alkaloidal assaying in America" and author of the first American book on the subject:

> The idea of having all medicaments of uniform, standard strength, is eminently good and proper, and all wish they were so, but how to make them thus uniform is the question agitating us all at present.... The prevailing sentiment of those who are expected to be the users of the Pharmacopoeia is opposed to the incorporation of, and insistence upon, definite stringent methods of assay or standardization. It is objected that we are not sufficiently qualified to conduct satisfactory assays, and, moreover, that in a large proportion of instances it would be impossible to decide upon the best method to adopt.... The great majority of druggists do not feel, and cannot be made to take, any interest in the matter, and cannot be forced to assay a preparation, and we submit that, for this one reason if for no other, the radical innovation of insisting upon standardized preparations would be decidely premature.
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> So long as the Pharmacopoeia is officinal only by courtesy, is not authorized by law, and infringement of its regulations does not meet with punishment, so long will it be useless to insist that a fluid extract or syrup shall contain a certain definite percentage of a certain ingredient.[19]

It was perhaps especially through investigation of such standardization methods that, before the 1890's research here and there began to take a significant, but modest part in pharmaco-industrial life. Nevertheless the effect of these humble beginnings should not be over-emphasized.

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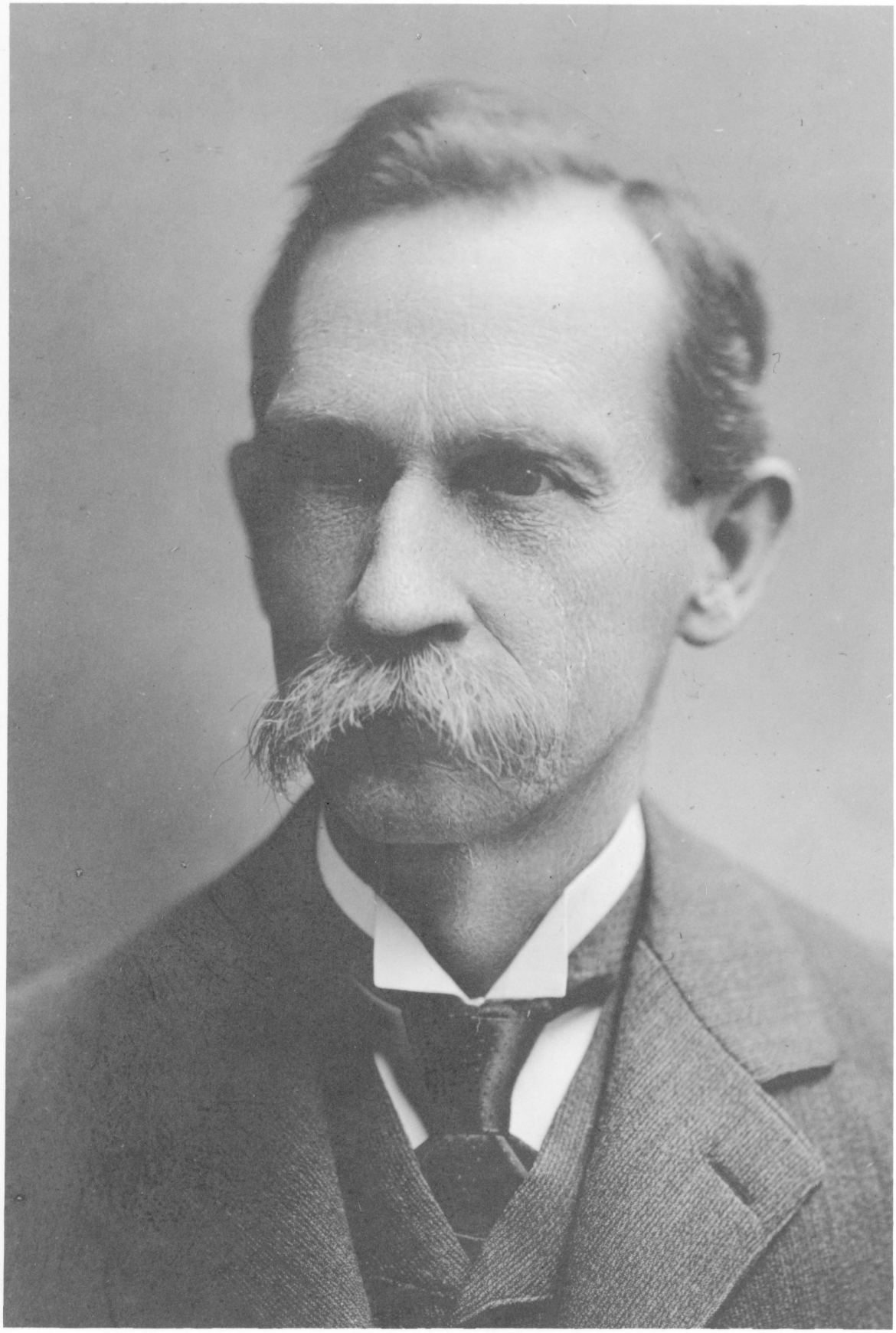
19. The Pharmaceutical Era, 32 (December, 1899), p. 450. This conservative counsel against admitting assays extensively into the 1890 U.S.P. represented a reversal of editorial position, "from careful consideration of the issues involved..."

ALBERT B. LYONS was responsible for the developmental work on chemical assays used by Parke-Davis to standardize its fluid extracts. He wrote the first American text on Pharmaceutical Assaying, published in 1886. After receiving an M. D. from the University of Michigan in 1868, Lyons had accepted a position as Professor of Chemistry at Detroit Medical College. In 1880 at the age of 39 he joined the staff of Parke, Davis and Company as a consulting chemist.



While there were yet few companies in American industry at large that supported research of any type, or for that matter even employed chemists, it may have been fairly common practice prior to 1900 for companies to purchase the results of a non-industrial scientist's research if applicable to the work of the company.[20] While this practice undoubtedly occurred in the pharmaceutical industry likewise, we thus far have found little evidence of it.

Before delving into the rise of company research departments let us examine some factors that either impeded or stimulated the development of systematic research programs in American industry and especially in the pharmaceutical industry.

Factors Affecting Early Research

Just as war-time demands have promoted the growth of many companies in American industry, they have also tended to stimulate research in industry -- especially in the chemical and pharmaceutical industries. During the War of 1812, the pharmacists had to develop methods to produce drugs that were supplied from abroad before trading with

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20. For information about individual pharmacists and scientists whose work was utilized by industry see Raymond F. Bacon, "Industrial Research in America," The Scientific Monthly, 2 (1916), pp. 226-230; Edward R. Weidlein and William A. Hamor, Science in Action, New York, 1931; George M. Beringer, "Pharmaceutical Research," The Journal of the American Pharmaceutical Association, 10 (February, 1921), pp. 89-96.

England was halted.[21] "During the Civil War, Congress established the National Academy of Sciences primarily as an advisory body for the federal government but also for the advancement of scientific research."[22]

One of the most important forces affecting industrial research was World War I. C. L. Parsons, Chief Chemist of the United States Bureau of Mines, said, "I think one of the potent basic influences in the development of the chemical industry was the sudden realization in 1914 and 1915 of our dependency on foreign countries for various kinds of chemicals. American manufacturers had only begun to support chemical research or even chemical control before the war. The greatest development of all which has come from chemistry during the war has been the realization by the American people that chemical research is necessary for the development of the country and that no industry can bring greater prosperity to America than the chemical industry and that no body of men is more necessary to our welfare than a carefully trained corps of thoughtfully educated chemists."[23]

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21. J. W. Sturmer, Pharmaceutical Era, 53 (1920), p. 131.

22. John B. Blake, "Scientific Institutions Since the Renaissance: Their Role in Medical Research," Proceedings of the American Philosophical Society, Vol. 101, No. 1 (February, 1957), pp. 47-48.

23. Charles L. Parsons, "Potent Influences in Chemical Progress," Drug and Chemical Markets, 9 (1921), p. 511.

Although a few pharmaceutical companies were doing research prior to World War I, the United States was still much dependent on Germany for many important drugs. The 1916 edition of New and Nonofficial Remedies listed 592 drugs and of these 228 were imported (in part) into the United States from Germany. Among these were such important drugs as aspirin, benzocaine, arsphenamine, neoarsphenamine, barbital and procaine.[24]

Hamor and Weidlein of the Mellon Institute point out that,

> In a number of our manufactures the interest in industrial research was aroused during or immediately after the World War. In wartime it was necessary for every industry of importance to try to do more, and to do more that was new, than had ever been required in a similar period of time under peace conditions. The entire United States became practically unified industrially, and this high-pressure industry called upon every bit of help that was procurable.
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> At the beginning of the war many manufacturers had never had occasion to ask for the aid of scientists; others had seen what scientific research had accomplished for various industries, but did not think that scientists could assist them very much. During the war, however, both groups found it essential to expend every possible effort to produce large quantities of well-known articles cheaply and quickly, and to manufacture new products just as expeditiously. Concluding under this urgent pressure that it was possible that the scientist could help, these companies gave the research laboratory its first great opportunity.[25]

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24. A. Lichtin and I. L. Schamberg, "The Dawn of American-Made Synthetic Drugs," mimeograph, n.d.; Kremers Reference File, University of Wisconsin (filed C39(E)II).

25. Edward R. Weidlein and William A. Hamor, Science in Action, New York, 1931, p. 39.

The National Research Council itself is another reminder that World War I demonstrated that the necessity for coordinated scientific research was applicable to industries as well as to modern warfare. This council was organized in 1916 primarily to stimulate and coordinate research on war problems. However, by executive order of the President of the United States (1918), this group was reorganized as a permanent body, and the announcement was officially made that "its essential purpose is the promotion of scientific research and of the application and dissemination of scientific knowledge for the benefit of the national strength and well being."[26]

In October, 1917, the Federal Trade Commission was granted authority ("Trading with the Enemy Act") to license responsible American citizens to operate patents owned by enemy aliens. "There were both immediate and long range effects of this act. The immediate effect was to provide the American people with needed drugs and chemicals. But even more important, this act freed the American pharmaceutical and chemical industries from foreign domination, and fostered their growth. The pioneer scientific workers during this period not only liberated American chemical research and the American chemical industry in their own day, but also helped to create the American technical genius

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26. George M. Beringer, "Pharmaceutical Research," Journal of the American Pharmaceutical Association, 10 (February, 1921), p. 91. It was noted in 1921 that there were no representatives from pharmacy on this council and no evidence that pharmaceutical research was to be given encouragement.

of today."[27]

The extent to which World War I and its aftermath proved to be a turning point, not only in the pharmaceutical industry but in many other industries also, is suggested by one dramatic fact,

> In 1899, the United States imported only 42 per cent of crude chemical raw materials, and the remainder in finished products, as against 73 per cent of crude materials in 1927.... This change has gradually taken place through the application of science to industry.... Until 1927 the balance of the trade in chemicals was consistently against the United States. In three of the last four years (1927-1931), however, exports have exceeded imports in value, and in 1930 the margin was larger than ever before.[28]

The reliance upon European countries -- especially Germany -- had been one factor that impeded the development of industrial research in America before World War I. This was due to a number of reasons. European countries were much further advanced in scientific work than the United States, and the educational facilities to train scientists were better in Europe. Many of the European governments, especially Germany, extended special privileges and support to their chemical industries to help them maintain their dominance on the world market. "The governments of Europe vie with one another in fostering chemical research, Germany most wisely doing this in her universities," Francis Venable observed. "We as a nation can not long afford to be behind them in this matter. In the close

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27. Lichtin and Schamberg, "The Dawn of American-Made Synthetic Drugs," mimeograph, n.d.; Kremers Reference File, University of Wisconsin (filed C39(E)II).

28. Weidlein and Hamor, Science in Action, New York, 1931, pp. 257-259.

competition of the near future we must depend upon these toilers of the laboratories for our supremacy in the world's markets."[29]

The chemical and pharmaceutical companies in the United States were handicapped by the wages they had to pay their employees, in comparison to cheaper wages abroad. Thus the United States companies found it hard to compete effectively; presumably this tended to make executives hesitate to invest in research.

This circumstance changed after World War I, W. H. Engels points out, because "thanks to the high tariffs on coal-tar products established by Congress, our chemical industry was able to maintain research laboratories, which were then beginning to develop new and improved medicinal chemicals."[30]

The attitude of management toward research and researchers frequently also impeded the advance of industrial research in the late 1800's and the early 1900's, according to R. F. Bacon, who said in 1916,

> ... many industrialists are even now certain that research will not pay. Some regard their technology as a hereditary art. Some have favorable raw material conditions or a large demand for their products, and are therefore disinclined to invest a very small portion of their earnings in a reserve of knowledge. Others have prospered

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29. Francis P. Venable, "Chemical Research in America," The Journal of the American Chemical Society, Vol. 28, No. 2 (February, 1906), pp. 137-138.

30. W. H. Engels, "Development of Chemicals for the Pharmaceutical Industry," The Journal of the American Pharmaceutical Association, 11 (1950), p. 86.

> because of high tariff, notwithstanding short-sighted management. But most of our industries are built upon stronger foundations. It is plain that the use of natural laws offers a more stable basis upon which to erect a manufacture and a more uniform source of profit than any structure built upon artificial conditions created by legislation. Moreover, the quality and value of a product are based upon the application of correct principles in its conception, preparation and use, and the correct principles can only result from scientific research.[31]

Part of the problem was that manufacturers often did not have an appreciation of the conditions necessary for the ultimate success of research work. Many manufacturers did not know how to properly select a research worker. Some did not fully understand the time required and the uncertainties in research, and expected results immediately.

That such problems were still a live influence in the general development of industrial research in 1915 is suggested by the fact that W. A. Hamor took pains to explain,

> A frequent difficulty encountered in the employment of researchers or in the establishment of a research laboratory, is that many manufacturers have been unable to grasp the importance of such work, or know how to treat the men in charge so as to secure the best results. The industrialists may not even fully understand just what is the cause of manufacturing losses or to whom to turn for aid. If he eventually engages a researcher, he is sometimes likely to regard him as a sort of master of mysteries who should be able to accomplish wonders, and if he can not see definite results in the course of a few months is occasionally apt to consider the investment a bad one and to regard researchers as a class, a useless lot. It has not been unusual for the chemist to be told to remain in his laboratory, and not to go in or about the works, and he must also face the natural opposition of the workmen to any innovations, and reckon with the jealousies of foremen

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31. Raymond F. Bacon, "Industrial Research in America," The Scientific Monthly, 1 (1916), p. 232.

and of various officials.[32]

Hence, a maturing of managerial attitudes, as of personnel and facilities, was needed before industrial research would clearly emerge from its "formative period." If, as seems likely, pharmaceutical management was, in origin or in knowledge, closer to science than the average industrialist, it would help explain why we have encountered no evidence of such cross-currents and pessimism during the early efforts to harness pharmaceutical industry to scientific research.

Indications in the literature that the American public did not have particularly high respect for chemists before World War I may have been part of both cause and effect with regard to the limited numbers of qualified research personnel. One observer warned, "There is a necessity for the further education of the public. The public, as a whole, is not aware of what a chemist professionaly is."[33]

The public work of the chemist was often obscured by technical details and his industrial achievements were cut off from public view by factory walls. "The chemist has the Great War to thank for leading him from behind the bowl and pestle of a drug mixer into the full light of

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32. W. A. Hamor, "The Value of Industrial Research," The Scientific Monthly, 1 (1915), p. 89.

33. William H. Walker, "Education for Research," Journal of Industrial and Engineering Chemistry, 7 (1915), p. 2.

public understanding and favor."[34]

There was a scarcity of gifted men to do research work before the early 1900's. The United States' educational programs in the sciences were far behind those of more advanced countries, especially Germany. Haynes indicates that,

> The dawning comprehension of the implications of research and its purposeful application to the practical problems of chemical manufacture are both closely related to the state of chemical education.
>
> It is to the everlasting credit of the German chemical industrialists of the nineteenth century that they systematized and organized research, turning a useful tool into a highly efficient precision instrument for accomplishing material progress. They could do so because, following Liebig's example, the laboratory technique of chemical instruction had been perfected and more than a score of brilliant teachers were training hundreds of competent, inspired chemists. The German chemical manufacturers -- themselves trained chemists -- recognized far in advance of their British and American contemporaries -- among whom a chemically trained man was an exception -- the key position that chemicals occupy in our modern industrial economy. With a nice appreciation of the possibilities of research aimed at definite objectives and having a plentiful supply of capable chemists available, they capitalized the values of research very profitably.[35]

It should be pointed out, however, that even before 1700 some aspects of chemistry were being covered in a course at Harvard on natural philosophy, later the subject commanded the dignity of a separate professorship in medical

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34. Editorial, "Our Chemical Independence," Drug and Chemical Markets, Vol. 4, No. 2 (1918), p. 6.

35. Williams Haynes, American Chemical Industry, Vol. I, New York, 1954, p. 392.

facilities were available for research and how little was being done when he returned to America in 1872 after five years in Germany to study chemistry. In his first academic position Remsen received no encouragement to pursue his research from the school officials; in fact they discouraged him.[37] In 1876 Remsen was offered the professorship of chemistry at the newly opened Johns Hopkins University, an institution which was instrumental in advancing scientific education in America.

> In the development of graduate instruction the influence of the John Hopkins University, which was incorporated in 1867 and opened in 1876, was paramount. Its first president, Daniel Coit Gilman, and a sympathetic board of trustees from the beginning emphasized research.... Thus a picked group of graduate students and fellows, working in close, informal relations in the seminars or laboratory with men who were themselves advancing knowledge, received an education in research. Leaving Hopkins for professorial posts elsewhere, they spread the gospel throughout the land.[38]

Thus it was not until the late 1870's and the 1880's that a few American colleges and universities offered educational programs in the sciences (mainly in chemistry) that approached the caliber of European institutions, especially Germany. This ready American source of new

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37. Ira Remsen, "The Development of Chemical Research in America," The Journal of the American Chemical Society, Vol. 37, No. 1 (January, 1915), pp. 4-5. When one of Remsen's articles was published in the American Journal of Science, he was actually made fun of at a faculty meeting.

38. Blake, "Scientific Institutions Since the Renaissance: Their Role in Medical Research," Proceedings of the American Philosophical Society, Vol. 101, No. 1 February, 1957), p. 49.

research personnel must have been significant -- if not even prerequisite -- to the upsurge of industrial research that came soon after the turn of the century.

When we speak of industrial research, for the most part we mean applied research (however one may define the term) and this was especially true prior to 1920 in most industries, including the pharmaceutical industry.

In Europe the advances during the last quarter of the century were both startling and more basic -- especially in organic chemistry, bacteriology, physiology and pharmacology. All helped to fertilize the growth of industrial chemistry in the pharmaceutical field, which Raymond Bacon, the first Director of the Mellon Institute, well characterized in a wider context, when he looked back across three decades from 1914:

> The replacement of natural dyes by the products of coal tar, the extension of our medical resources by the manufacture of synthetic medicines, has gone far to extend the appreciation of chemical work and to produce the general conviction that chemistry is an inexhaustible field of economic possibilities. Indeed, one natural product after another falls into the domain of chemical synthesis, and chemistry is becoming the important factor in the economy of the tropical products which are used for industrial purposes. As soon as the price of such a product exceeds a certain limit, organic chemistry enters the field and synthesizes it.... The basis of this marked development in organic chemical industries is the combined working of science and technology. The success of this intermingling is so obvious that I need not dwell on the point.[39]

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39. Raymond F. Bacon, "The Value of Research to Industry," Science, Vol. 40 (December 18, 1914), pp. 874-875.

Discussing the effect of some of the then recent advances on drug research, Bacon say,

> ...the teachings of physical chemistry have led to the study of the conditions of absorption of drugs by the various cells and tissue juices of the body, of the part played therein by osmosis, by electrolytic dissociation, by mass, and especially by the colloidal character of the substances concerned in metabolism. Such study associated with biological chemistry has pointed the way to new methods of research which promise well for a fuller understanding of the complexities of the processes that are comprised in the physiological actions for drugs.
>
> Despite the mass of material that has thus been accumulated, a scientific basis for the preparation of physiologically active compounds is but in its infancy. The possibility of precalculating the action of a drug from its chemical structure is as yet developed to but a limited extent, as has been repeatedly brought home during recent years by the discovery of new groups of compounds possessing valuable therapeutic properties, the physiological action of which was in no way anticipated. Indeed, the recognition of the therapeutic value of some of the earlier synthetic drugs was effected, as Keane has indicated, rather in accord with Priestley's belief that all discoveries are made by chance, and has been extended with some reminiscence of his view that scientific investigation was to be "compared to a hound, wildly running after and here and there chancing on game." The hypnotic activity property of sulphonal was a chance discovery; the physiological action of antipyrine was initially examinedon account of its supposed relation in chemical structure to kairine and allied febrifuges, which was subsequently proved to be incorrect; and the purgative properties of phenolphthalein became known from the results that followed its use to earmark, for administrative purposes, a certain kind of wine in Austria-Hungary. The commercial success of antipyrine... was followed by a hunt for further "game" and many a compound, such as acetanilide, has been called from the seclusion of chemical museums for the examination of its physiological properties.
>
> The recognition of the therapeutic value of such substances has been followed by inquiry into

> the relation of their chemical structure and physiological action, with the result that the study of this relation has since become more ordered and systematic.[40]

Thus it is readily seen that advances in the basic sciences during the late 1800's and early 1900's laid a foundation that enabled pharmaceutical research to reach a new level of refinement.

Many of the pharmaceutical firms employed chemists for quality control prior to 1900, and shortly thereafter many more employed chemists to do control work. There is little doubt that these chemists played a major role in the development of research in a number of the pharmaceutical companies. It appears that frequently when such chemists were not busy doing analytical work they conducted experiments to attempt to improve some of the existing products of the company. Sometimes this was done on the initiative of individual workers. The initial research at The Upjohn Company was centered around their first control chemist, F. W. Heyl, Ph. D. Leonard Engel points out that Heyl "was expected to develop laboratory tests to check the quality and uniformity of Upjohn products and assure their conformity with the food and drug law. He also hoped to do research on new products. But note the word also; control procedures were his major responsibility. Moreover, the new products which he had in mind were chiefly improvements in known drugs."[41]

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40. Ibid., pp. 375-376.

41. Leonard Engel, Medicine Makers of Kalamazoo, New York, 1961, p. 192.

There is little doubt that control chemists were also called upon from time to time to solve problems that arose in drug production processes. For example, Taylor points out that at Parke-Davis there were two or three men in the Analytical Department who were doing mainly "research work," and that two or three of the other chemists in this department were doing both routine control work and investigative work.[42]

George D. Beal, a former Director of the Mellon Institute, draws the same inference as we do in believing that research divisions often "germinated in the control laboratories of the manufacturers. A good bit of the research activity was probably expended at the beginning in process and product development."[43]

Apparently it was not only in the pharmaceutical industry that control work served as a stimulus for research because in his discussion of industrial chemistry in America, Charles E. Monroe, Dean of the Chemistry School of George Washington University (1926), notes that "a marked feature in the development of industrial chemistry during the last fifty years is the employment of educated chemists, at first in inspection and control work, and later in research work."[44]

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42. Frank O. Taylor to Glenn Sonnedecker, August 16, 1961; in personal file of M. K. W.

43. George D. Beal to G. Sonnedecker, March 1, 1961; in personal file of M. K. W.

44. Charles E. Monroe, "Industrial Chemistry," in Charles A. Browne, ed., A Half-Century of Chemistry in America: 1876-1926, Easton, 1926, p. 234.

A further influence on the maturing industrial pharmaceutical research, sometimes overlooked, is enactment of the first Federal Food and Drug Act in 1906.

Advocating this view, Weidlein and Hamor state, "Before 1906 only a few American pharmaceutical companies had research laboratories. Following the passage of the Federal Pure Food and Drug Act, however, the leading pharmaceutical houses found it desireable to provide for scientific staffs. This law, therefore, has not only been of immeasureable direct benefit to the public, but has also been of great indirect benefit to science and medicine by encouraging research."[45]

In evaluating the significance of the first Federal Pure Food and Drug Act, Paul N. Leech, Ph. D., Director of the Chemical Laboratory of The American Medical Association, notes:

> As the law had given the government chemists the power to analyze the official preparations, and to prosecute firms whose products were found wanting, it was not long before the business directors of the pharmaceutical firms, particularly of the smaller houses, began to realize the need of scientific controls of their products. In other words, many of the houses which never had scientific staffs, sooner or later, as the case might be, established laboratories for both chemical and biological assay of their products. This, in turn, has led to the creation of well-balanced scientific departments in every large pharmaceutical house in America [1928]... In the case of most of the pharmaceutical houses, their large staffs of today are one of the great

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45. Weidlein and Hamor, Science in Action, New York, 1931, p. 98.

> sources of protection to public health. These serious minded men engaged in the ultimate interests of public health, are frequently the ones who have the foresight to develop new worthwhile additions to Materia Medica. The Pure Food and Drugs Act, while it has been of great direct benefit, has also been of immeasurable indirect benefit for the impetus it has given to the establishment of the research laboratories in our leading pharmaceutical houses of today.[46]

In discussing what Upjohn did to meet the requirements of this new law, Leonard Engel says, "The Upjohn Company dealt with the problem in a way that was to have far reaching results. A chemist -- Upjohn's first scientist with a Doctor of Philosophy Degree -- was hired [In 1913] to work out improved methods of assaying drugs and controlling production. As happened also in a number of other pharmaceutical houses beside Upjohn, once the chemist and his aides had the control task in hand, they moved inevitably on to the investigation of new products, and then into independent research. Thus in Upjohn and several other companies, organized pharmaceutical research got its start."[47]

While this may have been true for a number of companies, there were notable exceptions. Yet, the evidence seems to support S. De Witt Clough, a former President of Abbott Laboratories, when he says, "During the fifty or more years prior to the passage of the Federal Pure Food and Drug Law the pharmaceutical industry was in a formative

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46. Paul N. Leech, "The Safeguarding of Drugs," in Julius Stieglitz, ed., Chemistry in Medicine, New York, 1928, pp. 404-405.

47. Engel, Medicine Makers of Kalamazoo, New York, 1961, p. 50.

period without its present clear conception of the real value of individual and group research.... I believe it is not an overstatement to state that the passage of the Federal Pure Food and Drug Law in June, 1906, as well as the Food, Drug and Cosmetic Law of June, 1938, did much to stimulate and encourage scientific research in the pharmaceutical industry."[48]

Was the patent system an important part of this picture? During the "formative period" here considered the pharmaceutical industry did not make extensive use of the patent system. There are several reasons why the patent system was not utilized more. First, there was relatively limited research being done in industry prior to 1920. And much of that done, for example on botanical and biological drugs and methods of assay, was probably not patentable. Little research then undertaken resulted in new chemical substances. Much early work involved developing processes, and some were patentable, but companies often preferred secrecy to protect their research investments, rather than divulge the results in a public patent. With the passing decades, beyond the formative period of research, the patent system came to serve more widely as a protection and stimulus.

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48. S. De Witt Clough, "The National Food, Drug and Cosmetic Law Instituted by the 1906 Act; Its Basic Value to Drug Industry," Food, Drug and Cosmetic Law Quarterly, Vol. 1, No. 3 (September, 1946), pp. 389-390.

