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THE EMERGENCE OF COOPERATIVE RESEARCH BETWEEN AMERICAN UNIVERSITIES AND THE PHARMACEUTICAL INDUSTRY, 1920-1940

BY

JOHN PATRICK SWANN

A thesis submitted in partial fulfillment of the requirements for the degree of

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PART I

INTRODUCTION TO COLLABORATIVE RESEARCH

CHAPTER 1

INTRODUCTION

Cooperative biomedical research between universities and industry in America emerged as a general movement between the two World Wars. The purpose of this study is to explore and interpret how and why this research developed, and to assess the significance of cooperative research from the standpoint of the university, the commercial organization, and therapeutics. "Research," as defined in the Oxford English Dictionary, and assumed throughout this study, is "a search or investigation directed to the discovery of some fact by careful consideration or study of a subject." The essence of this definition is that research is a deliberate endeavor to uncover new knowledge, or new interpretations of existing knowledge. A literature review of a subject, for example, is not research as defined above; its purpose is not to discover new knowledge, but to summarize what is already known about a topic. The molecular modification of a drug, on the other hand, is research, because this is a search for a new fact--in this case, a new drug. Research is by no means the exclusive pursuit of scientists, no more than knowledge itself is restricted to sciences. History, music, philosophy, sociology, art, economics, and other fields depend on research for their progress, too.

This project focuses on the history of scientific research, in particular the interactions relevant to biomedical research between two major estates of science in the United States, universities and industry. Since my emphasis is on research in the life sciences,

medical schools and the pharmaceutical industry receive primary consideration, although I mention other academic settings for biomedical sciences, such as departments of chemistry and (to a lesser extent) pharmacy schools. While the project is national in scope, a comprehensive investigation is unfeasible, at least for the purposes of a dissertation. Hence, I have restricted this study in some ways to maintain a manageable investigation in terms of limited time and space. These restrictions should not affect the accuracy of my interpretations, although only continued research in this area can substantiate this.

In the first place, I discuss in detail only the 1920s and 1930s. That collaborative research existed prior to this era, and that it proliferated from the 1940s onward, is uncontestable. But collaborative biomedical research sprouted as a systematic endeavor in America between World War One and World War Two. We can trace only scattered instances of collaboration prior to World War One, and after World War Two collaboration among the leading pharmaceutical firms and universities in general was a fait accompli. Second, the biomedical sciences encompass many fields, several of which are mentioned in this project (e.g., mycology, bacteriology, hematology, and neurology), but the weight of this study concerns pharmacology and chemistry, particularly medicinal chemistry. Pharmacology and chemistry were crucial to drug development in the period between the wars. Chemistry was important for synthesizing new drugs and isolating natural products such as insulin, liver extracts, and vitamins. Pharmacology was useful for designing new drugs for possible synthesis on the basis of anticipated

therapeutic action, and for testing experimental drugs in the laboratory. Chemistry and pharmacology were the most frequent foci of research interactions during this period.

Finally, I employ a series of representative case studies to illustrate the growth of collaborative research. I discuss three ideal typologies of cooperation, i.e., how the two sides worked together, in which I call upon numerous leading pharmaceutical firms and scientists representing many of the major research universities across the country as examples. Among the pharmaceutical companies, I emphasize Abbott Laboratories of North Chicago, Eli Lilly and Company of Indianapolis, Merck and Company of Rahway, New Jersey, Parke, Davis and Company of Detroit, and E. R. Squibb and Sons of New York. Among universities, scientists from Harvard, Illinois, Pennsylvania, Rochester, Toronto, Virginia, and Wisconsin receive much of the attention in this study. With the exception of perhaps one or two of these universities, the firms and institutions above occupied the upper echelons in terms of research orientation in the pharmaceutical industry and academe during the 1920s and 1930s.

This work is divided into four parts, each comprised of at least one chapter. Part I is a general introduction to collaborative research between industry and academe. Chapter 2 discusses the evolution of biomedical research in America, and the growing interest of various industries in research in general. Essentially, collaborative biomedical research awaited the emergence of biomedical sciences in America, and the awareness among industrial concerns that success was a function of their cultivation of research. Many biomedical sciences

established a foothold in American universities by the late 19th century. By the early 20th century, an increasing number of chemical, pharmaceutical, electrical, communications, and petroleum firms established research laboratories. World War One fueled both an interest among companies in establishing in-house research programs, and an interest among universities and firms in linking their intellectual, technical, and economic resources. A few pharmaceutical companies, most notably Parke-Davis and the H. K. Mulford Company of Philadelphia, were among the first American firms to entertain an interest in research of both an in-house and collaborative nature--as early as the 1890s. However, pharmaceutical firms, like companies in other industries, carried out joint work with academe on an ad hoc basis. Industries and academe did not pursue collaborative research systematically until after World War One.

Chapter 3 lays out the context for the following Parts by discussing general trends in the emergence of cooperative biomedical research. Cooperative research faced some formidable barriers that delayed its growth as a general movement in the United States. On one hand, biomedical scientists in universities had developed a mind set by the late 19th century by which many researchers were disposed to avoid contacts with drug companies. Their emphasis on fundamental research--research for its own sake, to contribute to the sum knowledge in a field--and their traditional deprecation of the patenting of medical discoveries imbued many academic biomedical scientists with a tainted image of the drug industry. Industry itself contributed to this image through questionable trade practices. However, some of the

leading pharmaceutical firms eventually helped erode this image during the 1920s and 1930s, by developing in-house research programs, by hiring prominent scientists from academe as researchers and research directors, by establishing special institutes and laboratories devoted to research, and by fostering at least some fundamental work in industry. Consequently, companies and academic scientists developed increasingly frequent research contacts, and by the early 1940s some firms had devised elaborate networks to maintain connections with university workers.

From the standpoint of the collaborators, joint work was a symbiotic arrangement. Companies with fledgling in-house research programs had to maintain open channels with universities to remain at the cutting edge of research. Even firms with established programs could not possibly cover every field of study, so they too depended on academic workers in some ways. University researchers in the interwar period needed to find support for their research programs at a time when funds from private foundations were gradually dwindling, and when the federal government had not yet initiated its mega-support of research in academe. Companies were a source of financial support for academic scientists, and they were increasingly a source of intellectual support as well, as more and more scientific talent moved into industry. From the standpoint of public health, collaborative efforts produced numerous valuable therapeutic agents, such as hormones, vitamins, anticonvulsant drugs, anesthetics, sedatives, chemotherapeutic agents, and other drugs. Without collaboration, the introduction of many of these drugs would have been delayed, and perhaps never have

come about.

This is not to say that cooperative research lacked any disadvantages. For example, the attraction of funding probably led more than a few academic scientists to focus on (industrial) problems in which they otherwise had little or no interest. Also, university workers and companies often entered into exclusive arrangements, whereby the collaborating firm had a monopoly on any discoveries made by the academic researcher. Arguably, such exclusive arrangements could inflate drug prices.

Parts II, III, and IV address typologies of collaborative research, with several examples. I do not contend that these are the only typologies; rather, these are the most obvious typologies I have been able to cull from my research so far. Each Part includes an introductory section which characterizes the typology and presents a few examples of the typology (in addition to the detailed chapters) in brief. Part II discusses the general consultantship, as exemplified principally by the relationship between pharmacologist Alfred Newton Richards of the University of Pennsylvania and Merck and between chemist Roger Adams of the University of Illinois and Abbott. In this typology, a single university scientist counseled a firm on a host of topics related to the broad development of a company's research programs. The general consultant advised the firm on his personal specialty and on several other areas, such as general company research policy, affairs requiring a liaison between the company and the academic community, and managerial aspects of the company's operations. Such consultants typically served their firms over many years, and

became so intimately involved in the internal affairs of a company that they could eventually become members of the company's board of directors. Richards and Adams each acted as general consultants to their firms for thirty years or longer, and each served on the board for several years.

Part III discusses a different breed of consultant, the specialist-consultant. The interactions of two pharmacologists at the University of Wisconsin--Arthur Loevenhart and Arthur Tatum--with a number of drug companies illustrate this typology, as do other examples mentioned in the introduction to Part III. Unlike the general consultantship, the specialist-consultantship actually involved interactions of one or more university workers with several companies, on a considerably narrower basis. The specialist-consultant's contact with companies rarely trespassed beyond his sphere of scientific expertise. Typically, the company engaged this consultant (often through fellowships or grants-in-aid) as an expert in a particular branch of chemistry, pharmacology, microbiology, or some other field.

Part IV deals with another typology of cooperative research, the specific project collaboration, in which a university group and a single pharmaceutical firm cooperated for the express purpose of developing a specific therapeutic agent. Once they accomplished their task, the two sides terminated the collaboration. I discuss some of the problems that could arise in this typology, and how other project collaborations avoided these problems, in the cooperative ventures between

1) Lilly and workers at the University of Toronto on insulin,

2) Harvard scientists and Lilly on a liver extract for pernicious

anemia, and 3) Lilly and researchers at the University of Rochester on a liver extract for secondary anemia. Finally, Chapter 8 concludes this study by briefly examining the continued interest in collaborative research today.

The historical literature lacks any kind of synthetic treatment of cooperative biomedical research as an entity all its own, even though it clearly involved circumstances unencountered in research contained within academe or industry, and even though it had a significant impact on therapeutics in the 20th century. Some secondary works on the history of biomedical research and the history of the pharmaceutical industry have been useful for this project. However, the primary resources for this study were manuscript collections of pharmaceutical firms and the collected papers of scientists who worked with industry. The latter was a particularly important resource for information on firms, since few drug companies maintain archives, and many of those that do retain records do not necessarily permit outsiders to make use of them. Ample manuscript sources existed to relate in detail several case studies illustrating the emergence of cooperative research, and to convey general trends in the growth of this type of research. Occasionally, when manuscripts did not shed sufficient light on an issue, I was able to make use of several interviews of collaborating academic and industrial scientists. These helped fill in some details lacking in the published and unpublished record. While the historian of the 20th century does not have as broad a perspective of his subject as the historian of earlier periods, the former sometimes has the enviable opportunity to meet with those who helped shape

his subject.

This project also relied, to a somewhat lesser extent, on patents and published scientific articles. Both were indispensable sources of information on the joint research per se. A history of biomedical research must utilize research publications; patents are a useful source as well. In the first place, they often relate the highlights of the work in a way intelligible to the nonscientist. Also, patents can be the source of disagreements and controversy within the academic and industrial communities, and between the two sides. Although it is impossible to avoid technical material in a work of this nature, I have tried to convey such material in a way understandable to a reader with little scientific background.

CHAPTER 2

BACKGROUND: THE EMERGENCE OF BIOMEDICAL RESEARCH AND INDUSTRIAL RESEARCH IN AMERICA

Development of the Biomedical Sciences

Cooperative biomedical research did not emerge on a broad scale in the United States until the 20th century. Indeed, the pharmacomedical sciences themselves did not emerge as distinct disciplines until the 19th century. The modernization of chemistry, for example, began under Lavoisier in the late 18th century. Alkaloidal chemistry arose in the early decades of the 19th century, principally through the efforts of Sertürner, Pelletier, and Caventou, as did organic and biological chemistry under Chevreul, Wöhler, Liebig, and other pioneers. Structural organic chemistry awaited the work of Kekulé, van't Hoff, and Le Bel in the middle decades of the 19th century. Other disciplines vital to pharmacomedical research can be traced to 19th-century Europe as well. Physiology flourished under many British (e.g., Sharpey and Foster) and Continental (Müller, Helmholtz, du Bois Reymond, Ludwig, Bernard, etc.) workers. Modern experimental pharmacology was a product of the 19th century too, principally through the efforts of Magendie, Bernard, Buchheim, and Schmiedeberg. Bacteriology emerged late in the century, following the discoveries of Pasteur,

Koch, and Behring.[1]

The major biomedical disciplines did not find a niche in American institutions until the last quarter of the 19th century. The social circumstances that facilitated the rise of these disciplines in Germany, such as a strong national system of secondary schools (the German Gymnasien), a widespread belief that higher learning was part of a nationalistic identity, and the active involvement (if not control) of the federal government in the policies and budgets of universities, were lacking in the United States.[2] Somewhat more direct influences also account for the delayed emergence of biomedical disciplines in America. For example, those within and outside of the medical profession who subscribed to antivivisectionist sentiment questioned the value of experimental biomedical research. The antivivisectionist movement was much stronger in Britain than the United States, but it nonetheless led several states to pass laws hindering vivisection in the late 19th century, such as the New Jersey antivivisection act of 1880. Such opinion was a source of frequent concern for many

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[1]Among the better introductions to these developments are Aaron Ihde, The Development of Modern Chemistry (New York: Harper and Row, 1964; New York: Dover, 1984); Karl E. Rothschuh, History of Physiology, trans. and ed. Guenter B. Risse (Huntington, N.Y.: Robert E. Krieger, 1973); B. Holmstedt and G. Liljestrand, eds., Readings in Pharmacology (Oxford: Pergamon Press, 1963; New York: Raven Press, 1981); and Hubert A. Lechevalier and Morris Solotorovsky, Three Centuries of Microbiology (New York: McGraw-Hill, 1965; New York: Dover, 1974).

[2]Robert E. Kohler, From Medical Chemistry to Biochemistry: The Making of a Biomedical Discipline (Cambridge: Cambridge University Press, 1982), 94.

biomedical scientists.[3] Also, the long-standing conflict between laboratory workers and clinicians impeded a smooth and rapid transfer of German biomedical science to the United States, as well as other countries.[4] However, American universities, medical schools, and agricultural colleges began fostering research in the biomedical sciences once biochemists like Russell Chittenden, physiologists like Henry Pickering Bowditch, and pharmacologists like John Jacob Abel returned from periods of study in Germany. From the 1870s on, a growing group of the better universities, including Johns Hopkins, Harvard, Pennsylvania, Michigan, and Yale, established centers for biomedical research.

Harvard Medical School established the first laboratory for experimental physiology in America in 1871. Henry Pickering Bowditch, who recently had returned from a period of study in Europe under physiologists Claude Bernard and Carl Ludwig, headed the new laboratory.

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[3]Richard H. Shryock, American Medical Research: Past and Present (New York: Commonwealth Fund, 1947), 68-69. On the antivivisectionist movement in Britain, see Richard D. French, Antivivisection and Medical Science in Victorian Society (Princeton: Princeton University Press, 1975).

[4]Ibid., 70-72; Gerald L. Geison, "Divided We Stand: Physiologists and Clinicians in the American Context," in The Therapeutic Revolution: Essays in the Social History of American Medicine, ed. Morris J. Vogel and Charles E. Rosenberg (Philadelphia: University of Pennsylvania Press, 1979), 67-90; Russell C. Maulitz, "'Physician Versus Bacteriologist': The Ideology of Science in Clinical Medicine," ibid., 91-107; and John Parascandola, "The Search for the Active Oxytocic Principle of Ergot: Laboratory Science and Clinical Medicine in Conflict," in Neue Beiträge zur Arzneimittelgeschichte: Festschrift für Wolfgang Schneider zum 70. Geburtstag, Veröffentlichungen der Internationalen Gesellschaft für Geschichte der Pharmazie, n.s. vol. 51, ed. Erika Hickel and Gerald Schröder (Stuttgart: Wissenschaftliche Verlagsgesellschaft, 1982), 205-227.

Five years later, in its inaugural year, Johns Hopkins appointed the Michael Foster-trained physiologist Henry Newell Martin to its biology chair. When William Henry Howell succeeded Martin in 1893, the name of the chair changed from "biology" to "physiology," reflecting physiology's increasing independence with respect to general biology. The University of Pennsylvania and the University of Michigan also opened laboratories of physiology in the 1870s.[5]

Modern biochemistry in America evolved from several sources. Russell Chittenden organized the first laboratory for experimental physiological chemistry in the Sheffield Scientific School at Yale in 1874. After spending a year of postgraduate work at Heidelberg, because he felt that ". . . in 1878 any American student desirous of making progress in physiological chemistry had no recourse other than going to Germany for the knowledge and experience he needed to help him on his way,"[6] Chittenden moved into the first chair of physiological chemistry in the United States in 1882. His department at Yale was the dominant force in biochemistry for the next three decades. Although the Sheffield School had no formal clinical connections, modern biochemistry also had strong roots in medical schools. However, by the 1890s only the better medical schools, such as Hopkins,

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[5]John Harley Warner, "Physiology," in The Education of American Physicians: Historical Essays, ed. Ronald L. Numbers (Berkeley: University of California Press, 1980), 60-63, and John F. Fulton, Physiology, Clio Medica: A Series of Primers on the History of Medicine, ed. E. B. Krumbhaar, vol. 5 (New York: Paul B. Hoeber, 1931), 102-107.

[6]Russell H. Chittenden, The Development of Physiological Chemistry in the United States, American Chemical Society Monograph Series (New York: Chemical Catalog, 1930), 27.

Pennsylvania, and Michigan, had a four-year course that permitted the establishment of preclinical disciplines like biochemistry. Medical schools, in general, did not emerge as major centers for training and research in biochemistry until the first two decades of the 20th century. At this time, more and more institutions followed the sweeping reforms in medical education that, among other things, emphasized the importance of a solid grounding in biochemistry and other sciences in the training of physicians. Finally, research in nutritional chemistry in agricultural experiment stations--particularly those stations in Wisconsin and Connecticut--contributed significantly to the knowledge base of modern biochemistry by the late 19th and early 20th centuries.[7]

Just as Chittenden was a leader of American biochemistry, John Jacob Abel was a leader of American pharmacology. Abel transformed the study of drugs in American medical schools from a didactic and descriptive exercise to a critical investigation of the action of drugs on tissues, on the basis of modern, experimental chemistry and physiology. He had spent six years in Europe, including study under Oswald Schmiedeberg, before returning to the United States to hold the first chair in modern experimental pharmacology at Michigan, in 1891. Abel moved to Hopkins two years later, where he established a center for research and training in pharmacology. In addition, Abel had a prominent role in the formation of a national pharmacological society in

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[7]The definitive study of the development of biochemistry as a discipline is Kohler, From Medical Chemistry to Biochemistry. See also Chittenden, The Development of Physiological Chemistry, and Stanley Leonard Becker, "The Emergence of a Trace Nutrient Concept through Animal Feeding Experiments," Ph.D. diss., University of Wisconsin, 1968.