An examination of the patents issued to E. R. Squibb and Sons illustrates one company's increased reliance on the patent system as a means of protecting research investments over the years. Prior to 1920 Squibb had been issued only one patent. What happened subsequently has been summarized by the Squibb executive, F. W. Nitardy:[49]

> It had not been customary for us to apply for patents on patentable developments in connection with our products or processes. Some requirements in this direction developed in the early Twenties, and as we found it both costly and not overly satisfactory to work with outside patent counsel on these matters, it was decided in April 1927 that we should engage a man to do this work in the plant. The first Squibb patent, above referred to, (U. S. 1,100,432) covered a method of sealing a bottle, devised by Mr. Hereth and issued June 16, 1914. A second patent was assigned to Squibb in 1922 (U. S. 1,005,228, Jan. 31, 1922) (Kober - Arsenicals). By 1930 we owned 17 domestic and 31 foreign patents, also 4 domestic and 2 foreign design patents. The number had grown to 149 domestic and 34 foreign patents, with 15 domestic and 5 Canadian design patents in addition, by June 1940.[50]

While the role of the patent system in early industrial research could be easily overemphasized, there remains

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49. F. W. Nitardy received a Ph. D. from Northwestern University in 1908 and from that time until 1917 he served as chief chemist of Scholtz Drug Company. In 1917 he joined E. R. Squibb and Sons as chief of the pharmaceutical manufacturing division. By 1919 he had risen to the position of General Superintendant in charge of Squibb's New Brunswick Chemical Plants and the Brooklyn Plants and Laboratories. From 1930 until his retirement (1943) he served as Vice-President in Charge of Manufacturing.

50. F. W. Nitardy, "Long Range Comparative Report (1916-1941)," presented to C. H. Palmer, Chairman of Board of Directors and L. P. Weicker, President, July 1, 1941; in Archives of the Squibb Institute for Medical Research Library, New Brunswick, N. J.

scarcely a doubt that the publication of research results played a significant role in encouraging scientific research. The first general journal for the publication of scientific papers was the American Journal of Science, founded (1818) by the chemist Benjamin Silliman of Yale University. In assessing the importance of this journal F. P. Venable said, "It stood for fifty years almost alone for the upbuilding of scientific investigation in America and can boast ninety years of great usefullness. Without some such journal there is little encouragement for research. The scientific man finds a keen delight in the search after truth but he also loves to impart his discoveries to others and to win the commendation of those who can understand and appreciate his work, and there must be some arena upon which controversies can be fought out and truth winnowed from the chaff."[51]

Only about seven years after The American Journal of Science was founded the Philadelphia College of Pharmacy published the first issue (1825) of the journal subsequently known as the American Journal of Pharmacy, which gained international recognition for its scientific as well as professional merit.

In 1879 Ira Remsen founded The American Chemical Journal, which flourished for thirty-five years until merged

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51. Venable, "Chemical Research in America," The Journal of the American Chemical Society, Vol. 28, No. 2 (February, 1906), p. 132.

into The Journal of the American Chemical Society (1914). Remsen said he thought his Journal, especially in the 1880's, had a stimulating influence on American Research[52] -- years that coincide interesting with the earliest consequential stirrings of pharmaco-industrial research.

Symptomatic of the upsurge of industrial research after the turn of the century (broader than pharmaceutical industry itself) was the need for a new Journal of Industrial and Engineering Chemistry, founded in 1908.

The Journal of the American Pharmaceutical Association was first published in 1912 as a more research-minded successor to the Association's Bulletin.

An examination of the early pharmaceutical and chemical publications reveals few reports of research conducted by the pharmaceutical industry.[53] Beginning in the early 1900's such reports began to increase gradually; however, not until about 1915 did industrial articles about pharmaceutical research appear more regularly. Prior to this time most of the investigative articles dealt mainly with standardization of drugs. In discussing the development of

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52. Remsen, "The Development of Chemical Research in America," The Journal of the American Chemical Society, Vol. 37, No. 1 (January, 1915), p. 6.

53. "In early years research reports from pharmaceutical industry were meager and not much more voluminous in 1899." E. V. Lynn, "A Century of Research in Pharmaceutical Chemistry in Schools of Pharmacy in the United States," American Journal of Pharmaceutical Education, 17 (1953), p. 183.

the Division of Medicinal Chemistry of the American Chemical Society, Maurice L. Moore of Smith, Kline and French Laboratories, observed a similar occurrence:

> The contributions to the early programs of the division dealt almost exclusively with pharmaceutical assays, improvements of pharmaceutical products, and discussions of drug standards which were made necessary by the passage of the Food and Drug Law of 1906. Papers of these problems predominated until well into the twenties. However, a few papers began [1921] to appear on the programs of the division which indicated the development of an interest in new drugs, especially those obtained synthetically.[54]

Throughout most of the period under discussion the American Pharmaceutical Association played an important role in attempts to prevent inferior or adulterated drugs from being placed on the market, and always had as one of its main objectives the improvement of "pharmaceutical science by diffusing scientific knowledge, fostering pharmaceutical literature, developing talent, stimulating discovery and invention, and encouraging home production and manufacture of drugs and medicines."[55]

Another group influence in bringing pharmaco-industrial research out of its adolescence stemmed from the American Pharmaceutical Manufacturers Association (founded 1908) and the American Drug Manufacturers Association (founded

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54. Maurice L. Moore, "Medicinal Chemistry," The Journal of Industrial and Engineering Chemistry, 44 (March, 1951), p. 577.

55. "The American Pharmaceutical Association: Its History, Objectives and Programs," mimeographed and distributed by American Pharmaceutical Association, 1959, in personal file of M. K. W.

1912). The proceedings of these associations show that at first they were mainly concerned with establishing standards for the manufacture of drugs, but a little later (after 1915 -- by now a not surprising date) those in annual assembly began to talk more about research in the drug industry.

Many factors, as we have seen, help account for tentious, pioneering research beginnings becoming visible in pharmaceutical industry after the 1880's and for their maturing by the second quarter of our century -- and at just this time -- as a central source of strength in the life of the industry. We have called attention to some of these major influences, whether encountered as research stimulus or impediment. With these in mind, let us now examine the development of systematic research in American pharmaceutical industry.

IV

RISE OF COMPANY RESEARCH AS A SYSTEMATIC ENDEAVOR

Looking back casually over the past quarter of a century or so, the immediate past of pharmaceutical industry, the view is dominated by the wider effectiveness of medication after the sulfonamide breakthrough, by the sharp upturn in industrial research after the 1920's, by the new-made glitter of elaborate research institutes. It tends to obscure, even to industrial representatives themselves,[1] decades before the 1930's, when industry was learning to be discontented with the role of using knowledge for production to the neglect of helping create knowledge, was making hard decisions about "unprofitable" research investments, was setting a pharmaceutical pattern and style for America rather than merely elaborating one.

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1. For example, John T. Connor felt we "cannot claim the pharmaceutical industry's significant contribution to that research is more than very recent; it actually dates back only about a quarter of a century." (Address of September 26, 1959 printed by Merck in The Search for New Weapons of Life, 1959, p. 1); and C. W. Pettinga felt that pharmaceutical industry could not refer meaningfully to organized research prior to the 1930's. (Interview with C. W. Pettinga, the Assistant to the Vice President of Research, Development and Control for Eli Lilly and Company, Indianapolis, December 15, 1961.

While commenting on research in the pharmaceutical industry at the dedication exercises of the Lilly Research Laboratories (1934) J. K. Lilly notes the increased interest that large-scale producers exhibited in research over the preceding 25 years. He points out that,

> Until the turn into the present century, large-scale producers limited their scientific endeavors to the use of established facts and current knowledge, but the past twenty-five years have witnessed a substantial advance into the field of real medical and chemical research. During this period, a fine spirit of co-operation between groups of scientists and the research and producing sections of large-scale operators has come into being. These joint endeavors have attained many large objectives and promise to continue thus, to the everlasting benefit of scientific medicine. Among the important therapeutic agents that have been developed through such efforts may be mentioned adrenalin, tryparsamide, thyroxin, viosterol, insulin, liver extract, parathyroid extract, ephedrine, and others of like importance.[2]

Since the role of the pioneer often is neither comfortable nor easy, we try here to bring back into remembrance and understanding those necessary precursors to the present vast research complex of American pharmaceutical industry.

Certainly systematic research found more than a few industrial proponents already in these earlier decades; and in fact as early as 1900 at least one pharmaceutical company had an organized research department. In a talk to

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2. J. K. Lilly, "Comments on Research in Manufacturing Pharmacy," in Lilly Research Laboratories: Dedication, Indianapolis, 1934, p. 5.

the Abbott Research Department, Ernest H. Volwiler, Ph. D., points out the fallacy in a belief that research is a creation of the present generation:

> We are prone to assume that research and scientific control are the property of the present generation; that before 1920, Abbott Laboratories like other pharmaceutical firms, was providing the physician with products of dubious value or even worthless junk. Let's get that idea out of our minds. Dr. Abbott himself really was our Company's first research man. He wasn't called that, but it was his keen power of observation which early sensed the possibilities of making better drugs. Many of them were alkaloids still in use today. True, some of the products used by physicians then, such as many vegetable concentrates and extracts, are regarded as practically worthless today. But we must remember that we are now blessed with more extensive knowledge and far better tools than were available thirty to sixty years ago. It is proper to say that our research attitude today is based on the same qualities of intense interest and eager inquiry which existed in the early days of the original Abbott Alkaloidal Company.
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> I have heard the statement that a quarter- or half-century ago it was easier to do research and to develop new products. It may seem that way, but the statement hardly bears analysis. Forty years ago our combined research staff numbered from six to ten people. Today's tools and services were still unknown. In spite of that, Abbott's small research staff in those days developed some new drugs specialties which are still important today...."[3]

Although Volwiler does not suggest that a systematic research program was begun by Dr. Abbott, he does recognize that the modest research efforts prior to 1920 or 1925 were

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3. Ernest H. Volwiler, "Goals for Abbott Research," (mimeograph) North Chicago, 1959, pp. 2-3; address delivered March 26, 1959; Abbott Historical File in the Abbott Research Library, North Chicago, Illinois.

an important and necessary step on the way to more sophisticated research programs.

We suggested that in the period between 1895 and 1920 research was first organized on a departmental basis in the pharmaceutical industry. This falls within the boundaries of the general industrial development as seen by C. E. Kenneth Mees, an authority on industrial research, when he states that "the first industrial research laboratories were organized, in the early years of this century...."[4] These statements about pre-1925 industrial research refer of course mainly to a vanguard.

It should be noted here that George D. Beal, Ph. D.,[5] a former Director of the Mellon Institute, believes that 1920 is too late a terminus when discussing the beginnings of organized research in the pharmaceutical industry. "In my opinion 1920 is not a good date to use in a classification," he comments, "for scientific research in the larger

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4. C. E. Kenneth Mees, The Path of Science, New York, 1946, p. 218.

5. George D. Beal (b. 1887) is a pharmacy graduate of Scio College (1907) in his hometown of Scio, Ohio; later receiving a Ph. D. in chemistry from Columbia University (1910). Beal began teaching at the University of Illinois School of Pharmacy in 1911 and remained there until 1926 when he was appointed Assistant Director of the Mellon Institute. From 1951 until his retirement (1959) he served as a Director of the Mellon Institute. Beal has been active in both pharmaceutical and chemical associations.

pharmaceutical houses was quite well organized by that time. A better year to use would be 1900."[6] While a number of the pharmaceutical firms employed scientists prior to the turn of the century, we believe that in most cases they were used mainly for quality control work.

Beal himself says, "It would be a fairly accurate statement to say that a good many groups have comparatively little idea as to when their research began because there was no clear-cut distinction between the study of present problems and looking toward the future."[7] In agreeing, we would point out further that the results of our investigation disclosed no indication of more than one or two companies that were systematically searching for new drugs prior to 1900.

Hamor, Weidlein and Leech's testimony (already cited in Chapter III), indicating that there were only a few pharmaceutical companies that had research laboratories prior to the passage of the first Federal Pure Food and Drug Act, tends to support the idea that the "formative period" of pharmaceutical research did not end by 1900.

By the turn of the century more emphasis was being placed on scientific methods, we certainly agree, rather than on the old trial and error approach to manufacturing drugs. Joseph Helfman, Editor of The Bulletin of Pharmacy,

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6. George D. Beal to Glenn Sonnedecker, March 1, 1961; in the personal file of M. K. W.

7. Ibid.

conveys the buoyant feeling of discovery and advance that pervaded pharmaceutical industry when he wrote to a scientific colleague at Christmastime in 1899:

> ...The most notable indications of an upward tendency during the past year have been observed here and there and denote that professional pharmacy is departing more and more from empiricism and progressing, on its manufacturing side, along truly scientific lines based on intelligent...investigation. This spirit is beginning to pervade the entire corps of pharmaceutical manufacturers and in consequence they have been devoting more attention to processes of assay, standardization, adjustment [of potency], and the various tests indicating the quality of the drug derivative -- fluid extract, powdered and solid extract, and the various substances which enter into the composition of pills, tablets and elixirs.
>
> The dispensing pharmacist shows a keener appreciation of the value of such tested products and this naturally has reacted on the manufacturer, causing the latter to exert himself more and more along lines of progress and development. We [Parke, Davis and Company] know that the chemists of other manufacturing houses are studying drugs more closely than in the past, are learning something of their composition and active principles, and are consequently recasting their processes of manufacture. In so far as we can speak for ourselves I can truly say that we have in the past twelve months devoted more brains and energy to an intelligent investigation of the material with which we have to deal than ever before. We have given considerable attention to Ergot, we are making a more thorough study of Cascara Sagrada, and at our instance Professor Freer[8] and his assistants are carefully

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8. Returning to the U. S. after receiving a Ph. D. (1887) at Munich, Paul C. Freer (b. 1862) taught chemistry at several American colleges before joining the faculty at the University of Michigan (1889) where he taught until 1905. His main research fields were the action of sodium on ketones and aldehydes; closed carbon chains; germicidal action of organic peroxides; and the esterification of halogen substituted fatty acids.

investigating Jamaica Dogwood and Cotton Root. We have also made a study of Passiflora Incarnata and several other drugs of minor importance. We are seeking to learn more and more of their peculiarities and of their composition so that we may have definite knowledge on which to base our processes of manufacture. All this is bound to bring about a great improvement in the vast line of products made by manufacturing pharmacists and dispensed by the retail pharmacist. The good work will undoubtedly gain impetus in the future and will be developed and expanded by such firms as are able to spend the money necessary. The inevitable result will be the discovery of new properties in well known drugs, the definite placing of many comparatively new drugs, and the abandonment of a number which are now held in esteem."[9]

Representative Pioneers of Industrial Research

Trying to pinpoint the birth date of a company research department can be illusory, but there are hard facts to suggest that Parke, Davis and Company pioneered meaningfully in developing a systematic approach to research in the pharmaceutical industry, and indeed stood among research pioneers in American industry at large.

Such investigations gained a strong initial stimulus when Parke, Davis and Company had the strength and boldness to grasp an opportunity that George Davis perceived one morning in September of 1894. His newspaper announced that von Behring and Roux had presented papers to the International Congress of Hygiene in Budapest about a serum treatment for

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9. Joseph Helfman to Edward Kremers, December 20, 1899. The Bulletin of Pharmacy, was established by George Davis of Parke, Davis and Company, and was closely associated with Parke-Davis.

diphtheria.[10] The announcement that an effective serum had been developed and demonstrated to be clinically effective stirred the entire scientific world. It culminated years of bacteriological research in Europe by such men as Loeffler, Yerson, Ehrlich, von Behring and Roux.[11]

George Davis rushed into his office that morning jubilant about the prospects of an effective treatment for diphtheria and determined to investigate the possibilities of producing diphtheria antitoxin for the American public.

The steps that Parke, Davis and Company took in the succeeding months proved to be extremely important, not only allowing them to be one of the very first American producers of diphtheria antitoxin, but as one result they hired their first research director.

Then as now, the advancing outer edges of the known often were linked to industry through university laboratories;

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10. A preliminary to the opening of immunization therapy had been the work by von Behring and Kitasato four years earlier when they produced animal immunity against tetanus and in their report introduced the term antitoxic.

11. It was the work of the remarkable Claude Bernard that actually helped to set the stage for all biological research, when in 1865 he published his book entitled An Introduction to the Study of Experimental Medicine. This book is still a classic today. For a discussion of the importance of Bernard's work see, M. L. Tainter and G. M. A. Marcelli, "The Rise of Synthetic Drugs in the American Pharmaceutical Industry," Bulletin of the New York Academy of Medicine, 35 (June, 1959), pp. 387-405.

and Parke, Davis and Company of Detroit found itself close at hand to the University of Michigan at Ann Arbor where two members of the medical faculty, F. G. Novy, M. D.,[12] and V. C. Vaughan, Ph. D., M. D.,[13] had attended the International Congress of Hygiene in Budapest. Immediately upon returning to Ann Arbor, they called a conference of the medical school faculty and reported to them the details of the studies presented by von Behring and Roux.

When the Company contacted the medical school to see if anyone there could help set up a department of bacteriology to produce diphtheria antitoxin it appears that they

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12. After receiving his B. Sc., M. Sc., Sc. D. and M. D., all from the University of Michigan (the latter in 1891), Frederick G. Novy (b. 1864) joined the faculty of the medical school of that university as an assistant professor of hygiene and physiological chemistry. His main research fields were the chemistry of bacteria; immunizing action of non-bacterial products; the etiology of diphtheria, yellow fever and the plague; and filterable virus. His memberships and honorary distinctions testify to his ability.

13. Victor C. Vaughan (b. 1851) was Professor of Physiological Chemistry, In Charge of Materia Medica" on the faculty of the School of Pharmacy, University of Michigan. ("Announcement of the School of Pharmacy of the University of Michigan," (1884-85). His name last appeared as a member of the School of Pharmacy faculty in the announcement for 1890-91, although he continued as a member of the medical school faculty. He was first appointed to the medical school faculty in 1876. Pharmacy students studied physiological chemistry from Vaughan's textbook.

were referred to Charles T. McClintock, Ph. D., M. D.[14]

For some years McClintock had been associated in biological work with one of the men who participated in the Budapest Congress, Dr. Vaughan.

A few days after Vaughan and Novy held their faculty conference, McClintock asked E. M. Houghton, M. D.,[15] if he would help him develop a bacteriological department for Parke, Davis and Company.[16] In a letter Dr. Houghton

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14. Charles T. McClintock came out of Bourbon County, Kentucky to take a Ph. D. (1892) and an M. D. (1894) at the University of Michigan, meanwhile serving as an assistant in the University of Michigan laboratories. Upon receiving his M. D. he took up work for Parke, Davis and Company to develop a method of producing diphtheria antitoxin. After completing some research on nucleins at the University of Michigan, he joined Parke-Davis on a full-time basis as the Director of their Biological and Research Laboratories. At the time he first began working for Parke-Davis he was 34. His main research fields were the etiology of hog cholera; etiology of vaccinia and smallpox; and serum therapy.

15. Elijah M. Houghton was a pharmacy graduate of the University of Michigan School of Pharmacy in 1893 and a year later received his M. D. from the Medical School of the same university, and served a year as an assistant in the department of pharmacology at the University of Michigan. At the age of 27 he joined the staff of Parke, Davis and Company to oversee the production of diphtheria antitoxin and to conduct biological research. In 1897 he was appointed Assistant Director of the Biological and Research Department of Parke-Davis and was promoted to Director of that department in 1911. His main research interests were ergot aseptic; pharmacological assay of heart tonic; pharmacology and pharmacological assay of active principles of suprarenal glands.

16. That both McClintock and Houghton had been associated for some years with Vaughan in biological work is reported by E. M. Houghton himself to O. W. Smith, December 3, 1923 (in the Historical File of Parke-Davis Research Library, Ann Arbor, Michigan.)

wrote on February 4, 1925, he discusses how he first became associated with the firm:

> Some time early in November, after Dr. McClintock had again discussed the matter with Parke, Davis and Company, he informed me that it had been decided that Parke, Davis and Company would take up the manufacture of Diphtheria Antitoxin on an experimental basis, and that they were going to start immediately; in fact, arrangements had been made whereby he was to produce Diphtheria toxin in Ann Arbor, and treat two or three horses in Detroit. This arrangement was made because he found it impossible to leave Ann Arbor at the time without seriously crippling some important research work that he was carrying out with Dr. Vaughan on the nucleins.
>
> From time to time, up until about the first of January, Dr. McClintock and I met and discussed the situation. Especially did it seem advisable that someone be in Detroit to carry on the work. As intimated, Dr. McClintock could not come, and the question arose, would I consider coming to Detroit. I considered the matter carefully with Dr. Cushny,[17] Professor of Pharmacology, my chief, Dr. Dock, Dr. Novy, and Dr. Vaughan, and they advised me, if arrangements could be made, to come to Detroit, as they believed that there was an opportunity for serving the medical profession, provided Parke, Davis and Company gave Dr. McClintock and myself a free hand to conduct a biological laboratory covering both bacteriology and pharmacology....
>
> About the middle of January, Dr. McClintock said that Mr. Wetzel [Secretary of Parke, Davis and Company] would like to have me come over to

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17. "The Scot A. R. Cushny (1866-1926), Professor of Pharmacology successively at the universities of Michigan, London, and Edinburgh, was a leader in his field, especially noted for his studies on digitalis and on antagonistic effects of optical isomers, and for his pathological studies on the heart and auricular fibrillation, and his development of Ludwig's filtration theory of urine-formation." (Arturo Castiglioni, A History of Medicine, E. B. Krumbhaar, trans., New York, 1941, p. 898.)

> Detroit to have a consultation with him about the possibility of taking up work in Detroit. I came over with Dr. McClintock in the middle of January, 1895, when Mr. Wetzel had a long talk with us. He assured me that there were great opportunities for work here, and that we should have practically as free a hand for developing scientific work in connection with Parke, Davis and Company as though we were connected with the University. Mr. Wetzel told me he had gone over the whole problem with Mr. George S. Davis, who was then General Manager, and this understanding was entirely agreeable to his wishes. Furthermore, he informed me that he had received letters from certain members of the medical faculty of the University of Michigan which indicated that I would be the proper man to take up the work. After considering the matter with Mr. Wetzel, an arrangement was made whereby I should report for work February 1, 1895 in Detroit....[18]

It was not until a year and a half later that McClintock completed his research at the university and was able to leave Ann Arbor permanently. Thus he did not join Parke, Davis and Company as a permanent employee until sometime in 1896, but during this interval he acted as a consultant and visited Detroit several times a week to oversee the work. Thus, as a result of Parke-Davis' desire to develop methods of producing diphtheria antitoxin, they employed their first research directors.

Although Houghton evidently did not have the title of Assistant Director of Research when he was first employed, it was understood that he would conduct biological research as soon as the production of diphtheria antitoxin was underway. The evidence so far uncovered seems to indicate

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18. E. M. Houghton to Mr. Mason, February 4, 1925; in the Historical File of the Parke, Davis and Company Research Library, Ann Arbor, Michigan.

the titles of Director of Research and Assistant Director of Research were established late in 1896 when McClintock joined the firm on a full time basis as the Director of Research.[19]

The selection of these two men to guide the research program was a turning point in the history of this firm because the success of early research probably was generated largely from their ability to conduct, plan, administer and encourage independent research. Both men had experience as university researchers and they had an appreciation of the conditions necessary for scientists to work productively.

That management agreed to give McClintock and Houghton a free hand in developing scientific work indicates management's appreciation for and belief in the value of research to their company. This was at a time, we should

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19. Some Parke-Davis publications list McClintock as Director of Research from 1895 to 1911, but we have found no reference to this title in company correspondence prior to the latter part of 1896. McClintock functioned as head of research and Houghton as the assistant head of research, although available records do not make clear what their full official titles were. For example, McClintock is listed in some sources as Director of Biological and Research Laboratories and in others as Director of Research. Houghton is referred to as Assistant Director of Research, Assistant Director of Biological and Research Laboratories, and Director of the Pharmacological Laboratory. Houghton used this latter title in several of his early publications (1900), and this can be explained by the fact that he was in charge of the pharmacological work. (See Historical File in the Parke-Davis Research Library, Ann Arbor, Michigan.)

CHARLES T. McCLINTOCK, believed to be the first full-time research director in American pharmaceutical industry, received a Ph. D. (1882) and an M. D. (1894) at the University of Michigan. After receiving his M. D. he began working for Parke, Davis and Company part-time, to develop methods for producing diphtheria antitoxin. Meanwhile he continued to conduct the research he and Dr. Vaughan had been doing at the University of Michigan on nucleins. Upon completion of this research late in 1896, he joined the staff of Parke-Davis as full-time Director of Research.

recall, when the majority of companies in American industry did not employ scientists.

The hiring of a research director was no mere gesture, for by 1900 we find mention of other research personnel and the research they were conducting.[20]

It took only a few months from the time they joined the Parke-Davis staff until Houghton and McClintock conquered the problems involved in producing diphtheria antitoxin, and thus Parke-Davis became one of the very first to introduce this valuable drug to the American market.

As soon as the problems of producing the diphtheria antitoxin were solved, Parke-Davis began biological research in an effort to develop antitoxins that would be effective against other diseases.[21] Initially this work was conducted by McClintock and an assistant, Louis Layson. Meanwhile, Houghton was busy experimenting with methods for assaying drugs physiologically. Thus during the first few years there were at least three scientists in the biological research department; and the records show that by 1900 there were at least five.

There were also several men in the Analytical Labor-

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20. Company correspondence, publications, and laboratory notebooks which I (M.K.W.) have examined in the Historical File of the Parke-Davis Research Library, Ann Arbor, Michigan.

21. Houghton to Mason, February 4, 1925, in Historical File of Parke-Davis Research Library, Ann Arbor, Michigan.

atory who were doing chemical research in addition to Aldrich, Hamilton, and others who were carrying out full time chemical research in the research department. Frank O. Taylor, who became associated with Parke-Davis in 1902, says, "The Analytical Department had about 12 or 13 men in it at that time. Two or three were doing largely what we would call 'research work,' two or three were doing both routine work and investigative work, with the Director, Dr. J. M. Francis, overseeing both types of work and doing some himself."[22] The research department at Parke-Davis prior to 1920 appears to have been preoccupied with biological research, reflecting the circumstances of its birth and the research specialties of its directors, reinforced by the exciting prospects for patients and for manufacturers alike that were offered by a whole new class of drugs, the "biologicals." Yet, Parke-Davis was conducting chemical research even prior to 1895, but the chemists were in the Analytical Department.[23] The Analytical Department continued

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22. Frank O. Taylor to Glenn Sonnedecker, August 16, 1961, in personal file of M. K. W.; for information about the number of individuals doing research prior to 1905 see transcriptions of interviews (kindly conducted by Dr. Alex M. Moore and Miss G. Losie) with Mr. Henry Devlin on August 2, 1961 and with Dr. Harvey Merker on July 6, 1961, on file in the Parke-Davis Research Library, Ann Arbor, Michigan.

23. There are conflicting reports as to whether Dr. McClintock was in charge of all research or only biological research. However, information collected from the Historical File in the Parke-Davis Research Library and from interviews and correspondence with Devlin, Merker and Taylor weighs heavily in favor of a view that McClintock was head of biological research only and that J. M. Francis, the Chief Chemist, was in charge of chemical research. However, there were some chemists in the Biological Research Department who did chemical work associated with biologicals.

to conduct some chemical research (in addition to the chemical research being done in the research department) as well as do the routine control work until Oliver Kamm, Ph. D.,[24] was employed (1920). At this time Kamm was placed in charge of all chemical research and a separate department for chemical research was established.[25]

Thus, after 1920 the main function of the Analytical Department was control work and J. M. Francis[26] continued

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24. Oliver Kamm received his B.Sc., M.Sc., and Ph.D. (the latter in 1915) at the University of Illinois. After serving as an instructor in chemistry at the University of Michigan for a year, Kamm returned to his alma mater and served as an assistant professor until 1920 when he joined the staff of Parke, Davis and Company as the Director of Chemical Research. At the time he began his long career in industrial research he was 32 years of age. His main research fields were organic synthesis; correlation between ionization and structure; relation between structure and physiological action; and the isolation of posterior pituitary principles.

25. Transcript of Merker's interview, July 6, 1961, in personal file of M. K. W.

26. John M. Francis (1867-1924) earned an A. B. (1887) at the University of Alabama; Master's (1889) while teaching chemistry at the University of Alabama, then took postgraduate course in organic chemistry at Johns Hopkins University. He remained on the faculty at the University of Alabama until he accepted a position as an assistant in the Analytical Department of Parke-Davis in 1892. By 1897 he had advanced to become head of the department, "supervised the firm's experimental work and in 1905 became chief chemist. He also superintended the firm's control department, which directed all processes employed in the manufacture of numerous chemical products...." He also worked in "weighing suggestions for new products... new processes of manufacturing... methods of improving the quality of preparations... and complaints from the trade and medical profession." (National Cyclopaedia of American Biography, Vol. 20, New York, 1929, p. 327.)

to head the Analytical Department as Chief Chemist, a position he held from 1905 to 1924, when Frank O. Taylor became Chief Chemist. As already pointed out, there were also men in the Analytical Department as early as 1902 who were devoting full time to chemical research.

More and more men took up their work at the benches, in both chemical and biological research between 1895 and 1920. That can be said even though in many laboratories the furnace long since consumed the exact figures. But Parke-Davis, for example, could list nineteen biological workers by 1917 (see Appendix B).

Circumstances that brought to Abbott Laboratories its first director of research show some interesting similarities to the experience at Parke-Davis.

Abbott chemists probably conducted some scientific research before the firm employed Ernest H. Volwiler[27] (1918), although not in a separately organized research department. Abbott maintained pharmacological and chemical laboratories as early as 1909, but these were mainly for quality control.[28] Several published articles indicate that "the

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27. After receiving his Ph.D. from the University of Illinois (1918) at the age of 25, Ernest H. Volwiler immediately joined the Abbott Laboratories as their Chief Chemist. In 1930 he was appointed Research Director of Abbott and in 1933 was promoted to Vice-President in Charge of Research and Development. From 1950 until his retirement in 1959 he served as President of Abbott Laboratories. His main research interests were anesthetics and barbiturates.

28. The Story of Abbott Alkaloidal Company, Chicago, 1909.

nucleus of a chemical research staff was formed" prior to World War I.[29]

When the war cut off our supply of foreign drugs, developing methods to produce some of these drugs became important, and Abbott stepped up its activities in this area.

While serving as Head of the Organic Chemistry Department at the University of Illinois, Roger Adams, Ph. D.,[30] developed laboratory methods for producing two drugs of German origin, barbital and procaine, which were vitally needed by our armed forces. "A prominent St. Louis company turned down his proposal to become their consultant in manufacturing these and other similar drugs. He then learned that Dr. Abbott was always keenly interested in new

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29. "American Chemical Industries: the Abbott Laboratories," The Journal of Industrial and Engineering Chemistry, 24 (May, 1932), p. 558; see also S. DeWitt Clough, "From Drug Store to 26-Acre Plant," Northwestern Druggist, 23 (November, 1922), p. 26; Elmer B. Vliet, "The Abbott Laboratories -- North Chicago Plant," The Chemical Bulletin, Vol. 14, No. 4 (April, 1927), p. 102.

30. After receiving his Ph. D. from Harvard University in 1912, Roger Adams (b. 1889) studied at the Berlin and Kaiser Wilhelm Institute for a year. Upon returning to the United States he accepted a position as an instructor in organic chemistry at his alma mater. In 1916 he accepted a position as an assistant professor at the University of Illinois and he has been associated with that institution ever since. Adams has received many scientific awards which testify to his eminence and renown. His main research fields were organic arsenical compounds, local anesthetics, chaulmoogric acid, and the chemistry of biphenyl derivatives.

ideas."[31] W. C. Abbott, M.D.,[32] and A. S. Burdick, M.D.,[33] liked the idea, and Roger Adams was employed as consultant. His first advice was that Abbott should employ Ernest H. Volwiler, who was about to receive his Doctor of Philosophy degree in organic chemistry (Spring of 1918) under Adams. Thus Volwiler began, as Research Chemist, a long and fruitful association with Abbott. He immediately set out to produce the desperately needed procaine and barbital,[34] "starting from laboratory research done by Dr. Adams. So urgent was the demand that only cursory laboratory and pilot plant experiments could precede actual production. The newly hired chemist plunged at once into his top priority

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31. Elmer B. Vliet, "The Abbott Story," mimeographed, March 16, 1950, in the Historical Files of Abbott Laboratories' Library, North Chicago, Ill.

32. Born in Vermont in 1857, W. C. Abbott received an M.D. at the University of Michigan in 1885. In 1886 he began a private practice in Ravenswood, Illinois, a Chicago suburb. He founded the Abbott Alkaloidal Company in 1899 and guided the destiny of the firm until his death in 1921. (E. B. Vliet, "The Abbott Laboratories -- North Chicago Plant," The Chemical Bulletin, Vol. 14, No. 1, p. 102.)

33. Born in DeRuyter, New York (1867), Alfred E. Burdick received an A. B. from Alfred University and in 1891 received an M.D. from Rush Medical College. He had a private practice for a number of years, before joining the staff of the Abbott Alkaloidal Company in 1904. He advanced steadily to positions of greater responsibility, becoming Vice-President of Abbott in 1916 and serving as President of the same firm from 1921 until his death in 1933. (E. B. Vliet, "Historical Sketch of Abbott Laboratories," on file in the Abbott Library, North Chicago, Ill.)

34. Ibid.

project, working as a technical laborer as well as a chemist."[35]

As soon as sufficient supplies of these drugs were produced, Dr. Volwiler was eager to begin research to develop new chemical drugs. Fortunately the Abbott management was also interested in expanding their research efforts. "Dr. Volwiler came to Abbott at a time when its leaders... were foreseeing the growing importance of research, development and production in the drug industry. All of them felt that a new era in pharmaceutical chemistry was at hand, an era that would bring people more relief from suffering than had ever been possible in previous human experience.

They were eager for Abbott to have a part in it, so chemists were added to the small group working in medicine, biology and pharmacy under J. F. Biehn, M.D.,[36] and Carl Nielsen. Among the able men who came to join in those early

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35. "Ernest Henry Volwiler: A Profile," Chicago, March 26, 1959; booklet published on the occasion of Dr. Volwiler's retirement as President of Abbott Laboratories.

36. J. F. Biehn (b. 1878) received an M.D. from Northwestern University in 1901 and after a year of postgraduate study at the same institution he began teaching bacteriology and sanitation at Dearborn Medical School. From 1904 to 1909 he served as bacteriologist of the Munic Laboratory in Chicago. In 1909, at the age of 31, he joined the Abbott Alkaloidal Company as Director of Scientific and Research Laboratories. His main research fields were methods of preserving vaccines; water analysis; hemolytic action of streptococci serums; pasteurization of milk; and antipneumococcus.

efforts were Norman Hansen[37], Elmer Vliet,[38] Floyd Thayer,[39] and Hugh Robinson."[40]

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37. Norman A. Hansen joined the staff at Abbott Laboratories as a plant chemist immediately after receiving a B. Sc. at the University of Illinois. At that time he was 25 years old. He served as a development chemist from 1926 to 1930, becoming manager of the Development Department in 1930. In 1946 he was appointed Director of Abbott's Product Development Laboratory.

38. Elmer B. Vliet received his B. Sc. (1918) and his M. Sc. (1926) from the University of Illinois. During 1919 he served as assistant research chemist for the U. S. Department of Agriculture. He joined Abbott in 1920, at the age of 23, as a research chemist and served in this position until 1935 when he was appointed manager of the Abbott Control Laboratories. He moved steadily up the management ladder at Abbott and presently is Chairman of the Abbott Laboratories' Board of Directors. His main research field was preparation and properties of synthetic medicinals and related compounds.

39. Floyd K. Thayer, at the age of 24, joined the staff of Abbott Laboratories immediately after receiving an M. Sc. at the University of Illinois in 1920. He served as a research chemist until 1925 when he became manager of the Chemical Sales Department. In 1953 he was appointed a Vice-President of Abbott Laboratories. His main research fields were mixed alkyl sulfates, anesthetics, and antiseptics.

40. Ibid. Dr. Biehn joined the Abbott staff in 1909; however, we do not know the extent of his work; a booklet published by Abbott in 1910 gives some indication: "One of the later features of the Company is its Scientific Laboratory, which is maintained for the convenience of the profession for the examination of urine, feces, blood, sputum, pathological tissue, etc. This laboratory which is in charge of Dr. J. Favil Biehn, for a number of years Director of the Laboratories of the Department of Health, City of Chicago, a practicing physician as well as a first-class physiologic chemist, also makes some bacteriological products, such as bacterins and antogenous vaccines for veterinary use, and is eventually to put out tuberculins, probably vaccines, and similar products." (St. Louis and Its Medical Institutions: A Souvenier of the Meeting of the American Medical Association at St. Louis, June 7th to 10th, 1910, published by Abbott; in Historical File of the Abbott Library.)

In 1919 Volwiler began formal research aimed at finding new and improved medicaments, as the Chief Chemist in charge of Abbott research (after 1930 with the title Director of Research). The Abbott research staff, ranging from six to ten men prior to 1925, made a number of valuable contributions by discovering such drugs as butacaine sulfate (Butyn), butyl aminobenzoate (Butesin), Butesin Picrate, and butethal (Neonal).[41]

The research staff was bolstered in 1922 when Abbott acquired the Dermatological Research Laboratories of Philadelphia. However, Dermatological Research Laboratories' research group continued to work in Philadelphia under the direction of George W. Raiziss, Ph. D.[42] Then in 1925, Volwiler began expanding his research staff, seeking out well trained men. By 1933 Abbott's scientific staff included twenty-nine persons in research, control and development.[43]

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41. Vliet, "The Abbott Story," March 16, 1950, mimeographed, on file in Historical File of Abbott Laboratories' Library; Volwiler, "Goals for Abbott Research," March 26, 1959, mimeographed; in Historical File of Abbott's Library.

42. The Russian-born (1884) George W. Raiziss received a Ph. D. in 1909 from Freiburg University. He began work as physiological chemist in the research department of a New York City Hospital in 1910 and served as a research chemist for the Rockefeller Institute, Matheson Lead Company, and General Electric Company prior to joining the Dermatological Research Laboratory in 1913 as Head of Chemical Research. At that time he was 29 years old. He was a specialist in dermatologicals and chemotherapy.

43. Ibid.

At the Upjohn Company circumstances surrounding employment of the first research director differed somewhat from those at Abbott and Parke-Davis. Upjohn employed Frederick Heyl, Ph. D.,[44] in 1913 to develop methods of assaying its products and to establish a system for quality control in production. As soon as Heyl and his first two assistants, Merrill C. Hart[45] and J. Fred Staley "had the control task in hand, they moved on to the investigation of new products, and then into independent research."[46] Heyl's research staff, which did not exceed three men prior to the 1920's, achieved a number of improvements in some of Upjohn's products through their work. At first Heyl was "chief chemist," but his title was "soon changed to director of the

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44. After Frederick W. Heyl received a Ph. D. from Yale University in 1908, he joined the faculty of the University of Wyoming as a professor of chemistry. In 1913, at the age of 28, he joined the staff of The Upjohn Company as Chief Chemist, a position he held until 1928 when he was appointed Vice-President in Charge of Research. Since his retirement (1945) he has served as a Research Consultant to the Upjohn Company. His main research fields were plants of therapeutic interest, especially digitalis, pollen, and ergot; lipoids; ergosterol; stigmasterol; and cortisone.

45. Merrill C. Hart received an M. Sc. from the University of Chicago in 1915 and an Sc. D. (h.c.) from Kalamazoo College in 1921. Hart joined Upjohn (1914) at the age of 23 as a research chemist; and in 1944 he was appointed Vice-President and Director of Research, a position he held until his retirement in 1949. His main research fields were phytochemistry; chemistry of corpus luteum and ovarian residue; and calcium metabolism.

46. Leonard Engel, Medicine Makers of Kalamazoo, New York, 1961, p. 50.

research division."[47]

Shortly after his arrival at Upjohn, Heyl began to work on digitalis to determine what caused the deterioration of digitalis tincture, and this work resulted in Upjohn introducing (1919) an oral tablet (Digitora) containing 0.85 grain of powdered digitalis leaf that was physiologically assayed, which remained one of Upjohn's leading products until the mid-1940's when digitoxin was developed.

From limited information available to us, it appears that Eli Lilly and Company organized a formal Scientific Division shortly after the turn of the century (prior to 1910), and by 1911 or 1912 was conducting research on a systematic basis. We know that Lilly employed a chemist, a botanist, and a pharmacologist and probably a few other scientists prior to 1909, but no evidence has been available that indicates any of them had research as an important function in the early years.[48]

An examination of Lilly's organization chart for 1908 lends support to the idea that the main function of the Scientific Division was quality control. The organization chart "lists four groups comprising the Scientific Division:

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47. Ibid., p. 51.

48. G. H. A. Clowes, Lilly's Director of Research, pointed out that "Research work in the Lilly Laboratories may be said to date from the period some fifty years ago when Mr. J. K. Lilly, returning from college [1882] and working single-handed in a small laboratory, succeeded in establishing standards for the alkaloidal contents of the more important fluid extracts and tinctures then manufactured by the company. Soon thereafter a chemist and a botanist and somewhat later a pharmacologist were added to the research staff." (Lilly Research Laboratories: Dedication, Indianapolis, 1934, p. ix.)

(1) Testing chemicals, oils, etc., (2) Assaying and standardizing, (3) Physiological testing, and (4) Botanical examinations."[49]

In 1909 a decision was made to construct a building to be known as the Scientific Building. This was begun in 1910 and completed and occupied in 1911. The research staff was then considerably enlarged. George H. A. Clowes[50] points out that, "The growth of this department was so continuous that within a decade the research work overflowed into adjoining buildings."[51]

"Systematic organic chemical research began in 1912 and a Synthetic Department was established. In 1913 the

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49. Archives of Eli Lilly and Company to Keith Weikel, March 1, 1962, in personal file of M. K. W. Not receiving access to the company archive nor exact references to company documents, we have relied upon information obtained by correspondence with Company-designated representatives, Dr. C. W. Pettinga and Mrs. Sally Denhart, wherever unpublished information about Eli Lilly and Company is cited.

50. In 1919, the English-born G. H. A. Clowes joined the research staff at Lilly after studying at the Royal College of Science in London, Berlin University, the Pasteur Institute and the University of Gottingen. Clowes received a Ph. D. from the University of Gottingen in 1899 and came to the United States in 1901. He began working (1901) at the New York State Cancer Laboratory and remained there until 1919, when he joined the research staff of Eli Lilly and Company. In 1920 he was appointed Research Director. His main research was concerned with cancer, emulsions, colloids and adsorption, and adsorbed alkaloids.

51. Lilly Research Laboratories: Dedication, Indianapolis, 1934, p. ix.

Scientific Division was completely reorganized."[52]

Of thirty-five persons listed on the scientific and research staff in 1912, we infer that up to three-fifths of them could have been engaged in research.[53]

The development of a formal research program at E. R. Squibb and Sons began about 1922 when Paul M. Giesy, Ph. D.[54] was employed as Director of Research at the Brooklyn Research Laboratory (chemical research), probably the beginning of Squibb's chemical research department. As early

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52. Archives of Eli Lilly and Company to Keith Weikel, March 1, 1962, in personal file of M.K.W.

53. Ibid. These thirty-five persons were engaged as follows:

Departments	Personnel
Analytical Department	9
Biological Department	3
Botanical Department	4
Chemical Research Department	5
Experimental Research Department	5
Library	4
Pharmaceutical Development and Economics	2
Scientific Supervision of Manufacturing	3
Custodian	1
	35

54. Prior to receiving a Ph. D. from Columbia University, Paul M. Giesy was employed as an assistant chemist by the U. S. Department of Agriculture (1912-14) and the Procter and Gamble Company (1914-15). He served as a research chemist for the Calco Chemical Company from 1920 until 1922, when he became Director of the Chemical Research Laboratory of E. R. Squibb and Sons, a position he held until 1926 when he resigned and went into education. At the time he joined Squibb he was 32 years old. His main research fields were dyestuffs and placental hormones.

as 1911, however, the firm set up a research laboratory in the Brooklyn plant,[55] even though progress appears to have been very limited until Giesy arrived. In a special report (1931), F. W. Nitardy observes:

> The reputation of the House of Squibb was built through the research work done by him [E. R. S.] on the production of pharmaceutical, medicinal chemicals and specialties. As long as he lived Dr. [E.R.] Squibb preferred to do his own research work, and published the results thereof in current pharmaceutical, chemical and medical literature, later (beginning with 1882) in the Ephemeris, his private journal, the latter covering a period of about twenty years and representing nearly 3,000 pages.
>
> After Dr. Squibb's death (in 1900) research received less atention for a time, until in 1911 a Research Laboratory was organized under Dr. Virgil Coblentz[56] who had the help of three assistants.
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> The laboratory continued until 1916 but was not as productive as it could have been primarily for lack of proper selection of problems and neglect to record the results. There is no record of what was worked on or accomplished in those years.... After 1916 the laboratory continued with

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55. F. W. Nitardy, "Long Range Comparative Report (1916-1941)," submitted to Lowell P. Weicker, President of E. R. Squibb and Sons in 1941, in the Archives of the Squibb Institute for Medical Research Library, New Brunswick, New Jersey.

56. The son of a Cincinnati pharmacist, Virgil Coblentz graduated from Wittenberg (Ohio) College Academy and the Philadelphia College of Pharmacy (1882). While managing the family pharmacy he served for two years as professor of materia medica and toxicology at the Cincinnati College of Pharmacy. This inspired him to go to Germany to continue his education. After receiving a Ph. D. at the University of Berlin (1891), he joined the faculty of the New York College of Pharmacy as a professor of pharmacy and chemistry, resigning this position in 1911 to become chief chemist for E. R. Squibb and Sons. His memberships and awards testify to considerable stature.

> one man devoting his entire time to research under conditions similar to those prevailing earlier. Solargentum [Mild Silver Protein] and Protargentum [a combination of silver and gelatose] were created in 1918, but there is no other result on record.[57]

The development of Squibb's research on a truly departmental and more vigorous basis began shortly after Giesy became Director of Research (1922), when he installed a "system for initiating research work, keeping protocols of all experiments, and recording results, positive as well

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57. Research Work in the House of Squibb: Brief Survey of its History, Present Status, and its Effect on the Future of the House. A Supplement to the Annual Report for 1930, submitted by F. W. Nitardy to the Executive Office, March 24, 1931; in Archives of Squibb Institute for Medical Research Library. In the Annual Report for 1930 Nitardy sheds further light on the development of research at Squibb when he says, "Although it would readily be acknowledged that research is fundamental to our business, little seems to have been done in this field after 1890, when Dr. Squibb's personal activities in research declined [due to failing health]. Such work as was done was not reported and personal association with people in important positions in the plant prior to 1917 has not brought to light any information or any suggestions of any accomplishments after the work of Dr. Squibb as recorded in his publications. Ten years ago [1921] the laboratory had 'one research chemist'. An effort by the Plant Management (1919) to have research work properly recorded and reported was overruled. So much attention and effort was required in improving plant conditions generally about this time that effective organization for research did not occur until after the serious business slump in 1921." Annual Report for the Year of 1930 on the Operation of the Brooklyn Laboratories and New Brunswick Chemical Division, presented to C. H. Palmer, President and Theodore Weicker, Vice-President by F. W. Nitardy, Vice-President in Charge of Manufacturing, April 4, 1931, pp. 48-49.

as negative...."[58] In 1923 Geisy began adding chemists, and within five years the research staff at the Brooklyn laboratory included fourteen chemists, four assistants and the director of research.[59]

In addition to the chemical research, which was done at the Brooklyn plant, Squibb also conducted some research at their "Biological and Research Laboratories" at New Brunswick. E. R. Squibb and Sons Research and Biological Laboratories (incorporated September 26, 1913) began producing biologicals early in 1914, and acquired John F. Anderson, Ph. D.,[60] as Director the following year. Information on the staff, caliber, or extent of the research endeavor at New Brunswick[61] could not be recaptured -- but it could not have occupied more than one or two senior

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58. Ibid.

59. Ibid.

60. After receiving an M.D. (1895) from the University of Virginia, John F. Anderson studied in Europe and upon returning to the United States he accepted a position with the U. S. Public Health Service as an assistant surgeon (1898). Anderson remained with the Public Health Service, serving as Director of the Hygienic Laboratory from 1909 until 1915 when he resigned to become director of E. R. Squibb and Sons Research and Biological Laboratory. At the time he joined Squibb he was 37 years old. He served as a Vice-President of Squibb from 1919 until his death in 1956. His major research was concerned with the standardization of disinfectants, control of vaccine virus, studies upon anaphylaxis and serum sickness.

61. Now the site of the famous Squibb Institute for Medical Research.

research men.[62]

So far we have discussed research beginnings in several companies that were founded as business enterprises. An institution not founded as a profit-making organization also played an important role in early pharmaceutical research, and eventually was absorbed into pharmaceutical industry. "...The Dermatological Research Laboratories had their inception in 1912 through the generosity of a philanthropic citizen of Philadelphia who financed the scientific work for a period of four years. Shortly after his demise, the estate was settled and further financial grants from this source were discontinued."[63] Initially, Dermatological Research Laboratories was organized as a voluntary unincorporated association and, with the consent of the donor, Jay Frank Schamberg, M.D.,[64] was appointed Director. Schamberg secured the services of two skilled

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62. The entire research budget for the New Brunswick laboratory was $6,248 in 1924 (Ibid.).

63. "Report of the Dermatological Research Laboratories to the Board of Trustees of the Philadelphia Polyclinic and College for Graduates in Medicine," 1918, in Historical File of the Abbott Library, North Chicago, Ill.

64. Jay F. Schamberg (b. 1870) received his M.D. from the University of Pennsylvania in 1892. After graduating he remained in the Philadelphia area and began to practice medicine. In 1912 he was appointed Director of the Dermatological Research Laboratories. In 1919 he was appointed Professor of Dermatology and Syphilology at the University of Pennsylvania Graduate School of Medicine. Schamberg was a specialist in syphilology; diseases of the skin; acute contagious diseases and eruptive fevers.

scientists (1912) to help him conduct the research -- John A. Kolmer, M.D.,[65] a pathologist and George W. Raiziss, Ph. D., an organic chemist.

At first their work was devoted to investigating the cause of psoriasis and means of improving its treatment. "During the course of this work, we felt that our laboratories were so organized as to permit broader investigative research without material increases of expenditure. We thereupon entered upon research in the newly established science of chemotherapy."[66]

Soon after, World War I began. Recognizing that the United States' supply of arsphenamine (Salvarsan) -- the exciting specific discovered by Ehrlich for treatment of syphilis -- might be cut off, Dermatological Research Laboratories set out to develop methods to produce this compound.

> After some months of experimentation, we succeeded in the spring of 1915 in preparing salvarsan. At the meeting of the American Dermatological Association, held in May, 1915, in New York City, we detailed our work and presented a paper on the technical nature of this compound....

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65. John A. Kolmer received his M.D. from the University of Pennsylvania in 1908. He served as a pathologist at the Philadelphia Hospital of Contagious Diseases (1908-1918) and became associated with the Dermatological Research Laboratory in 1913 at the age of 27. In 1919 he was appointed a professor of pathology and bacteriology at the University of Pennsylvania. Kolmer was a specialist in immunity, pathology, and bacteriology.

66. Ibid.

We prepared and distributed salvarsan under the name of arsenobenzol to hospitals and physicians throughout the United States from December, 1915, to June, 1916. At this time we received a letter from the American [patent] licensee stating that he had received a large shipment of salvarsan from abroad and that he would expect us to cease the preparation and sale of arsenobenzol. While we had not bound ourselves by any agreement to do so, we felt that the purpose which we had in mind had been accomplished, and we immediately discontinued the preparation and distribution of this product. We then resumed our scientific work and devoted our time exclusively to the purpose for which the laboratories had been organized.... By this time our laboratories had become entirely dependent upon our own efforts for their maintenance; we had accumulated an amount of money which would carry on the work of the laboratories for several years. We were most anxious to conserve this fund for the support of our research work. Our laboratories were, of course, not instituted nor were they conducted for commercial ends."[67]

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67. Ibid. The report contains further explanation of one of the fascinating pharmaceutical episodes of World War I that may be of interest to record: "In November, 1915, there was manifested evidence of the exhaustion of the supply of the German product in the United States. Our laboratories began to receive numerous communications from physicians and hospitals asking us whether we could supply this drug as they had difficulty in securing it. We thereupon had an interview with the American licensee of the German company, and found that the supply of salvarsan in the United States was indeed virtually exhausted. We took the position that, despite the fact that salvarsan was protected in the United States by comprehensive patents, there was a moral obligation upon us to prepare and supply the drug in view of the fact that there was an interruption of its importation; it was inevitable that this condition of affairs would lead to physical suffering and extension of disease. After a long conference with the American licensee of the German company he agreed that he would not interfere with our supplying the drug as long as he could not secure it, but that as soon as he again received a supply of salvarsan from abroad, he would inform us of the fact and would then call upon us to cease the marketing of our product."

In another three years the Dermatological Research Laboratories became a corporation in which profits from the distribution of their products were placed in a fund for the "support of medical research and the development of new antisyphilitic remedies and new chemotherapeutic drugs."[68]

By 1921 the demand for products of the Dermatological Research Laboratories had so increased that they moved from their original laboratory in the basement of Polyclinic Hospital to a four-story building of their own. At this time the research staff is said to have consisted of nineteen scientists.

The Dermatological Research Laboratories advanced chemotherapeutic research in America -- developing several products still in use today.

In 1922, Schamberg and Kolmer decided that it was not possible for them to provide the proper attention to affairs of the corporation without jeopardizing their medical work. So they sold Dermatological Research Laboratories to Abbott Laboratories (1922), thus ending the life of a remarkable institution, but at the same time adding to the research resources of another firm.[69]

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68. "History of D. R. L." (mimeograph, n. d.); in Historical File of the Abbott Library.

69. As a part of the sales contract it was agreed that George W. Raiziss was to become the Director of the Dermatological Research Laboratories and be in charge of the production of its products for distribution by Abbott Laboratories. With the proceeds of the sale Schamberg and Kolmer founded and endowed the Research Institute of Cutaneous Medicine. (Ibid.)

Physical Facilities

In addition to the employment of a qualified research staff, company management must provide them with the proper physical facilities to carry out their work. Such facilities probably varied as widely as the size of the research staffs employed during this early period.

In most companies, research began in a small one-room laboratory, which expanded in the wake of a growing research staff and program. While at least one company constructed a building specifically for research as early as 1902, there were other strong companies that as late as 1920 still confined their own research to a one-room laboratory.

In 1901 the stockholders of Parke, Davis and Company voted "to increase the capital stock of the corporation from $1,200,000 to $2,500,000, the main purpose being to provide means with which to build an elaborate and separate laboratory for purely scientific work. These various scientific departments have previously been scattered over several existing laboratories given up mainly to manufacturing and each has grown until the available space and conveniences have become entirely inadequate. The present plan is to bring them into coordination which is essential for best results and to provide them with every facility which modern scientific progress makes necessary."[70]

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70. "A New Scientific Laboratory," Bulletin of Pharmacy, 15 (1901), p. 52.

It appears that McClintock probably played an important role in encouraging management to erect a research building. He proposed such a building in a letter he wrote to the General Manager, William M. Warren:

> From the time you took charge of the work, each year there has been talk of a special laboratory for the scientific departments of the House. Each year this has had to give way for building for manufacturing purposes. It seems to me that the time has come when that building should be provided for.
>
> Speaking broadly, reputation is the best asset which Parke, Davis and Co. has and, as it appears to me at least, the work done in its scientific departments has and will add more to that reputation than any other work undertaken by the Firm. Could we have a laboratory dignified in appearance and in appointments, the favorable impression produced on our many visitors would, I think, be of great value. If we can show people that we have better facilities for developing work, for testing drugs, for finding out in advance as to whether a given remedy is or is not of value, it will place us in a unique position among manufacturing pharmacists....
>
> There is still further the fact that men of sufficient ability to be experimentors must be allowed, within reason, some privileges that cannot be granted the general employees of the laboratory. This could be arranged for in a separate building without causing friction or hard feelings.
>
> The prosperity of the Firm as a whole and of this Department in particular, it appears to me, amply justifies the expense of a handsome, well-equipped laboratory. I know but little of building and building materials, or of the cost, and while I have not given detailed thought to the matter my impressions are that we should have something like the following:
>
> A three-story building, with basement, approximately 160 to 175 ft. in length by 60 ft. in width. In architecture it should be plain but handsome. My own impressions would be favorable to a dark grey brick, but of this I know but little.