1908, and the establishment of a journal devoted to pharmacology in the following year.[8]

Insofar as the biomedical sciences emerged in America as functions of medical schools in the late 19th and early 20th centuries,[9] their disciplinary status was closely tied to the reforms in American medical education in this period, as mentioned above. Institutions in the upper echelons initiated reforms by the 1880s, and many of the rank and file medical schools joined in the reforms in the first two decades of the 20th century. The American Medical Association, the Association of American Medical Colleges, and a few private foundations, such as the Rockefeller and Carnegie Foundations, spearheaded these changes. In the first place, higher entrance requirements plunged medical school

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[8]John Parascandola, "John J. Abel and the Early Development of Pharmacology at the Johns Hopkins University," Bulletin of the History of Medicine 56 (1982):512-527; idem and Elizabeth Keeney, Sources in the History of American Pharmacology (Madison: American Institute of the History of Pharmacy, 1983); and David Cowen, "Materia Medica and Pharmacology," in The Education of American Physicians: Historical Essays, ed. Ronald L. Numbers (Berkeley: University of California Press, 1980), 95-121.

[9]For example, few university chemistry departments adopted biochemistry as a sister of organic, analytical, and other established fields of chemistry. Only a fraction of those departments that did offer biochemistry taught it in a satisfactory way--at least as far as medical schools were concerned. Abel opposed separate Ph.D. programs for pharmacology; he preferred that the pharmacologist have a solid training in chemistry and physics, prior to work leading to the medical degree. An alternative degree-granting source for pharmacology--schools of pharmacy--did not develop on a significant scale until the 1930s. See Robert E. Kohler, "Medical Reform and Biomedical Science: Biochemistry--A Case Study," in The Therapeutic Revolution: Essays in the Social History of American Medicine, ed. Morris J. Vogel and Charles E. Rosenberg (Philadelphia: University of Pennsylvania Press, 1979), 30; Parascandola, "Abel and the Development of Pharmacology," 523; and idem and John Swann, "Development of Pharmacology in American Schools of Pharmacy," Pharmacy in History 25 (1983):95-115.

enrollments. Consequently, schools had to align themselves with universities for economic support, since student fees were no longer sufficient to subsidize faculty salaries and expensive laboratory facilities. University administrations thus assumed many of the roles that medical faculties had formerly controlled, such as guidance over budgets, hiring, and other policy matters. Second, the traditional position of the faculty member as a part-time teacher and part-time outside practitioner (fees were inadequate for the faculty to rely on the former alone for support) changed, to the professor-researcher. In part, this was a move to accommodate the new scientific medicine. Finally, after 1890 an increasing number of medical schools expanded the curriculum to four years and instituted minimum requirements for admission--at least two years of college work. This elevated the M.D. to resemblance of a graduate degree, and allowed specialized study of preclinical biomedical sciences apart from clinical work. Thus, medical reforms in the late 19th early 20th centuries institutionalized biomedical sciences, enabling them to avoid purely service functions and flourish on their own as independent disciplines.[10]

The Rise of Industrial Research

The development of industrial research in America hinged on various factors. First, it depended on progress in the natural sciences. The 19th century was a period of considerable growth for physics,

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[10]Kohler, "Medical Reform and Biomedical Science."

chemistry, and biology. Synthetic organic chemistry, electricity and magnetism, and bacteriology, for example--the application of which established many industries on a solid, scientific basis--made great strides during the 19th century. Of course, research in different industries did not progress at the same rate, simply because the sciences supporting these industries did not develop at a parallel pace. But the chemical, electrical, pharmaceutical, petroleum, and other industries had a vast scientific base to draw on by the late 19th century. Second, an institutional network was necessary to facilitate the application of science. In the United States, such a network had been growing since the second quarter of the 19th century, through the founding of several schools of applied science and technology. Beginning with the Rensselaer Polytechnic Institute in 1825, such institutions were established in the 1840s (the Sheffield Scientific School at Yale and the Lawrence Scientific School at Harvard), 1860s (the Massachusetts Institute of Technology, the Columbia University School of Mines, and the Worcester Polytechnic Institute), and later in the century (e.g., the Case School of Applied Science and the Throop Polytechnic Institute (now the California Institute of Technology)). In addition to these private institutions, many government-supported schools of applied agriculture and mechanical arts arose in the second half of the century through the Morrill Land Grant Act of 1862, the Hatch Act (1887), and the second Morrill Act of 1890.

Finally, the development of industrial research depended on: 1) the ability of industrialists to recognize the importance of science, and how this could relate to the success of their companies,

and 2) the willingness of scientists to work on a full- or part-time basis with firms. American industrialists, to be sure, could draw on many precedents in modern history that illustrated the value of organized scientific research in industry: for example, the mobilization of French scientific resources in the late 18th century, which contributed significantly to military and communications technology; the application of science to improve optical technology, principally under Carl Zeiss in Germany; and most notably, the rapid growth of the German synthetic chemical industry in the final third of the 19th century, which gave birth to the modern industrial research laboratory. That industries were able to offer academic scientists higher salaries and better equipment than universities drew an increasing number of university scientists to industry, although some academic workers resisted these attractions (see Chapter 3).[11]

Until about the turn of the 20th century, American industrial research was generally the province of the lone scientist and inventor; occasionally, firms called on outside consultants for their expertise. Examples of the independent workers and consultants who developed innovations for various industries abound, throughout the 19th century.

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[11]Howard R. Bartlett, "The Development of Industrial Research in the United States," in Research--A National Resource, 2 vols., Report of the Science Committee to the National Resources Committee (vol. 1), Report of the National Research Council to the National Resources Planning Board (vol. 2) (Washington, D.C.: Government Printing Office, 1938-1941), 2:19-25; Kendall Birr, "The Roots of Industrial Research," in Harold Vagtborg, Research and American Industrial Development: A Bicentennial Look at the Contributions of Applied R and D (New York: Pergamon Press, 1976), 27-29; and George H. Daniels, Science in American Society: A Social History (New York: Alfred A. Knopf, 1971), 318.

The discoveries of several of these scientists revolutionized some industries. Benjamin Silliman, Jr., of the Sheffield Scientific School, examined petroleum samples from a Pennsylvania site for speculators in the 1850s. He found that one of the distillates could serve as an excellent and comparatively inexpensive illuminating agent--thus giving rise to petroleum refining. Soon after the Civil War John Wesley Hyatt, with formal background in chemistry, developed the versatile plastic, celluloid. In the late 1880s, Charles M. Hall discovered a commercially viable method to produce aluminum, which eventually benefited many industries. Other contributions by independent workers, such as those of Elias Howe to the textile industry and Alexander Graham Bell to communications, are too well known to recount here. The point is that industrial research, for the most part, was unorganized during the 19th century. Most industrialists believed that the manufacturer's job was to manufacture; new ideas to improve manufacturing could be purchased or otherwise appropriated. Typically, investors offered little support for research, until they had evidence that a worker's results indicated likely commercial application. While some highly successful results derived from these solitary researchers, by and large their work was inefficient, duplicative, and had little direction.[12]

There were some exceptional cases. For example, the Pennsylvania Railroad hired chemist Charles Benjamin Dudley as an analyst in 1875.

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[12]Bartlett, "Industrial Research in the United States," 25-34; Daniels, Science in American Society, 318; and Raymond F. Bacon, "Industrial Research in America," Scientific Monthly, 2 (1916):226-230.

On the basis of his analyses, Dudley developed specifications for many of the materials vital to Pennsylvania Railroad, including tallows used in locomotive cylinders, lard oil for signal lights, and the steel used to make the firm's rails. The value the company placed on Dudley's work can be seen in the growth of his laboratory at Pennsylvania Railroad, from about two untrained assistants when he accepted the position to nearly three dozen trained chemists when he retired. In 1834, physician-chemist Samuel Luther Dana established what was probably the first industrial research laboratory in America, for the Merrimack Manufacturing Company, a textile firm in Lowell, Massachusetts. Among his many contributions to Merrimack and the textile industry in general, Dana improved the processes of calico printing and the bleaching of cotton prior to printing. The most notable example of an organized industrial laboratory of the 19th century was Thomas Edison's facility at Menlo Park, New Jersey, established in 1876. While his accomplishments are too well known to repeat here, it is worth mentioning that the continuously high level of activity of his laboratory is partially explained by the dozens of workers Edison employed to design, build, and test apparatus.[13]

The modern industrial research laboratory emerged in America in the early 20th century. Prior to World War One, those industries born in the laboratory, and those firms big enough to afford research programs, were the first to establish research facilities:

It is significant that most of the early laboratories

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[13]Bartlett, "Industrial Research in the United States," 25-26, 29-31, and Birr, "Roots of Industrial Research," 31-32.

> appeared in industries such as electricity or chemicals. Not only were they relatively new industries, with no traditional inertia from the past, but in these industries there were large firms with sufficient financial resources and stability to support the laboratories; and a rapidly changing, competitive technology made successful research imperative for the sponsoring firm. Older industries, such as iron and steel, and those where no giants existed were relatively slow to bring science into their activities, and a great differential still exists.[14]

Firms from the chemical, pharmaceutical, electrical, and petroleum industries founded research laboratories in this period: General Electric, Bell Telephone, Parke-Davis, Du Pont, Westinghouse, Standard Oil and Eastman Kodak. World War One had a significant impact on the development of industrial research in the United States. New industrial research laboratories arose, and extant laboratories expanded, to replenish increasingly scarce imported commodities and to meet the technological needs of a wartime government.

Industrial researchers took part in many projects during the war. General Electric and Western Electric, for example, worked closely with university and government scientists in the development of an effective listening device for submarine detection. Industry also played an important part in the production of high-quality optical glass to replace the interrupted supply from German companies. The American chemical industry, Du Pont in particular, managed to alleviate shortages of many goods for which America had depended on Germany in the past. Chemical firms developed means to process naturally occurring nitrates--essential to explosives, and they produced synthetic materials used in smokeless powder. Pharmaceutical firms supplied

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[14]Daniels, Science in American Society, 319.

many Germany-controlled therapeutic agents during the war, such as anesthetics, sedatives, and antimicrobial drugs.

The pressing wartime needs called for emergency measures, which industry actively carried out. The Secretary of the Navy established the Naval Consulting Board in 1915 to help organize vital research. While the Board included some members from academe and government, most of its members were from industry. Although its major activity was the screening of inventions submitted by the public, the Board facilitated the involvement of major firms in such problems as submarine detection. Industrial researchers also worked on many of the problems which the National Research Committee organized. Overall, research-based mass-production came of age during the war, and a significant proportion of American industry thereafter increasingly manifested an interest in research.[15]

Industrial research grew significantly between the two World Wars. On the basis of the following tabulation, derived from fairly comprehensive surveys of all industries by the National Research Council, the interwar expansion of industrial research was only temporarily set back by the Depression. From the mid-1920s to World War Two, the total number of industrial laboratories more than doubled and

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[15]A. Hunter Dupree, Science in the Federal Government: A History of Policies and Activities to 1940 (Cambridge, Mass.: Harvard University Press, Belknap Press, 1957; New York: Harper and Row, Harper Torchbooks, 1964), 302-325; Bartlett, "Industrial Research in the United States," 35-37; and Birr, "Roots of Industrial Research," 32.

the total research staff tripled.[16]

Year	Laboratories	Research Staff
1927	1000	19,000
1931	1625	32,000
1933	1575	27,000
1938	1769	44,000
1940	2264	58,000

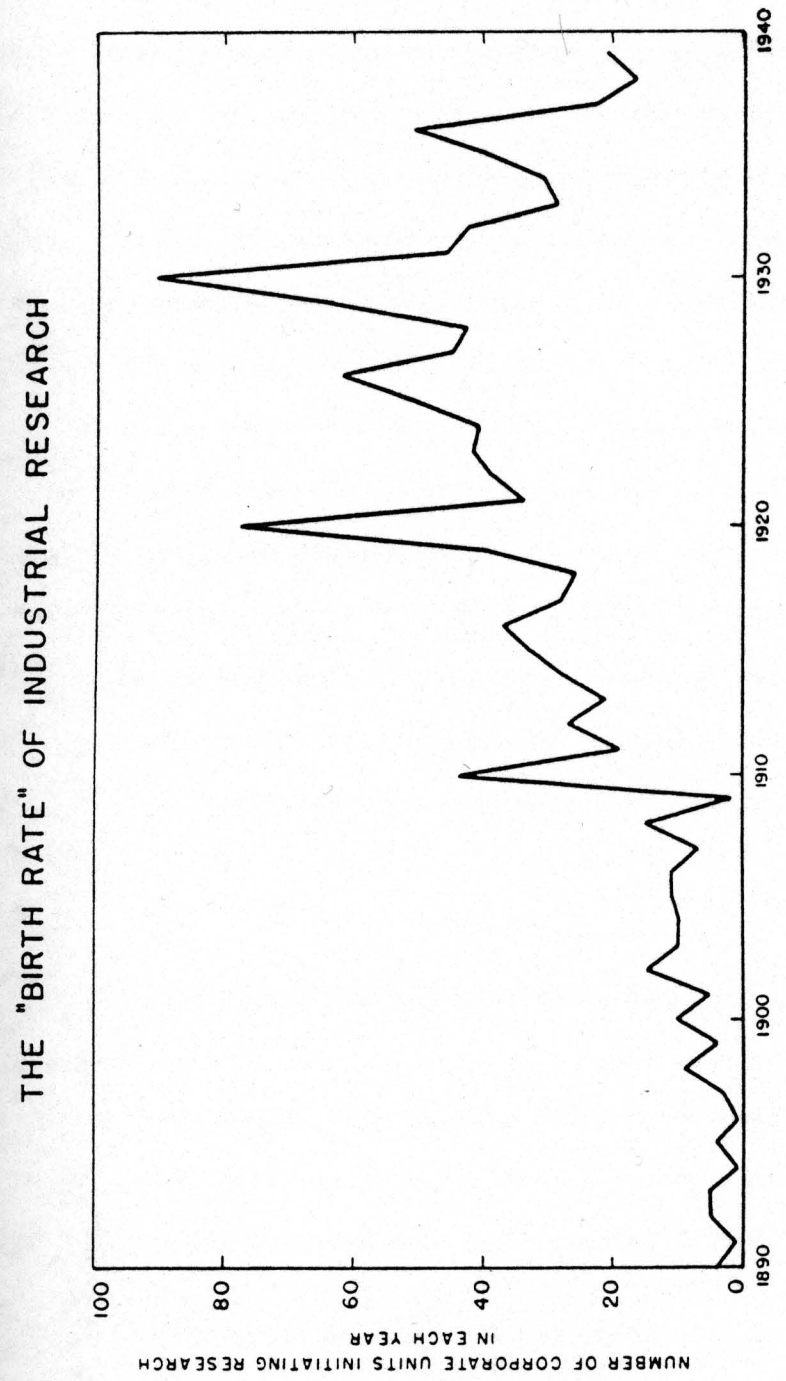
For comparative purposes, the change in total research staff for 200 companies existing throughout the period of these surveys was as follows: 1927, 10,000; 1931, 14,000; 1933, 11,000; 1938, 16,000; 1940, 18,000. The NRC surveys clearly suggest an overall growth of interest in research within American industry.[17] The number of large industrial research laboratories increased during the period between the

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[16]Clarence J. West and Ervye Risher, "Industrial Research Laboratories of the United States, Including Consulting Research Laboratories," 3d ed., Bulletin of the National Research Council, no. 60 (1927); Clarence J. West and Callie Hull, "Industrial Research Laboratories of the United States, Including Consulting Research Laboratories," 5th ed., ibid., no. 91 (1933); Callie Hull, "Industrial Research Laboratories of the United States, Including Consulting Research Laboratories," 6th ed., ibid., no. 102 (1938); idem, "Industrial Research Laboratories of the United States, Including Consulting Research Laboratories," 7th ed., ibid., no. 104 (1940); Birr, "Roots of Industrial Research," 40-41; and Franklin S. Cooper, "Location and Extent of Industrial Research Activity in the United States," in Research--A National Resource, 2:174 (Figure 44). Note that the tabulation includes consulting laboratories, although the majority of the data pertain to company laboratories. The National Research Council conducted earlier surveys of industrial research laboratories, but these were not as comprehensive as the 1927 and later surveys.

[17]Cooper, "Location and Extent of Industrial Research," 174 (Figure 44). These data should be qualified to the extent that it is difficult to identify, much less quantify, total research staff in a firm. Companies did not necessarily differentiate the functions of their technical staff and their research staff. For example, research could very well have been an occasional function of personnel who also had quite different responsibilities in the plant. This distinction is not clear in the National Research Council surveys. However, the surveys clearly indicate a trend of increasing research activity in industry between the two World Wars.

Figure 1. Graph of the "birth rate" of industrial research in the United States, showing the number of companies in all industries which established research as a recognized function in each year from 1890 through 1939 (from Research--A National Resource, 2:176).


THE "BIRTH RATE" OF INDUSTRIAL RESEARCH
NUMBER OF CORPORATE UNITS INITIATING RESEARCH IN EACH YEAR
0
20
40
60
80
100
1890
1900
1910
1920
1930
1940

wars. In 1921 only fifteen firms had research staffs of at least 50, but by the late 1930s this group swelled to 120 companies. A handful of these firms, representing one percent of all companies listed in the 1938 NRC survey, employed one-third of all research personnel by that year.[18] Disparities in the level of research activity also existed from industry to industry, as measured by the proportion of research personnel among an industry's total employees. The chemical (including the pharmaceutical) industry by far was the leader here, throughout the interwar period. Moreover, the same four industries--petroleum, rubber products, electrical machinery, and instruments--were consistently the most research intensive industries behind the chemical industry, from 1920 to 1940.[19] Thus, by the end of this period, research had become a function of much of American industry, although a small number of firms in the chemical, electrical, and other industries cultivated research much more intensively than the rest of industry.

Interactions between Academe and Industry

At the turn of the 20th century, some university scientists were acting as consultants to industry; by and large, however, the main means by which universities and industries maintained contact was

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[18]Bartlett, "Industrial Research in the United States," 38.