> This, as it appears to me now, taking all things into consideration, should be located on the river front, the most showy site we have and one which would be freest from dust and smoke.
>
> In this building should be housed the Biological and Analytical Departments, and probably the Herbarium and general library. The finishings of the interior would, of course need most careful consideration and I would suggest that we look into the plans and general arrangement of the foremost laboratories of the country, in particular those of the Chicago University. It might be that it would be advisable to have architects who have built some of these laboratories plan ours. I will give the matter more detailed thought and study and will be able to suggest a number of things, particularly in regard to planning the interior of this Department."[71]

In perfecting the plans for its research building and equipment "the best laboratories of the country were visited and critically examined by experts. Their defective features were eliminated from our plans, while the best ideas were incorporated in them."[72] A few years earlier (1897), McClintock visited research laboratories in European countries to determine their methods of production and their research procedures.[73] This probably stimulated his ambitions for a new company laboratory, and he may well have brought back some ideas from European research laboratories

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71. C. T. McClintock to William M. Warren, January 4, 1901; in the Historical File of the Parke-Davis Research Library, Ann Arbor, Michigan.

72. "Our New Research Laboratory," Pharmacal Notes, No. 2 (1901), p. 39.

73. McClintock to Wetzel, April, 1897, in Historical File of Parke-Davis Research Library.

that were incorporated into Parke-Davis's scientific building. Taylor points out that both Houghton and Francis also made a trip to Europe "to look over various types of laboratories and to get ideas on what might be the best set-up for Parke-Davis."[74]

When Parke, Davis and Company erected its scientific laboratory in 1902 at a cost of $250,000, it became one of the very first companies in American industry at large to construct a building largely for research. The famous General Electric Research Laboratory was started a year earlier at Schenectady, New York, in an already existing building. (For pictures of Parke-Davis' early research building see Appendix D.)

A few years later Eli Lilly and Company decided "to construct a building to be known as the Scientific Building." This was started in 1910 and completed in 1911. By 1934 the Lilly research staff had outgrown this building, and the new Lilly Research Laboratories were opened.

Expanding research staffs made it necessary by the 1930's for a number of other companies to erect buildings devoted specifically to research. For example, Merck and Company opened the Merck Research Laboratories at Rahway, New Jersey, in 1933; and in 1938 both the Squibb Institute for Medical Research and the Abbott Research Laboratories

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74. F. O. Taylor to M. K. Weikel, June 30, 1962, in personal file of M. K. W.

were dedicated. Prime research was becoming a necessity for any company that desired to be in the vanguard of the industry. Research advances by several companies in the 1920's spoke eloquently of the potential, and the opening up of the field of sulfa-compounds by Domagk made the conquest of bacterial infections a visible goal.

Typical Work

From the first research facilities and research staffs came improvements such as the biological standardization and clinical testing of drugs, aimed at providing the physician with more uniform and more effective drugs.

The first American product standardized by physiological assay (1897) was a fluidextract of ergot; interestingly, this same preparation eighteen years earlier apparently was the first chemically standardized botanical product produced in America. According to Sir Henry Dale, the methods that had been laid down by Paul Ehrlich to measure the activity of early antitoxic sera provided the principles on which rests "all sound later work on the biological assay of remedies."[75]

E. Mark Houghton was responsible for introducing

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75. Sir Henry Dale, "Chemical Ideas in Medicine and Biology," in Lilly Research Laboratories: Dedication, Indianapolis, 1934, p. 22.

physiologically standardized products to American medicine. Houghton began this work while still a member of the medical faculty at the University of Michigan. "I may inform you," he once wrote, "that the work on pharmacology, especially physiological testing, was inaugurated by myself during the summer of 1894 at the University of Michigan, and I brought to Parke, Davis and Company the idea of determining the activity of certain unknown drugs that could not be tested by chemical means through the use of lower animals. Experiments were conducted at this time in Ann Arbor which convinced me that pharmacology as a medical science could be applied to a considerable number of problems that confront the manufacturing pharmacist."[76]

Herbert C. Hamilton, a member of the Parke-Davis research staff, notes that a number of scientists had worked on various methods of assaying ergot prior to Houghton's work, but that Houghton was the first to propose a physiological assay for a commercial preparation of ergot. Hamilton notes that,

> Wiggers fed 9 grains of an extract he called "ergotin" obtained by alcoholic extraction, to a cock and caused convulsions and death. This probably occurred too quickly for the typical bluing of the comb to appear since he noted only that the comb became cold.
>
> Bonjean obtained an aqueous extract

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76. Houghton to Mason, February 4, 1925; in Historical File of Parke-Davis Research Library, Ann Arbor, Michigan.

purified by precipitation with alcohol to which he also gave the name "ergotine." This caused the typical bluing of comb and wattles and a narcotic condition which demonstrated to him that it contained the therapeutic agent.

Kobert, in carrying out investigations of ergot bodies in 1884, used all the laboratory animals including cocks, frogs, pigs, rabbits, cats and dogs. He used also the isolated uterus of the sheep and considered this the most suitable method of testing ergot, but as a second and final test it must produce abortion in pregnant animals with no other untoward effect.

Jacobi's work in 1897 was probably the most important to that date because he carefully checked up his chemical investigations by means of physiological tests. He noted its action on the uterus, on the cocks comb and on blood pressure, the three characteristic effects of this drug.

All the work recorded to this time has been on experimental bodies with no reference to standardization of commercial products. Houghton, in 1898, proposed, in a paper before this /American Pharmaceutical/ Association, applying the Cock's Comb Method for the routine assay of commercial ergot preparations, the method of administration then followed, being that of feeding the crude drug, and by means of a catheter introducing fluid preparations into the rooster's crop.

About this time the work of Barger, Carr, and Dale, who wrote voluminously at this period, seemed to have cleared up much of the uncertainty regarding the identity and character of the active constituents of ergot. They showed that different constituents were responsible for the different physiological effects noted. Thus they demonstrated that the aqueous extract as well as an alcoholic can contain an active agent. Ergotoxine, an alkaloid, appears to be the agent causing the bluing of the cock's comb, p-oxyphenylethylamine or tyramine is the pressor agent although the alkaloid acts in this way too, while B-iminazoylethylamine or histamine is the principle which acts on the non-pregnant uterus and in most cases lowers the blood pressure of anesthetized dogs and rabbits.

> This work shows conclusively why no assay method based on the amount of any one active constituent present is adapted to the standardization of this drug.[77]

After his success with ergot, Houghton continued to develop physiological assays for other drug preparations, such as digitalis, strophanthus and cannabis. (For Houghton's work on ergot, see Appendix C.)

Seeing physicians' acceptance of these physiologically standardized fluidextracts, other companies began to assay some of their preparations physiologically. As early as 1908, for example, the organization chart of Eli Lilly and Company listed physiological testing as the task of one of the four groups comprising the Scientific Division.[78]

In the immediately preceding years, the firm is recalled as making a special endeavor to bring into its laboratories up-to-date academic knowledge that would serve this purpose.[79]

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77. Herbert C. Hamilton, "Pharmacological Assaying," The Journal of the American Pharmaceutical Association, 8 (January, 1919), p. 52.

78. Archives of Eli Lilly and Company to M. Keith Weikel, March 1, 1962.

79. Transcript of interview conducted with Dr. Harvey Merker, in the personal file of M. K. W.

While some firms were assaying some of their products by physiological methods prior to World War I,[80] apparently in the early 1920's some companies still did not utilize physiological assays.[81]

By the turn of the century some segments of the industry were providing physicians with drugs whose strength and action were standardized by either chemical or physiological assays. Not later than 1901 another measure was initiated to provide the physician and patient with more reliable drugs. At this time Parke, Davis and Company instituted a systematic method of clinically proving all medicinal agents before marketing them. While clinical tests were nothing new, this may well have been the first American company to develop a formal system of clinically

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80. For example an advertisement of H. K. Mulford in 1909 states, "The H. K. Mulford Company standardizes ONE HUNDRED AND TWENTY-ONE MORE VEGETABLE DRUGS AND PREPARATIONS than is required by the United States Pharmacopeia. The U.S.P. requires the chemical standardization of 56. The H. K. Mulford Company standardizes 177. The U.S.P. does not require physiological testing of drugs. The H. K. Mulford Company physiologically tests 50 pharmaceutical and biological preparations. In addition to this, we make a bacteriological or clinical test of 38 of our preparations." (The Pharmaceutical Era, 42 (March, 1909), p. 16.)

81. For example, E. R. Squibb and Sons "did not at that time apply physiological tests to Fluidextract [of] Ergot...." ("Long Range Comparative Report (1916 to 1941)," July 1, 1941, presented to Carleton H. Palmer, Chairman of the Board of Directors, and Lowell P. Weicker, President of E. R. Squibb and Sons, by the Vice-President in Charge of Manufacturing; in the Archives of the Squibb Institute for Medical Research Library, New Brunswick, New Jersey).

testing their drugs prior to placing them on the market.

The clinical testing of drugs was proposed already in the Middle Ages by the great Arabic clinician, Avicenna (980-1037),[82] who argued for use of the human body, because testing a drug on a lion or a horse might not give the same results as on man.[83]

By the latter part of the nineteenth century clinical evaluation of new drugs had become quite common in Europe.

Other features of the broadening research programs ranged from problems involved in the production of a drug to more fundamental and complex problems of determining the etiology of certain diseases. The scope of the work by at least one research staff covered such diverse areas as pathology, cytology, bacteriology, nutritional chemistry, biology, pharmacology, physiology, pharmacy and chemistry.

Much early research in the American industry studied immunity and development of antitoxins, stimulated by the basic European work then commanding attention. A few years

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82. In a list of rules for testing drugs he gave in his encyclopedic Canon, J. P. Bull tells us, Avicenna "suggests that in the trial of a remedy it should be used in its natural state upon uncomplicated disease, that two opposed cases be observed, and that the study be made of the time of action and of the reproducibility of the effects." ("The Historical Development of Clinical Therapeutic Trials," Journal of Chronic Diseases, Vol. 10, No. 3 (September, 1959, p. 221.)

83. A. C. Crombie, in Avicenna, Scientist and Philosopher, edited by G. M. Wickens, London, 1952, p. 89.

after the introduction of diphtheria antitoxin, serums were developed to treat such conditions as puerperal fever, erysipelas, scarlet fever, and malignant tumors.

Some products developed or introduced during the "formative period" are still in use today. An old and notable product from this time is epinephrine. In 1895 Parke, Davis and Company hired a Japanese chemist, Jokichi Takamine,[84] as a consultant and began to market a potent starch-splitting enzyme, which he had developed, called Taka-Diastase. Takamine worked on a number of problems as the firm's consultant, but probably most important was research that led to the isolation of crystalline epinephrine. In the late 1890's a number of scientists were trying to isolate pure epinephrine. John J. Abel, M.D.,[85] of Johns

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84. The Japanese-born Jokichi Takamine received a Doctor of Chemical Engineering degree from Glasgow University (1880) and a year later received a Doctor of Pharmacy degree from the same institution. Takamine served as a chemist for the Japanese government and for several companies prior to coming to the United States in 1890. He spent several years trying to interest the American distilling industry in a starch-splitting enzyme he developed as a consequence of his college studies. In 1895 at the age of 41 he was employed by Parke-Davis as a research consultant, a position he held until his death (1922). His major fields of research were diastatic ferments and the active principles of the suprarenal glands.

85. John J. Abel (b. 1857) attended the University of Michigan and Johns Hopkins University prior to studying at several European universities (1884-1890). He received an M.D. from the University of Strasbourg in 1888. Upon returning to the United States he accepted a position at the University of Michigan as a lecturer on materia medica and therapeutics. In 1893 he accepted a position as professor of pharmacology at Johns Hopkins University. He is considered one of the most brilliant and influential of early pharmacologists in America.

Hopkins University, Otto von Furth, Ph.D., of Strassburg, Germany, T. B. Aldrich, Ph.D.,[86] and J. M. Francis (the latter two men being from Parke, Davis and Company). All had made progress. Nevertheless, it was Takamine who turned the final trick and successfully isolated pure, crystalline epinephrine (marketed by Parke-Davis in 1900 as Adrenalin).

Although research prior to World War I was heavily preoccupied with "biologicals," there were also efforts to develop chemical drugs. For example, an examination of early laboratory notebooks at Parke-Davis indicates that in addition to work on the development of biologicals and methods of standardizing various products, this firm was attempting to develop disinfectants, germicides, antiseptics, antipyretics, sedatives, anesthetics and mercurials.[87] A number of products resulted from this early work, and among these was Formadine,[88] an antiseptic dusting powder developed

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86. After receiving a Ph.D. (1892) from University of Jena, Thomas B. Aldrich was employed as a chemistry teacher in several high schools. In 1893 he accepted a position as an associate physiological chemist at Johns Hopkins University. In 1898, at the age of 37, he joined the Parke-Davis staff as a research chemist. His major research fields were new derivatives of phenylmethylpyrazolons; derivatives of chlorotone and brometone; isolation and synthesis of adrenalin; pituitrin and enzymes.

87. Notebooks listing titles of Parke-Davis' research projects, 1903-1910, in Parke-Davis Research Library, Ann Arbor, Michigan.

88. Iodized condensation product of formaldehyde and salicylic acid, containing about 56% iodine.

by Eric Clemmensen, a German chemist employed by Parke-Davis.[89]

About 1920 more emphasis was being placed on chemical research. Abbott Laboratories initiated research about this time to develop more effective local anesthetics, hypnotics, and sedatives. These efforts resulted in the discovery of butacaine (Butyn)[90] and butethal sulfate (Neonal).[91]

Most of the research during the early 1900's in pharmaceutical firms dealt with human diseases; however, there was some research to determine the causes of certain animal diseases. Newell S. Ferry,[92] who joined Parke-Davis in 1908 and headed research in bacteriology, discovered the cause of canine distemper, a feat that bacteriologists in Europe and America had been attempting for many years.[93]

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89. Taylor to Sonnedecker, August 16, 1961; in personal file of M. K. W.

90. Procaine derivative, with butyl group in place of ethyl, and propanol in place of ethanol.

91. N-butyl ethyl barbituric acid.

92. Newell S. Ferry received his Ph.D. at Yale (1898) and his M.D. at Johns Hopkins University in 1902. From 1903 to 1908 he taught pathology, bacteriology and physiology at the Tennessee Medical College. In 1908 at the age of 32 he accepted a position as senior research bacteriologist for Parke-Davis. His main fields of research were animal diseases, especially canine distemper and equine influenza; bacterial antigens; pollen and protein extracts, bacteriology and immunology of infectious diseases; and bacterial toxins.

93. W. E. King to Mr. Allee, March 25, 1915; in the Historical File of the Parke-Davis Research Library, Ann Arbor, Michigan.

W. E. King, M.D.,[94] Assistant Director of Research, points out his firm's extensive work on hog cholera:

> For over fifteen years the research laboratory of Parke, Davis and Co. has conducted practically a continuous line of experiments and investigations on Hog Cholera. This work has been zealously prosecuted without financial return. Several times experimental hog cholera vaccines have been developed and tested out in the field in the Middle West and ultimately dropped because they did not yield sufficiently uniform results to warrant placing them on the market. Much of the hog cholera work which has been done has been limited solely to the study of the specific cause of the disease and the elucidation of the study of filterable viruses and ultramicroscopic organisms."[95]

Even before 1920 at least one firm was attempting to develop products to treat such dreaded diseases as polio, cancer and tuberculosis.[96]

While most research during the "formative period" is what we would consider "applied research," some could be considered "basis research." For example,

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94. Walter E. King received an M.D. from Detroit Medical College in 1914. Prior to receiving his medical degree King served as a research bacteriologist for Parke-Davis (1905-1908). From 1908 to 1910 he served as a bacteriologist at Kansas State University. In 1910, at the age of 33, he returned to Parke-Davis as Assistant Director of Research. His major fields of research were the oral administration of antitoxins and toxins, hog cholera, filterable viruses, and the viability of bacteria.

95. Ibid.

96. Information about research on such products is in the Historical File of the Parke-Davis Research Library, Ann Arbor, Michigan.

> Dr. G. H. A. Clowes, who joined Lilly in 1919, first devoted his time to a comprehensive study of those fundamental problems in the borderline field between physics and chemistry on the one hand and physiology and pathology on the other. In 1920 in order to facilitate the study of living protoplasm and to throw light on the physics and chemistry of certain vital processes, arrangements were made to carry out a part of the work with simple marine organisms in the Marine Biological Research Laboratories at Woods Hole, Massachusetts. Dr. Clowes wrote at that time, "The scientific research both here and in Woods Hole is immensely valuable from an educational and development standpoint, to say nothing of the fresh leads that must inevitable open up as a result of the work."[97]

Sir Henry Dale, pointed out Lilly's support of basic research when he said, "I recently visited the Marine Laboratory at Woods Hole, and there saw Dr. Clowes and some of his staff, who had been working through the summer on problems of fundamental biology, in happy association with distinguished academic workers in the same field; and I brought away with me the conviction that there was no need here to urge on an enlightened directorate the claims of research having no immediate or visible relation to its business, but of immense value in keeping alive the scientific initiative and mental enterprise of those who also serve its interests more directly, and in helping them to establish and to retain their proper rank in scientific fellowship."[98]

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97. Archives of Eli Lilly and Company to M. Keith Weikel, March 1, 1962, personal file of M. K. W.

98. Dale, "Chemical Ideas in Medicine and Biology," in Lilly Research Laboratories: Dedication, Indianapolis, 1934, p. 31.

Additional insight into the type and scope of research conducted can be obtained by examining the titles of articles published by the research departments of several firms during the "formative period" (Appendix A; see also Appendix B and C).

The investigations by early research staffs were quite diversified, and it is not our purpose in the present context to examine all types of work they were doing, but rather to exemplify the character of these early American efforts.

V

RESEARCH ADMINISTRATION AND PERSONNEL

One factor impeding the development of industrial research in America, we have noted, was that some managements did not grasp the importance of research or appreciate the conditions necessary for scientists to carry out their work properly.

That the managerial attitude in the 1920's often fell short of venturing upon a systematic research program seems implied by Earl P. Stevenson, Research Director of Arthur D. Little, Inc., when he said, "Instead of a guerilla attack, involving casual work here, duplication there, and general chaos, the great opportunity of organized research, ably directed, sufficiently financed and sustained in prosecution, is evident. Such an enterprise requires imagination, courage and faith in its sponsors. It is a most attractive speculation.

"Organized industrial research is a speculation which is of growing appeal to those who are endowed with the vision to comprehend its possibilities and the means to act."[1]

Executives of several pharmaceutical companies had the

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1. Earl P. Stevenson, "The Frontier of Industry," The Scientific Monthly, 22 (April, 1926), p. 288.

foresight, early in the 1900's to recognize the advantages of an organized research program. This is evident in company literature and policies. For example, Eli Lilly and Company first established research as a matter of policy in 1899, "To contribute to the progress of medicine by developing new and superior agents through research."[2] In voicing this policy Lilly management recognized the importance of research, and in the ensuing years they took vigorous steps to give this policy reality.

In the first issue (1894) of Therapeutic Notes, Parke, Davis and Company stated its conviction of the importance of advancing both medical and pharmaceutical science,

> We hold that the manufacturing chemist should lend his superior resources to the advancement of both medical and pharmaceutical science; that he ought not to act altogether from a selfish pecuniary motive, but should have in view the general well-being of humanity and, as tending to this end, the continued progress of medicine and pharmacy.
>
> In pursuance of this belief, we have expended large sums in therapeutic, physiological and chemical research; employed able botanists in exploring the habitats and studying the characteristics of new drugs; promoted exhuastive physiological experiments to determine their therapeutic value; made expensive tests in our laboratory to determine the most available form of preparation; and have then placed, free of cost, at the disposal of the medical profession, samples of the same for clinical experimentation, until the medicinal value was ascertained. Where no therapeutic worth was found, the drug has been relegated to deserved oblivion....[3]

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2. Archives of Eli Lilly and Company to M. Keith Weikel, March 1, 1962.

3. Therapeutic Notes, Vol. 1, No. 1 (February, 1894), p. 1.

Although this initial declaration may smack of a testimonial it does illustrate that management appreciated the potential of systematic research, and this appreciation was further attested by an article that appeared in another Parke-Davis publication, Pharmacal Notes, seven years later (1901):

> Ever since the establishment of our biological laboratories in 1894 we have sought to utilize them for something more than mere routine production and assay of standard antitoxins and vaccines. Mindful of rapid progress of bacteriology, of its brilliant promise for the future, and of the labor which many men throughout the world are now devoting to the discovery of biological remedies for infectious disease, we have not hesitated to employ a large staff of research workers, who conduct original investigations; to give them every needed appliance, and to exempt them from all routine duties. For the most part this work has justified itself, and our plan for the first year of the century is to prosecute, more energetically than ever before, a series of experimental researches into the etiology, the pathology of various infectious diseases -- problems bearing directly on our manufacturing work.[4]

Thus by the turn of the century the management of Parke-Davis had enough research already on record to make an effective promotional use of the achievement, which had reached out for new products, for improvements of the old and, more fundamentally, for understanding the etiology of certain diseases. This research support applied not only to the biological department but also to the analytical department where several men were conducting chemical research aimed at developing new products.

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4. "A Notable Accession to our Staff of Scientific Workers," Pharmacal Notes, 8 (1901), p. 19.

Thus Lilly and Parke-Davis are two examples of companies that not only recognized the value of systematic scientific research, but were willing to demonstrate their conviction by turning some of their resources into active research programs. Management in a number of other companies recognized the importance of systematic research early in the present century but for some reason (possibly financial) limited their scientific work to development of quality controls for their products or to the development of methods for producing already known drugs -- efforts that were important, despite a more limited scope. For example, that W. C. Abbott, the founder of Abbott Laboratories, and the early Abbott management recognized the value of scientific research in the early 1900's is evidenced by company documents. However, not until about the beginning of the third decade of the present century did Abbott support scientific work aimed at the development of new synthetic drugs. Prior to this any scientific work conducted by Abbott was mainly concerned with quality control and development of methods to produce already known drugs.

According to Elmer Vliet, one of the first research chemists employed by Volwiler, the man largely responsible for promoting systematic research at Abbott was Alfred S. Burdick, M.D., who became president of Abbott Laboratories following W. C. Abbott's death (1921). Burdick had "a keen appreciation of the importance of research. He was responsible in large measure for the rapidly widening scope

of activity and the emphasis on research that characterized this concern."[5] In an earlier publication Vliet attributes the growth of research at Abbott to Burdick's "enthusiastic appreciation and thorough understanding of scientific research, and his faculty of fostering cooperative contacts with investigators in universities, clinics and hospitals...."[6]

It is our impression that probably the majority of the pharmaceutical houses followed a pattern much like that of Abbott: recognizing the value of scientific research early in the 1900's but not conducting substantial, systematic research aimed at developing new products until sometime during the second or third decade of the century.

The importance of management recognizing an employee's aptitude for research work was stressed by W. R. Whitney, Director of the General Electric Research Department, when he said, "Probably almost every manufacturing plant develops among its workmen, from time to time, men who are practically endowed with aptitude for research in their line. They are usually the inventors of the company. They are often

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5. Elmer Vliet, "Historical Sketch of the Abbott Laboratories," prepared for the Historical Section of the American Pharmaceutical Association (August, 1933), mimeographed, in Historical File of the Abbott Library, North Chicago, Illinois.

6. E. B. Vliet, "The Abbott Laboratories -- North Chicago Plant," The Chemical Bulletin, Vol. 14, No. 4 (April, 1927), p. 103.

discoverers in spite of opposition. They are always trying new things. They are almost of necessity somewhat inefficient in the routine production. In many plants they are merely endured, in a few they are encouraged. To my mind their proper utilization is a safe investment. A research laboratory assists in such a scheme."[7]

Although Whitney was speaking mainly of the importance of recognizing the aptitude to do research possessed by some men employed in routine production, the same can be said for recognizing the aptitude possessed by some men engaged in more or less routine scientific work to do research. Interestingly, in discussing the personnel of the biological department and the analytical department of Parke-Davis, Taylor attributes the early progress of this firm to getting employees to do developmental work. Taylor observes, "at the time I began work in the Analytical Laboratory it included both routine analytical work and various types of research as did also the Biological Department. If a man showed interest in any new problems he was quickly given some in addition to routine work. I know because I got a few. This was to my mind one of the secrets of the progress of Parke, Davis and Company, getting anyone who was at all interested in developmental work."[8]

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7. W. R. Whitney, "Research as a Financial Asset," The Journal of Industrial and Engineering Chemistry, 3 (June, 1911), p. 431.

8. F. O. Taylor to G. Sonnedecker, August 16, 1961, in personal file of M. K. W.

The backgrounds of men engaged in research in the pharmaceutical industry during the "formative period" were rather diverse. Among the different scientific disciplines represented in the early scientific staffs were physicians, chemists, pharmacists, bacteriologists, botanists, chemical engineers, pharmacologists, veterinarians, pathologists, physiologists, and cytologists.

The degrees possessed by early industrial research scientists included some Doctor of Philosophy and Doctor of Medicine degrees; others had Master of Science or Bachelor of Science degrees. Some of the men obtained all their degrees in American institutions, while others had degrees from both American and European universities.

While most of the men were Americans, there were some European scientists conducting research in the American pharmaceutical industry during the "formative period." One similitude in the backgrounds of these men would be their lack of experience in industrial research -- almost a lack by force of circumstance until late in the period here discussed. A number of the early research men in the pharmaceutical industry had previous research experience, however, as members of university faculties.

It would be of interest to examine some of the administrative procedures, such as the keeping of research records, that were followed in some early research. Unfortunately, little of such information apparently has survived the passing decades. We do know that early in the 1900's

some companies kept very detailed records of their research work, while other firms did not observe a formal system for recording results until the early 1920's. Looking at the method of recording research results used (as early as 1904) by the Department of Experimental Medicine at Parke-Davis we can discern some resemblances to procedures employed in industry today.

According to C. T. McClintock the Department of Experimental Medicine was doing both the routine work of quality control and biological research work.[9] Some insight

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9. C. T. McClintock to E. G. Swift, August 25, 1904, in the Historical File of the Parke-Davis Research Library, Ann Arbor, Michigan. If the Department of Experimental Medicine was not coextensive with the biological research area at least it encompassed various kinds of biological research other than clinical research. While certain company documents and the recollections of Frank O. Taylor suggest the idea that the sole function of the Department of Experimental Medicine was clinical research, McClintock's testimony concerning a broader scope is given further credence by a very concrete description of the work of the Department of Experimental Medicine in a company-sponsored publication; see "A Home of Science," Bulletin of Pharmacy, 17 (November, 1903), pp. 456-459.

It is my impression (M.K.W.) after reviewing company documents and laboratory notebooks that the title Biological and Research Laboratories was broader than the title Department of Experimental Medicine, which seems to have concerned more specifically the section for quality control and research work on biologicals, as distinguished from the section concerned mainly with the production of biologicals.

However, by 1910 the title Department of Experimental Medicine was being used specifically to denote the department that was solely responsible for clinically testing all drug preparations prior to placing them on the market. At this time (1910) the Department of Experimental Medicine was a separate department, not part of either biological or chemical research. For information on this see, C. T. McClintock to E. G. Swift, July 2, 1910, in Historical File of the Parke-Davis Library, Ann Arbor, Michigan.

into procedure as well as research records of this department is provided by the following rules:

1. Whenever it is desired to take up a new subject for investigation a card designed for the purpose should be obtained from the library attendant which should have entered upon it the subject of experimentation, the name of the worker, the number of room and date. The card is then to be returned to the attendant who will issue a numbered book.