[19]David Charles Mowery, "The Emergence and Growth of Industrial Research in American Manufacturing, 1899-1945," Ph.D. diss., Stanford University, 1981, 120.

through graduates who had become industrial employees. As more and more firms developed an interest in research during the early decades of the 20th century, different avenues opened to foster links. The industrial fellowship was the most frequent source of contact. Chemist Robert Kennedy Duncan pioneered the systematic use of industrial fellowships in academe at the University of Kansas in 1907. The seriously inefficient state of American industry, which Duncan attributed to the failure of industry to make use of research, and the manufacturer's lack of experience in scientific research convinced the chemist to institute the research fellowships. Typically, the fellow, a graduate student working under the direction of Duncan, devoted nearly all of his time (with the exception of a few hours of teaching each week) to the fellowship research, for the full term of the contract (a minimum of two years). The stipend varied from fellowship to fellowship, from about $500-1500 per annum. Any discoveries became the exclusive property of the sponsor, but the firm usually had to pay the fellow a royalty of ten percent of the net profits on any marketed discovery. While the company had the right of approval over any publications stemming from the fellowship, the fellow had the right to use the work in a thesis or dissertation. At the expiration of the fellowship, the sponsor typically had some obligation to employ the fellow, for a minimum of three years. The chancellor arbitrated any differences between the firm and the fellow.[20]

Duncan's fellowships offered the firms research expertise at a

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[20]Robert Kennedy Duncan, "On Industrial Fellowships," Journal of Industrial and Engineering Chemistry 1 (1909):600-602.

fairly modest expense. From the standpoint of the fellow, it was a source of support both during and--if he made satisfactory progress on the fellowship--after his graduate studies. Duncan personally derived no material benefits from the fellowships:

> [The fellowship scheme] can only be carried out through a professor of industrial chemistry who regards it as a sacred trust. It is, therefore, necessary, positively necessary that the professor of industrial chemistry should, so far as any material sense is concerned, gain absolutely nothing, otherwise his donors would not trust him with the details of their secret processes, nor would his fellows trust him with their progress.[21]

By 1909 firms were supporting ten fellowships under Duncan, worth a total of nearly $11,000 annually in stipends (excluding any possible royalties). Duncan moved to the Mellon Institute of Industrial Research and School of Specific Industries at the University of Pittsburgh in 1911, where his system of industrial fellowships flourished. The value of the fellowships grew to about $40,000 in 1911 and $238,000 by 1918. In 1929, two years after the Mellon Institute had separated completely from Pittsburgh, 135 fellows were working on contracts worth a total of $700,000.[22]

Various other fellowship programs between universities and industry emerged about the time of Duncan's experience at Kansas. MIT, for example, established the Research Laboratory of Applied Chemistry in 1908. Research contracts between the Laboratory and industrial

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[21] Ibid., 602. Although Duncan personally felt industrialists would not trust him if he wanted to make some money, we will see many examples in Parts II, III, and IV of both academic scientists and industrialists who would take issue with such a belief.

[22] Ibid., 602-603, and Mowery, "Growth of Research in American Manufacturing," 257-258.

to the often narrow subject of a fellowship or grant--industry hired academic consultants for both narrow and broad problems. When Standard Oil of New Jersey decided to establish a research program in 1919, it hired physicist Robert A. Millikan of the University of Chicago and chemists Ira Remsen of Johns Hopkins and Warren K. Lewis of MIT for their expert advice. Roger Adams helped shape company policies through long-term consultantships at Du Pont and Abbott Laboratories.[25]

Universities, companies, and the federal government organized bodies to promote cooperative research between academe and industry. As mentioned above, MIT's Research Laboratory of Applied Chemistry stimulated interactions between that institution and various industries. The University of Washington instituted a Bureau of Industrial Research in 1916 "to provide industry with applied engineering skills and expertise on a consulting basis," and "to train engineers and, increasingly, Ph.D.'s in chemistry or physics for industrial research positions." The University of Oklahoma established a similar organization, the Industrial Research Department, in the following year.[26] Other bodies sought to stimulate cooperation on a wider basis. For example, the Engineering Foundation, which represented the research interests of civil, mechanical, electrical, mining, and metallurgical

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[25]Thackray, "University-Industry Connections," 220; D. Stanley Tarbell and Ann Tracy Tarbell, Roger Adams: Scientist and Statesman (Washington, D.C.: American Chemical Society, 1982); and Part II of this study.

[26]David C. Mowery, "British and American Industrial Research: A Comparison, 1900-1950," paper presented at the Anglo-American Conference on the Decline of the British Economy, Boston University, [August] 1983, 26.

engineering societies, sponsored numerous collaborative projects over many years in the 1930s. Also, academic and industrial researchers had many common interests in organizations like the American Chemical Society and the American Institute of Chemical Engineers.[27]

The National Research Council was particularly active in fostering cooperative research between universities and industry during the 1920s and 1930s. The National Academy of Sciences created the NRC in 1916, at the request of President Wilson, to identify and organize scientific research vital to preparation for a wartime emergency. The Council consisted of several divisions and committees representing various fields, whose members came from all the major estates of science: universities, industry, government, and private research laboratories. The Academy, again at Wilson's request, made the NRC a permanent body at the end of the war. Through its National Research Fund, established in 1925, the Council was able to secure pledges of several millions of dollars from a few companies to support fundamental research (although this was much less than the NRC hoped to raise from industry). With the onset of the Depression, however, the fund collapsed.[28]

In a somewhat more successful attempt to stimulate interactions between industry and universities, the Division of Chemistry and Chemical Technology of the NRC started a program in 1926 linking problems of interest to industry with academic researchers. Firms presented

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[27]Bartlett, "Industrial Research in the United States," 38, and Thackray, "University-Industry Connections," 216.

[28]Lance E. Davis and Daniel J. Kevles, "The National Research Fund: A Case Study in the Industrial Support of Academic Science," Minerva 12 (1974):207-220.

the Division with various topics requiring investigation, and the Division located the appropriate academic worker for the problem. "After appreciable progress had been reported," the Division revealed the identity of the company interested in the problem to the scientist, and vice versa. Thereafter, the two parties dealt directly with each other--if they wished to continue the work. It is not clear how long this program lasted, but in its first year the Division engineered 25 different links between firms and universities.[29] The Council's Division of Engineering and Industrial Research, and the Division of Research Extension, also encouraged cooperation between academe and industry by sponsoring conferences emphasizing potential research connections between universities and companies.[30]

Thus, many avenues existed for the propagation of research interactions between academe and industry. Fellowships could be arranged directly or by a third party. Consultantships were less common than fellowships, but they could bring the academic scientist into much closer contact with a firm than a fellowship. Universities, professional societies, and even an organ of the federal government developed programs to facilitate cooperative research. Both estates of science took advantage of this network of contacts. Interactions were well under way before the end of World War One, and grew significantly during the 1920s. The effect of the Depression was temporary at most,

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[29]William J. Hale, "Cooperative Research between Industries and Universities," Annual Survey of American Chemistry 1 (1925-1926):250-257, and idem, ibid. 2 (1927):395-397.

[30]Albert L. Barrows, "The Relationship of the National Research Council to Industrial Research," in Research--A National Resource, 2:367.

because interactions were stronger than ever by the beginning of World War Two.

Early Research and Interactions with Academe in the Pharmaceutical Industry

Research did not become a function of the pharmaceutical industry in general until after World War One, but this is not to say that research was absent prior to the war. As the case with other industries, a few pharmaceutical firms had assembled scientific staffs by the turn of the 20th century. Parke-Davis of Detroit and Mulford of Philadelphia were among the first firms to establish a science-based industry. Science first gained a foothold in the pharmaceutical industry through the standardization of drugs--an essential component of quality control since its purpose is to create a uniform strength of an active ingredient. Parke-Davis was one of the first American companies to attempt to produce standardized drugs. The firm hired chemist Albert Lyons in 1880, who soon devised a method to standardize ergot, on the basis of the assumption that ergot's activity was due to a particular chemical component in the fungus, and that through chemical manipulations one could determine the amount of that component in samples of crude ergot. By 1883 Parke-Davis had introduced twenty chemically assayed fluidextracts of botanical drugs. A few other firms, such as Lilly and G. D. Searle, followed suit in the 1880s. For example, J. K. Lilly went to work in the laboratory of his father's firm immediately after graduating from the Philadelphia College of

firm immediately after graduating from the Philadelphia College of Pharmacy in 1882; within a decade Lilly hired a chemist and a botanist to assist in control work.[31]

Science moved further into the pharmaceutical industry in the 1890s, when firms began manufacturing diphtheria antitoxin following Emile Roux's announcement in 1894 that he had developed a method to produce the antitoxin on a large scale. In the process, companies initiated early links with academic researchers. Here, Mulford and Parke-Davis were the early leaders. Late in 1894 Mulford President Milton Campbell hired Joseph McFarland, a member of the Philadelphia Board of Health and the Medico-Chirurgical College, to produce diphtheria antitoxin and possibly other biologicals. This move "was the first direct effort on Campbell's part to enact a policy of active product development through laboratory science."[32] McFarland soon acquired the assistance of faculty members of the University of Pennsylvania Veterinary School to produce the drug, and Mulford arranged for the Laboratory of Hygiene at Pennsylvania to test the antitoxin. By 1900 Mulford was producing nearly a dozen different biologicals, including tetanus antitoxin, anti-streptococcus serum,

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[31]Malcolm Keith Weikel, "Research as a Function of Pharmaceutical Industry: The American Formative Period," M.S. thesis, University of Wisconsin, 1962, 29-36; David L. Cowen, "The Role of the Pharmaceutical Industry," in Safeguarding the Public: Historical Aspects of Medicinal Drug Control, ed. John B. Blake (Baltimore: Johns Hopkins Press, 1970), 73; and Jonathan Michael Liebenau, "Medical Science and Medical Industry, 1890-1929: A Study of Pharmaceutical Manufacturing in Philadelphia," Ph.D. diss., University of Pennsylvania, 1981, 107-109.

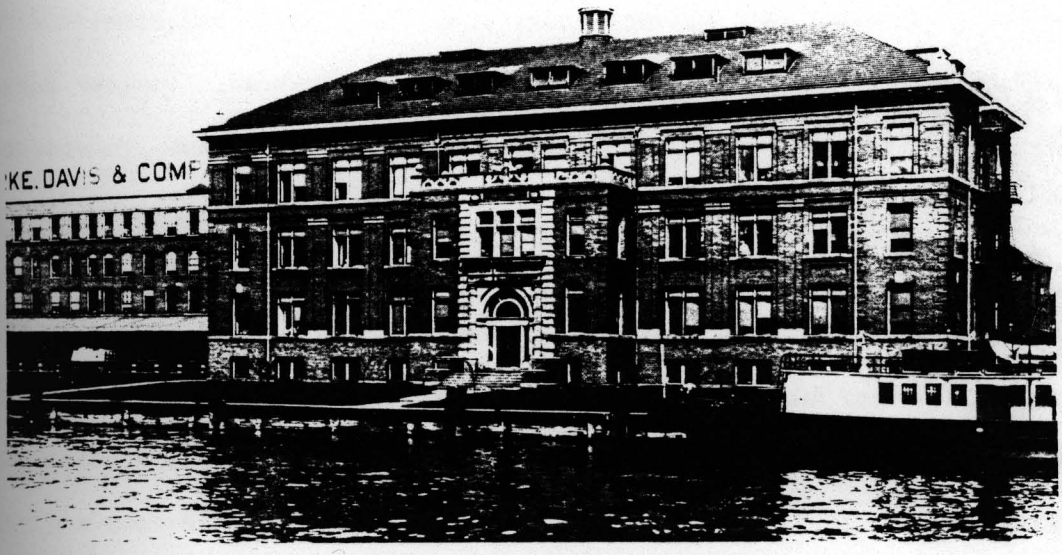
[32]Liebenau, "Medical Science and Medical Industry," 186.

Parke-Davis also developed an interest in diphtheria antitoxin soon after Roux's announcement, and like Mulford, tapped a nearby academic institution for assistance. The Detroit firm had maintained some contact with the University of Michigan, particularly through Lyons, a Michigan graduate, so Parke-Davis turned to this university for assistance in producing diphtheria antitoxin. Michigan was also a logical place to seek advice, since the Dean and a faculty member of the medical school had attended the meeting where Roux announced his discovery. Elijah M. Houghton, a research assistant in pharmacology at Michigan, joined Parke-Davis early in 1895, and Charles McClintock, a research assistant in bacteriology, followed Houghton the next year. The firm immediately established a research laboratory in biology, in which McClintock served as Director of Research and Houghton as Assistant Director of Research. The two were able to produce diphtheria antitoxin within a few months. Thereafter, Houghton focused on biological standardizations of various botanical drugs--a field he pioneered--while McClintock turned his attention to the production of other biologicals. Biological research dominated Parke-Davis until the 1920s, when the firm established a separate department of chemical research. Parke-Davis' early commitment to research also is indicated by its construction of a separate building for research in 1902--one of the first among all industries in America.[34]

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[34]Weikel, "Research as a Function of Pharmaceutical Industry," 68-79, 97-104, and Peter Stechl, "Biological Standardization of Drugs before 1928," Ph.D. diss., University of Wisconsin, 1969, 60-82.

Figure 2. The Parke, Davis and Company Research Laboratory, established in Detroit in 1902. This was the first building in American industry to be erected as a research facility (from Parke-Davis at 100; UW neg. no. 10273 C-3).


KE. DAVIS & COMP

Interest in biologicals also thrust Lederle Laboratories of Pearl River, New York, into research activity. Chemist Ernst Joseph Lederle, a former President of the Board of Health of New York City, assembled a small but well-trained staff to enter the field of biologicals. However, Lederle's interest came well after (1906) Parke-Davis and Mulford's work in this area.[35]

A few other firms established scientific staffs and facilities in the late 19th and early 20th centuries. Smith, Kline and French of Philadelphia set up an analytical laboratory in 1893, headed by chemist Lyman Kebler. The firm soon built up the equipment and staff of the laboratory, but the company accomplished little in the way of original investigations before World War One. Kebler's group primarily provided a testing laboratory rather than a development laboratory.[36] Upjohn of Kalamazoo, Michigan, hired the Yale-trained chemist Frederick Heyl in 1913 to direct its new research division. Heyl and his colleagues carried out some studies on new products, but their chief responsibility was control work. Lilly's small scientific staff grew enough that the firm constructed a Scientific Building in 1911. By the following year the Indianapolis company could have had as many as a score of its personnel engaged in research on such topics as new synthetic drugs.[37]

A few firms thus had assembled at least the rudiments of a research staff by World War One. Efforts at cooperative research in

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[35]Jonathan M. Liebenau, "Scientific Ambitions: The Pharmaceutical Industry, 1900-1920," Pharmacy in History 27 (1985):4-6.

[36]Liebenau, "Scientific Ambitions," 6-10.

[37]Weikel, "Research as a Function of Pharmaceutical Industry," 86-89.

this period existed on a rudimentary level as well. Generally, companies dealt with only one or two academic institutions, and typically contracted with university workers for control work. Thus H. A. Metz Laboratories of New York hired two Columbia biochemists as consultants, to run occasional quality control checks on its products. Mulford engaged the Laboratory of Hygiene at Pennsylvania as a biologicals testing laboratory, and pharmacologist Torald Sollmann, a consultant to the firm, worked out a process to increase the potency and shelf life of Mulford's products. Charles LaWall of the Philadelphia College of Pharmacy was a consultant to Smith, Kline and French, periodically from 1895 to 1905. Parke-Davis occasionally worked with University of Michigan scientists. Mulford, Parke-Davis, and perhaps a few other companies arranged for regional hospitals to test their products, a measure that was voluntary in this period.[38]

Cooperative research was still a fledgling enterprise before the war, with little resemblance to the systems and networks of contracts that emerged in the 1920s. In part, this was because research itself was relatively undeveloped and unorganized in firms with an interest in research, and in part for reasons that are discussed in the following chapter.

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[38]Ibid., 67-68, 105-106, 128; Liebenau, "Medical Science and Medical Industry," 19, 109-110, 188-191, 294-295, 334-335, 363; and "Contract between H. K. Mulford Co., of Philadelphia, PA., and Dr. Torald Sollmann, Cleveland, Ohio," 1 March 1900, Torald Sollmann Papers, Allen Medical Library, Case Western Reserve University, Cleveland, Ohio.

CHAPTER 3

OVERVIEW OF THE RISE OF UNIVERSITY-INDUSTRY INTERACTIONS IN BIOMEDICAL RESEARCH

Biomedical research interactions between American universities and the pharmaceutical industry emerged on a systematic basis between 1920 and 1940. Some circumstances existing since the 19th century--circumstances that, taken together, put the academic medical researcher in a unique position compared to other colleagues in the university--had impeded cooperative research between these two sectors of American society. In the first place, while applied research was a ubiquitous component of the American university of the late 19th century, increasing numbers of academic researchers in the last quarter of that century returned from abroad imbued with a Germanic emphasis on fundamental research, i.e., research for the sake of adding to the sum of knowledge in a field. Such a frame of mind was incompatible with an enterprise as utilitarian as the pharmaceutical industry. Second, American medical researchers were not disposed to work with the pharmaceutical industry because of traditional disapproval of the patenting of health-related processes and products. Questionable practices by some drug companies, too, helped create a tainted image of this industry.

The industry itself, however, helped erode this image. Beginning around the turn of the 20th century, but primarily after the First World War, company executives increasingly emphasized the value of research, both in word and deed. Research staffs in many companies grew significantly during the 1920s and 1930s, as did research budgets.

Qualitatively, some firms began to foster in-house fundamental research programs, although the weight of industrial research interests was practical in nature. Pharmaceutical firms also helped elevate their status among academic workers by employing prominent scientists, often as research directors. Companies reinforced this new image of a research-conscious industry in the 1930s by establishing special laboratories and institutes devoted to research, and by supporting fundamental work in universities through direct grants-in-aid and awards administered by scientific societies.

As a result, from 1920 to 1940 more and more university workers turned to drug companies, and vice versa, for intellectual, technical, and economic support. Academic scientists and firms developed a variety of relationships, which are discussed in Parts II, III, and IV. Cooperative endeavors typically benefited both sides. University researchers enjoyed a variety of direct and indirect benefits, most notably, a source of support for their research programs in an era prior to large-scale government involvement in the support of research. Companies depended on universities for research personnel and know-how, necessities to remain competitive in the modern pharmaceutical industry. Collaboration produced many drugs that contributed appreciably to companies' sales and profits. Public health shared in the benefits of cooperative research. Many important anesthetics, hormones, sedatives, anticonvulsants, antiinfectives, and other therapeutic agents derived from joint work by universities and drug firms.