2. The library attendant will properly fill out cards for the alphabetical and numerical card files.

3. When commencing on a new subject for investigation a bibliography should be compiled giving very brief abstracts of the work already done on the subject, citations, etc., and placed in the record book.

4. The records should be written in ink by the person doing the work, writing only on one side of the paper.

5. The record should be in sufficient detail so as to show exactly how the experiments were made and the results obtained. It is desirable that the record be made the day when the experiments are made, and as far as possible be the original records, not copied from notes.

6. All kimographic tracings should be properly folded and filed in the book in the proper place.

7. The pages of the book should be numbered and the contents properly indexed on the third pages of cover.

8. All records and experiments as far as possible should be finished by Saturday noon and the record books turned over to the library attendant, who will return them the following Monday.

9. Whenever any specifications are given to the Purchasing, Control or other Departments for any supplies for experimental purposes or for the manufacture of a new product, copy of such specifications must be filed in the record,

and before the specifications are sent out they must be countersigned by the director in charge.

10. When an experimental product is made for pharmacological or bacteriological study a record should be made giving complete information of its method of manufacture, etc., as far as possible.

11. When an experimental product is turned over for laboratory study it should be accompanied by a brief statement of its physical and chemical properties.

12. When an experimental product is turned over for further laboratory study it should be labeled with the number of the original record book on the subject, for example, label Experimental Product R/ 99. In case a second lot of experimental product is made according to the original or modified formula it should be labeled Experimental Product R/ 99 A; a third product would be R/ 99 B, etc.

13. When an experimental product is turned over for laboratory study it should be accompanied with a statement from the research worker, briefly giving his views as to the probable use of the product.

14. When experimental products are referred for further laboratory study the library attendant will make out a new temporary book cover which will bear the same number as the original book, and proper entry made on the cards in the index.

15. The records of the results of pharmacological and bacteriological work shall be kept in detail and referred at the end of the week to the proper parties as already suggested under previous rules. When such work is complete the records shall be returned to the library attendant who will compile them with the chemical records and refer them to the director in charge for further consideration.

16. If a review of the results of the laboratory work shows that an experimental product will probably be of clinical value, sufficient quantities of the product will be ordered, an appropriate letter prepared by the director in charge and sent out to such clinicians as it is deemed advisable.

17. One month after the samples for clinical trial are sent out a follow up letter is to be prepared by the director in charge, and to be sent to those clinicians who have not reported.

18. Two months after the samples are sent out a consideration of all the laboratory and clinical results should be made and a decision rendered as to the advisability of placing the product on the market. If the decision is a negative one it should be properly recorded with reasons for such decision, and copy filed.

19. Where it is deemed advisable to add the product to our list, proper recommendation should be made to the General Manager and to such other interested parties as is thought proper. Such recommendations should be accompanied with material for circulars, labels, etc.

20. If the product is finally placed on the market a request should be made that samples of the manufactured lots before they are sent out should be referred to the Department of Experimental Medicine for O. K. until such time as it is deemed advisable to have other parties held responsible for them.

21. Copies of all advertising material, circulars, etc., should be submitted to the Department of Experimental Medicine for criticism before being sent out and copies filed with the other data on the subject.

22. Copies of all specifications, memorandums, reports, letters, etc., pertaining to the product which may not have been mentioned previously should be filed in proper order in the records.[10]

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10. "Rules for Recording the Work of the Department of Experimental Medicine," 1904, in Historical File of the Parke-Davis Research Library, Ann Arbor, Michigan.

Selecting and Financing Research Projects

In most of the companies the research director and/or the chief chemist and the company executives -- general manager, vice-president, or president -- usually decided what projects would be worked on by the research staff. As early as 1924, however, at least one company (Parke, Davis and Company) had appointed a research committee to select research projects.

When O. W. Smith, President of Parke-Davis, appointed a research committee in 1924 he said,

> I believe it will be of considerable advantage to condense and unify the direction of our Medical and Chemical Research work by placing it in the hands of a special committee, such committee to be known as the Research Committee....
>
> The Research Committee will have for its purpose the general direction of all research work. It will decide what problems should be investigated; methods of keeping records; determine what practical results may be utilized from the investigations (i.e., whether new products, improvements of processes, papers, etc.).
>
> The activities of the Committee should be of such a character as to stimulate the best efforts of the individual research worker without in any way detracting from the initiative and originality of the worker. The whole purpose of the committee should be exerted for the purpose of developing the best results for the advancement of medical knowledge pertaining to prophylaxis and therapeutics.
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> ...I believe the Committee should meet regularly at a set time and place, perhaps as frequently as once a week or once in every two weeks.[11]

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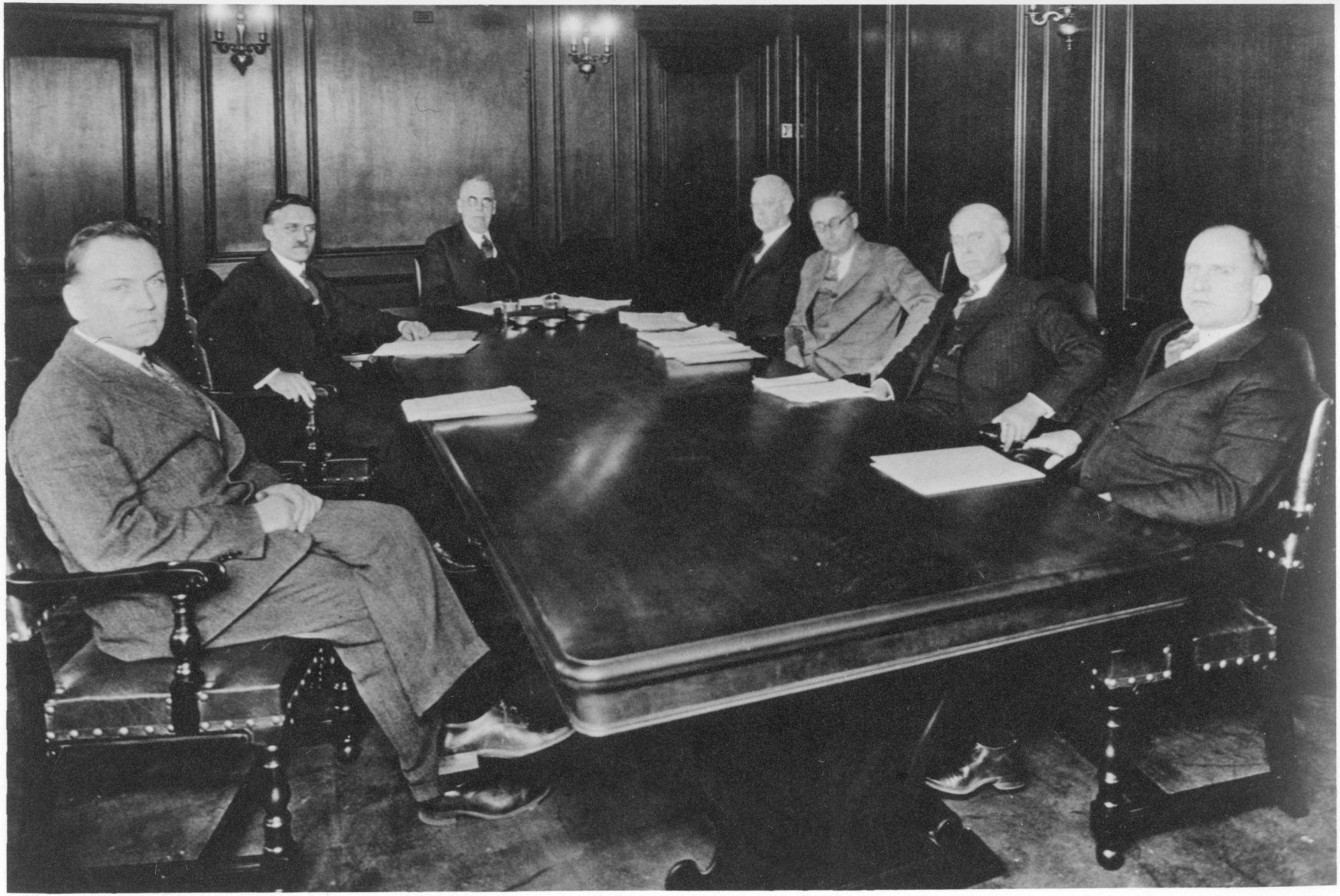
11. O. W. Smith to E. M. Houghton, February 5, 1924, in Historical File of the Parke-Davis Research Library, Ann Arbor, Michigan. Smith appointed the following men to the Research Committee: E. M. Houghton, F. O. Taylor, L. T. Clark, O. Kamm, A. W. Lescohier, and C. H. Briggs.

PARKE-DAVIS' RESEARCH COMMITTEE, from left to right consisted of Oliver Kamm, Head of Chemical Research; Frank O. Taylor, Chief Chemist; E. Mark Houghton, Director of Biological and Research Laboratories; Wilbur L. Scoville, Head of Analytical Department; A. W. Lescohier; W. E. King, Assistant Director of Biological and Research Laboratories; and L. T. Clark. The original Research Committee, appointed in 1924 by O. W. Smith, President of Parke-Davis, consisted of all the men mentioned above except Scoville and King. C. H. Briggs, a member of the original committee, retired in 1925 and was replaced by Scoville as Head of the Analytical Department and probably also as a member of this committee. W. E. King was the Assistant Director of Research, which would explain his presence at what appears to us to be a meeting of the Research Committee. The Research Committee was responsible for the general direction of all research work, including the selection of research projects, determining methods of keeping records and deciding whether new products should be added to the firm's line.



Individual researchers usually reported to the director of research and the director reported to one of the company executives. For example, at Upjohn the research men reported to Heyl and he reported to S. R. Light, the General Manager of Upjohn.[12]

Few records of early research expenditures have survived through the passing decades.[13]

Thus we have no clear picture, as yet, of how much money pharmaceutical companies were spending on research during the "formative period."

One example just after the close of the period here considered may be cited, if we bear in mind the lack of evidence that it is representative. By 1924 one prominent company was spending $73,823 on chemical research; by 1927 this same company was spending $122,192 on chemical research; and by 1930 (after the economic crash) this had declined to $100,379.

In addition to these expenditures on chemical research, the company was spending some money on biological research. In 1924, $6,248 went into biological research, increasing

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12. Transcript of interview with Frederick Heyl, kindly conducted by G. F. Cartland, November 6, 1961, in personal file of M. K. W.

13. For example, although Parke-Davis has preserved considerable information about its early research, the firm has not been able to locate any early budgets which indicate how much they were spending on research during the "formative period." This has also been the case with other companies we have obtained information about.

by 1927 to $53,148, and then declined to $47,805 by 1930.[14]

Industry-Sponsored Research

There is evidence which suggests that several pharmaceutical companies were cooperating with university scientists prior to 1920. For example, while discussing the work of the Department of Experimental Medicine at Parke-Davis in 1904, McClintock said, "An attempt is being made to isolate and grow the organism causing Texas Fever in Cattle. This work is being carried on in conjunction with Dr. Novy of the University of Michigan."[15] Joseph Helfman also implied that Professor Freer of the University of Michigan was doing some work in 1899 for Parke-Davis when he said, "...at our instance Professor Freer and his assistants are carefully investigating Jamaica Dogwood and Cotton Root."[16] We have also pointed out previously that Abbott Laboratories employed Roger Adams, a faculty member of the University of Illinois, as a consultant in 1917.

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14. Annual Report (1930) on the Operation of the Brooklyn Laboratories and the New Brunswick Chemical Division, presented to C. H. Palmer, President of E. R. Squibb and Sons, by F. W. Nitardy, Vice-President in Charge of Manufacturing, April 8, 1931, p. 51.

15. C. T. McClintock to E. G. Swift, August 15, 1904, in Historical File of the Parke-Davis Research Library.

16. Joseph Helfman to Edward Kremers, December 20, 1899, in Kremers Reference File, University of Wisconsin.

Thus some pharmaceutical companies had the collaboration of university scientists at a time when there was still a relatively tenuous link between university scientists and American industry at large.

There is considerable discussion in the literature about the lack of cooperation between industrial and university scientists prior to World War I.

W. A. Hamor points out that one reason for the limited cooperation between industrial and university scientists was the secrecy that surrounded much industrial research. Hamor said:

> In this matter of the dissemination of knowledge concerning industrial practice, it must be evident to all that there is but little cooperation between manufacturers and the universities. Manufacturers and especially chemical manufacturers, have been quite naturally opposed to publishing any discoveries made in their plants, since "knowledge is power" in manufacturing as elsewhere, and new knowledge gained in the laboratories of a company may often very properly be regarded as among the most valuable assets of the concern. The universities and the scientific societies, on the other hand, exist for the diffusion of knowledge, and from their standpoint the great disadvantage of the above policy is the concealment of knowledge, for it results in a serious retardation of the general growth and development of science in its broader aspects, and renders it much more difficult for the universities to train men properly for such industries, since all textbooks and general knowledge available would in all probability be far behind the actual manufacturing practice. Fortunately, the policy of industrial secrecy is becoming more generally regarded in the light of reason, and there is a growing inclination among manufacturers to disclose the details of investigations, which according to tradition would be carefully guarded. These manufacturers appreciate the fact that public interest in chemical achievements is stimulating to further fruitful research, that helpful

> suggestions and information may come from other investigations upon publication of any results, and that the exchange of knowledge prevents many costly repetitions.[17]

Although there is apparently much less secrecy today in industrial research than before World War I, industry has not completely cast off this traditional attitude of "trade secrecy." Jack Cooper, Ph.D., Director of Pharmacy Research and Development Division at Ciba Pharmaceutical Company recently pointed this out by saying,

> ...In my opinion there is an even greater weakness in the approach of industrial circles to pharmacy research as represented by the so-called "trade secret" philosophy. In this illusory world of exaggerated notions of superiority are buried all sorts of ridiculous advantages claimed to be of economic value to the holder of the secret. In their anxiety to protect such theoretical and unchecked advantages, many organizations have built a wall around their pharmacy research groups behind which are hidden unknown men holding unknown inventions close to their chests. Their ideas and practices become ingrown, fail to be subjected to the fine comb of outside analysis and criticism and grow stale from lack of intercourse with other men and other ideas. These pharmaceutical prisoners do not speak nor do they publish and no forum provides an opportunity to praise or ridicule their accomplishments.[18]

However, the restricted cooperation between industry and university scientists was not all the fault of industry. Arthur D. Little pointed this out in 1913 when he said,

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17. W. A. Hamor, "The Value of Industrial Research," The Scientific Monthly, 1 (1915), p. 89.

18. Jack Cooper, "The Pharmacist and Research," American Journal of Pharmacy, 132 (May, 1960), p. 162.

> In view of the evidence offered by Germany of the far-reaching benefits resulting from the close co-operation which there obtains between the university laboratory and the industrial plant, it must be admitted with regret that our own institutions of learning have, speaking generally, failed to seize or realize the great opportunity confronting them. They have, almost universally, neglected to provide adequate equipment for industrial research, and, what is more to be deplored since the first would otherwise quickly follow, have rarely acquired that close touch with industry essential for familiarity and appreciation of its immediate and pressing needs.[19]

Some universities were better equipped for industrial research, in both attitude and facilities; and among those Little mentioned as collaborating effectively with industry were the Massachusetts Institute of Technology, Cornell University, and the Universities of Wisconsin, Illinois, Kansas, and Pittsburgh. But relatively few universities had established facilities for industrial research early in the present century.

Although benefitting pharmacy as an eventual client industry, it interests us more particularly as expressing a trend and time when the first formal industrial fellowship system was established by Robert Kennedy Duncan at the

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19. Arthur D. Little, "Industrial Research in America," The Journal of Industrial and Engineering Chemistry, Vol. 5, No. 10 (October, 1913), p. 14. For further discussion of university-industry cooperation toward the close of the period under discussion see: "Co-operation between University and Industry," Journal of Metallurgical and Chemical Engineering, 13 (1915), p. 885; H. P. Talbot and W. H. Walker, "University and Industry," The Journal of Industrial and Engineering Chemistry, 8 (1916), p. 61; C. P. Steinmetz, "Scientific Research in Relation to the Industries," The Journal of the Franklin Institute, (1916), p. 711; A. E. Kennelly, "Industrial Research and the Colleges," The Journal of the American Institute of Electrical Engineers (1917), p. 757.

University of Kansas.

> The idea of this System was conceived by Dr. Duncan in 1906, while in attendance at the Sixth International Congress of Applied Chemistry in Rome.... Through visits of inspection to factories, laboratories, and universities of some European countries, and through conversation with industrialists and scientists [prior to the Congress], he had become impressed at various places with the spirit of cooperation that existed between technology and science which made for the advancement of both. At the same time, he became aware, more than ever before, of the fact that much of American chemical industry, from the standpoint of manufacturing efficiency, was in a weak condition. The absence of the application of scientific research methods was one reason for this state of affairs, and Dr. Duncan was led to propose a remedy in Industrial Fellowships. His plan was to assist manufacturers who desired to break away from tradition and to make even more scientific that production already well on the road from tradition to science.
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> Upon his return from Europe to accept the chair of industrial chemistry in the University of Kansas, Dr. Duncan arranged for the establishment of the first Industrial Fellowship in January, 1907.[20]

Five years later Duncan was called to the University of Pittsburgh to inaugurate his "system" in a Department of Industrial Research. There he gained the respect of the Pittsburgh financiers Andrew W. Mellon and Richard B. Mellon, who placed the Industrial Fellowship System on a permanent basis (1913) as the Mellon Institute of Industrial Research.[21] Especially identified with pharmaceutical research during thirty-two years at the Institute was George D. Beal, first as Assistant Director, then as a

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20. Industrial Fellowships, Pittsburgh, 1924, pp. 2-3.

21. Ibid., p. 4.

Director of Research (1926-1958).

Just before Duncan's program took its final form as the Mellon Institute, Albert Cushman founded (1910) The Institute of Industrial Research in Washington, D. C. This Institute's Division of Foods, Drugs and Agriculture was equipped to conduct drug research.[22]

The far-reaching influence of the concept as well as the existence of the Mellon Institute, and the need laid bare by World War I for larger resources devoted specifically to the chemical and pharmacological study of medicinal substances, are evidenced by a proposal for a specialized research institute voiced by the editor of The Journal of Industrial and Engineering Chemistry, in 1918. Said Editor C. H. Herty:

> A few days ago we asked a well-known organic chemist, one who has been particularly successful in working out methods for the manufacture of certain much-needed coal-tar medicinals, "Suppose during your researches you made some new compound which you believed would prove more efficacious against certain diseases than any of the known compounds whose details of manufacture you have solved, where would you turn to have it tested thoroughly?" He replied, "I don't know."
>
> ...The negative answer was not surprising, rather it was confirmatory. It is a peculiar situation that exists in this country today. The three great commercial applications of the so-called "coal-tar chemicals" are, first, explosives, for which means are never lacking for the thorough testing of new products; second, dyestuffs, for which fortunately the equipment testing as to standard, fastness, durability and aesthetic suitability is simple, inexpensive and

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22. For information about this institute see The Institute of Industrial Research, Washington, D. C., 1912.

accessible to every worker; third, medicinals, and here the problems of investigation become much more complex and the responsibility even greater. Rarely does the chemist possess the technique for their testing; he must rely upon the pharmacologist and the physiologist to determine the therapeutic value of his product.

In university circles there is often lacking that spirit of cooperation between several classes of research workers which would insure a thorough examination of these new products of the organic chemical laboratory, or, if the spirit be willing the means for conducting tests may be limited, especially now when universities' finances are so severely contracted. In a few manufacturing establishments provision is made for animal experimentation, but these facilities are entirely inadequate and not available to all chemists.... And still people suffer, though much suffering has been alleviated by discoveries made in other lands.

...The importance of the intimate cooperation of these workers [chemists and biologists] is evidenced by the work on the synthesis of a new anti-syphilitic drug which was recently accomplished in the laboratories of the Rockefeller Institute for Medical Research.... Similar institutions, however, are few in number and the capacity for works of this kind is necessarily restricted.

...A suggestion had been advanced which seems to cover the situation admirable, namely that an institution somewhat analogous to the Mellon Institute be founded, in which adequate provision for laboratory tests of all kinds be made and to which through the establishment of fellowships, manufacturing organizations could send well-trained young men for working out specific problems. Cooperation should be established between this institution and the organic laboratories of universities, as well as with the hospitals of the country.

An institute of this character would prove a great stimulus to the creation of more adequate research facilities within manufacturing establishments for the great glory of the Mellon Institute lies, it seems to us, not so much in the actual results obtained under its roof as in the indirect creation of research departments

> in industries which first caught the full significance of research through the fellowships established in that institution.[23]

Herty's proposal precipitated considerable discussion among members of the American Chemical Society, and this organization initiated plans to sponsor such an institute. Many men noted advantages to be gained and suggested how an institution of this type might be set up and operated. However, plans for an institute for drug research aborted because of controversy over who should control it and over procedures under which it should operate.

Paul N. Leech, Director of the Chemical Laboratory of the American Medical Association, warned the medical profession that dangers as well as benefits could come from the proposed drug research institute. Leech said,

> In view of the agitation to found an institute for cooperative research as an aid to the American drug industry under the auspices of the American Chemical Society, it will be well for the medical profession to be on its guard against too enthusiastic propaganda on the part of those engaged in the laudable enterprise of promoting the American chemical industry. Unless it is, it may be inflicted in the future, as in the past, with a large number of drugs that are either useless, harmful or unessential modifications of well-known pharmaceuticals....
>
> On the other hand, the constructive possibilities of chemistry in the service of medicine should serve as a stimulus for American research.... Obviously the American chemist has the opportunity of showing his resourcefulness in aiding the public health of America and the world.

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23. C. H. Herty, "War Chemistry in Alleviation of Suffering," The Journal of Industrial and Engineering Chemistry, 10 (September, 1918), pp. 673-674.

> In this connection, a cooperative institute devoted to purely scientific drug research, and governed in such a manner as to inspire confidence in its humanitarianism and unbiased judgement, should serve a most commendable purpose. The hopes of American men of science are for a monumental research institution -- cooperative with all allied professions -- and as the Chicago Chemical Bulletin stated, "Stripped of all professional or commercial pettishness and not dominated by any one group of scientists."[24]

The main reason this institute never was established lies in apprehensions such as Leech voiced; that is, the problem that one organization or one group of scientists would try to control the institute.[25]

We have already mentioned evidence that some pharmaceutical firms were linked with collaborating university

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24. Paul N. Leech, "American Made Synthetic Drugs-II," The Journal of the American Medical Association, 73 (September, 1919), pp. 758-759.

25. For information about the proposed drug research institute see: J. J. Abel, "A National Institute for Drug Research," The Journal of Industrial and Engineering Chemistry, 10 (December, 1918), p. 969; P. A. Levene, "An Institute of Chemotherapy," The Journal of Industrial and Engineering Chemistry, 10 (December, 1918), p. 970; A. S. Loevenhart, "An Institute for Research in Synthetic Organic Chemistry," The Journal of Industrial and Engineering Chemistry, 10 (December, 1918), pp. 971-973; F. R. Eldred, "An Institute for Medicinal Research," The Journal of Industrial and Engineering Chemistry, 10 (December, 1918), pp. 973-975; D. W. Jayne, "Institute for Research on Synthetic Drugs," The Journal of Industrial and Engineering Chemistry, 10 (December, 1918), pp. 975-976; E. R. Weidlein, "Remarks Concerning Suggestions for Central Medicinal Research Laboratory," The Journal of Industrial and Engineering Chemistry, 10 (December, 1918), p. 976; F. E. Stewart, "Proposed National Institute of Drug Research," The Journal of the American Pharmaceutical Association, 8 (1919), pp. 256-260.

scientists around the turn of the century. The further linkage of industrial and academic science through graduate fellowships comes within view by 1917.

Making what must have been one of the earliest pharmaceutical awards of its kind, F. E. Watermyer, President of Fritzsche Brothers of New York City, announced in May, 1917, the establishment of a fellowship ($500 annually) at the University of Wisconsin School of Pharmacy.[26] Fritzsche Brothers' vanguard position in this respect becomes understandable not only from its German antecedence, but from the importance that the American firm's own research had in gaining a leading position in the field of essential oils and related products.[27]

A further example -- and there may have been others -- was the fellowship Frederick Stearns and Company was sponsoring by 1920 ($500 annually) at the University of Michigan for research in pharmacy.[28]

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26. Manuscript left by Edward Kremers, in Kremers Reference File at the University of Wisconsin (C31(a)I:Fellowships). The work conducted by the recipients of this fellowship covered such topics as the terpene problem of Monardas, the derivatives of thymol and carvacrol, the two isomeric phenols of two closely related species of Monarda, and a special study of a chameleon-like derivative of thymoquinone.

27. Edward Kremers and George Urdang, History of Pharmacy, 2nd ed., Philadelphia, 1951, p. 435.

28. Callie Hull, "Funds Available in 1920 in the United States of America for the Encouragement of Scientific Research," Bulletin of the National Research Council, Vol. 2, No. 9 (1921), p. 45.

During the third decade of the century, somewhat beyond our present concern, there was an increase in the pharmaceutical industry's support of research activities in academic institutions and research institutes. For example, in 1922 E. R. Squibb and Sons established a fellowship at the Mellon Institute, which secured for the "firm the opportunity of using this well-known institution for researches on medicinal products and such other products as fall into our line."[29]

By 1930 Squibb was supporting research in a number of other universities, such as fellowships at the Sterling Chemical Laboratory of Yale University, the University of Minnesota, and the University of Pittsburgh Dental School.[30]

"In 1921 Eli Lilly and Company adopted the policy not only of supporting abstract scientific work on fundamental problems, which might have no immediate practical bearing, but also of publishing freely those results that are of practical value in the belief that only by full publicity and interchange of results and ideas can rapid progress be made in any field of research. Such a policy... should secure co-operation from universities and research institutions and enable the company to add to its scientific staff

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29. F. W. Nitardy, Report on Progress in the Plants -- April, 1922 to April, 1923, April 4, 1923, presented to C. H. Palmer, President of E. R. Squibb and Sons.

30. Nitardy, Annual Report for 1930, April 8, 1931, p. 51.

those who are looking for opportunities to carry on investigations on fundamental problems requiring considerable time and facilities."[31]

The year after Lilly established this policy they became associated with the University of Toronto in the development and production of insulin.

Recalling this achievement during the dedication of the Lilly Research Laboratories (1934), co-discoverer Sir Frederick Banting said,

> When the first report of insulin was made at New Haven in December, 1921, Dr. G. H. A. Clowes offered to put the resources of the Eli Lilly Company at our disposal whenever we felt that our laboratory experiments had reached the point at which their practical co-operation might be of benefit. About April, 1922, we accepted his kind offer. From this time the Eli Lilly Company collaborated with us and were of the greatest assistance in the development of the large-scale production. There was an intimate reciprocation of all results between the two laboratories....
>
> In the autumn of 1922 the product was still extremely impure and we were experiencing great difficulty with deterioration and sensitization reactions. By the middle of November the Eli Lilly Company were first able to effect a very substantial purification and concentration of the product by developing the iso-electric method of precipitation. This product had the added advantage of being reasonably stable. The yields at that time were still very small, but by January (1923), as a result of work carried out in the Connaught Laboratories and the Eli Lilly Company, we were able to provide insulin to about 250 clinicians.[32]

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31. Archives of Eli Lilly and Company to M. Keith Weikel, March 1, 1962, in personal file of M.K.W.

32. Sir Frederick Banting, "The Early Story of Insulin," in Lilly Research Laboratories: Dedication, Indianapolis, 1934, p. 19.

This significant example dramatizes the more fruitful bond that had developed by the 1920's between pharmaceutical industry and graduate departments burgeoning in American universities.