Barriers to Cooperative Research

Impediments to interactions between academic scientists and pharmaceutical companies existed on both sides. These obstacles slowly dissolved after the turn of the 20th century,[1] in part because university researchers during the Progressive era were more willing than in the past to address their work to the needs of society. Also, many drug companies realized after World War One the importance of research for success. Consequently, firms fostered research through large-scale research programs within industry, and through contacts with academic research programs.

The roots of one of the more significant barriers within American universities rested in the concept of fundamental research,[2] as it emerged in the United States in the late 19th century. Prior to this, American universities were typically religious in character, and emphasized the improvement of all mental faculties such as observation, reasoning, and memory by training them on difficult and abstract material, such as Greek, Latin, and mathematics. However, the subjects per se were not as important to the 19th century educator as their use in developing the faculties to function efficiently in whatever field the

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[1]Barriers to cooperative research, of course, never dissolved completely. For example, it is not uncommon today to find university researchers who refuse to do industry-selected problems.

[2]By fundamental, or basic, research I mean learning for its own sake, to supplement the sum understanding in a field without consideration of any other use. When I refer to applied research (below), I mean learning for the sake of utility or public benefit other than pure intellectual elevation.

student chose to enter.[3] Thus educator Joseph Payne remarked that the aim of education was

> quickening and strengthening the powers of observation and memory, and forming habits of careful and persevering attention; it should habituate the pupil to distinguish points of difference and recognize those of resemblance, to analyze and investigate, to arrange and classify. It should awaken and invigorate the understanding, mature the reason, chasten while it kindles the imagination, exercise the judgement and refine the taste.[4]

Research, specifically fundamental research, did not become a function of universities in America until the last quarter of the 19th century. The intimate relationship between fundamental research and higher education was an innovation of German universities in the 19th century. This relationship spread to American universities as scientists and scholars returned from abroad, infected with the notion of "Wissenschaft" as a "dedicated, sanctified pursuit" of phenomena, "not the study of things for their immediate utilities, but the morally imperative study of things for themselves and for their ultimate meanings."[5] This concept of "Wissenschaft" as a search for ultimate meanings sprang from German idealism of the 18th and early 19th centuries, which maintained close connections with universities through Kant (at Königsberg), Schelling (at Jena and Berlin), Hegel (at Berlin) and others. Unlike French and English universities of the 18th and early

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[3]See Walter B. Kolesnik, Mental Discipline in Modern Education (Madison: University of Wisconsin Press, 1958), 3-29.

[4]Quoted in ibid., 18.

[5]Richard Hofstadter and Walter P. Metzger, The Development of Academic Freedom in the United States (New York: Columbia University Press, 1955), 373.

19th centuries, the German philosophical faculty achieved a status equal to the faculties of law, medicine, and theology.[6] Prior to the emergence of the basic biomedical sciences like physiology and biochemistry in the early 19th century, the German idealists' search for certainty helped shape a philosophical science of medicine, beginning around the turn of the 19th century.[7]

As the basic sciences began to make their way into German universities,[8] the empirical methods of the natural and physical sciences clashed with the a priori approach to understanding of the idealists. Eventually, the empirical approach to science developed by Justus von Liebig in chemistry, Johannes Mueller and Carl Ludwig in physiology, Wilhelm Wundt in psychology, and many others, established this methodology for the many disciplines that arose in German universities in the 19th century. However, "the idealistic mood lingered over the German universities long after it was severed from the circumstances of its origin," and "pure" learning, characterized by scrupulous investigation, marked German academic research later in the 19th century. Basic courses became the province of the Gymnasien, and fields in

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[6]Ibid., 370-372, and Joseph Ben-David and Awraham Zloczower, "Universities and Academic Systems in Modern Societies," Archives européennes de sociologie 3 (1962):50-53.

[7]See Guenter B. Risse, "Kant, Schelling, and the Early Search for a Philosophical 'Science' of Medicine in Germany," Journal of the History of Medicine and Allied Sciences 27 (1972):145-158.

[8]See, for example, Ben-David and Zloczower, "Universities and Academic Systems," 53-57.

engineering were relegated to the Technische Hochschulen.[9]

Americans emigrated to German universities throughout the 19th century, primarily in the 1870s, 1880s, and 1890s. Peak emigration came in 1895-1896, when over 500 Americans enrolled in German institutions. That study in Germany was cheaper (even when including the cost of travel) than study at some of the better universities in the United States played some part in a student's decision to spend time at a German university, but the intellectual challenge alone was overwhelmingly attractive for most.[10] In the 1890s Harvard philosopher Josiah Royce reflected on the lure of study in Germany:

> German scholarship was our master and our guide. . . . The air was full of suggestion. . . . One went to Germany still a doubter as to the possibility of the theoretic life; one returned an idealist, devoted for the time to pure learning for learning's sake, determined to contribute his Scherflein to the massive store of human knowledge, burning for a chance to help build the American University.[11]

Several American universities--some new, such as Clark, Stanford, and Chicago, and some refurbished, such as Harvard, Yale, and Cornell--followed the lead of Johns Hopkins in 1876 by establishing graduate research programs based on the German model. By 1900 some state universities--Wisconsin, California, and Michigan--established graduate

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[9]Hofstadter and Metzger, Development of Academic Freedom, 372 (quotation) and 374; Laurence R. Veysey, The Emergence of the American University (Chicago: University of Chicago Press, 1965; Phoenix Books, 1970), 126-127; and Ben-David and Zloczower, "Universities and Academic Systems," 49.

[10]Veysey, Emergence of the American University, 130, and Merle Curti, The Growth of American Thought, 3d ed. (New York: Harper and Row, 1964), 566.

[11]Quoted in Veysey, Emergence of the American University, 130.

research programs as well. The number of doctorates conferred by American universities increased from zero in 1861 to 164 in 1890, and the postgraduate population in America rose from about 200 students in 1871 to nearly 3000 in 1890.[12]

Qualitatively, American higher education slowly became enamored of Germanic scholarly pursuit without regard to practicality. An early Register of Johns Hopkins proclaimed that the Baltimore university "provides advanced instruction, not professional, to properly qualified students, in various departments of literature and science."[13] Clark University was established in 1888 as a graduate school alone, which was indicative of the feeling of some that the pursuit of pure learning did not benefit from the popular precept that bigger (enrollment) was better. Few American educators were as ardently supportive of fundamental research as psychologist G. Stanley Hall, the first President of Clark University. He likened research-oriented professors to prophets, freed from the "routine and rules of common college life," in an atmosphere devoid of the practical components of Francis Bacon's "House of Solomon": "In the new 'House of Solomon' they should have the best equipment, the largest pay, the freest air; for thus not merely the university, but the nation, receives with due honor its anointed prophets."[14] Hall's image of the university clearly was free of

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[12]Hofstadter and Metzger, Development of Academic Freedom, 377-379, and Curti, Growth of American Thought, 569.

[13]Quoted in Veysey, Emergence of the American University, 149.

[14]G. Stanley Hall, "Research the Vital Spirit of Teaching," Forum (New York) 17 (1894):561-562.

utilitarian considerations:

> The common sense of it all is, that the university should rest solely on the love of knowledge, and the true investigator refines, and over and over returns to, his method and thought till it is simple and direct, great but easily mastered because [it is] stated in a way to present the least possible resistance.[15]

Fundamental research incontestably played an important part in the development of the American university in the late 19th century, but the latter also had a well-established utilitarian component.[16] For example, the Morrill Land Grant Act of 1862, the Hatch Act of 1887 (which established agricultural experiment stations), and the second Morrill Act of 1890 (which helped subsidize the agricultural colleges established under the 1862 Act) provided for practical instruction in many universities. By the turn of the 20th century, the American university emerged as an amalgam of fundamental and applied research functions:

> In the one view, research was an activity to be initiated and directed from within the university. The searcher was to be independent, not only with respect to his conclusions, but to his choice of an area of work. To fill the gaps in knowledge that continuing inquiry revealed, to conduct investigations as the logic of a discipline directed--these were to be the functions of academic inquiry. Practical results might be forthcoming, but inquiry should be allowed to push against any of the frontiers of knowledge, and not merely

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[15] Ibid., 570.

[16] Richard Harrison Shryock, "American Indifference to Basic Science during the Nineteenth Century," Archives internationales d'histoire des sciences, no. 5, October 1948:50-65, analyzes the social and scientific factors in the failure of fundamental work to take hold in America in the first half of the 19th century. For an apology of the value of practical instruction in the university, analogous to Hall's support of fundamental research, see, e.g., Edmund Janes James' inaugural address as President of the University of Illinois, "The Function of the State University," Science 22 (1905):609-628.

> along that border where material benefits were promised. . . [But] the graduate school in the American university was only one of a heterogeneous group of divisions. In the other schools and departments [for example, agriculture, commerce, engineering, and business administration], research was often geared to external and ulterior purposes.[17]

Notwithstanding the presence of practical interests, the strength of fundamental research in universities probably played some part in the reluctance of biomedical researchers to collaborate with pharmaceutical companies. Many physiologists, biochemists, pharmacologists, and other biomedical scientists spent time in Germany in the late 19th and early 20th centuries, including some of the most prominent workers in their fields. Pharmacologist John J. Abel of Johns Hopkins spent seven years in Germany; physiological chemist Russell Chittenden of Yale and physiologist Jacques Loeb, who spent nearly twenty years at Chicago and California before moving to the Rockefeller Institute, also brought German ideals of pure learning to America. These disciplines certainly faced practical obligations in settings such as medical and agricultural schools,[18] but such "service roles" did not lead to the abandonment of pure learning in the biomedical sciences. For example, Hopkins physiologist Henry Newall Martin felt that physiology "should be cultivated as a pure science absolutely independent of any

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[17]Hofstadter and Metzger, Development of Academic Freedom, 381-382.

[18]For example, see Robert E. Kohler, From Medical Chemistry to Biochemistry: The Making of a Biomedical Discipline (Cambridge: Cambridge University Press, 1982); Gerald L. Geison, "Divided We Stand: Physiologists and Clinicians in the American Context," in The Therapeutic Revolution: Essays in the Social History of American Medicine, ed. Morris J. Vogel and Charles E. Rosenberg (Philadelphia: University of Pennsylvania Press, 1979), 67-90; and Russell C. Maulitz, "'Physician Versus Bacteriologist': The Ideology of Science in Clinical Medicine," in ibid., 91-107.

so-called practical affiliation."[19] Chittenden, the father of American biochemistry, developed a successful modus vivendi between purely theoretical work and practical instruction at the Sheffield Scientific School.[20] Abel, Chittenden's counterpart in pharmacology, believed that, once established, pharmacology would "yield valuable results for the practical man." He emphasized, however, that pharmacology "is not therefore an applied science, like therapeutics, but is one of the biological sciences, using that word in its widest sense."[21]

It was one thing for biomedical researchers to spend time training physicians and other professionals, but working with industry was an entirely different matter. Until the early 20th century, drug companies by and large had no interest in research. There were a few exceptions, such as Mulford and Parke-Davis (see Chapter 2), but even the exceptional cases had little or no interest in fundamental work. Even after research (including some fundamental studies) had become a function of the pharmaceutical industry, Abel refused to do any work for drug firms:

> I personally would not think of working on a problem suggested to me by any firm anywhere. Usually, problems of this nature could be worked out very well in the laboratories of the firms since they almost always concern questions of what I might call applied pharmacology. A pharmacologist of any training or ability should have so many problems of his own awaiting solution that he should not spend his time on matters

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[19]Quoted in Geison, "Divided We Stand," 71.

[20]Kohler, From Medical Chemistry to Biochemistry, 97-101.

[21]John J. Abel, "The Methods of Pharmacology, with Experimental Illustrations," Pharmaceutical Era 7 (1892):105.

of little theoretical importance for his science.[22]

The high value placed on fundamental research in American universities, therefore, helped impede any movement for collaboration with pharmaceutical firms on strictly applied work. Traditional disapproval of medical patents by physicians and biomedical scientists also presented a barrier to cooperative work from within academe. The Code of Ethics that the American Medical Association adopted in 1847 explicitly decried medical patents: "Equally derogatory to professional character is it, for a physician to hold a patent for any surgical instrument, or medicine."[23] Patenting of discoveries generally did not generate among physical scientists the repugnance which many biomedical scientists had for patenting.[24] Harvard bacteriologist Hans Zinsser proclaimed why physicians and medical researchers had such an aversion to medical patents:

> The invention of an improvement in the mechanism of automobiles, or of a shoe-buckle, concerns matters of convenience or luxury, and can be dispensed with easily by those who are forced to do without them. The relief of the sick and the prevention of unnecessary sorrow by the maintenance of individual and public health are matters in a different category. As soon as we are in possession of the knowledge of principles or methods which can contribute to these purposes their free utilization becomes a public necessity; and any procedure which inhibits their most rapid and effective application to

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[22]John J. Abel to William deB. MacNider, 5 April 1935, John Jacob Abel Papers, Alan Mason Chesney Archives, Johns Hopkins University, Baltimore, Maryland [hereafter Abel Papers]. I am indebted to John Parascandola for this and all other letters cited from the Abel Papers.

[23]From Code of Ethics of the American Medical Association, chap. 2, art. 1, sec. 4, reproduced in Chauncey D. Leake, ed., Percival's Medical Ethics (Baltimore: Williams and Wilkins, 1927), 226.

[24]Richard H. Shryock, American Medical Research: Past and Present (New York: Commonwealth Fund, 1947), 140.

> the needs of the community would seem to us as unjustified as the cornering of the wheat market or the patenting of the process of making bread.[25]

Abel, too, questioned the ethics of patenting medical discoveries: "I have always considered it unethical for a medical man, and especially for a research worker who is supported by a university and foundations, to take out patents."[26]

The American pharmaceutical industry did not make significant use of the patent system until after World War I. For example, Edward R. Squibb, founder of E. R. Squibb and Sons, proclaimed, "I do not myself think that anything should be patented by either physician or pharmacist; I am sure that the patient would not be benefited thereby." Indeed, the Squibb company held only one patent by 1920.[27] The German pharmaceutical industry held the vast majority of American patents on therapeutic agents prior to World War One. Several American firms received licenses to produce these patented drugs after the United States government abrogated German-owned patents under the Trading With the Enemy Act of 1917.[28] Before the war, drug companies protected

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[25]Hans Zinsser, "Problems of the Bacteriologist in His Relations to Medicine and the Public Health," Presidential address delivered to the Society of American Bacteriologists, Philadelphia, 29 December 1926, Journal of Bacteriology 13 (1927):161.

[26]John J. Abel to S. Lloyd Johnson, 21 September 1935, Abel Papers.

[27]F. E. Stewart, "Is It Ethical for Medical Men to Patent Medical Inventions?," Journal of the American Medical Association 29 (1897): 586 (Squibb quoted from his discussion following this paper), and F. W. Nitardy, "Long Range Comparative Report (1916-1941)," typescript, 1 July 1941, 43, "Research, 1900-1925," Archives, E. R. Squibb and Sons, New Brunswick, New Jersey (hereafter Squibb Archives].

[28]See Williams Haynes, American Chemical Industry, 6 vols. (New York: D. Van Nostrand, 1945-1954), 3:481-508, 512-515.

their processes through secrecy;[29] the American Medical Association had long censured this means of protection as well as patenting.[30]

It may seem incongruous to conceive of an unwillingness within academe to cooperate with the pharmaceutical industry on the basis of anti-patent bias, given the actual paucity of patent activity by American firms. However, there was no reason for university scientists to doubt that American firms would turn to patents to protect their research investments--much like the German industry--once they established research programs.[31] To effect the latter, of course, required the cooperation of academic researchers. In a sense, drug companies in the late 19th and early 20th centuries were damned if they did and damned if they did not, with respect to collaboration with universities. On one hand, it was difficult for academic scientists to take firms seriously as potential collaborators until they developed an interest in research. On the other hand, once firms established research programs of their own, they would in all likelihood (based on the experience of German firms) become more aggressively patent-minded. As the relationship between university scientists and drug firms evolved in the early decades of this century, interest in research was a more

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[29]Malcolm Keith Weikel, "Research as a Function of Pharmaceutical Industry: The American Formative Period," M.S. thesis, University of Wisconsin, 1962, 56-57, and Jonathan Michael Liebenau, "Medical Science and Medical Industry, 1890-1929: A Study of Pharmaceutical Manufacturing in Philadelphia," Ph.D. diss., University of Pennsylvania, 1981, 92-93.

[30]Code of Ethics of the American Medical Association, chap. 2, art. 1, sec. 4, in Leake, Percival's Medical Ethics, 226.

[31]This is precisely what Mulford did; see Liebenau, "Medical Science and Medical Industry," 197.

important precondition to cooperation. Academic biomedical scientists themselves began seeking patents in the 1920s and 1930s (see below).

The pharmaceutical industry itself was perhaps the biggest barrier to collaborative research. In the first place, the distant, embarrassing relatives of such respectable firms as Parke-Davis, Squibb, and Lilly--the manufacturers of Wendell's Ambition Pills, Old Sachem Bitters, William Radam's Microbe Killer, and other questionable nostrums--certainly did not help the image of respectable pharmaceutical companies. The companies discussed in this study were far removed (and they attempted to remove themselves far) from the so-called "patent" medicine makers. However, that the latter began to mimic methods by which respectable firms advertised their products to physicians and in medical journals, by the late 19th century, worsened the situation for the comparatively small group of ethical firms. In addition, even respectable firms marketed a fair share of dubious home health care items, which probably confused distinctions between nostrum makers and ethical firms. The efforts of muckraking journalists, the American Medical Association, the American Pharmaceutical Association, and others, to expose the fraud of the "patent" medicine makers helped to differentiate respectable companies from the latter.[32]

Second, while the ethical industry per se was not to blame for the inundation of "patent" medicines, it had its share of practices

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[32]The definitive histories of "patent" medicines and health quackery are James Harvey Young, The Toadstool Millionaires: A Social History of Patent Medicines in America before Federal Regulation (Princeton: Princeton University Press, 1961), and idem, The Medical Messiahs: A Social History of Health Quackery in Twentieth-Century America (Princeton: Princeton University Press, 1967).

that seemed questionable to physicians and medical researchers. As mentioned above, for example, firms relied on secrecy to protect their products. Also, companies that published scientific papers rarely published anything negative about their products in this period before the war.[33] Even in the late 1930s, Merck pharmacologist Hans Molitor said that only positive results were usually published from industrial laboratories, although "non-publication of results, particularly of negative ones, is not necessarily due to a desire to keep them secret, but more often is caused by the impossibility of finding a periodical willing to allot sufficient space to the publication of data which interest only a small minority of its readers."[34] The type of experience Abel had with a firm could damage the reputation of an otherwise respectable drug company. According to the Hopkins pharmacologist:

> Even reputable houses will do things that tend to damage men. About ten years ago [c. 1900] one of our large and reputable houses put on their labels and stated in pamphlets that their preparation of the suprarenal principle was made by a method of Professor John J. Abel, of the Johns Hopkins University, Medical School, etc. etc. My friends immediately called my attention to these labels and asked me if I had "supplied this firm with a method." I wrote to the firm at once stating that I should publish a card in every medical journal in the country calling attention to the injury that was being done to me in these statements which implied that I had given them a "method." [I] furthermore stated that

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[33]As late as 1946, K. K. Chen, a well-respected pharmacologist with Lilly, informed a colleague, "As a rule, I do not publish any negative results from various investigations" (K. K. Chen to Chauncey D. Leake, 8 April 1946, box 44, "Lilly Research Laboratories (K. K. Chen), Jan.-June 1946," Chauncey D. Leake Papers, National Library of Medicine, Bethesda, Maryland.

[34]Hans Molitor, "Merck Institute of Therapeutic Research: Sixth Annual Report (1938)," 19-page typescript, 8, box 30, "Merck Institute, 1931-1940," Alfred Newton Richards Papers, University of Pennsylvania Archives, Philadelphia, Pennsylvania [hereafter Richards Papers].

> while I could not and did not wish to keep manufacturers from making use of my work, I must insist that they should state in their literature that this method was obtained from my [published] papers . . .[35]

The firm soon acquiesced. It is not clear how extensively respectable firms made free use of the names of researchers in advertisements, but the publicity generated from just a few such affairs could damage a company's reputation.

Given all of the above, it should not be surprising that, by the beginning of the period between the two World Wars, academic scientists had a tainted image of industrial pharmaceutical work. As one indication of this image, consider the reaction of scientists when Max Gottlieb--the creation of Sinclair Lewis and bacteriologist Paul De Kruif, whom De Kruif based on Jacques Loeb--abandoned academic life to work for the fictional pharmaceutical firm, Dawson T. Hunziker and Co., Inc. Scientists lamented, "'How could old Max have gone over to that damned pill-peddler?'" and "'Of all the people in the world! I wouldn't have believed it! Max Gottlieb falling for those crooks. . . . I wish he hadn't gone wrong!'"[36] Arrowsmith was a novel, but the depiction of the alarm and dismay of his academic colleagues when a respected scientist joined a drug company reflected the opinion of many biomedical scientists and physicians about connections with industry.

For example, around 1910 Cornell pharmacologist Robert A. Hatcher

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[35]John J. Abel to [Robert] Hatcher, 31 January 1910, Abel Papers.

[36]Sinclair Lewis, Arrowsmith (New York: Harcourt Brace Jovanovich, 1925; New York: New American Library, Signet Classics, n.d.), 132. For an interesting historical discussion of Arrowsmith, see Charles E. Rosenberg, No Other Gods: On Science and American Social Thought (Baltimore: Johns Hopkins University Press, 1976), 123-131.

agreed to abstract all available literature on the physiological action of caffeine for the Coca-Cola Company; this involved neither personal comments nor original research by Hatcher. When Torald Sollmann, a pharmacologist at Western Reserve University, heard about the agreement between Hatcher and Coca-Cola, he informed the Cornell worker that Hatcher's reputation would suffer a very severe shock if it became known that he had done the work for them, and if the firm chose to misuse the abstracts."[37] Hatcher's friend Abel tried to assure the former there was nothing improper in abstracting literature for a firm, but Hatcher nonetheless felt "certainly sicker of this thing than I have even been of anything I can recall. I never make resolutions, but I do hope I may not get into such a fix again."[38]

Like Hatcher, other pharmacologists sought Abel's advice from time to time about the propriety of collaborating with companies. For example, in the early 1930s Alfred Newton Richards of Pennsylvania approached the Hopkins pharmacologist for an enlightened opinion about an offer Merck made Richards, to serve as a consultant to the firm (see Chapter 4). North Carolina pharmacologist William MacNider like-

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[37]Robert A. Hatcher to [John J.] Abel, 28 January 1910, Abel Papers. Sollmann himself had worked much closer with a firm (albeit a respectable pharmaceutical company) than Hatcher's proposed abstracting services for Coca-Cola. Sollmann had concluded an agreement with Mulford in 1900, whereby the firm paid him $100 monthly and furnished equipment and supplies for his exclusive services to Mulford as a consultant. The agreement lasted for at least six months. See "Contract between H. K. Mulford Co., of Philadelphia, PA., and Dr. Torald Sollmann, Cleveland, Ohio," Torald Sollmann Papers, Allen Medical Library, Case Western Reserve University, Cleveland, Ohio (I thank John Parascandola for this document).

[38]Abel to Hatcher, 31 January 1910, and Robert A. Hatcher to [John J.] Abel, 2 February 1910, Abel Papers.

wise sought Abel's counsel. A pharmaceutical company wanted MacNider to evaluate the therapeutic value of one of its new plant extracts. MacNider was seriously considering the offer, even though he normally was reluctant to cooperate with industry: "I must say that I have almost a phobia concerning becoming mixed up with commercial enterprises, and also receiving money for such work. My innate reaction is against it . . ."[39] We have already seen that Abel personally opposed cooperative work, on the basis that applied pharmacological research was more the province of industrial laboratories than universities. He also believed that, if academic workers were less cooperative with industry, firms by necessity would have to establish their own research programs, which would be all the better for industry (and academic pharmacologists):

> My own opinion in regard to professors of pharmacology doing work for firms is that they had better not. I mean to say that a man will be better satisfied with himself in the long run if he can keep out of it. The firms can get good men from abroad (for that matter, in this country), if they will treat them as scientifically trained men should be treated. If no reputable pharmacologist who holds a chair will do hack work or expert work for them, I think that they will get men of their own as the foreign firms do and as one of the large firms in this country has done.[40]

Biomedical scientists and physicians took stands against commercial work collectively as well as individually. As already mentioned, for

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[39]William deB. MacNider to John J. Abel, 29 May 1931, Abel Papers. Abel sometimes did counsel his colleagues that cooperative work seemed acceptable to him, as when A. N. Richards sought his advice on a possible consultantship with Merck; see Chapter 4.

[40]Abel to Hatcher, 31 January 1910. The American firm Abel referred to was Parke-Davis, which had hired pharmacologist E. M. Houghton from the University of Michigan in 1895.

example, the American Medical Association censured the patenting of medicines. At the 48th (1896) annual meeting of the Association, in Atlanta, "a delegate was refused permission to register because he had applied for a patent; he had not even obtained a patent."[41] Prior to the period between the wars, members of the Society for Experimental Biology and Medicine introduced a stipulation into the Society's Constitution, expelling anyone from the Society who published deliberately favorable analyses of foods and drugs for manufacturers. The Society used this stipulation to remove one of its members.[42]

No scientific society in the United States took as strong a stance against industrial work as the American Society for Pharmacology and Experimental Therapeutics (ASPET), whose vast majority of members were M.D.s. According to the original ASPET Constitution, framed when Abel and a small group of pharmacologists established the Society in 1908, "No one shall be admitted to membership who is in the permanent employ of a drug firm," and "Entrance into the permanent employ of a drug firm shall constitute forfeiture of membership."[43] A decade later, however, a movement involving a handful of members (including Abel) was underfoot to eliminate the ASPET ban. This small group did not succeed, but sentiment to remove the clauses grew over the 1920s and

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[41]Stewart, "Is It Ethical to Patent Inventions," 586.

[42]S. J. Meltzer to A. S. Loevenhart, 20 December 1919, box 3, "Personal Correspondence, P-Q," Arthur Salomon Loevenhart Papers, University of Wisconsin Archives, Madison, Wisconsin [hereafter Loevenhart Papers].

[43]From Article III of the Constitution, reproduced in K. K. Chen, ed., The American Society for Pharmacology and Experimental Therapeutics, Incorporated: The First Sixty Years, 1908-1969 (n.p.: American Society for Pharmacology and Experimental Therapeutics, 1969), 184.

1930s, as the tainted image of the pharmaceutical industry slowly dissipated.

Erosion of the Tainted Image

Several developments within the pharmaceutical industry between World War One and World War Two helped erase the academic biomedical community's disparaging view of this industry, and thereby opened the way for widespread cooperation between industry and academe. The most significant developments were: 1) a major industry-wide change in attitude, emphasizing the value of research, and an active application of this philosophy (including the support of some fundamental research); 2) employment of prominent scientists, often as directors of company research; and 3) establishment of special research laboratories and research institutes.

Some firms, as we saw in Chapter 2, had developed an interest in research in the late 19th century. These companies--most notably Parke-Davis and Mulford--developed rudimentary research interactions with a few university scientists. However, research in the pharmaceutical industry did not emerge on a wide scale until after World War One.[44]

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[44]The development of post-World War One research in the pharmaceutical industry has not previously received significant attention from historians. For a relatively brief overview of the subject, see John Parascandola, "Industrial Research Comes of Age: The American Pharmaceutical Industry, 1920-1940," Pharmacy in History 27 (1985):12-21.

Research in this period grew, not out of quality control work,[45] but out of product development. While government regulation, through the Biologics Control Act of 1902 and the Pure Food and Drug Act of 1906, led to the introduction of science-based control work in a number of firms, such work was geared to the improvement of existing products and processes.[46] How significantly could this increase a firm's capital? The industry grew rapidly after World War One, when firms actively began turning out new therapeutic products. Research programs were essential to this new primary function of industry.

The neglect of product development by American manufacturers became quite obvious during World War One, once wartime conditions forced German firms to interrupt drug supplies to the United States. German pharmaceutical firms had introduced some of the leading analgesic, anesthetic, hypnotic, antimicrobial, and other agents, and employed a variety of trade practices to maintain control of the markets for these drugs in the United States. As the war dragged on, a dearth of these drugs set in, and prices skyrocketed. After the government abrogated German patents near the end of the war, American pharmaceutical firms soon filled the demand for these drugs, partly because many firms already had trained staff on hand for control work, and partly because

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[45]Some control chemists and pharmacologists also found time to work on new products, but by and large their primary responsibility was in the control laboratory; see Weikel, "Research as a Function of Pharmaceutical Industry," 52-53.

[46]Liebenau, "Medical Science and Medical Industry," 84, 237-279, and Ramunas A. Kondratas, "Biologics Control Act of 1902," in The Early Years of Federal Food and Drug Control (Madison: American Institute of the History of Pharmacy, 1982), 8-27.

outside scientists assisted some firms, such as Roger Adams' cooperation with Abbott (see Part II). Essentially, this enabled many firms to get their collective foot in the product development door.[47]

If American firms learned anything from their German counterparts after the war, they learned that research was fundamentally important to remain at the cutting edge of practical therapeutics. Thus Alfred S. Burdick, President of Abbott Laboratories, proclaimed, "Research is fundamental and vital. Without it real progress is impossible, in spite of occasional evanescent success."[48] According to Carlton Palmer, President of Squibb, his firm could not neglect in-house research:

> We cannot afford to discontinue all research work even though we connect with the Mellon Institute and use their data to solve our bigger problems. Just whether we need any additional men or whether we do not possess men on our present staff sufficiently qualified to take charge of our research work I leave to you to decide. But I do feel that we should have a regular research department . . .[49]

Lilly President Josiah K. Lilly recognized the need for a solid foundation of chemists, pharmacologists, biologists, pharmacists, and clinicians "to insure a steady stream of useful and profitable specialties to Eli Lilly and Company."[50] From the time he assumed the chief

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[47]See, e.g., Liebenau, "Medical Science and Medical Industry," 313-315, and Haynes, American Chemical Industry, 3:311-326.

[48]Quoted in Herman Kogan, The Long White Line (New York: Random House, 1963), 119.

[49]Carleton H. Palmer to F. W. Nitardy [Plant Superintendant at Squibb], 30 March 1922, "M(1): Research and Development, General, 1920s," Squibb Archives.

[50]J. K. Lilly to Eli Lilly and J. K. Lilly, Jr., 27 April 1926, "J. K. Lilly, Jr., Letters to and from Mr. Lilly, 18 Feb. 1926-11 Sept. 1931," XCAc, Archives, Eli Lilly and Company, Indianapolis, Indiana [hereafter Lilly Archives]. See also Josiah K. Lilly, "Comments on Research in

executive position of Merck and Company in 1925, George Merck planned a research laboratory of the highest order, on a level equal to the best academic laboratories:

> To do research worthy of the name, to do research which will bring to industry true recognition of its contribution to the advance of knowledge, industry must have at its disposal genuinely creative minds so placed and so protected that their mental powers of thought, study, and imagination can concentrate on problems of great difficulty.[51]

These and other pharmaceutical company executives put their strong convictions about research into action. Abbott, for example, was appropriating about $100,000 annually for research by the late 1920s, and it had a research and control staff of 29 by 1933.[52] Upjohn's research staff had grown to a similar size by this time.[53] Merck's research program grew slowly in the 1920s, but this changed in the next decade; from 1931 to 1940, Merck annual research expenditures ballooned from $146,000 to $906,000 (the latter sum was four percent of the company's

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Manufacturing Pharmacy," in Lilly Research Laboratories: Dedication (Indianapolis: [Eli Lilly and Company,] 1934), 5-6, and Gene E. McCormick, "Josiah Kirby Lilly, Sr., the Man," Pharmacy in History 12 (1970):64-65.

[51]George W. Merck, "An Essential Partnership: The Chemical Industry and Medicine," Industrial and Engineering Chemistry 27 (1935):739 (quotation), and Max Tishler, interview by Leon Gortler and John A. Heitmann, Wesleyan University Library, 14 November 1983, 28-29, transcript, Center for the History of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania.

[52]Kogan, Long White Line, 120, and Elmer B. Vliet, "The Abbott Story," lecture delivered at the Research-Development-Control Dinner, Abbott Auditorium, [North Chicago, Illinois,] 16 March 1950, 15-page typescript, 12, "Abbott--History," Archives, Abbott Laboratories, North Chicago, Illinois [hereafter Abbott Archives].

[53]Leonard Engel, Medicine Makers of Kalamazoo (New York: McGraw-Hill, 1961), 91.

total sales for 1940).[54] Squibb had only a handful of researchers at the end of World War One, but by 1928 the firm's research staff totaled at least 15 (not including scientific personnel at its biologicals laboratory), with a research budget of about $200,000 each year.[55] Lilly, by the mid-1930s, had one of the largest research and control staffs in the industry. Its personnel in analytical, organic, and biochemistry; pharmacology; bacteriology and immunology; and other divisions amounted to over 70, 40 of whom held graduate or professional degrees.[56] Parke-Davis had built up such a research program that, in 1924, President Oscar W. Smith appointed a research committee, which included a physician, a Ph.D. in pharmacology, and a Ph.D. in organic chemistry. Smith charged the committee to

> . . . decide what problems should be investigated; [devise] methods of keeping records; determine what practical results may be utilized from the investigators; . . . stimulate the best efforts of the individual research worker without in any way detracting from the initiative and originality of the worker. . . . I trust that this Committee will be able to push forward the selection of whatever problems may be decided upon as rapidly and conclusively as possible and in such a manner as to enhance the scientific standing and material welfare of Parke, Davis and Company. In carrying out its duties, I believe the Committee should meet regularly at a set time and place, perhaps as frequently as once a week

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[54]Merck and Company, The Merck Corporation: Annual Report, 1931, and "Merck and Co., Inc. and Consolidated Domestic Subsidiaries: Analysis of Research and Development Expenses," one-page typescript, 15 November 1951, box 29, "Budget, 1953," Richards Papers.

[55]F. W. Nitardy, "Research and Library Work," 7-page typescript (unpaginated), 24 March 1931, 6, Squibb Archives, and E. R. Squibb and Sons, "Annual Report," typescript, 8 April 1931, 49, "Research, 1900-1925," Squibb Archives.

[56]Lilly, Lilly Research Laboratories: Dedication, 118.

or once in every two weeks.[57]

Not all of the leading pharmaceutical firms displayed a firm commitment to research during the period between the World Wars. Smith, Kline and French, for example, had sales of $8-9 million by the mid-1930s (slightly higher than Abbott's sales in the same period), but the company employed only eight researchers, who received only $70,000 in support annually at this time.[58] However, most of the leading pharmaceutical companies were becoming more and more aware of the value of research, and willing to invest in personnel, equipment, and facilities. When chemist Max Tishler moved from Harvard to Merck in 1937, he was most impressed by the industrial laboratory--its personnel, facilities, and the first-rate scientific work that was coming out of Merck at the time.[59]

Parts II, III, and IV, and to some extent the following section, address the type of research that many companies engaged in. Generally, industry had to rely on itself for present and future support of industrial research, as J. K. Lilly argued: "It should be recognized, also,

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[57]O. W. Smith to [E. M.] Houghton, 5 February 1924, historical file, Parke-Davis Research Library, Ann Arbor, Michigan (copy in C(38)a, Kremers Reference Files, F. B. Power Pharmaceutical Library, University of Wisconsin, Madison, Wisconsin). The members of the Committee were E. M. Houghton (Chairman), F. O. Taylor, C. H. Briggs, L. T. Clark, O. Kamm, and A. W. Lescohier. The following year, Wilbur Scoville replaced Briggs, and W. E. King joined the committee; see Weikel, "Research as a Function of Pharmaceutical Industry," 124-125.

[58]John Francis Marion, The Fine Old House (Philadelphia: SmithKline, 1980), 130, and Gabriel P. Becker, "A Study of the History and Development of Abbott Laboratories," M.B.A. thesis, University of Louisville, 1956, 48.

[59]Tishler, interview by Gortler and Heitmann, 14 November 1983, 31-32.