Moreover, in accepting and institutionalizing industrial research as never before, the private, university and company laboratories were finding common ground at a higher level. It signified that the formative stage had come to an end. Research as a function of pharmaceutical industry was completing a metamorphosis that brought the industry itself to a more mature stage.

V

SUMMARY

To see in perspective the evolution of research in the pharmaceutical industry we must keep in mind that not until the mid-1800's did pharmaceutical production in America become visibly industrial. Between 1850 and 1900 a number of companies that are prominent today were established, and the structure of the industry began to solidify.

Among factors found to have affected the development of research in American industry, not the least was the iron demand of war, with World War I probably providing industry with a pivotal thrust at the turning point into scientific self-reliance and creativity, just as the Civil War seems to have put down the last barricades to an industrial revolution in American drug production as in the economy at large. The Federal Pure Food and Drug Act of 1906 was seen as an indirect stimulant to research in the drug industry. Chemical and pharmaceutical journals and associations established mainly during the latter part of the 1800's and the early 1900's played their part in cultivating requisite knowledge and whetting research ambitions.

Among factors that delayed vigorous development of research in American industry, we noted a dependence on

European countries -- especially Germany -- for many of our drugs and chemicals; the long wait before many American educational programs in the sciences were functioning at the research level of European institutions; and management's limited appreciation for research as a sound risk for investment. If we are to comprehend what might account for research remaining beyond the practical possibilities in the planning of most industrialists, some impressions beyond the facts we have marshalled should be taken into account. Before World War I, an expanding population and an improving system of communication and transportation placed markets of dimensions theretofore unknown at the disposal of adventuresome entrepreneurs. Faced with opportunity to exploit the new advantages of large-scale industry, through free-wheeling enterprise, the relationship of science to the immediate world of industrial entrepreneurs must have seemed abstruse and remote, too little needed as an industrial tool to command much of their thought or capital.

The purpose of manufacturers was to manufacture things. There were a great many things waiting to be made. Ideas for additional new things could be had from scientists and inventors, who perhaps by definition were dissociated from the work-a-day world of commerce, business and factories. A shrewd business man could buy or borrow ideas from a professor or inventor without paying him to work on something he might or might not ever discover or make practical.

It perhaps came to seem reasonable and needful to absorb this inventive function into the manufacturing enterprise itself when:

(a) Mass production put industry on a scale where the costs of such an unpredictable enterprise as research could be borne -- could be afforded -- as a business speculation or risk investment;

(b) The complexity of applied science became such that new products and new industries more and more required teams of researchers and coordinated planning. This could be best afforded by large-scale industry, which stood to benefit; and if industry was to put in such large sums, it was better to have the effort entirely under the control and surveillance of management -- rather than financing independent agencies or researchers for the major effort;

(c) As the rate of population growth slowed down and the number of large-scale manufacturing units increased after the end of the 19th century, there were not so many fortunes waiting to be plucked by making the host of things based on old knowledge, which an exploding country and population had demanded. Instead of making old things for ever new markets, there was an increasing pressure to make new things for old markets;

(d) At least with respect to American pharmaceutical industry, the legal requirements after 1906 made scientific personnel within the plant more or less a necessity; and these individuals were almost certain to be exponents of the fruitfulness of science for industry, centers of propaganda for what science could do. Management was getting manpower, equipment, and ideas within their walls, with a potential for research and suggesting industrial science and research even before there were noticeable research beginnings.

While these impressions may be applicable to a large proportion of American industries -- including the pharmaceutical industry -- there were exceptions. These exceptions pointed the way and proved to the more skeptical industrialists that research could serve as a valuable tool for industry. We found that the management of at least one or two pharmaceutical firms recognized the potential of organized scientific research programs late in the 1800's and early 1900's.

Their predecessors were a few particularly ambitious community pharmacists attempting to develop better methods of preparing drugs they dispensed in their pharmacies, or supplied at wholesale to outlying pharmacies and medical practitioners. In the 1870's the attention of some drug firms had turned to an investigation of the active principles

of vegetable drugs, and efforts were made to find additional plants that possessed therapeutically active constituents. During the 1880's the scientific endeavor of the drug industry centered around chemical standardization methods for drugs of natural origin.

The attention of the American drug industry turned to the exciting biologicals during the early part of the 1890's, and some firms employed scientists to help them produce biologicals that had been discovered abroad. We also noted that physiologically standardized preparations were introduced to American medicine at this time.

Around the turn of the century some efforts to develop or improve chemical drugs became visible. The First World War markedly increased activity in research aimed at developing new synthetic drugs.

The first attempt to depict the history of pharmaco-industrial research in its formative stage, focusing upon a few companies in the vanguard of the industry, involves a complex development that merits further studies if we are to have adequate understanding of the range and character and diverse levels of early research in the pharmaceutical industry.[1]

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1. For example, further research should be conducted to uncover how much firms were spending on research during the early years; to evaluate more thoroughly the effect of government legislation -- such as tariff and patent legislation; to clarify the American role in the development of chemical and physiological standardization, and the clinical evaluation of drug preparations; and to learn more about administrative procedures utilized in early research departments.

The evidence has mounted during this study confirming that Parke, Davis and Company not only was a pioneer in pharmaceutical industrial research, but was the first company to formally employ a research director, and the first company in American industry at large to construct a building specifically for scientific work (1902). The scope and breadth of the Parke-Davis research staff and the research they conducted all testify to the sophisticated research program of this firm during the "formative period." In his presidential address before the American Chemical Society, Arthur D. Little, lists Parke, Davis and Company among a group of companies in American industry at large that possessed excellent research laboratories.[2]

From the limited information that was available to us about early research at Eli Lilly and Company, it appears that this company also played an important part in the development of research in the industry.

Frank O. Taylor pointed out recently that there are many factors which have contributed to the development of research as a function of the pharmaceutical industry. Taylor said,

> The thing that comes first, the seed from which all research develops, is what we might call the "Spirit of Research" -- an active desire for the improvement of medicinal products; for

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2. Arthur D. Little, "Industrial Research in America," The Journal of Industrial and Engineering Chemistry, Vol. 5, No. 10 (October, 1913), p. 17.

> the development of new products; for understanding of how these products work; for the understanding of diseases and their diagnosis, prevention, or cure. These medicinal products may come from various sources, botanical, chemical, or biological.
>
> Active research work may develop around many places such as analytical laboratories, control laboratories for all varieties of medicinal preparations, biological laboratories, various manufacturing laboratories, etc. Yes, a manufacturing laboratory can do what is essentially "research work;" not often, that is true, but I personally know of instances.... It may be that because of the availability of proper scientific apparatus the Control Laboratory has sometimes been the nucleus around which research has begun but we should remember the "Spirit of Research" manifests itself in many ways and grows out of many phases of the whole pharmaceutical field.[3]

That the "spirit of research" was growing and the "formative period" was coming to an end by 1920 in American industry becomes clear from Maurice Holland's analysis:

> By far the most significant single factor in the twenty years between 1920 and 1939 was the phenomenal growth of research in industry. From fewer than 300 laboratories in the early twenties to over 2,300 in 1939; from a few thousand research workers to over 70,000 and from a national expenditure of 100 million dollars to approximately 400 million is the bare statistical record. But the mere measure of size and numbers is only one quantitative basis of comparison. The uniform adoption of industrial research by American industry as a whole, regardless of size of company, field of industry, or geographic location was equally impressive....
>
> ...Research became solidly anchored in the bedrock foundations of American industry. Industrial executives, bankers, and even stockholders of industrial corporations took keen interest in the research activities of their companies; they were "sold on research."

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3. F. O. Taylor to M. Keith Weikel, June 30, 1962, in personal file of M. K. W.

> In brief, the 1920's and 1930's might be characterized as the era of "first growth" in the industrial research crop of laboratories. The phenomenal rate of expansion not only stretched the supply of qualified research workers but conclusively answered the question: "Why do research?" The industrial executive, backed by his banker and encouraged by the active interest of his stockholders, answered: "Research is a paying investment -- it is the best form of industrial insurance!"[4]

As the formative period was coming to a close more of the pharmaceutical firms were conducting systematic research work and the companies with established research departments were expanding their staffs and their physical facilities. A number of drug companies had the research staff and facilities that would allow them to play an important role in the new era of the exciting chemotherapeutics -- sulfonamides and antibiotics -- that was just ahead; and these very discoveries tended to make research a necessity for any company that desired to be in the vanguard.

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4. Maurice Holland, "Research in America and Europe," in C. C. Furnas, ed., Research in Industry, New York, 1948, pp. 500-501.

APPENDIX A

TYPICAL PUBLISHED RESEARCH OF REPRESENTATIVE PHARMACO-INDUSTRIAL LABORATORIES

This list of titles of the published research papers from several research departments provides some insight into the type and scope of research work being conducted in several firms during the "formative period." One must remember, however, that these lists are only representative of the work that was published by these departments.

We should keep in mind some of the limitations of these lists. The Parke-Davis list, covering the years 1912 to 1938, does not include any of the reprints of publications from the Analytical, Pharmaceutical, or Experimental Medicine Departments. This list goes somewhat beyond the years of our present interests, thus making information available for further investigations or for comparative purposes.

The list of Upjohn's research publications represents the first sixty publications of its research laboratory and covers a span of years from 1914 to 1930.

The list of articles published from Dermatological Research Laboratories represents all the papers published by the scientists of this institution from 1912 to 1921.

EXHIBIT I

REPRINTS OF PUBLICATIONS FROM THE RESEACH DEPARTMENT

PARKE, DAVIS & COMPANY, DETROIT, MICH.

The present system of collecting reprints of articles published from the Research Laboratory was begun in 1912. In 1931 reprints of chemical research articles published during the years 1920-1930 were added to this list (see Nos. 389-432). Reprints of many of these articles are available and will be sent upon request, but those publications marked with an asterisk are no longer available.

The list does not include reprints of publications from the Analytical, Pharmaceutical or Experimental Medicine Departments.

1. On the Administration of Diphtheria Toxin in a Collodion Sac. By E. C. L. Miller. (*Journal of Infectious Diseases*, Vol. 8, January, 1911, pp. 50-65.)

2. A Further Contribution to Our Knowledge of Insecticides—Fumigants. By Chas. T. McClintock, H. C. Hamilton and F. B. Lowe. (*Journal of the American Public Health Association*, Vol. 1, April, 1911, pp. 227-238.)

3. Duboisia Hopwoodii—A Histological Study. By Oliver A. Farwell. (Reprinted from *Merck's Report*, Vol. 20, May 1, 1911.)

4. Etiology of Canine Distemper. By Newell S. Ferry. (*Journal of Infectious Diseases*, Vol. 8, June, 1911, pp. 399-420.)

5. The Resistance of Smallpox Vaccine to the Coal-tar Disinfectants. By Chas. T. McClintock and Newell S. Ferry. (*Journal of the American Public Health Association*, Vol 1, June, 1911, pp. 418-419.)

6. Production of Immunity with Over-Neutralized Diphtheria Toxin. By Chas. T. McClintock and Newell S. Ferry. (*Abdruck Aus Dem Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten*, Abt. 1, Originale, Bd. 59, July 15, 1911, pp. 456-464.)

7. Soaps from Different Glycerides—Their Germicidal and Insecticidal Values Alone and Associated with Active Agents. By H. C. Hamilton. (*Journal of Industrial and Engineering Chemistry*, Vol. 3, August, 1911, pp. 582-584.)

8. The Sleepy Grass of New Mexico: A Histological Study. By Oliver A. Farwell. (*Merck's Report*, Vol. 20, October, 1911, pp. 271-273.)

9. Some Observations on the Physiological Action of Sleepy Grass. By A. W. Lescohier. (*Merck's Report*, Vol. 20, October, 1911, pp. 271-275.)

10. An Investigation of the Depressor Action of Pituitary Extracts. By Carey P. McCord. (*Archives of Internal Medicine*, Vol. 8, November, 1911, pp. 609-620.)

11. The Physiology of the Pituitary Gland and the Actions of Its Extracts. By Carl J. Wiggers. (*American Journal of Medical Sciences*, Vol. 141, April, 1911, pp. 502-515.)

12. A Physiological Investigation of the Treatment of Hemoptysis. By Carl J. Wiggers. (*Archives of Internal Medicine*, Vol. 8, 1911, pp. 17-38.)

13. Notes on Catgut Sterilization: A Preliminary Report. By Willard H. Hutchings. (*Annals of Surgery*, Vol. 54, July, 1911, pp. 693-695.)

14. The Relations of Pyogenic Microorganisms to the Etiology and Treatment of Skin Diseases. By Henry Rockwell Varney. (*Ohio State Medical Journal*, December, 1911.)

15. A Micrococcus with Unusual Characteristics as a Factor in a Resistant Dermatosis Resembling Acne Vulgaris. By Henry Rockwell Varney and L. T. Clark. (*Journal of Cutaneous Diseases*, Vol. 30, February, 1912, pp. 72-78.)

16. Serum Treatment of Hemorrhage and Blood Dyscrasias. By A. W. Lescohier. (*New York Medical Journal*, Vol. 95, February 3, 1912, pp. 223-229.)

17. Further Studies on the Bacillus Bronchicanis, the Cause of Canine Distemper. By Newell S. Ferry. (*American Veterinary Review*, Vol. 41, April, 1912, pp. 77-79.)

18. The Pharmacopœial Requirements for Cannabis Sativa. By H. C. Hamilton. (*Journal of the American Pharmaceutical Association*, Vol. 1, March, 1912, pp. 200-203.)

19. The Heart Tonic Unit. By H. C. Hamilton. (*American Journal of Pharmacy*, Vol. 84, March, 1912, pp. 97-103.)

20. Studies on the Etiology of Equine Influenza. By Newell S. Ferry. (*Veterinary Journal* (London), Vol. 19, April, 1912, pp. 185-197.)

21. A Method for the Bacteriological Standardization of Disinfectants. By Tatsuzo Ohno and H. C. Hamilton. (*American Journal of Public Health*, Vol. 2, May, 1912, pp. 331-338.)

22. Physiological Testing. By E. M. Houghton. (*American Druggist*, July and September, 1911, and January and April, 1912.)

23. Bacillus Bronchisepticus (Bronchicanis): The Cause of Distemper in Dogs and a Similar Disease in Other Animals. By Newell S. Ferry. (*Veterinary Journal* (London), Vol. 19, July, 1912, pp. 376-391.)

24. On Feeding Young Pups the Anterior Lobe of the Pituitary Gland. By T. B. Aldrich. (*American Journal of Physiology*, Vol. 30, July, 1912, pp. 352-357.)

25. A Practical Portable Incubator. By Newell S. Ferry. (*Abdruck Aus Dem Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten*, Abt. 1, Original, Bd. 65, Heft 4/5, 1912, pp. 412-413.)

26. Tobacco Extracts: Their Comparative Values as Insecticides. By W. O. Hollister. (*Journal of Economic Entomology*, Vol. 5, June, 1912, pp. 263-267.)

27. The Pharmacological Assay of Pituitary Preparations. By H. C. Hamilton. (*Journal of the American Pharmaceutical Association*, Vol. 1, October, 1912, pp. 1117-1119.)

28. Pituitary Extracts in Obstetrics and Gynecology. By A. W. Lescohier and O. E. Closson. (*Journal of the Michigan State Medical Society*, Vol. 11, October, 1912, pp. 650-657.)

29. Biological Products—Veterinary. By Robert H. Wilson. (*American Veterinary Review*, Vol. 41, September, 1912, pp. 668-681.)

30. The Isolation and Cultural Characteristics of Bacillus Acne. By Edwin M. Stanton. (*Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten*, Original, Bd. 66, Heft 5/7, 1912, pp. 386-389.)

31. Studies on Hog Cholera. By Walter E. King and Robert H. Wilson. (*Journal of Infectious Diseases*, Vol. 11, November, 1912, pp. 441-458.)

32. Studies on the Virus of Hog Cholera. By Walter E. King and F. W. Baeslack. (*Journal of Infectious Diseases*, Vol. 12, January, 1913, pp. 39-41.)

33. The Physiological Activity of Cannabis Sativa. By H. C. Hamilton, A. W. Lescohier and R. A. Perkins. (*Journal of the American Pharmaceutical Association*, Vol. 2, January, 1913, pp. 22-30.)

34. The Iodine Content of the Small, Medium and Large Thyroid Glands of Sheep, Beef and Hogs. By T. B. Aldrich. (Original Communications, Eighth International Congress of Applied Chemistry, Vol. 19, 1912, pp. 9-14.)

35. Studies on the Virus of Hog Cholera. By Walter E. King and Robert H. Wilson. (*Zeitschrift für Immunitatsforschung und Experimentelle Therapie,* Bd. 16, Heft 3, 1913, pp. 367-376.)

*36. On the Cultivation of the Treponema Pallidum (Spirochæta Pallida). By F. W. Baeslack. (*Journal of Infectious Diseases,* Vol. 12, Jan., 1913, pp. 55-67.)

37. Studies on the Gonococcus, I. By Carl C. Warden. (*Journal of Infectious Diseases,* Vol. 12, Jan., 1913, pp. 93-105.)

38. Studies on the Virus of Hog Cholera. By Walter E. King, F. W. Baeslack and George L. Hoffmann. (*Journal of Infectious Diseases,* Vol. 12, March, 1913, pp. 206-235.)

39. Bacillus Bronchisepticus—Its Relation to Canine Distemper. By N. S. Ferry. (*American Veterinary Review,* Vol. 43, April, 1913, pp. 16-30.)

40. Drug Influence on Extrasystoles of the Mammalian Heart. By Carey P. McCord. (*Interstate Medical Journal,* Vol. 19, Oct., 1912, pp. 870-880.)

41. The Employment of Protective Enzymes of the Blood as a Means of Extracorporeal Diagnosis. I.—Sero-Diagnosis of Pregnancy. By Carey P. McCord. (*Surgery, Gynecology and Obstetrics,* Vol. 16, April, 1913, pp. 418-421.)

42. Tribromo-tert-Butyl Alcohol, $C_4H_7OBr_3$. By T. B. Aldrich. (*Journal of the American Chemical Society,* Vol. 33, March, 1911, pp. 386-388.)

43. On Feeding Young White Rats the Posterior and the Anterior Parts of the Pituitary Gland. By T. B. Aldrich. (*American Journal of Physiology,* Vol. 31, Nov., 1912, pp. 94-101.)

44. The Rationale of the Use of Adrenalin in the Treatment of Asthma. By Carey P. McCord. (*Medical Record,* Vol. 83, March 8, 1913, pp. 431-432.)

45. Standardization of Disinfectants: Some Suggested Modifications. By H. C. Hamilton and T. Ohno. (*American Journal of Public Health,* Vol. 3, June, 1913, pp. 582-588.)

46. Preventive Measures Against Equine Influenza Based on Its Bacteriology. By N. S. Ferry. (Report of the Proceedings of the United States Live Stock Association, December, 1912, p. 127.)

47. Correcting Water. By H. C. Hamilton. (*Bulletin of Pharmacy,* Vol. 27, August, 1913, pp. 330-335.)

48. Duration of Immunity Following Small-pox Vaccination. By A. W. Lescohier. (*Journal of the American Medical Association,* Vol. 61, Aug. 16, 1913, page 487-490.)

49. On Crystalline Kombe-Strophanthin. By D. H. Brauns and O. E. Closson. (*Journal of the American Pharmaceutical Association,* May, June and July, 1913, Vol. 2.)

50. A Comparative Study of Antigens for the Wassermann Reaction. By H. R. Varney and F. W. Baeslack. (*Journal of the American Medical Association,* Vol. 61, Sept. 6, 1913, pp. 754-757.)

51. The Treatment of Tetanus. By Charles T. McClintock and Willard H. Hutchings. (*Journal of Infectious Diseases,* Vol. 13, Sept., 1913, pp. 309-320.)

52. Spirochæta Suis, Its Significance as a Pathogenic Organism, Studies on Hog Cholera. By Walter E. King and George L. Hoffmann. (*Journal of Infectious Diseases,* Vol. 13, Nov., 1913, pp. 463-498.)

53. Time Recorder for Kymograph Tracings. By Oliver E. Closson. (*Journal of Pharmacology and Experimental Medicine*, Vol. 5, Jan., 1914, pp. 235-238.)

54. U. S. P. Menstrua. By H. C. Hamilton. (*American Journal of Pharmacy*, Vol. 86, Feb., 1914, pp. 56-61.)

55. Numerical Variations of the White Blood Cells in Mice Inoculated with Transplantable Adenocarcinoma. By F. W. Baeslack. (*Zeitschrift für Immunitatsforschung und Experimentelle Therapie*, Bd. 20, Heft 5, 1914, pp. 421-435.)

56. A Study of the Germicidal Action of the Ultraviolet Rays. By E. M. Houghton and L. Davis. (*American Journal of Public Health*, Vol. 4, March, 1914, pp. 224-240.)

57. Some Phenomena Involved in the Life History of Spirochæta Suis—Studies on Hog Cholera. By W. E. King and R. H. Drake. (*The Journal of Infectious Diseases*, Vol. 14, March, 1914, pp. 246-250.)

58. The Sterilization of Adrenalin Solutions. By L. W. Rowe. (*American Journal of Pharmacy*, Vol. 86, April, 1914, pp. 145-149.)

59. Infection and Immunity: A Review. By N. S. Ferry, Ph.B., M.D. (*Journal of the American Pharmaceutical Association*, Vol. 3, April and May, 1914.)

60. Disinfection—What Disinfectant is the Most Generally Applicable for Clinical, Surgical and Sanitary Purposes? By H. C. Hamilton. (*Therapeutic Gazette*, Vol. 38, May, 1914, pp. 311-315.)

61. Study of the Bacteriology of the Posterior Nasopharynx in Scarlatina. By N. S. Ferry, M.D. (*Medical Record*, Vol. 85, May 23, 1914, pp. 934-935.)

62. Some Experiences with Bacterial Vaccines in Scarlatina. By Guy L. Kiefer, M.D., D.P.H., and N. S. Ferry, M.D. (*Medical Record*, Vol. 85, May 23, 1914, p. 936.)

63. A Sero-enzyme Test for Syphilis. By F. W. Baeslack, M.A., M.D. (*The Urologic and Cutaneous Review*, Vol. 18, May, 1914, pp. 234-238.)

64. Bacteriology and Control of Acute Infections in Laboratory Animals. By N. S. Ferry, Ph.B., M.D. (*Journal of Pathology and Bacteriology*, Vol. 18, 1914, pp. 445-455.)

65. The Bacteriological Standardization of Disinfectants. By H. C. Hamilton and Tatsuzo Ohno. (*American Journal of Public Health*, Vol. 4, No. 6, p. 163.)

66. The Pineal Gland in Relation to Somatic, Sexual and Mental Development. By Carey P. McCord, M.D. (*Journal of the American Medical Association*, Vol. 63, July 18, 1914, pp. 232-235.)

67. The Sero-enzyme Test for Syphilis. By F. W. Baeslack, M.D., M.A. (*Journal of the American Medical Association*, Vol. 63, Aug. 15, 1914, pp. 559-563.)

68. A Case of Contagious Broncho-pneumonia Caused by Bacillus Coli Communis. By Edwin M. Stanton. (*American Veterinary Review*, Vol. 14, May, 1914, pp. 233-235.)

69. Local Anesthetics—Some Comparative Physiological Reactions. By Oliver E. Closson. (*Journal of the Michigan State Medical Society*, Vol. 13, Oct., 1914, pp. 587-597.)

70. Potassium Tellurite as an Indicator of Microbial Life. By Walter E. King and Lewis Davis. (*American Journal of Public Health*, Vol. 4, Oct., 1914, pp. 917-932.)

71. Further Studies with Reference to Spirochetes Observed in Swine —Studies on Hog Cholera. By Walter E. King, Raymond H. Drake, and Geo. L. Hoffmann. (*Zeitschrift für Immunitätsforschung und Experimentelle Therapie*, Vol. 22, 1914, pp. 347-371.)

72. The Pharmacy of Adrenalin. By C. P. Beckwith. (*Journal of the American Pharmaceutical Association*, Vol. 3, November, 1914, pp. 1547-1554.)

73. A Study of the "Tellurite Reaction" with the Colon-typhoid Group and other Organisms. By Lewis Davis, S.M. (*Centralblatt für Bakteriologie Parasitenkunde und Infektionskrankheiten*, 75 Band, 1914, pp. 180-192.)

74. An Expanding Root Canal Filling. By George Bailey Harris, D.D.S., Sc.M. (*Items of Interest*, Vol. 36, Dec., 1914, pp. 881-886.)

75. On the Presence of Histidine-like Substances in the Pituitary Gland (Posterior Lobe). By T. B. Aldrich. (*Journal of the Chemical Society*, Vol. 37, Jan., 1915, pp. 203-208.)

76. Inoculation Experiment with Pure Culture of Spirochæta Hyos—Studies on Hog Cholera. By Walter E. King and Raymond H. Drake. (*Journal of Infectious Diseases*, Vol. 16, Jan., 1915, pp. 54-57.)

77. What is the Best End-Point of the Reaction in the Frog-Heart Method of Digitalis Assay? By H. C. Hamilton and L. W. Rowe. (*Journal of the American Pharmaceutical Association*, Vol. 4, January, 1915, pp. 108-112.)

78. The Glands of Internal Secretion and Their Importance as Therapeutic Agents. By Carey P. McCord. (*Journal of the American Pharmaceutical Association*, Vol. 4, March, 1915, pp. 293-297.)

79. Cannabis Sativa. By H. C. Hamilton. (*Journal of the American Pharmaceutical Association*, Vol. 4, April, 1915, pp. 448-451.)

80. The Pineal Gland. By Carey P. McCord. (*Interstate Medical Journal*, Vol. 22, No. 4, April, 1915, pp. 354-370.)

81. The Filterability of Bacillus Bronchisepticus: With An Argument for a Uniform Method of Filtration. By N. S. Ferry. (*Journal of Pathology and Bacteriology*, Vol. 19, No. 4, April, 1915, pp. 488-493.)

82. The Pineal Gland in Relation to Somatic, Sexual and Mental Development. By Carey P. McCord. (*Journal of the American Medical Association*, Vol. 65, Aug. 7, 1915, pp. 517-520.)

83. The Correct Name for the Hemlock Spruce. By Oliver A. Farwell. (*Bulletin of the Torrey Botanical Club*, Vol. 41, Jan. 8, 1915, pp. 621-629.)

84. The Proper Time to Collect Sanguinaria. By O. A. Farwell. (*American Journal of Pharmacy*, Vol. 87, March, 1915, pp. 97-98.)

85. Notes on the Michigan Species of Polygonatum. By O. A. Farwell. (*Bulletin of the Torrey Botanical Club*, Vol. 42, May, 1915, pp. 247-258.)

86. Belladonna and Hyoscyamus. By O. A. Farwell. (*American Journal of Pharmacy*, March, 1915, pp. 99-101.)

87. Notes on Michigan Liliaceae. By O. A. Farwell. (*Bulletin of the Torrey Botanical Club*, Vol. 41, June 16, 1915, pp. 351-358.)

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EXHIBIT II

The Upjohn Company and Scientific Research

Tucked away in an obscure place on the last few pages of the catalog is a list of the research publications from the research laboratories of The Upjohn Company. While some houses have gained considerable prestige by advertising research and also by distribution of reprints of articles, few of our salesmen appreciate the fact that the published record of our own research laboratory is second to none. Study this list carefully and note the wide range of subjects, and the character of the scientific journals in which this work was reported. Perhaps you have certain doctors who would be interested.

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4. Some Constituents of the Root of Brauneria Augustifolia. J. Am. Chem. Soc. *37, 1769* (1915).
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EXHIBIT III

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2—Research Studies in Psoriasis.
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By G. W. Raiziss and H. Dubin. Journal of Biological Chemistry; XVIII, No. 2, 297 (1914).

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By G. W. Raiziss, H. Dubin and A. I. Ringer. Journal of Biological Chemistry; XIX No. 4, 473 (1914).

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By M. E. Trist and J. A. Kolmer. Archives of Pediatrics; Vol. XXXII, No. 11 (Nov., 1915).