Figure 3. The Parke, Davis and Company Research Committee, pictured here sometime in the late 1920s. Members are (clockwise, beginning at the left foreground) Oliver Kamm, Director of Chemical Research; Frank O. Taylor, Chief Chemist; Elijah Mark Houghton, Director of Biological and Research Laboratories; Wilbur L. Scoville, Head of the Analytical Department; A. W. Lescohier, General Manager; Walter E. King, Assistant Director of Biological and Research Laboratories; and Lawrence T. Clark, Junior Director of Biological and Research Laboratories (from C(38)a, Kremers Reference Files, F. B. Power Pharmaceutical Library, Madison, Wisconsin; UW neg. no. 10271 C-3).



that it must be a prosperous and reasonably profitable concern that essays to support, financially, extensive research. In short, [industry] must supply its own endowment."[60] Thus, research had to pay its own way to have a future in industry, i.e., it had to be translated into profit margins. Company executives, after all, were not going to invest hundreds of thousands of dollars in something without a return. Oscar Smith established a research committee at Parke-Davis, in part, to "enhance the material welfare of Parke, Davis and Company," and the General Superintendent of Squibb emphasized that, "I do not believe we are in [a] position at this time to spend money on research work concerning products we manufacture or might manufacture that would not be likely to yield profitable results in a business way . . ."[61]

The Director of Research at Lilly, G. H. A. Clowes, suggested to President J. K. Lilly and Vice-President Eli Lilly that "our scientific reputation is now [1929] so firmly established that we can afford to be somewhat more exacting and discriminating than heretofore" in the selection of in-house research projects and in the support of research proposals from outside the company. Clowes outlined three categories of drug use, categories which he felt should be kept in mind when allotting research funds: 1) occasional use (e.g., antitoxins), 2) temporary use (e.g., ephedrine, a decongestant, and antisyphilitic arsenicals), and 3) regular use (e.g., insulin, and liver extracts for pernicious anemia (see Part IV)). Clowes felt that, in terms of comparative

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[60]J. K. Lilly, "Research in Manufacturing Pharmacy," 6.

[61]F. W. Nitardy to P. M. Giesy, 11 April 1924, "M(1): Research and Development, General 1920s," Squibb Archives.

consumption, regularly used drugs would turn more profit for the company than temporarily used medications, and the latter would be more profitable than occasionally used items. However, he went on to propose several others factors to be taken into account when considering a research proposal, such as patentability of the drug or process, prevalence of the disease for which a drug is to be used, and projected cost to the patient.[62]

Research in the pharmaceutical industry was not entirely geared to immediate practical benefit. By 1921, Lilly supported fundamental research by Clowes in Indianapolis, and the company funded a unit at the Marine Biological Laboratory in Woods Hole, Massachusetts, where Clowes and other Lilly scientists took regular retreats in the Summer.[63] Some of the basic research in Indianapolis included studies of the physicochemical nature of drug adsorption, and the mechanisms of anesthesia. Clowes summarized his Lilly-sponsored research at Woods Hole as studies of

> . . . 1) the mechanism underlying growth . . . and pathological growth as it occurs in cancer; 2) the mechanism underlying the penetration of drugs, anesthetics, germicides, etc., into living cells and the mode of action in the protoplasm of the cells, and 3) the mechanism underlying specificity, immunity, etc.[64]

Clowes incisively recognized in this type of fundamental work an impor-

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[62]G. H. A. Clowes to J. K. Lilly and Eli Lilly, 25 January 1929, "G. H. A. Clowes, Correspondence, 1925-1956," XRDc, Lilly Archives.

[63][G. H. A. Clowes,] "Report of Scientific Research Work for Year Ending November 1st, 1921," 18-page typescript, "G. H. A. Clowes--Report of Scientific Research Work, Year Ending 1 Nov. 1921," XRDe, Lilly Archives.

[64]Ibid., 1.

tance beyond the value of basic research in and of itself:

> There is one point upon which considerable stress should be laid and that is the necessity of securing the recognition, respect and confidence of scientific and medical organizations and individuals all over the world. The greater the authority with which we can speak when we do speak, the greater will be our prestige and the more certain we shall be of establishing the scientific standing of the laboratory and improving the status of Eli Lilly and Company in the eyes of the medical profession. For this reason it may pay to spend a great deal of time on the scientific intricacies of problems from the solution of which there may be no immediate commercial return.[65]

Fundamental research became a battle cry for companies later in the period between the wars, when the pharmaceutical industry opened several research institutes and laboratories (see below). It was not a case where firms were merely paying lip service to basic research, in the presence of prominent academic scientists. Firms actually were engaging in more and more of this type of research by the end of the 1930s. The experience during the 1920s and 1930s established a fundamental research consciousness in the pharmaceutical industry that eventually thrust it ahead of other industries, in terms of output of this type of research. For example, a 1955 survey of basic research in industry, in which the surveyor counted industrial publications not concerned with specific product or process applications, reported that seven drug firms were among the twenty most active American firms in publication of basic research.[66]

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[65][G. H. A. Clowes,] "Preliminary Report of Research Department for Year Ending October 20th, 1921," 10-page typescript, 3-4, "G. H. A. Clowes, Preliminary Report, Research Dept., 1921," XRDe, Lilly Archives.

[66]J. C. Fisher, "Basic Research in Industry," Science 129 (1959):1653-1657. The drug companies that placed among the top twenty were Merck (ranked 5th, 90 publications), Lilly (12th, 54), Upjohn (15th, 44),

That company executives wanted to establish research programs is clear. That they really understood how to establish a research program was another matter. For example, we saw that Carleton Palmer of Squibb was sure that he wanted his firm to have a research department, but he was not quite sure how or whether to add to his research staff. George Merck was solidly behind research at his firm. When he would walk around the laboratories, talking to the bench scientists, "he would get all excited about what people were telling him. He didn't understand it, but you could see he was getting all excited about it."[67] This is not surprising, since Palmer, Merck, and many other executives in the drug industry between 1920 and 1940 were businessmen, not scientists. Thus they, and even executives with some scientific background like the Lillys and Alfred Burdick of Abbott, turned to scientists to create research departments.

Several firms hired major scientists to head their research departments. John F. Anderson joined Squibb in 1915 as Director of the Research and Biological Laboratories. Anderson, twelve years earlier, had been the first to identify Rocky Mountain spotted fever, and suggested the wood tick (Dermacentor andersoni) as the probable vector. He had served in the United States Public Health Service since 1901, and he was the Director of the Service's Hygienic Laboratory from 1909

Burroughs Wellcome (U.S. branch; 16th, 35), and Abbott and Parke-Davis (19th, 32 each); the author lists American Cyanamid as 4th with 107 publications, but does not include Lederle, which produced 60 of Cyanamid's publications. Thus I include Lederle among the top 20.

[67]Tishler, interview by Gortler and Heitmann, 14 February 1983, 29.

until the time he joined Squibb.[68] Ernest Volwiler, the first Ph.D. student of Roger Adams, joined Abbott as a research chemist the same year he graduated from Illinois, in 1918. Volwiler was named Chief Chemist in 1920, and quickly assembled a string of impressive therapeutic discoveries, most notably in the group of hypnotics and sedatives. He became Director of Research at Abbott in 1930.[69] George Henry Alexander Clowes studied chemistry in his native England and took a Ph.D. in that field at Göttingen before emigrating to the United States in 1901. His first position in the States was at the New York State Institute for the Study of Malignant Disease in Buffalo, as a research chemist. Clowes soon developed an interest in cancer research, and became part of a small circle of pioneering researchers in that field. He worked in the Chemical Warfare Service and at the Marine Biological Laboratory at Woods Hole from 1917 to 1919, when he accepted the Lillys' offer to organize a research program in Indianapolis as Director of Research.[70]

Other firms soon followed suit. Parke-Davis hired Oliver Kamm,

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[68]Francis C. Wood," John F. Anderson, 1871-1958," Transactions of the Association of American Physicians 72 (1959):13-14, and "Dr. John F. Anderson, 1871-1958," Squibb Sales Bulletin [34](1958):541-542.

[69]"Testimonial Dinner Tendered by His Friends and Associates in the Scientific Divisions to Dr. Ernest H. Volwiler in Appreciation of His Notable Services to Abbott Laboratories, to Science, and to Mankind since May 1, 1918," [Chicago, Illinois,] 26 March 1959, mimeograph, Abbott Archives.

[70]George H. A. Clowes, Jr., "George Henry Alexander Clowes, Ph.D., D.Sc., LL.D. (1877-1958): A Man of Science for All Seasons," Journal of Surgical Oncology 18 (1981):197-217, and M. E. Krahl, "Obituary: George Henry Alexander Clowes, 1877-1958," Cancer Research 19 (1959): 334-336.

an organic chemist on the faculty of the University of Illinois, in 1920 as Director of Chemical Research. Hoffmann-La Roche was establishing a research program independent of its parent firm in Switzerland when it appointed physiologist Friedrich Gudernatsch (Ph.D., German University, Prague, 1910) as Director of Research Laboratories in 1929. Gudernatsch had spent several years prior to this appointment on the faculty of the Cornell Medical College; throughout his Directorship Gudernatsch was a visiting professor at New York University.[71] George Merck, on the recommendation of Princeton physical chemist Hugh Taylor,[72] invited a rising organic chemist at Princeton, Randolph Major, to head research at his firm. Major joined Merck as Director of Pure Research in 1930. Sharp and Dohme engaged pharmacologist John Krantz, of the University of Maryland School of Pharmacy, briefly (1927-1930) as Director of Pharmaceutical Research. A long-time faculty member at Johns Hopkins Medical School, George Harrop, came to Squibb in 1937 as Director of the Squibb Institute for Medical Research.

In addition to these well-respected research directors, many bright young scientists came to work for pharmaceutical companies in the 1920s and 1930s. For example, among those hired were pharmacologist David Macht (beginning in 1925) at Hynson, Westcott, and Dunning; biochemist George Cartland (1927) at Upjohn; pharmacologist K. K. Chen (1929) and biochemist M. E. Krahl (1933) at Lilly; pharmacologist Harry van Dyke (1938) at Squibb; and chemists William Ruigh (1930), Karl Folkers

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[71]American Men of Science, 8th ed., s.v. "Gudernatsch, Dr. Friedrich."

[72]Tishler, interview by Gortler and Heitmann, 14 November 1983, 28-29.

(1934), Max Tishler (1937), and pharmacologist Hans Molitor (1932) at Merck.

The proliferation of research (including some basic research) and a growing migration of respected scientists to industry were the most significant factors in the erosion of the tainted image of industrial work between 1920 and 1940. On the other side of the collaboration, we cannot neglect the impact of the Progressive Era. Those scientists not already inclined to consider the practical application of their work became increasingly mindful of the social relevance of their research in the early 20th century. Even as stalwart a defender of research for its own sake as G. Stanley Hall accepted utilitarian research:

> Fifteen years ago [1893] it was quite commonly assumed that pure science ranked not only far above, but must pedagogically precede applied science. . . . But I think that now, scientific values being equal or even approximately so, the problem that promises most useful results would always be preferred, even for pedagogic reasons.[73]

Science, journalism, education, and other parts of American society increasingly addressed the needs of cities, factories, consumers, the infirm, and so on. Pharmacomedical scientists, no matter how staunchly devoted to fundamental research, were in a strategic position to contribute significantly to these causes through the eradication of disease. Cooperation between universities and industry for the good of society was entirely in line with Progressive thought.[74]

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[73]Quoted in Veysey, Emergence of the American University, 125 n. 12.

[74]For example, in John Dewey's Democracy in Education (1916) we read,

> The isolation and exclusiveness of a gang or clique brings

The Rise of Research Laboratories and Institutes

Several leading, research-conscious firms in the pharmaceutical industry established special research units in the 1930s, such as the Merck Research Laboratory, which included the Merck Institute for Therapeutic Research (founded in 1933), the Lilly Research Laboratories (1934), the Squibb Institute for Medical Research (1938), and the Abbott Research Laboratories (1938). Some companies, like Parke-Davis and Lilly, had established research laboratories as early as the first decade of this century. The difference between these and the above-mentioned institutions founded in the 1930s is that the earlier laboratories only went so far as to establish a comparatively rudimentary level of science in the pharmaceutical industry, whereas laboratories established in the 1930s contributed to the general stream of pharmacomedical sciences.

The research laboratories and institutes typically opened with much fanfare. Major scientists and others from universities, the federal government, and private research foundations addressed assemblies of prominent scientists and physicians at the dedication

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> its antisocial spirit into relief. But this same spirit is found wherever one group has interests "of its own" which shut it out from full interaction with other groups, so that its prevailing purpose is the protection of what it has got, instead of reorganization and progress through wider relationships. . . . The essential point is that isolation makes for rigidity and formal institutionalizing of life, for static and selfish ideals within the group.

(from John Dewey, John Dewey: The Essential Writings, ed. David Sidorsky (New York: Harper and Row, Harper Torchbooks, 1977), 223).

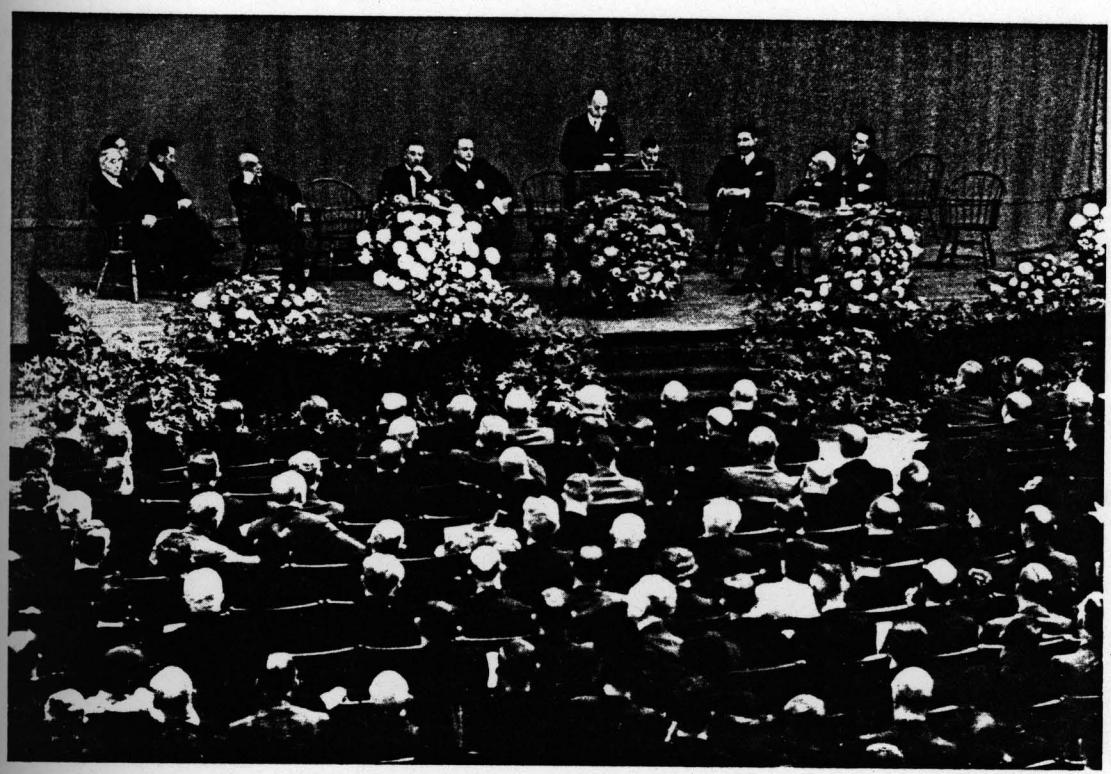
ceremonies of these research units. The speakers at the Merck Research Laboratory dedication, for example, included Surgeon General Hugh S. Cumming, industrialist Lammot du Pont, and British pharmacologist Henry Dale. Dale, Irving Langmuir of the General Electric Research Laboratory, pharmacologist Carl Voegtlin, of the United States Public Health Service, Frederick Banting of insulin fame, and the discoverers of the value of liver in anemias, George Minot and George Whipple, were among the speakers at the dedication of the Lilly Research Laboratories.[75]

In their addresses to these distinguished audiences, the executives and research directors of these firms emphasized the high level of scientific work--even fundamental work--to be expected from these research units, the need for closer cooperation between universities and the drug industry, and the separate status of these research units with respect to the business interests of the firm. George Merck informed his audience in Rahway, New Jersey, that the Merck Research Laboratory was made up of an applied research department, the Merck Institute of Therapeutic Research, and a "Pure Research division" devoted "to the study and preparation of new chemicals of scientific interest." G. H. A. Clowes reminded the Lilly audience of his company's support of basic research:

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[75]"Merck Research Laboratory Dedicated," Merck's Report and Price List 42 (1933):82-85, and Lilly, Lilly Research Laboratories: Dedication. See also The Field and the Work of the Squibb Institute for Medical Research 1, no. 1 (1938); "Squibb Institute for Medical Research Dedicated October 11," Squibb Sales Bulletin 14 (1938):513-521; and Addresses: Dedication of Research Building, Abbott Laboratories, North Chicago, Illinois, October 7, 1938 (North Chicago, Ill.: Abbott Laboratories, 1938).

Figure 4. Dedication ceremonies for the Squibb Institute for Medical Research, held at the Rutgers University gymnasium, 11 October 1938. Guest speakers on stage are (left to right) Robert Clarkson Clothier, President of Rutgers University; William H. Cole, Professor of Physiology at Rutgers (partially hidden); John F. Anderson, Vice-President and Director of the Squibb Biological Laboratories; Abraham Flexner, Director of the Institute for Advanced Study at Princeton; August Krogh, Professor of Physiology at the University of Copenhagen; George A. Harrop, Director of the Squibb Institute; George R. Minot, Professor of Medicine at Harvard Medical School (at podium); Russell M. Wilder, Head of the Section on Internal Medicine at the Mayo Clinic; Carleton H. Palmer, President of Squibb; Theodore Weicker, Chairman of the Board at Squibb; and Lowell Weicker, also of Squibb (from Field and the Work of the Squibb Institute for Medical Research 1, no. 1 (1938):2; UW neg. no. 10274 C-3).