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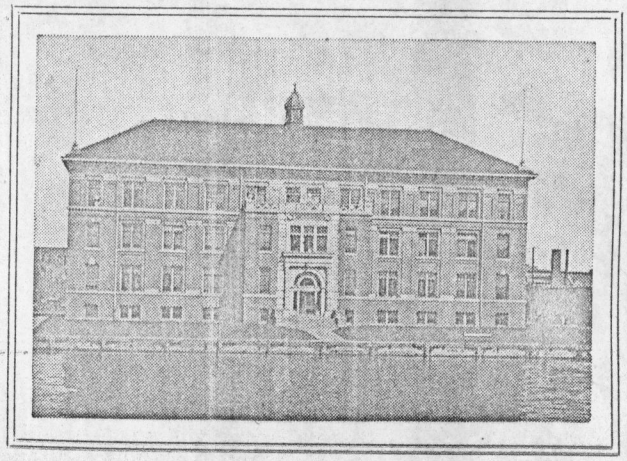
APPENDIX B

PROGRAM OF PARKE-DAVIS® LABORATORY WEEK (1917) FOR VISITING PHYSICIANS

The first "Laboratory Week" was held by Parke-Davis in 1914 to provide instruction to physicians in new methods of diagnosis and treatment. An examination of this program for the 1917 "Laboratory Week" provides the names of nineteen men who were conducting independent research in biologicals. A study of the topics presented during this week is suggestive of the scope of interests of the scientific staff in the Parke-Davis Research Laboratories.

PROGRAM OF LABORATORY WEEK FOR VISITING PHYSICIANS



BY THE
RESEARCH LABORATORY OF
PARKE, DAVIS & CO.
DETROIT, MICHIGAN
JUNE 25-29, 1917

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T. B. Aldrich, Ph.D., - - - - Biological Chemistry.

F. W. Baeslack, M.A., M.D., - - Pathology and Cytology.

L. Davis, S.M., - - - - - Biological Chemistry.

R. H. Drake, M.A., - - - - - Bacteriology.

A. D. Emmett, Ph.D., - - - - Nutritional Chemistry.

N. S. Ferry, Ph.B, M.D., - - - - - Bacteriology.

M. C. Hall, Ph.D., D.V.M., - - - - Parasitology.

H. C. Hamilton, M. S., - - - - - Chemistry.

H. P. Hoskins, D.V.M., - - - Animal Diseases.

A W. Lescohier, M.D., - - - - - Biology.

L W. Rowe, B.S., - - - - - Pharmacology.

C. P. McCord, A.B., M.D., - - - - Physiology.

G. J. Walters, Ph.D., M.D., - - - - Pathology.

H. C. Ward, M.S., - - - - - - Bacteriology.

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* The above list includes only members of staff engaged in independent research work, not assistants in the Research Division, or the Technical Staff of the Biological Manufacturing Division.

ENROLLMENT AND RECEPTION.

GENERAL INTRODUCTORY ADDRESS.

E. M. HOUGHTON,
Director, Research and Biological Laboratories.

ACTIVELY IMMUNIZING AGENTS.

N. S. FERRY.

Living, virulent viruses. Attenuated viruses: smallpox vaccine; anthrax vaccine; antirabic vaccine (Pasteur, Högyes and Cömming methods); blackleg vaccine; sensitized bacterial vaccine (Besredka's method). Dead viruses: bacterial vaccines; sensitized vaccine (modification of Besredka's method). Bacterial products: exotoxins (diphtheria, tetanus, botulismus); endotoxins; extracts (agressins—natural, artificial).

INTERNAL SECRETIONS.

CAREY PRATT McCORD.

(I). THE INTERNAL SECRETORY SYSTEM.

The significance of the internal secretory organs in body economy. The internal secretory system as a mechanism for integrating the diverse functions and activities of the body's organs and tissues. The vegetative mechanisms of the body. The interrelations of the internal secretory organs.

(II). GLANDULAR THERAPY.

General principles, terminology, hormones, substitution therapy, pluriglandular therapy. The uses and limitations of glandular therapy.

(III). CLINICAL TYPES OF INTERNAL SECRETORY DYSFUNCTION.

Clinical manifestations of perversions of functions of glands of internal secretion. Pluriglandular syndromes. Abnormalities of growth and differentiation. Psychic disturbances arising from perversions of the endocrinous system.

(IV). CLINICAL TYPES OF INTERNAL SECRETORY DYSFUNCTION.

A continuation of the previous discussion of the perversions of internal secretory functions as seen clinically. The frequence of such cases. Etiology. Symptomatology. Diagnosis. Therapy Lantern demonstrations.

SERUM THERAPY.

A. W. LESCOHIER.

Antitoxic and antibacterial serums in relation to passive immunity. Accepted serums, therapeutic indications, modes of administration and results of use. Experimental serums.

PROTEIN SENSITIZATION.

N. S. FERRY.

History, phenomena, review of various anaphylactic diagnostic tests, with a practical demonstration of anaphylactic reactions in both man and animals.

RABIES.

G. WALTERS.

History. Epidemiology; exploded fallacies; manner of transmission; source of infection; pathology; clinical and laboratory diagnosis; prophylaxis; legal prevention; Pasteur treatment of human and animal patients.

TUBERCULINS.

A. W. LESCOHIER.

Indications for use of tuberculin products in diagnosis and treatment. Brief review of the theories as to the action of tuberculins. Discussion of the tuberculin reaction. The different forms of tuberculin, with methods of application.

EXPERIMENTAL SYPHILIS.

F. W. BAESLACK.

The Spirochaeta pallida—historical sketch of the search for the cause of syphilis. The experimental research in syphilis. Cultivation of the Spirochaeta pallida. Experimental syphilis in rabbits.

TRIP TO PARKEDALE BIOLOGICAL FARM, ROCHESTER, MICHIGAN.

DEMONSTRATIONS.

R. H. WILSON,
M. J. SMEAD,
L. A. MAZE.

The propagation of experimental animals and maintenance of large animals for biological purposes.

THE CANCER PROBLEM.

F. W. BAESLACK.

Brief historical review. The period of experimental research in cancer. The theories regarding the cause of cancer—their relation to each other in the light of modern research. Mutation in cancer. Recoveries from cancer. Cancer immunity. Diagnosis of cancer. Therapeutic agents employed in cancer. Ferments in the blood of cancer patients. Lantern slide demonstration.

POLIOMYELITIS.

H. C. WARD.

Pandemics in both Europe and America stimulative of scientific inquiry concerning the cause of infantile paralysis. Etiological studies in other laboratories. United States epidemic of 1916 and subsequent lines of research.

Presentation of evidence indicating the nature and action of the virus, its viability, pathogenicity, and methods of conveyance. Difficulties involved in establishing protection against this disease. Present status of medicinal and biological therapeutic agents. Available methods for controlling infection. Importance of progressive work.

POLLEN DISEASES.

N. S. FERRY.

History, role played by pollen and secondary infection, and rationale of expectant, bacterial vaccine, specific serum, and pollen extract treatments.

COMPLEMENT FIXATION IN TUBERCULOSIS.

F. W. BAESLACK.

General discussion of the application of complement fixation reaction to the diagnosis of tubercular infections. Resume of tests conducted.

OZENA.

H. C. WARD.

Ozena described and illustrated. Importance emphasized by a marked tendency to family infection and chronicity. Theoretical relationship to

syphilis, tuberculosis, pneumonia, diphtheria, and to the vital problem of infection carriers.

Presentation of our recent study of fifty cases. Indication of the etiological factors probably involved. Employment of experimental vaccines, including both autogenous and stock preparations. Present outlook.

BLOOD STUDIES.

G. WALTERS.

History of hematology; blood pathology; cytology; coagulation; interpretation of cell counts; effects of coagulation time upon surgical procedure; agencies for clinical correction of adverse blood conditions; selection of therapeutic substances; results.

PARASITOLOGY.

MAURICE C HALL.

Prevalence of parasitism in general and in the United States in particular. Methods of examining feces for evidences of parasitism, and the theory underlying these methods. Anthelmintics and insecticides—discussion of a few of the more important.

SCIENTIFIC RESEARCH, THE BASIS OF PHARMACEUTICAL PROGRESS.

DR. J. M. FRANCIS,
Chief Chemist.

INFORMAL DISCUSSIONS.

LABORATORY DEMONSTRATIONS.

The Laboratory Demonstrations will be given in eight sections, so arranged that all of the subjects will be presented once to each member of the party during the week. These demonstrations, with discussions, will consist of the following:

I. RAT SARCOMATA, TREPONEMA AND SPIRILLI.

F. W. BAESLACK.

Sarcomata transplantable in rats. *Treponema pertenue* (yaws). Spirillum Novyi (relapsing fever).

II. EXPERIMENTAL WORK ON GLANDS OF INTERNAL SECRETION.

CAREY PRATT McCORD.

Internal Secretion.—Anatomic and histologic preparations of the several internal secreting organs demonstrating:

(1). The sources of materials for glandular therapy.

(2). The structural basis for endocrinopathic lesions.

III. DISEASES OF UNKNOWN ETIOLOGY.

W. E. KING.

General scope of microbiological field. One conspicuous break in the development of the science ultravisible viruses. List of specific infectious diseases of unknown etiology.

General consideration of filterability. Fallacies of filtration work. Demonstration of different types of filters and methods of filtration, including the Bechhold "ultra filter." Illusrated study of a filterable virus.

IV. DIETARY DEFICIENCY DISEASES.

A. D. EMMETT.

(1). Vitamines.—Relation to infantile scurvy, beriberi and pellagra.—Demonstration of the effect of a vitamine-free diet upon pigeons, producing avian polyneuritis beriberi in man.

(2). Amino acids.—Relation to the maintenance, growth and development of the animal body.—Demonstration, showing the influence upon rats of with-holding certain amino acids from the diet.

V. (a) ANIMAL PARASITES.

MAURICE C. HALL.

Exhibition of various species of parasites.

(b) METHODS OF EXAMINING FECES.

MAURICE C. HALL.

Demonstration of methods of examining feces for evidences of parasitism: the simpler equipment and the more elaborate equipment and apparatus.

VI. BLOOD COAGULATION STUDIES.

G. WALTERS.

Surgical application of coagulating substances; theory of tissue repair and wound healing; interpretation of results.

VII. (a) PHARMACOLOGICAL ACTION OF DRUGS.

L. W. ROWE.

Demonstration of physiologic reactions used in testing the activity of extracts of drugs and internal secreting glands.

(b) DISINFECTANTS AND INSECTICIDES.

H. C. HAMILTON.

Phenol coefficients or germicidal values of some representative disinfectants, with description of methods for obtaining these values.

VIII. POLIOMYELITIS.

H. C. WARD.

Illustrates studies on the geographical distribution of poliomyelitis. Presentation of cases. Limits of the laboratory diagnosis. The filterable virus of Flexner, and micro-organisms reported from other sources.

Experimental difficulties of proving etiological relationship. Laboratory animals under present observation. Culture and microscopic preparations.

APPENDIX C

SOME TYPICAL RESEARCH PAPERS

E. M. Houghton's paper (1898) on "Ergot Aseptic" permits insight into his early work on the development of a physiological assay for ergot. E. M. Houghton and H. C. Hamilton's paper on "Veratrone" gives an indication of the level of sophistication of some of the early industrial research (1905).

EXHIBIT I

ERGOT ASEPTIC.

BY E. M. HOUGHTON, Ph.C., M.D.

Reprinted from The Therapeutic Gazette,
July 15, 1898

Many attempts have been made to isolate the active constituents of ergot, or to produce a satisfactory preparation of the drug for hypodermic administration. Owing to the fact that pharmacologists thus far have not been able to agree upon what should be considered the active constituents of ergot, and the great difficulty of isolating the chemical constituents already studied, it seemed to me best to endeavor to obtain a preparation which would represent as nearly as possible the activity of prime samples of ergot, rather than to attempt to obtain any of the constituents of the drug in pure form.

It is not necessary to mention the importance of having a reliable preparation of ergot for hypodermic administration always on hand when prompt action of the drug is desired. Especially desirable is this in obstetric practise, since it so frequently happens that at the critical moment the patient is vomiting, or the stomach is otherwise not in condition to absorb the drug when administered by the mouth.

It is a well known fact that much of the crude ergot, and its preparations, on the market vary very greatly in strength, or may be entirely inert; consequently it seemed advisable to adopt some method of physiological assay. Having this in view, various methods of determining from physiological experiments the real activity possessed by ergot were investigated. I finally decided to adopt the reaction manifested in roosters when fed with this drug. From times prehistoric it has been observed that in fowls, swine, and other animals, as well as man, fed with ergotized rye, or with bread prepared from the flour of such grain, for a considerable length of time, the poisonous action of the fungus is frequently manifested by gangrene and sloughing of the peripheral parts, as the comb of fowls, ears of hogs, and ears, nose, fingers and toes of man. Two particular types of ergot poisoning have been observed in man, viz., ergotismus gangrenosus and ergotismus spasmodicus. Kobert, and his pupil Grünfeld, were the first to employ the method of feeding ergot to roosters in order to determine the activity of the crude drug, or of the products isolated from it. However, these investigators employed the reaction only for experimental purposes. It seemed to me, after careful investigation, that it would be advisable, and of vastly more importance to medical practitioners, to employ this reaction not only as a check on experimental work, but as a means for determining the active properties of the crude ergot before its manufacture into the various pharmaceutical preparations, and to test the completed preparations by the same means. With this end in view I have examined during the past three years several hundred samples of the crude drug as it appeared upon the American market, and finished preparations taken from the druggists' shelves. Many of the samples were almost inert, while the remainder varied greatly in activity. Indeed, not long since I had occasion to reject several samples of the drug which were forwarded to me for examination, the aggregate quantity represented by them amounting to over 20,000 pounds. This method of testing was employed also by Jacobi last year in an elaborate experimental research. My experience leads me to conclude that not more than from fifty to seventy-five per cent. of the drug, or its preparations, offered for sale is suitable for medicinal use.

In taking up the study of ergot aseptic I shall present the views of some of the leading pharmacologists who have made extended researches on ergot. It has been shown that the fungus contains acid salts of potassium, sodium, etc., and various organic constituents, as coloring matter, fats, methylamine, etc. These several constituents are of little importance if contained in preparations designed for internal administration, since none of them are physiologically active, but they may be a source of irritation when injected subcutaneously. Pharmacologists in general agree that ergot contains at least three active constituents, viz., ergotinic acid, sphacelinic acid, and cornutin. Ergotinic acid (the impure form of which is known as sclerotinic or sclerotic acid, and combined with mannin is known as scleromuscin) is a glucosidal body, readily soluble in water but almost insoluble

in alcohol; it decomposes easily under bacterial or chemical influences. Consequently, when taken internally in the various preparations of the drug it is quickly split up by the processes of digestion, or by bacteria contained in the alimentary canal. Dragendorff and Podwyssotzki were the first to call attention to this constituent, and claimed, because they found that it stopped the laid-bare frog's heart in diastole, that it was the active constituent to be depended upon for the production of ergot effects. The later work of Kobert, his pupil Grünfeld, and others, has shown that it has no influence on the uterus, not even when gravid. Since it is decomposed and not absorbed from the alimentary canal, except possibly in the minutest quantities, it is not objectionable when contained in preparations for oral administration, but is to be especially guarded against in fluids designed for hypodermic use, since when administered in this manner it is slowly absorbed into the system — in fact (according to Kobert), it acts as a long-irritating foreign body, frequently resulting in abscess. As much as three per cent. of sclerotic acid may be obtained from some of the preparations of ergot on the market. I will add several volumes of strong alcohol to this fluid extract of ergot, and you can better appreciate this fact, since the voluminous precipitate thrown down consists almost entirely of this constituent. When subcutaneously injected in a very dilute condition, sufficient quantities may be absorbed to produce the general symptoms noted when the drug is introduced directly into the intravenous system — that is, the irritability of the central nervous system is lessened. The action of ergotinic acid on the spinal cord is manifested by paresis, weakness of the limbs, etc., large doses producing complete motor and finally sensory paralysis. Blood-pressure is also lowered, from the action of the acid on the vasomotor centers, while its sedative action on the brain is manifested by stupor.

I have repeatedly confirmed these statements by subcutaneous and internal administration of the ergotinic acid to roosters, and to pregnant animals in various stages of gestation.

Ergot affords one of the many instances where, possibly by a wise provision of Nature, a crude drug contains active constituents having antagonistic actions. Sphacelinic acid, which is also known by the names of sphacelotoxin and sphacmotoxin, is a resinous substance almost entirely insoluble in water, but readily soluble in alcohol. It has not been obtained in a pure condition, as it is very easily decomposed by chemical manipulations. It is held that this substance is responsible for the ergotismus gangrenosus. This constituent was first obtained by Kobert, and later extensively studied by Grünfeld, who concluded that while it had marked pharmacologic properties it could not be used therapeutically. This opinion, however, was disputed last year by Jacobi, who holds that the active constituent of ergot is the nitrogen-free resin, sphacelotoxin, which occurs in the drug in combination with basic substances, especially with secalin and ergo-chrysins. Jacobi carried out many extensive experiments upon fowls and pregnant animals, the results of which seem to prove that his claims are correct. Grünfeld found that the gangrene of the peripheral parts caused by large doses of sphacelinic acid is due partially to a local action upon the walls of the arterioles, and partially to a direct action on the vasomotor centers, resulting in a narrowing of the caliber of the vessels, followed by the pouring out of a hyaline substance, this condition finally terminating in complete paralysis of the walls of the arterioles; peristalsis of the intestine is markedly increased, ulceration of its walls may occur, and extravasations into the mesentery may also be noted. Sphacelinic acid, because of its direct stimulant action upon the motor centers of the central nervous system, and its local action on the vessels, produces a marked rise in blood-pressure. Also from its action on the motor centers and its local action on unstriped muscle fiber, it produces tonic contractions of the uterus.

The third constituent, the alkaloid cornutin, is believed by Kobert to be the active constituent desired. But this seems scarcely possible, since the best crude drug contains only a fraction of one per cent. of it. Tanret held cornutin to be a decomposition product of ergotinin, while Jacobi, as already mentioned, believes that we should ascribe the therapeutic value of the drug to the sphacelinic acid contained. Jacobi, however, also thinks that cornutin may in part explain the oxytocic action of ergot. Cornutin possesses very weak basic properties. Like sphacelinic acid, it is only extracted by an alcoholic menstruum. Its salts are somewhat soluble in water. Cornutin is said to be the cause of ergotismus spasmodicus. Mainly because of its irritation upon the medulla, it produces

in mammals increased blood-pressure, slowing of the pulse, etc., large doses resulting in tetanic convulsions. However, very small doses, as claimed by Kobert, produce, through action on the motor centers of the lumbar cord, strong clonic contractions of the gravid uterus, simulating those observed during the normal act of parturition. Especially do these results occur when cornutin is administered subcutaneously.

In general we may conclude from what has already been said that the desired action of ergot is due to the pharmacologic properties of the contained sphacelinic acid and cornutin, or their salts. It appears well-nigh impossible to separate these constituents, since the solubilities of both are much alike, but for practical purposes this is of little importance, as they have much the same physiologic action and can be readily separated from the sclerotic acid, which has an opposite action.

With the purpose of obtaining a preparation of ergot which should contain a large percentage of sphacelinic acid and cornutin and as small quantities of sclerotic acid and inert substances as possible, the following experimental work was carried out:

The crude drug employed was carefully standardized by feeding to cocks and noting the reaction manifested by the comb and wattles. The selected drug was ground and divided into a large number of small parcels, which were then percolated with various solvents. The several extracts obtained, and the exhausted drug left in the percolators, were each tested by feeding to fowls, and the results compared. The menstruum found to produce an extract having the most marked physiologic properties was selected. This menstruum, however, extracts a certain amount of sclerotic acid, which, while it is not harmful (as already stated) for internal administration, was removed from the preparation designed for subcutaneous injection. Since the free acids and the acid salts contained in a fluid extract of the drug are very irritating when administered hypodermically, they were neutralized. The fluid was finally concentrated until one part represented two parts of the crude drug. The finished product was found to be almost entirely non-irritating, but would not keep, owing to the ready decomposition of its constituents. Instead of using alcohol or seeking out some antiseptic which would preserve the fluid, it seemed much more desirable to have the fluid placed in containers holding sufficient for one injection, the filled and sealed containers to be then sterilized. The results were entirely satisfactory. The completed ergot aseptic consists, therefore, of a non-alcoholic fluid preparation of ergot from which the inert substances and ergotinic acid have been removed. The irritating acids and acid salts have been neutralized, the finished product appearing in small glass bulbs, each holding sufficient for one injection. The bulbs, after being filled, and the necks sealed, are then rendered completely sterile by fractional steam sterilization. It is now over a year since the bulbs which I have here were filled, and you see the contained fluid is even now perfectly clear and transparent. A recent test has shown that the contained fluid has retained its physiologic properties apparently unimpaired.

Of far more importance to the physician than the chemic and physical properties is its physiologic action. I have carried out many experiments on various kinds of animals — dogs, cats, rabbits, etc. — which show conclusively that ergot aseptic has the active properties of sphacelinic acid and cornutin. Blood-pressure is raised; peristalsis of the intestine is increased when intravenous injections are administered to dogs and rabbits; gangrene of peripheral parts occurs when it is given to cocks, and expulsion of the contents of the uterus follows when ergot aseptic is administered subcutaneously or internally in proper doses, to pregnant animals at various periods of gestation.

Thus far the clinical results reported by those who have employed it in practise indicate that it is non-irritating and produces prompt and efficient results. Since I am not engaged in obstetric practise I shall leave the final decision of the therapeutic value of ergot aseptic in the hands of the medical profession at large.

However, before closing I find it incumbent upon myself to again state that it is my opinion after several years' careful testing of ergot by pharmacologic methods, that crude ergot, or its pharmaceutical preparations, should never be employed for medicinal purposes except they be carefully tested for physiologic properties, as the chemist is unable to tell whether this drug and its preparations are active or inert. And for the purpose of testing the crude drug ergot, or any of its pharmaceutical preparations, the reaction noticed in roosters seems to be the most reliable and most readily carried out. The blackened and gangrenous appearances produced in the

comb and wattles of fowls is well shown in the accompanying colored plate, which is an exact reproduction of an oil painting made from life.

To my colleague, Mr. J. M. Francis, is due the credit of having overcome the pharmaceutical difficulties in the way of manufacturing ergot aseptic.

EXHIBIT II

VERATRONE.

Reprinted from The Therapeutic Gazette, January, 1905

By E. M. Houghton, Ph.C., M.D., and H. C. Hamilton, M.S.

Some years ago one of us[1] had a series of experiments undertaken for the purpose of devising fluid preparations of such of our old and tried drugs as ergot, digitalis, etc., suitable for oral and hypodermic use. The chemistry of this class of drugs was, and still is, in such a chaotic state that it was deemed advisable to branch off the beaten paths of pharmacy, ignore for the most part the results of chemical investigation, and adopt the pharmacologic method for obtaining suitable preparations for therapeutic purposes. This, from the physician's point of view, would seem to be a most rational procedure, since it makes very little difference in the treatment of disease what the chemical properties of a given drug may be, provided it produces when administered to the patient the desired pharmacologic action, with the least amount of irritation or other untoward effects.

In brief, the method of studying these drugs and obtaining the desired preparations has been as follows: The U. S. P. fluid extracts, since they represent to the best of our knowledge the therapeutic properties of these drugs, were taken as standards. The normal physiologic action of these was determined upon suitable animals and recorded. Samples of prime crude drug were then percolated with various menstrua, and the resulting percolates were tested upon animals and the reactions compared with the standards previously established. Thus step by step as a percolate was obtained or was modified by subsequent treatment its qualitative and quantitative activity was determined.

For full reports of the work on ergot see Therapeutic Gazette, July 15, 1898, "Ergot Aseptic," and Therapeutic Gazette, July 15, 1903, "A Pharmacological Study of an Aseptic Preparation of Ergot Devised for Hypodermic and Internal Administration;" and on digitalis see *Medicine* for August, 1903, "An Attempt to Obtain a Uniformly Active, Sterile, and Non-irritating Preparation of Digitalis for Subcutaneous and Internal Administration."

The therapeutic results obtained from the use of the ergot aseptic, ergone, and digitalone were the incentive for making an extended study of veratrum viride. As already intimated, the chemistry of veratrum viride is very much involved; likewise pharmacologists and therapeutists differ greatly in their views. Thus, Wood and Brunton claim that the activity of the plant depends principally upon jervine and rubijervine (veratroidine), and recognize that the action of these constituents may be modified to a certain extent by traces of pseudojervine, cevadine, veratrine, etc. On the contrary Cushny holds that the therapeutic properties of the drug for the most part depend upon the contained veratrine, and that from a pharmacological point of view it serves no useful purpose in therapeutics. Many practitioners speak highly of veratrum viride as an agent for controlling the sthenic symptoms of a beginning pneumonia, eclampsia, etc. Some physicians go so far as to believe it to be almost a specific for the latter disease. At best the subject is a debatable one. In any case where the drug is to be employed, particularly if for injection, it is almost axiomatic that it should be of uniform activity, non-irritating, and sterile.

Many preparations of veratrum viride were made and tested for activity upon the circulatory and respiratory systems, the kymograph (see Fig. 1) being employed for registering the pharmacological reac-

[1] E. M. Houghton.

tions. The irritating properties were determined by injecting the preparations subcutaneously into guinea-pigs, the animals being chloroformed a few hours later and post-mortem examination made. Finally, when the results of the experiments showed that the desired preparation had been obtained, a detailed pharmacological study of it was made. It was found, as in the case of ergone and digitalone, that the finished preparation would not keep without the use of an antiseptic. Chloretone, about four grains to the ounce, was again found to answer all purposes, as it prevented bacterial infection and rendered the injections less painful. Since the preparation had been obtained in the same way, and was combined with chloretone, it seemed desirable to designate the new product "veratrone," in keeping with similar preparations of the drugs just named.

Veratrone is a clear, amber-colored, non-alcoholic, aqueous fluid, having a pleasant odor and a slightly bitter taste. Its pharmacologic activity has been adjusted to one-fourth the strength of the U. S. P. fluid extract by determining the minimum lethal dose per gramme of body weight for frogs of the same species and weight, kept under uniform conditions, comparing the results with those obtained from the injection of known quantities of the U. S. P. fluid extract of veratrum viride.

The sterility of the preparation, when kept under as nearly the same conditions as would be found in a drug store, was repeatedly tested. Samples were planted on several varieties of culture media and placed under the most favorable conditions for growth. Subsequent examination of these plants showed in each instance that the fluid was aseptic.

In order to determine the amount of irritation produced by hypodermic administrations, a number of guinea-pigs were injected with the new preparation, fluid extract veratrum viride, Norwood's tincture, etc., suitable corrections being made so that each injection would represent the same amount of crude drug. On chloroforming the animals to death some hours later and making a post-mortem examination, it was clearly manifest that the irritation produced by veratrone was decidedly less than resulted from the injection of the other preparations. As another evidence of the irritating properties of veratrone as compared with the other preparations of the drug just mentioned, it was found that dogs showed less discomfort, nausea, and other evidences of irritation when it was given per stomach. This may in part have been due to the local anesthetic action of the chloretone.

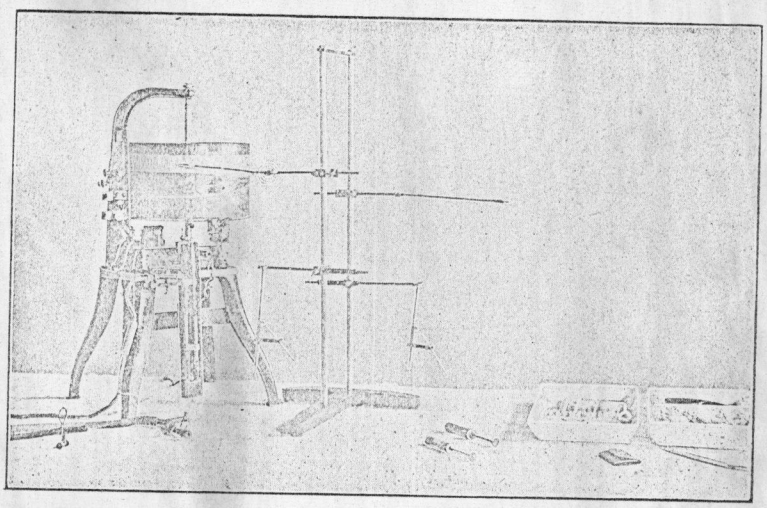


FIG. 1.

Veratrone, when applied to the isolated frog's heart, produced at first a more prolonged and stronger systole, but this was soon followed by an irregular contraction of the heart muscle, one part of the muscle being contracted, while another was relaxed—a sort of peristaltic wave, passing over the ventricle, which soon ceased beating and remained in systole.

In order to determine the action of the preparation upon the circulatory and respiratory systems, a number of experiments were made upon dogs, the results being recorded on a kymograph (see Fig. 1).

The following tables and tracings, which are typical, show the action of the new preparation to be essentially the same as that of the U. S. P. preparation, differing from it only quantitatively:

TABLE NO. 1.

Dec. 8, 1904. Experiment No. 5. Dog, weight 11 kilogrammes; a very quiet animal. This experiment was made to show the general action of veratrum viride.

Time.	Temperature.	Respiration per minute.	Pulse rate per minute.	Remarks.
9.20 A.M.	102.8° F.	18	112	Normal.
9.40 "	102.8° F.	16	106	Normal.
10.05 "	102.6° F.	20	114	Normal.
10.15 "	.....	...	.....	Given 2 Cc. veratrone undiluted subcutaneously. The animal does not whine or show other evidence of pain.
10.19 "	.....	...	.....	Respiration quickened, tongue begins to hang out of the mouth. Snaps his jaws together.
10.21 "	.....	...	.....	Begins to be nauseated, and respiration becomes slow and spasmodic.
10.25 "	.....	...	.....	Emesis occurs. Respiration ceases.
10.28 "	.....	...	.....	Still nauseated. Deep respiration. Animal lies prone, but moves about readily when disturbed, showing great muscular weakness.
10.29 "	101.4° F.	Irregular gasps.	70 and irregular.	
10.33 "	.....	...	.....	Begins to move about and show signs of recovery.
10.45 "	100.8° F.	10	76	
10.59 "	100.4° F.	4	82	Still nauseated. Lies prone, but shows much improvement.
11.15 "	99.2° F.	6	75	
11.20 "	.....	...	.....	Becoming drowsy, lies prone. Less nausea.
11.30 "	99° F.	8	76	Resting.
11.45 "	98.2° F.	16, irregular.	74	Resting. Does not like to be disturbed.
12.10 P.M.	98° F.	12, irregular.	124, irregular.	
1 "	97.4° F.	6, irregular.	136, irregular.	
2.30 "	94.3° F.	16	154	
4.23 "	96.6° F.	22	128	

Before the following morning the dog made a good recovery. No treatment was given except to keep the animal near a radiator.

TABLE NO. 2.

Dec. 9, 1904. Experiment No. 7. Dog, weight 5 kilogrammes; quiet female. See tracing for details. Anesthetic—chloretone and morphine. Artificial respiration.

Time.	Pulse rate per minute.	Blood-pressure.	Remarks.
4.38 P.M.	168	34 m.m. mercury.	Normal.
4.40 "	.....	.....	0.2 Cc. veratrone injected into femoral vein, diluted with physiological salt solution to 5 Cc.
4.41 "	81	21 m.m. mercury.	Heart action somewhat irregular and tending to go into diastole.
4.50 "	63	29 m.m. mercury.	Heart action more regular.
5.15 "	76	15 m.m. mercury.	
5.15+ "	.....	.....	2 Cc. veratrone injected into femoral vein, diluted to 5 Cc. with saline.
5.17 "	Rapid and irregular.	46 m.m. mercury.	No preliminary fall in blood-pressure. (See note.)
5.22 "	96	27 m.m. mercury.	Pulse regular.
5.30 "	112	21 m.m. mercury.	
5.31 "	.....	.....	5 Cc. veratrone injected into femoral vein.
5.34 "	165	54 m.m. mercury.	Quite regular heart action.
5.41 "	Quick and irregular.	24 m.m. mercury.	Experiment discontinued.

NOTE.—The heart action is very tumultuous, several partial beats being followed by very strong beats with marked diastole and systole.

This experiment, since the animal was supplied with artificial respiration, shows very clearly, as there was 5 Cc. injected at one time, more than twice the fatal dose (2 Cc.) (see Experiment 8), that death depends upon respiratory failure. So long as sufficient air is supplied, the circulation, while both heart action and blood-pressure may be profoundly disturbed, will take care of itself.

Dec. 10, 1904. Experiment No. 8. Dog, weight 4.5 kilogrammes. Anesthetized with chloretone and morphine. (See tracing for details.) This experiment was designed to show the action of large doses of the drug upon the respiration. The respiration normally was very slow and prolonged. Two Cc. of veratrone diluted to 5 Cc. with saline was injected into the femoral vein. As soon as the drug was injected the animal gave a few quick gasps and the respiration ceased. Very quickly there was a fall in the blood-pressure, followed in a few seconds by a pronounced rise, the heart becoming very irregular at the same time. This continued for about two minutes, when the heart action became very feeble, accompanied by a rapid fall in blood-pressure. In four minutes after the respiratory standstill the heart ceased to beat.

This experiment shows very clearly that the animal died of respiratory paralysis, the circulatory changes following this paralysis being largely due to the accumulation of CO_2 in the blood.

Dec. 10, 1904. Experiment No. 9. Dog, weight 12.8 kilogrammes. Anesthetized with chloretone and morphine. (See tracings for details.) This experiment was designed to show the action of veratrone in small doses upon the respiration. Normal rate of respiration 14 per minute. Injected 0.25 Cc. veratrone diluted to 5 Cc. with saline solution into femoral vein. The respiration was at once slowed to eight per minute and somewhat irregular. In about five minutes the rate had increased to eleven beats per minute, and a little later became normal. When the experiment was discontinued the blood-pressure showed a temporary fall followed by a partial rise, gradually falling to a point much below normal, where it remained fairly constant for a few minutes, and then returned to nearly normal. The pulse was much slowed, but remained quite regular.

This experiment shows the therapeutic possibilities of the drug, especially upon the circulation and respiration, viz., slowing of the respiration and pulse rate, accompanied by a fall in blood-pressure.

A study of these and many other experiments on the circulatory and respiratory systems shows that we may draw the following conclusions regarding its action:

Small or therapeutic doses slow and deepen the respiration, decrease the pulse rate, and produce a fall in blood-pressure.

Toxic doses first of all produce momentary stimulation of the respiratory center, resulting in a few quick gasps, followed by respiratory paralysis and death from asphyxia.

Little need be said regarding the therapeutic uses of this preparation. As already intimated, authorities differ greatly as to the advisability of prescribing any preparation of veratrum viride. Those who recognize the drug as of value are agreed that its range of usefulness is limited almost entirely to its employment as a means of reducing arterial action. Sometimes, as in typhoid fever and other similar conditions, it should not be employed even though it apparently is indicated. Wood claims that for the controling of "true sthenic arterial excitement," in any disease except gastritis, veratrum viride may be employed as a prompt, thoroughly efficient, and "very safe remedy" as "it is almost incapable of producing death in a robust adult, unless used with great recklessness and in repeated doses." A number of French writers believe it is the best remedy to employ in sthenic pneumonia. Where digitalis is contraindicated veratrum viride may be of much service. It is looked upon with the greatest favor perhaps for the treatment of eclampsia, many writers believing it to be the best means available for controlling the symptoms. In general it may be employed with great success wherever venesection would be practiced, with the advantage to the patient of being bled into his own veins. Whenever employed, sufficient doses should be administered to produce decided physiological effects, but care should be exercised not to push the dose too far.

Usually 1 to 2 Cc. (15 to 30 minims) as an initial dose per os, and half that quantity subcutaneously, is sufficient to elicit a physiological effect, but the physician must be guided by the symptoms manifested by the patient.

As would be expected from its pharmacological action, this new preparation does not differ essentially in its medicinal properties from other preparations of the drug, except that it can be used with a greater degree of certainty on account of its uniform strength, with less inconvenience to the patient because of the elimination of irritating and inert substances found in other preparations, and, since it is sterile, with less danger of infection.

Veratrone has been employed in several hospitals in the treatment of various diseases, and has been found to produce the desired therapeutic effects. It has been employed particularly in the treatment of eclampsia, and is looked upon with especial favor by those employing it. The report of Dr. E. L. Hunt, of the Worcester City Hospital, Worcester, is typical of several, received:

"You will perhaps recall that about seven months ago you sent for trial a preparation of veratrum viride, containing 25 per cent of the fluid extract preserved in chloretone for hypodermic use.

"We have had opportunity to use the preparation in several cases of puerperal eclampsia and one of severe uremia in acute nephritis, in all of which convulsions ceased as soon as the patient reacted to the drug—*i.e.*, after the pulse fell to 90 per minute or below, our aim in its administration being to keep pulse below 70.

"Your preparation in our experience has shown excellence in the following respects:

"1. It has so far shown no deterioration on keeping, hence is of uniform activity.

"2. Its subcutaneous use is not followed by local irritation.

"3. A smaller dose than of the official tincture seems to be efficient, probably due to its less irritating character.

"So far then as our still limited experience goes, the preparation should commend itself to all practitioners who believe in the veratrum treatment of eclampsia. It seems very desirable to have a preparation suitable for hypodermic use, and your preparation seems to be a step in that direction.

"I make the above statement by permission of Dr. Wheeler, Visiting Obstetrician of the Hospital."

CONCLUSIONS.

Veratrone is a stable, uniformly active, non-alcoholic, but slightly irritating, sterile preparation of veratrum viride, of one-fourth the strength of the U. S. P. fluid extract. It is always ready for use without dilution, and can be administered orally or subcutaneously for the prompt control of sthenic respiratory and circulatory symptoms, as in beginning pneumonia, eclampsia, etc.

EXPLANATION OF TRACINGS.

The tracings are to be read from left to right.

At the bottom the broken line records seconds or minutes. Immediately above are the blood-pressure tracings taken directly from the carotid artery.

The upper tracing in experiment No. 7 is taken directly from the ventricle of the heart by means of the myocardiograph (see Fig. 1), the down stroke of the tracing being made by the systolic movement of the heart, and the up stroke by the diastolic movement.

In experiments No. 8 and No. 9, the upper tracings show the respiratory movements, as recorded by an electrical signal, which makes a down stroke at each inspiration.

APPENDIX D

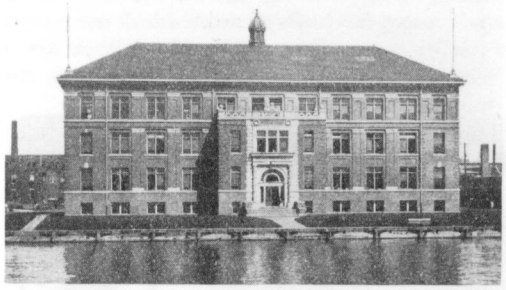
FIRST RESEARCH BUILDING IN AMERICAN PHARMACEUTICAL INDUSTRY

This is one of the best available sets of pictures and description of Parke-Davis' first research building (1902). A brief description is also given of the general type of work done in each area of the new building.

A HOME OF SCIENCE.*

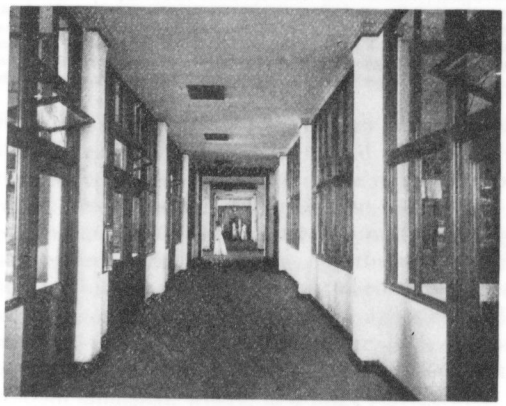
The New "Laboratory of Medical Research" of Parke, Davis & Co.—An Illustrated Description of its Chief Features—The Elaborate Means Employed for Conducting Biological and Chemical Investigations.

Pharmacists from all over the United States have journeyed to Detroit during the last year to inspect the new Research Laboratory of Parke, Davis & Co. The marked interest which has thus been shown, and the deep significance to pharmacy which lies behind



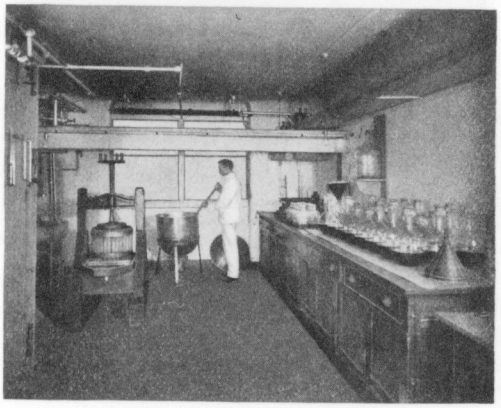
The building itself. This splendid structure stands directly upon the shore of the Detroit River. It is 160 feet long, 60 feet deep, and three stories high, with a basement under all. The construction is thoroughly fireproof. The walls are built of hard paving brick with stone trimmings; the floors are made of steel and cement, and the roof is tiled.

the establishment of this elaborate home of medical and pharmaceutical science, warrant the BULLETIN in bringing the building to those of its readers who have been unable to visit it in person.



Biological Department: A view down the right corridor of the first floor. Operations in the various laboratories on either side may be clearly seen by the visitor as he passes along with the guide who points out the various features of interest. At the remote end of the corridor is a doorway leading into the anteroom of the cold storage chamber, where a temperature of about 2° C. is constantly maintained.

The chief features of the laboratory are indicated by the pictures, and by the textual descriptions which accompany them; we shall for the most part let these tell their own story. It may be said at the outset, though, that in this one building are centralized all the appliances for scientific work which modern skill and experience have developed. The leading laboratories of Europe and America, private and public, were searched for ideas in laboratory construction, in apparatus, in advantages of every kind; and the net result of this search was brought together in a building which will be a model for many years to come.



Biological Department: The laboratory for the preparation of beef bouillon, which is used as the culture medium in the process of manufacturing antitoxins. The bouillon is prepared in the steam-heated copper kettle in the background. Upon the left is the apparatus for expressing the fluid from the beef. On the right are freshly charged flasks, stoppered with sterile cotton, while on the extreme left edge of the picture may be seen the corner of an autoclave in which the flasks and their contents are sterilized before being sent up to the planting room; in the latter room the germs are grown in the medium, and the toxins which they develop are injected into the horse for the purpose of developing the *anti*toxin.

TAKING A TRIP THROUGH THE BUILDING.

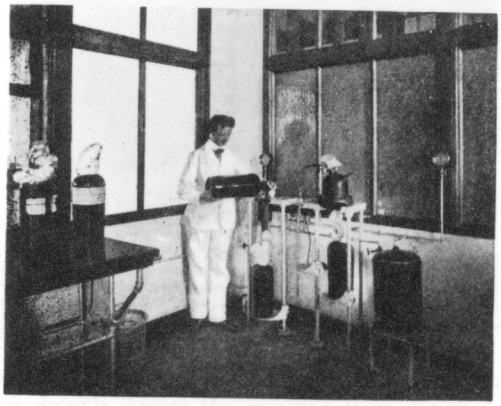
The reader will get a clearer idea of the laboratory if he imagines himself to be taking a trip through it in reality. The building itself, shown in our first illustration, is favorably located directly on the river front, a block distant from the main portion of the manufacturing plant in the rear. Let the visitor suppose, then, that he is walking up the front steps seen in the first engraving. He at once finds himself in a wide, open hall; from this corridors run to

* Published in: Bulletin of Pharmacy, 17 (November, 1903) pp. 456-459.

the right and to the left, and straight in front is a double iron stairway leading to the floors above.

THE FIRST FLOOR: BIOLOGICAL PRODUCTS.

This first floor is devoted to the biological products of the house. As we walk down the right corridor we see rooms in which the various toxins are prepared for injection in the horses and other animals over in the biological stables. In one room, for instance, the germs are planted in the media contained in flasks; another serves as an incubator for keeping the flasks warm to allow the germs to grow; in still another the toxins which these germs have thus developed are separated from the liquid by

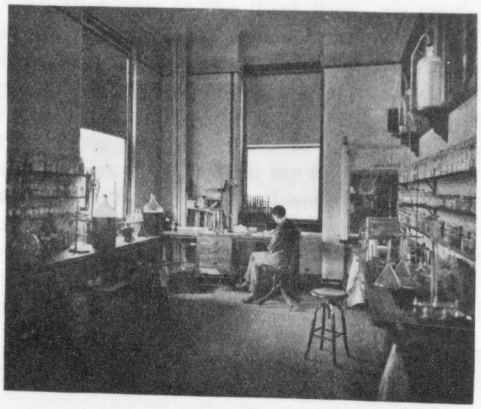


Biological Department: After the horses have undergone treatment with the toxin until they are immune, the blood is drawn, and the clear serum containing the antitoxin is separated from the clot and siphoned off into sterilized glass tubes. These are removed to the laboratory, and the serum is then passed under pressure through sterile porcelain filters, in the manner shown above, after which it is tested and bottled ready for the market.

filtration; and so on through many others. Down the left corridor, on the other hand, the visitor sees rooms, separated from those of the right corridor to avoid any possible contamination, in which the serums and vaccines, brought from the biological stables in crude form, are put through the final stages of manufacture and purification—rooms where the serums are filtered through sterilized filters or porcelain cylinders under high pressure, where the vaccine is ground with glycerin into a smooth emulsion, where, in a huge refrigerator, this emulsion is placed to "ripen" for several weeks, and where the products, finally complete, are put in bulbs and tubes, labeled, and prepared for the market.

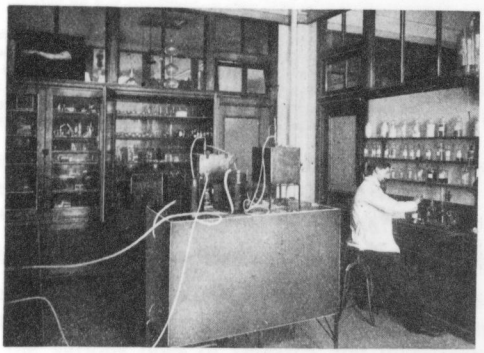
THE SECOND FLOOR: BIOLOGICAL RESEARCH.

Ascending the broad double staircase now, we come to the second floor, occupied by the Department of Experimental Medicine. A long corridor runs from end to end of the building, and on either side of it are numbers of elaborately equipped little laboratories for work in bacteriology, physiological



Laboratory of Pharmacology on the Second Floor: This is a view of one of the rooms in which the physiological assay of drugs is performed. These include such important extracts as digitalis, convallaria, strophanthus, Indian cannabis, ergot, squill, aconite, etc., and such active principles as digitalin, strophanthin, and others that cannot be assayed chemically, but for which a reliable standard of strength is urgently demanded by the medical profession. A great variety of animals are used in this work; these are conveyed directly to the laboratory by a small elevator that communicates directly with a vivarium in the basement.

assaying, animal chemistry, and pharmacology. A large and well-trained staff of scientific specialists is constantly at work here striving to improve existing pharmaceutical, chemical, and biological products, and to bring new ones forth, in order that dreaded

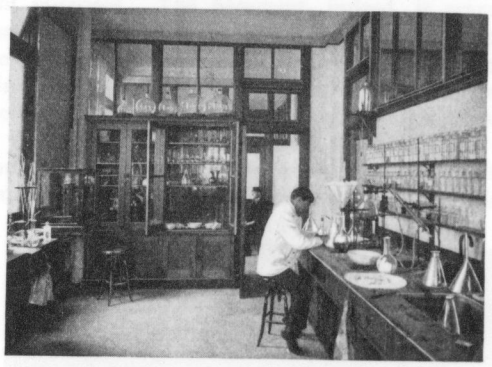


A Room for Research in Bacteriology. This is one of several laboratories in which bacteriological work is being done by specialists with a view to discovering agents and methods which will do for other contagious diseases what antidiphtheritic serum has done for diphtheria, or vaccine virus for smallpox. The large apparatus shown in the center of the room is an incubator, and on top of it are two additional incubators, each being kept at a special temperature for a particular purpose. At the left is a wall case filled with glass apparatus elaborate in design and costly in character. Glass partitions at the top of the side walls permit the equal diffusion of light—a feature which is very essential.

diseases and epidemics may be robbed of their terrors.

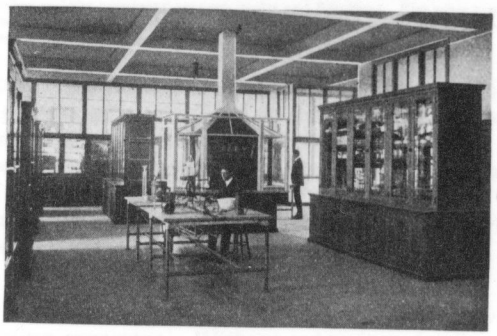
THE LIBRARY AND HERBARIUM.

It should be said that the library of the Research Laboratory is located also on the second floor. A well-lighted and large room is devoted to it directly in the center and in front, and this is supplied with reading tables and other conveniences. Two additional rooms are required for the overflow—more



A Room for Research in Organic Chemistry: being one of several rooms where such problems are worked out as pertain to new synthetic products and the like, chloretone being a marked example. This and the two preceding views were taken on the second floor—a floor given up to the Department of Experimental Medicine, and containing 16 such laboratories, each of which is 14 by 23 feet in size.

than 6000 volumes being comprised in the collection. And directly across the corridor from the library, and facing the rear, is the herbarium of 30,000 specimens—one of the most complete in America, representing the flora of every country on the globe. On the second floor, too, and flanking the library at



The Analytical and Experimental Department in Chemistry on the Third Floor: This large and beautifully lighted and furnished apartment occupies the upper story of the Research Laboratory. It has a floor area of nearly ten thousand square feet. In the foreground is a work-table described in the text under the next view. To the right is a handsome quartered-oak cabinet filled with glittering apparatus; a similar cabinet may be seen in the distance, while beyond the glass partition, in the background, is the Laboratory of Experimental Pharmacy.

either side in the front of the building, overlooking the river, are the offices of the two prominent directors of the biological departments.

THE THIRD FLOOR: THE ANALYTICAL DEPARTMENT.

Ascending now to the third floor, we reach the department which seems a little more familiar to the pharmacist. This is occupied by the analytical and experimental departments in chemistry. Several of the engravings show views of this floor, and it does not therefore seem necessary to add much by way of description. Suffice it to say that on one side are examined and tested the chemicals purchased or manufactured for use in the preparation of the firm's products, and here also are assayed the finished products themselves. This in general comprises the routine work of the analytical department; and it is

Analytical and Experimental Department: To the right may be seen a number of "working sections," each 14x15 feet in extent and separated from one another by low partitions—a plan that affords the necessary isolation for individual work and yet does not interfere with lighting, heating, and ventilation. In the foreground is a large work-table of iron with alborine-stone top. This table, as well as those in the working sections, is fitted with hot and cold water supply, steam, compressed air, mechanical vacuum, gas, and water at high pressure for use with the aspirator pump. To the left may be seen a large hood of glass and iron, fitted with steam and sand baths, with special provision for ventilation.

done on the right half of the floor in the compartments shown in one or two of the pictures.

On the other side of this third floor is

THE EXPERIMENTAL DEPARTMENT IN CHEMISTRY.

Here likewise, as on the second floor, a corps of chemical and pharmaceutical specialists are engaged in the various lines of research and investigation, endeavoring to enrich pharmacy and medicine by perfecting old remedies and bringing such new ones forward as will be real and necessary additions to the materia medica. A dark-room for polariscopic and spectroscopic work is situated near the center of this department, and rooms are also set apart for

combustions, glass-blowing, and the generation of offensive gases. A model balance room, located on this floor, is shown in one of our pictures.

AN INTERESTING BASEMENT.

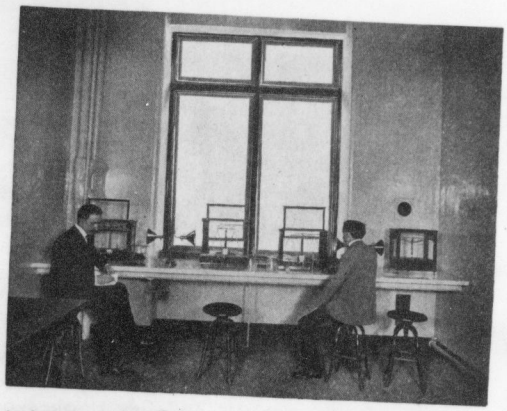
We have now made a hurried visit to the three main floors of the building, but in reality there are two additional floors, and both of them serve important purposes. The basement, indeed, is scarcely less interesting than the main floors. In addition to the heating and ventilating apparatus which it contains, there are modern machines for supplying compressed air, vacuums, and water under high pressure to the work tables throughout the building. An improved refrigerating apparatus supplies arctic-zone coolness to the refrigerators on the various

Analytical and Experimental Department: In each working section are two large windows through which pours a flood of light that is diffused by reflection from the white adamantine walls. Ample cabinets containing shelving and drawers are provided, with about thirty-five linear feet of table surface and the necessary reagent racks and furniture. The table tops are constructed of maple, laid on in strips, then bolted together; the whole being stained black and finished with paraffine.

floors. Then there are the several means of sterilizing flasks, glassware, and other material, including a steam autoclave; and at one end of the basement are the "vivaria"—rooms where are kept a small supply of the live animals used on the floors above for purposes of experimentation and physiological assay.

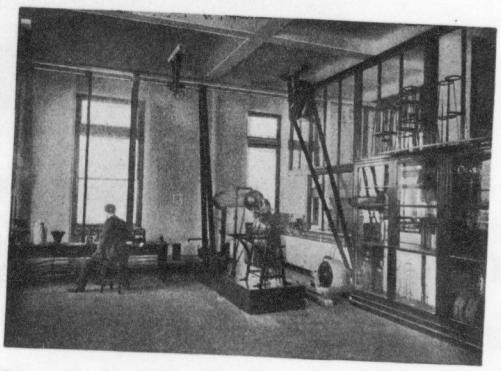
FINALLY—THE ATTIC.

In the attic, finally, is another portion of the ventilating apparatus. Without going into details it is sufficient to say that fresh air is forced into each room by a large fan in the basement, and drawn out by a large fan in the attic. The building is heated by steam delivered under high pressure from the central power-plant of the establishment, through a conduit 700 feet long. It is carried directly to the attic, where the pressure is reduced to one atmosphere, and the steam passed through pipes to radiators in the rooms below. The radiators are used only in the coldest weather, as the fresh air supplied through the conduits is usually sufficiently warm to make the



Analytical and Experimental Department—The Balance Room: The principal feature of this room is a shelf of polished Italian marble, fourteen feet long, two and one-half feet wide, and two inches thick, supported by iron beams set in the outer wall of the building. This excellent arrangement prevents vibration, as contact with the inner walls or floor of the room is entirely avoided.

rooms comfortable. It is an interesting and suggestive fact that there are several miles of piping in this building—a statement which indicates at once the size of the Research Laboratory and its completeness of equipment.



Laboratory of Experimental Pharmacy: This fine, well-lighted room is 20x60 feet in size. It is equipped with large pieces of apparatus, including drug mills, ointment and mass machines operated by electric power. A small steam vacuum pan may be seen in the center of the picture. In other parts of the room, not shown in the engraving, are percolators, evaporating pans, and refrigerating apparatus of the most convenient kind, and sinks and closets for washing and drying apparatus.

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