> . . . [J. K. Lilly] and Mr. Eli Lilly fully appreciated the value of fundamental research and were not only willing but eager and anxious that we should conduct investigations in certain fields in which there could be no possible hope of any commercial return. . . . What question could there possibly be regarding association with an organization directed by men holding such an enlightened point of view?[76]

Abbott Research Director Ernest Volwiler touched on the need for closer cooperation between industry and universities: "Your presence here today to join in the dedication of this new research building shows your belief that new steps forward in hygiene must come about through the mutual efforts of the medical arts and all the accessory sciences; of the university and industry; of the individual worker in science and the highly organized group." J. K. Lilly Chairman of the Board of the Indianapolis firm, recalled that many therapeutic agents--"adrenalin, tryparsamide, thyroxin, viosterol, insulin, liver extract, parathyroid extract, ephedrine"--derived from collaborative work.[77] George Merck proclaimed that the Merck Institute operated as a foundation independent of Merck and Company, a proclamation that President Carleton Palmer echoed five years later in his dedication address of the Squibb Institute: "In fact, this Institute for Medical Research stands separate and distinct from the business activities of Squibb. It replaces none of our manufacturing research. That goes on as before. The new Institute is an addition; it will be conducted in the

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[76]"Merck Research Laboratory Dedicated," 82, and G. H. A. Clowes, "Address by Dr. George H. A. Clowes," in Lilly Research Laboratories: Dedication, 53-54.

[77]Ernest H. Volwiler, "Introduction," in Addresses: Dedication of Research Building, Abbott Laboratories, 4, and Lilly, "Research in Manufacturing Pharmacy," 5.

interests of science only."[78]

The separate nature of the Institutes of these two New Jersey firms warrants special attention, because interests outside of science proper forced Merck--and presumably Squibb--to legally detach these Institutes from the firms. Merck had planned to establish a pharmacological research laboratory to test Merck products and conduct other research since 1931. The firm equipped the laboratory and engaged a Viennese pharmacologist, Hans Molitor, to head the program (see Chapter 4). However, when Molitor arrived in the United States to begin his work, in September of 1932, he discovered a most surprising turn of events:

> Mr. [George] Perkins [Vice-President of Merck] asked me today what really a "vivisection" experiment means, and told me that the permit for performing such experiments, for which Dr. Major had applied, had been refused by the State of New Jersey. . . . It seems to me--speaking confidentially--a little bit of "Schildbürgerstreich" [i.e., a foolish act] to equip a new laboratory and engage a pharmacologist, without being sure that both of them will be permitted to work.[79]

The New Jersey State Legislature had passed an act for the prevention of cruelty to animals in 1880, which imposed a fine of up to $250 and a jail sentence of up to six months, for violations.[80] According to an amendment to this act in 1915,

> Nothing in this act contained shall be construed to prohibit

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[78]"Merck Research Laboratory Dedicated," 82, and Carleton Palmer, "Welcome," The Field and the Work of the Squibb Institute for Medical research 1, no. 1 (1938):3.

[79]Hans Molitor to [A. N.] Richards, 28 September 1932, box 32, "Hans Molitor, 1932-1933," Richards Papers.

[80]Acts of the One Hundred and Fourth Legislature of the State of New Jersey, and Thirty-sixth under the New Constitution, 1880, chap. 157.

> or interfere with any properly conducted scientific experiments or investigations, which experiments or investigations shall be performed only under the authority of the Board of Health of the State of New Jersey, the said Board of Health being hereby granted power to authorize the conduct of such experiments or investigations by agricultural stations and schools maintained by the State or Federal government, medical societies, universities, colleges and philanthropic institutions having among their corporate purposes investigation into the causes, nature and mode of prevention and cure of diseases in men or animals . . .[81]

Thus, Merck and anyone else wishing to conduct experiments with animals in New Jersey had to seek a permit for such investigations. In other states, by comparison, some firms were not only working with animals, but operating their own clinical research units.[82]

Merck applied for a permit in the late Summer of 1932. Before granting the permit, the New Jersey Department of Health asked that Merck 1) inform the Department how it proposed to use animals, and 2) incorporate the pharmacology laboratory separately from the company.[83] In the meantime, the consultant who originally suggested that

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[81]Acts of the One Hundred and Thirty-ninth Legislature of the State of New Jersey, and Seventy-first under the New Constitution, 1915, chap. 160, sec. 17.

[82]Lilly, for example, established the Lilly Laboratory for Clinical Research in the Indianapolis City Hospital in 1926. Originally, the Laboratory evaluated clinical reports on Lilly products from outside clinics, but soon it emphasized original investigations. See Kenneth G. Kohlstaedt, ["The Lilly Laboratory for Clinical Research,"] 23-page typescript, n.d., "History of the Lilly Laboratory for Clinical Research, 1926-1958," XRDuc, Lilly Archives; Leon G. Zerfas, interview by Gene E. McCormick, Camby, Indiana, 22 and 25 October 1968, 6-8, 23, 26-32, 36, 41-42, transcript, Lilly Archives; and Kahn, All in a Century, 123.

[83]Minutes of a meeting of the Department of Health of the State of New Jersey, 13 September 1932 and 6 December 1932, New Jersey State Division of Archives and Records Management, Trenton, New Jersey [hereafter New Jersey State Archives; for these and other materials from this collection, I am indebted to David Cowen].

Merck organize a laboratory for pharmacological research, pharmacologist A. N. Richards of the University of Pennsylvania, assured the President of the Department of Health he was fully confident that Merck's pharmacology department would contribute significantly to therapeutics.[84] The Rahway firm incorporated its pharmacology laboratory separately from the firm, in line with the laws of the State of New Jersey and the wishes of the Department of Health.[85] On 10 January 1933, the day after Merck filed a certificate of incorporation with the New Jersey Secretary of State, the Department of Health authorized the Merck Institute of Therapeutic Research to conduct experiments on animals.[86] Molitor soon developed a policy in the Merck Institute of using dogs and cats as little as possible, and reducing the number of experiments requiring animals to be sacrificed at the end of an investigation. He even designed a bloodless method to measure peripheral circulation in

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[84]Randolph T. Major to A. N. Richards, 29 December 1932, box 30, "Merck Institute, 1931-1940," Richards Papers; A. N. Richards to Charles I. Lafferty, 30 December 1932, ibid.; and A. N. Richards to A. Haines Lippincott, ibid.

[85]One of the stated purposes of the Merck Institute was reproduced verbatim from the 1915 amendment: "The purposes for which this corporation is formed are: the investigation into the causes, nature and mode of prevention and cure of diseases in men and animals . . ." (from Certificate of Incorporation of the Merck Institute of Therapeutic Research, art. 2, in "Certificate of Incorporation and By-Laws of Merck Institute of Therapeutic Research," 8-page mimeograph, n.d., p. 1, Archives, Merck and Company, Rahway, New Jersey [hereafter Merck Archives]).

[86]Ibid.; Minutes of a meeting of the Department of Health of the State of New Jersey, 10 January 1933, New Jersey State Archives; and Department of Health of the State of New Jersey, Fifty-sixth Annual Report of the Department of Health of the State of New Jersey, 1933 (Trenton, N.J.: n.p., 1933), 19-20.

animals.[87]

That these Institutes were legally separated from the firms is certain. That they were economically separated is an entirely different matter. Neither the Merck Institute nor the Squibb Institute were self-sustaining; we shall soon see that they were still beholden to the company. To be sure, the American Society for Pharmacology and Experimental Therapeutics felt this way. When ASPET member Harry van Dyke left academe to head the Division of Pharmacology of the Squibb Institute, the Society expelled him from membership, in accordance with its Constitution.[88] The Squibb pharmacologist argued that he merely acted as a consultant to Squibb, that he had as much freedom to pursue his research as a university scientist. (ASPET had, by this time, formally permitted members to consult with industry in a Constitutional amendment; see below.) To support his contention, van Dyke cited Carleton Palmer's address at the Squibb Institute dedication (see above), and he sent ASPET a letter from Director Harrop, which reiterated that van Dyke's status "is quite analogous to that of a university professor and that as Director of the Squibb Institute I could assure him that both he and his staff would have the same freedom

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[87]Hans Molitor, "Merck Institute of Therapeutic Research: Third Annual Report," 20-page typescript, 15 January 1936, 9-11, box 30, "Merck Institute, 1931-1940," Richards Papers, and idem and Michael Kniazuk, "A New Bloodless Method for Continuous Recording of Peripheral Circulatory Changes," Journal of Pharmacology and Experimental Therapeutics 57 (1936):6-18.

[88]Charles M. Gruber to Harry B. van Dyke, 13 July 1938, Minutes and Records, vol. 5, 1938-1939, Archives, American Society for Pharmacology and Experimental Therapeutics, Bethesda, Maryland [hereafter ASPET Archives; I thank John Parascandola for documents cited from this collection].

and support as the members of any university department."[89] These arguments did not convince ASPET Treasurer Charles Gruber. He felt that van Dyke was an employee of Squibb rather than a consultant, since he derived his full salary from the company.[90] The Executive Council of ASPET must have concurred, because they unanimously rejected van Dyke's appeal to be reinstated in the Society.[91]

For the present purposes, detailed examination of each of the research institutes and laboratories would be out of place. However, a brief discussion of the organization, evolution, and type of work at one of these research units, the Merck Institute, should convey some idea of how these units operated toward the end of the period under study, and to what extent they contributed to the breakdown of barriers to collaborative work. While the Merck Institute had a Board of Trustees (consisting of Merck and Company executives), Scientific Directors (Molitor and other Merck scientists), and Scientific Advisors (outside scientists),[92] Molitor was given much freedom in setting up

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[89]H. B. van Dyke to Charles M. Gruber, 14 July 1938, ibid.; H. B. van Dyke to G. Philip Grabfield, 21 November 1938, ibid.; and George A. Harrop to G. Philip Grabfield, 22 November 1938, ibid.

[90]Charles M. Gruber to H. B. van Dyke, 21 July 1938, ibid.

[91]Minutes of the 30th Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics, 26 April 1939, ibid.

[92]The Board of Trustees (George Merck, George Perkins, and Joseph Rosin) supervised the financial aspects of the Institute; the Scientific Directors (Molitor, Randolph Major, William H. Engels, and Dickinson Richards (a consultant to Merck on medical affairs)) determined research problems for the Institute; and the Scientific Advisors (A. N. Richards, William B. Castle, and Henry Dakin) offered counsel on the general policies of the Institute. See Molitor, "Merck Institute: Sixth Annual Report," 18, and The Merck Institute for Therapeutic Research ([Rahway, N.J.:] Merck Institute for Therapeutic Research, 1942), unpaginated

Figure 5. The Merck Research Laboratory, established in Rahway, New Jersey, in 1933. The Laboratory housed the Division of Pure Research, the Division of Applied Research, and the Merck Institute for Therapeutic Research (from Merck Sharp and Dohme International Review 21, no. 2 (1983); UW neg. no. 10276 C-3).

[p. 3].



the Institute. Molitor's goal was to build up the Merck Institute in such a way that it would improve relations between universities and industry in biology and medicine:

> At present the Merck Institute is probably still regarded by the outside world as a commercial laboratory; it will be my greatest success if this opinion can gradually be changed, and I shall do everything in my power to accomplish this task. I think that it can be done if the present management of Merck and Co. Inc. is not changed and [if] its research policy remains unaltered.[93]

The Merck Institute struggled for space and personnel during the 1930s. Until it moved into its own three-story building in 1940, the Institute was confined to three rooms (excluding animal quarters) in the Merck Research Laboratory, totalling about 1000 square feet. In addition to Director Molitor, the Institute had only one other employee with a degree--and he was a chemical engineer. But Molitor was imaginative. First, he employed medical students during the Summers. Second, most of his technicians were high school youth. Molitor trained them himself, and encouraged them later on to take classes on a part-time basis at area universities. Eventually, he arranged for a few of these technicians to do graduate work at New York University, which agreed to allow them to work on thesis topics relevant to their work at the Merck Institute. Finally, Molitor arranged for a consulting pathologist from an area hospital to work about one afternoon a week at the Institute. By 1937, the Institute employed another pharmacologist (Klaus Unna), and two years later Merck transferred a biochemist

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[93][Hans Molitor,] "Merck Institute of Therapeutic Research: Its Organization at Present and in the Future," 18-page typescript, c. January 1935, 4, attached to Hans Molitor to [A. N.] Richards, 18 January 1935, box 30, "Merck Institute, 1931-1940," Richards Papers.

to the Institute.[94]

The Merck Institute generally addressed three types of research problems: research having no immediate application to therapeutics, i.e., fundamental work; evaluation of experimental compounds submitted by Merck chemists and others, i.e., developmental research; and biological assays of established drugs, i.e., quality control work. The Institute typically conducted bioassays on such Merck products as tryparsamide, arsphenamines, B complex vitamins, vitamin K, and vinyl ether.[95] Most of the developmental work in the Institute concerned experimental drugs from Merck chemists, but Molitor believed that this should be expected of a commercially supported laboratory. Still, Molitor's group spent a significant portion of their time testing experimental drugs for outsiders (see below).[96] Molitor blamed himself for the steady decline of fundamental work in the early years at the Institute:

> I would like to emphasize at this point again, that the Board of Trustees of the Merck Institute has not only never opposed

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[94]Molitor, "Merck Institute: Organization," 12-14; idem, "Merck Institute of Therapeutic Research: Fifth Annual Report," 19-page typescript, c. January 1938, 3-4, box 30, "Merck Institute, 1931-1940," Richards Papers; idem, "Merck Institute for Therapeutic Research: Seventh Annual Report," 19-page typescript, 19 January 1940, 7-8, ibid.; and Merck Institute for Therapeutic Research, [28].

[95]Molitor, "Merck Institute: Organization," 3, 18; idem, "Merck Institute of Therapeutic Research: Fourth Annual Report," 11-page typescript, c. January 1937, 7, box 30, "Merck Institute, 1931-1940," Richards Papers; idem to [A. N.] Richards, 2 December 1938, 36-page (partially paginated) report, [14], [21], [30], [33], ibid.; and Molitor, "Merck Institute: Seventh Annual Report," 10-12.

[96]Hans Molitor to [A. N.] Richards, 6 March 1936, box 30, "Merck Institute, 1931-1940," Richards Papers, and Molitor to Richards, 2 December 1938, 8.

> research work of the abstract, fundamental type, but on the contrary has encouraged it. What I mentioned before in connection with pressure of urgent work [on the pharmacology, toxicology, and pathology of new drugs], represents entirely my own personal feeling. If anyone is to blame for the gradual sliding of the Merck Institute into developmental research it is I, and perhaps the circumstances; but certainly not our Board of Trustees.[97]

Some of the fundamental problems the Institute investigated were the influence of anesthetics on nerve currents, the mode of action of curare, the effect of pain on the circulatory system, and the influence of oxygen deficiency in arterial blood on the liver.[98]

As part of his goal to use the Merck Institute to improve relations between universities and industry, Molitor formed contacts with academic workers and publicized the work of the Institute, in a number of ways. He and other Institute staff presented papers at scientific and professional meetings regularly, the cost of which Merck at least partially subsidized. For example, in 1937 alone Institute personnel attended six major meetings, including meetings of the American Medical Association, the Federation of Biological Societies, and the American Chemical Society.[99] The Institute actively published its results as well. Molitor's group produced over 30 papers in the first five years of the Institute, and about 50 papers from 1939 through 1941.[100] Molitor and

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[97]Molitor to Richards, 2 December 1938, 10-11.

[98]Molitor, "Merck Institute: Organization," 1, and Molitor to Richards, 2 December 1938, 4.

[99]Molitor, "Merck Institute: Fifth Annual Report," 7, and Molitor to Richards, 2 December 1938, [15] (lists travel expenses for 1933 through 1938).

[100]For a bibliography of Institute publications through 1941, see Merck Institute for Therapeutic Research, [39-43].

another member of the staff presented lectures at the Rutgers College of Pharmacy on a regular basis, and Molitor made frequent visits to academic workers in a number of Eastern and Midwestern universities, particularly A. N. Richards' group at Pennsylvania.[101]

The most notable way the Merck Institute interacted with the academic community was by testing experimental drugs for university scientists. Molitor believed such work was the province of the industrial pharmacology laboratory, not the university pharmacology department:

> The determination of the toxicity of a new compound has become to a large extent a standardized procedure, offering little opportunity for startling discoveries, but requiring a great deal of time, expense and, particularly in chronic toxicity experiments, space for the housing of animals. . . . Such a procedure probably requires greater facilities than those existing in the majority of university laboratories and more time than many academic investigators are willing to spend on a problem of a semi-routine character . . . The task of providing the required data remains therefore, rightly or wrongly, in most instances that of the manufacturer, and it is probably this type of work for which a non-academic research laboratory should primarily be prepared.[102]

A large portion of the Institute's developmental research could be devoted to testing new drugs for university workers. In 1935, for example, Molitor and his co-workers tested 30 new drugs, 16 of which came from outsiders. Apparently, there was no preponderant class of drugs the group tested for university scientists, just a variety--chemotherapeutic agents, anticonvulsants, hypnotics, and so on.[103]

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[101]Molitor, "Merck Institute: Fifth Annual Report," 7-8.

[102]Molitor, "Merck Institute: Sixth Annual Report," 4-5.

[103]Molitor, "Merck Institute: Third Annual Report," 19, and idem, "Merck Institute: Sixth Annual Report," 16.

Figure 6. Graphs of the growth of the Merck Institute of Therapeutic Research, 1933-1938, in terms of increase in personnel and increase in inventory (from Hans Molitor to [A. N.] Richards, report, 2 December 1938, Fig. 1, box 30, "Merck Institute, 1931-1940," Alfred Newton Richards Papers, University of Pennsylvania Archives, Philadelphia, Pennsylvania).

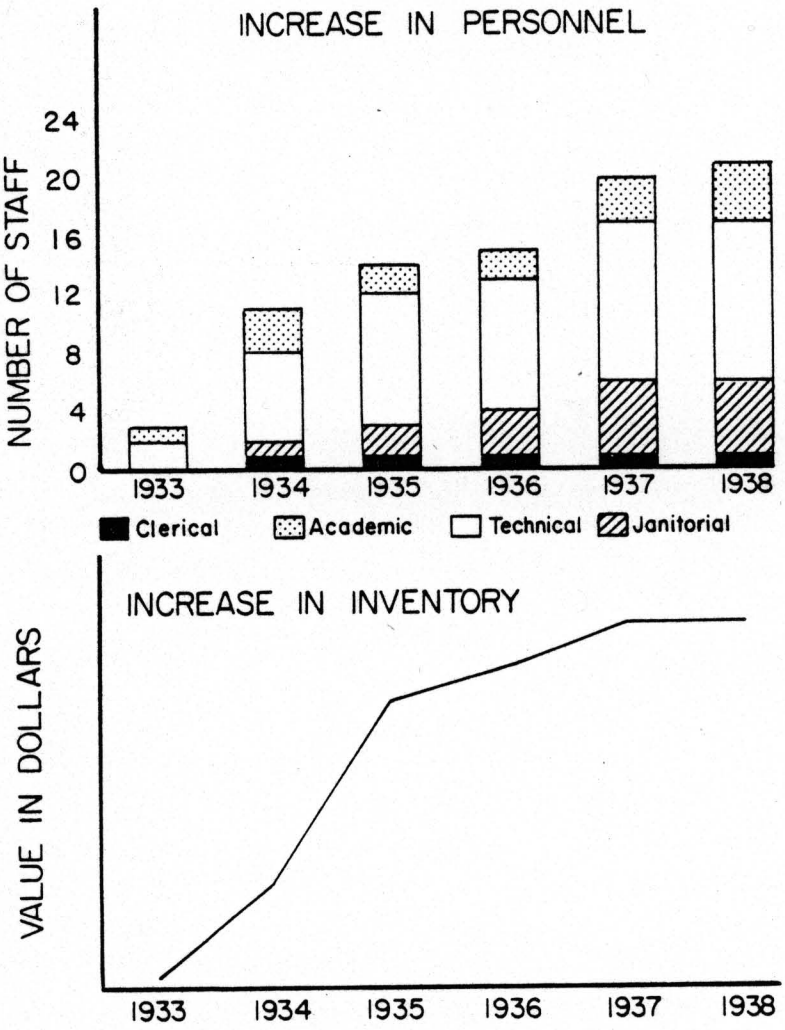
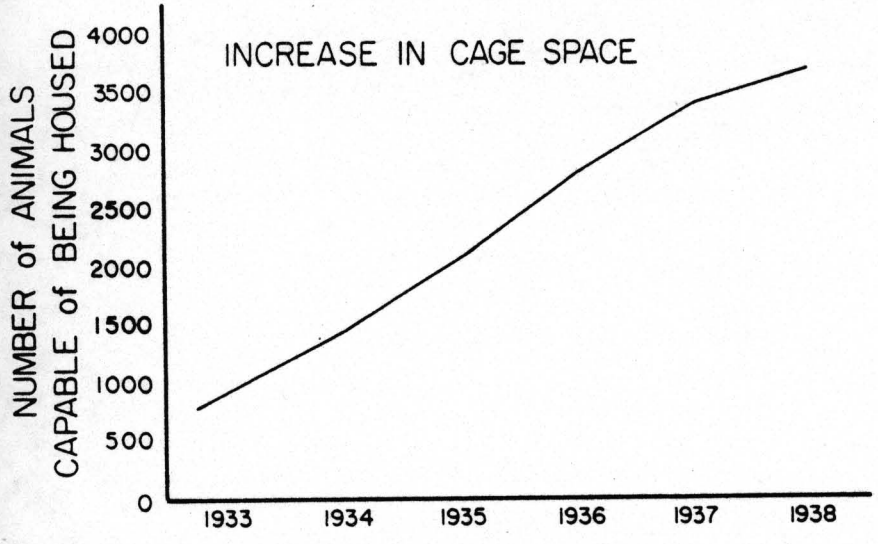

INCREASE IN PERSONNEL
NUMBER OF STAFF
24
20
16
12
8
4
0
1933
1934
1935
1936
1937
1938
Clerical
Academic
Technical
Janitorial
INCREASE IN INVENTORY
VALUE IN DOLLARS
1933
1934
1935
1936
1937
1938

Figure 7. Graphs of the growth of the Merck Institute of Therapeutic Research, 1933-1938, in terms of increase in cage space for laboratory animals and increase in publications (from Hans Molitor to [A. N.] Richards, report, 2 December 1938, Fig. 1, box 30, "Merck Institute, 1931-1940," Alfred Newton Richards Papers, University of Pennsylvania Archives, Philadelphia, Pennsylvania).


INCREASE IN CAGE SPACE
NUMBER of ANIMALS CAPABLE of BEING HOUSED
4000
3500
3000
2500
2000
1500
1000
500
0
1933
1934
1935
1936
1937
1938

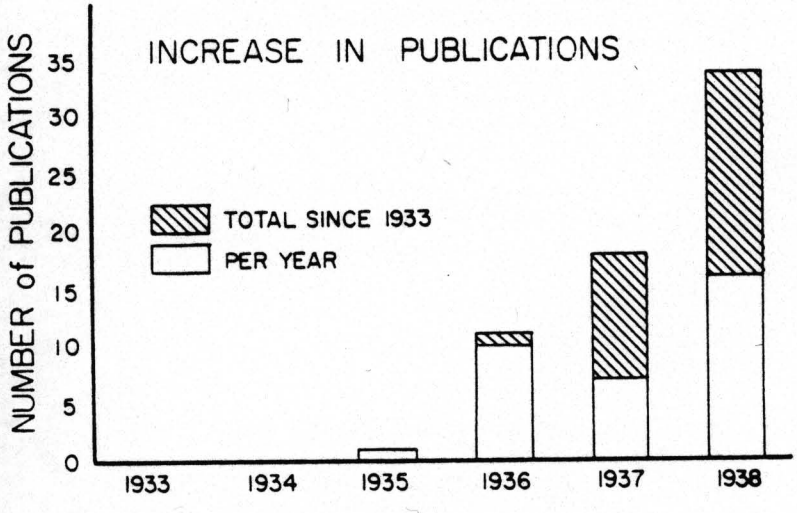
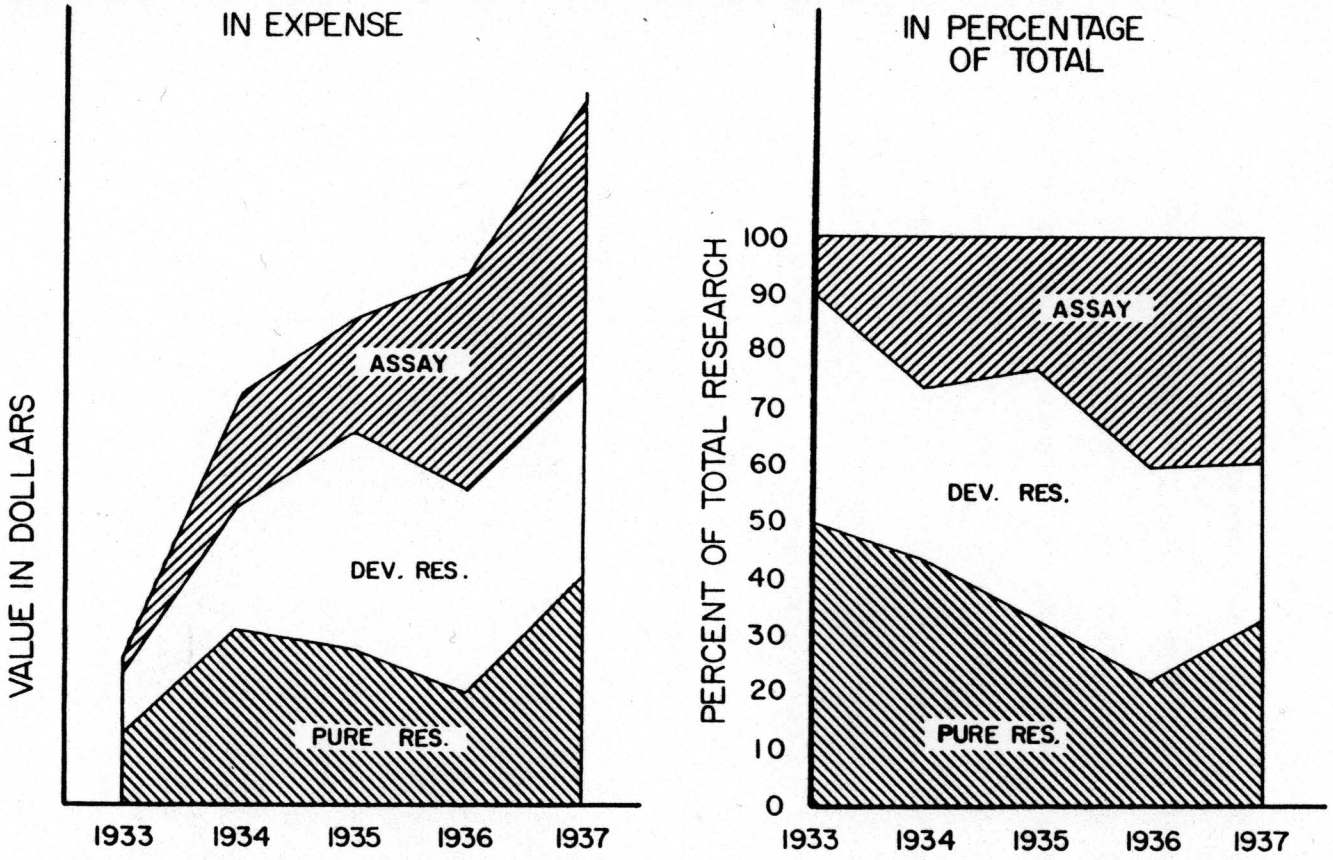

INCREASE IN PUBLICATIONS
NUMBER of PUBLICATIONS
35
30
25
20
15
10
5
0
TOTAL SINCE 1933
PER YEAR
1933
1934
1935
1936
1937
1938

Figure 8. Graphs of the changing distribution of work at the Merck Institute of Therapeutic Research, 1933-1937, for pure (or fundamental) research, developmental (or applied) research, and bioassays on therapeutic agents. Distribution is pictured in terms of expense of the work involved and the percentage of the total work in the Institute (from Hans Molitor to [A. N.] Richards, 2 December 1938, report, Fig. 2, box 30, "Merck Institute, 1931-1940," Alfred Newton Richards Papers, University of Pennsylvania Archives, Philadelphia, Pennsylvania).

DISTRIBUTION OF RESEARCH



All of the factors discussed in the preceding sections--the growing interest in and support of research in the pharmaceutical industry, the slow migration of prominent academic scientists to industry to organize and direct company research programs, the movement of promising young scientists into industrial positions, the academic scientist's growing concern for the social relevance of his work in the Progressive Era, and the sudden emergence of a cluster of industrial research institutes and laboratories--helped erode the barriers to collaborative biomedical research between the two World Wars. Successful collaborations early in this period, such as the work between Roger Adams and Abbott on barbital and procaine (Part II), and the introduction of insulin through the joint efforts of the University of Toronto and Lilly (Chapter 6), fueled the fire of cooperative work. Abbott President Alfred S. Burdick's address to the American Pharmaceutical Manufacturers' Association, in the early 1930s, testified to this change of venue in cooperative biomedical work:

> I also want to stress cooperation in research. There never was a time, for instance, when the university men were so eager to collaborate with commercial houses as they are now. I remember when we first started in, the average college professor working in the field was a haughty creature. He would not be tainted with commercialism in any form. His research was academic, for purposes of science. I may say that is all changed. They are just as eager to have friendly relations with commercial houses as any other type of men. In fact, they come to me almost every day or every few weeks--men connected with universities that are following certain lines of research, whose funds have run out or are not available on account of the present depression, eager and anxious to make commercial connections with people who will finance them. Some of these things have great promise. It would really be for the benefit of mankind if some of you men who have surplus funds, if any of you have and I hope you have,

would consider some of these possibilities.[104]

Growth of University-Industry Interactions

Parts II, III, and IV discuss in some detail how and why university scientists and pharmaceutical firms worked together during the formative era of collaborative research, and what each side got out of the joint work. Here I will consider some general aspects of collaborative work, specifically, the growth of contacts between academe and industry, and the nature of such contacts by the end of the period under study--as evinced by Lilly, one of the leading, research-oriented firms in the industry. The latter, especially, will convey a sense of how far university-industry connections evolved by the early 1940s.

Companies typically supported research in universities during the 1920s and 1930s through fellowships or grants--cash payments, usually for a specific period, made either to the professor to disburse as he saw fit or to a student working under that professor, in the form of a stipend. The fellow or grantee often was obligated to file regular progress reports with the company. The specific terms of these awards varied from company to company and from fellowship to fellowship within each firm. Some fellowships were purely philanthropic, but by and

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[104]Alfred S. Burdick, "Research," address at the Annual Meeting of the American Pharmaceutical Manufacturers' Association, Greensboro, North Carolina, 18 May 1932, Proceedings of the American Pharmaceutical Manufacturers' Association, 1931-1932:373-374.

large fellowships served immediately strategic purposes.[105] For example, the company could insist on choosing the research topic it supported, as a means to supplement or even substitute for in-house research.[106] Also, the firm could make prior arrangements for the disposition of any discoveries made in the professor's laboratory.[107] A firm often awarded a grant or fellowship simply to maintain an open channel of communication with a researcher at the cutting edge of a particular field.[108]

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[105]The Lilly Fellowship for the Study of Chemistry at the Johns Hopkins University, for example, was a philanthropic fellowship. It awarded a $1000 stipend to an Indiana resident for study at the Baltimore university; see Callie Hull and Clarence J. West, "Fellowships and Scholarships for Advanced Work in Science and Technology," 2d ed., Bulletin of the National Research Council, no. 72 (1929):62. One could argue, of course, that such publicized "philanthropic" fellowships had strategic value--improving a firm's image. However, in terms of a company's research interests, such a fellowship was of marginal relevance at most.

[106]See, e.g., the J. K. Lilly Fellowship no. 28 and no. 29 at the Purdue University College of Pharmacy, and the Parke, Davis and Company Fellowships in the Department of Chemistry at the Iowa State College of Agriculture and Mechanic Arts, in idem, "Fellowships and Scholarships for Advanced Work in Science and Technology," 3d ed., ibid., no. 94 (1934): 67, 120.

[107]Several examples can be seen in the arrangements Wisconsin pharmacologists Arthur Loevenhart and Arthur Tatum made with the many firms they collaborated with, discussed in Chapter 5.

[108]See, e.g., Squibb General Superintendent F. W. Nitardy to P. M. Giesy, 28 August 1923, "M(1): Research and Development, General, 1920s," Squibb Archives:

> . . . we might contribute to the expenses of people who would . . . in return [keep] us informed on what was going on and what new things were under investigation, so that if anything of particular interest to E. R. Squibb and Sons were under investigation, we would have first hand information on it and could get in touch with the investigator personally if the case should warrant it. This, as you will see, is just for the purpose of linking the House up in some sort of a direct form with all the medical research work that is done in public institutions.

One way to arrive at an estimate of the growth of university-industry research interactions in this period is to examine the increase of fellowships. Research Information Service of the National Research Council published surveys of fellowships in science and technology in 1923, 1929, and 1934.[109] The data pertaining to academic fellowships subsidized by pharmaceutical firms are summarized below.[110]

Year	Companies	Fellowships	Total Amount
1923	4	8	$6,300
1929	6	19	$13,200
1934	10	40	$37,050

The surveys certainly suggest an increasing level of interaction between biomedical scientists in universities and the pharmaceutical industry. However, we should not look at these data as a comprehensive picture, because the actual number and value of fellowships--and perhaps the number of companies as well--were much higher. Companies were not

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[109]Research Information Service, "Fellowships and Scholarships for Advanced Work in Science and Technology," Bulletin of the National Research Council, no. 38 (1923); Hull and West, "Fellowships and Scholarships," 2d ed.; and idem, "Fellowships and Scholarships," 3d ed.

[110]I have made some assumptions in tabulating the data, where information was incomplete. For the 1929 survey, I assumed Upjohn awarded five fellowships at Kalamazoo College, the number the firm awarded according to the 1923 survey. Also, the 1929 survey did not state the amount of the Squibb fellowships at California, Hopkins, and Wisconsin; thus, the value of these fellowships is not reflected in the "Total Amount" column, although I counted Squibb and its three fellowships. For the 1934 survey, I again assumed that Upjohn offered five fellowships at Kalamazoo College, and that Parke-Davis offered three fellowships at Iowa State (the number the firm awarded in 1929). Several companies in the 1934 survey did not state the amount of some of their fellowships: Abbott (1), Lilly (2), Parke-Davis (3), and Squibb (1). While I counted the companies and these seven fellowships, the value of the latter are not included under "Total Amount."

always willing to divulge the names of the groups they were supporting, for fear that competitors might get wind of their research activities and interests. The university worker, too, could be reluctant to publicize the fact that he was receiving support from a firm. For example, he could have felt his colleagues would look askance at any of his publications throwing a good light on a supporting firm's product.[111]

More accurate information on fellowship support is available from a few leading companies for selected years during the period under study. This at least will give us a fair idea of the level of support which some firms were willing to accord research in universities. From 1925 to 1930, Squibb's fellowship support increased significantly, as the firm's total research budget grew: 1925, $18,400; 1926, $15,900; 1927, $18,000; 1928, $22,400; 1929, $30,200; and 1930, $48,609. Overall, fellowships represented one-seventh of the total research expenses for these years.[112] Thus, Squibb seems to have relied on university laboratories as an important additional source of research. Upjohn instituted a major fellowship program in 1933. The firm awarded a dozen fellowships each year, ranging from $1800 to $5000, and the fellows spent the year at Upjohn.[113]

Merck also invested a major sum in academic research fellowships

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[111]For example, see Tatum's connections with Abbott in Chapter 5.

[112]E. R. Squibb and Sons, "Annual Report," 8 April 1931, 51, "Research, 1900-1925," Squibb Archives. Squibb supported a fellowship at least at one private research institution, the Mellon Institute, which is included in the data. However, the bulk of Squibb's fellowships went to academic workers.

[113]Engel, Medicine Makers of Kalamazoo, 89-90.

by the late 1930s. In 1939, that firm funded 17 projects at 11 institutions for a total of $38,500. Unlike the case with Squibb in the late 1920s, Merck's fellowships amounted to no more than about five percent of its total research expenses.[114] Reliable information exists for selected years throughout this period for Lilly. In 1925, on the heels of its successful and widely publicized collaboration with the University of Toronto on insulin, Lilly formed research contacts with academic workers at eleven institutions.[115] Unfortunately, the amount of Lilly's support is unknown. Five years later, following other major collaborations--with Harvard and with Rochester on liver extracts for anemias--Lilly's fellowship activity grew. The company established 17 fellowships in 14 universities, worth nearly $32,000.[116] By 1942 this sum increased to over $87,000 annually, representing 45 fellowships in 27 academic institutions. On the basis of the firm's 1943 research budget, fellowships accounted for about eleven percent of all research expenditures.[117]

As seen by Merck, Squibb, Upjohn, and Lilly, industry and academe interacted more and more during this period. Also, scientists began

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[114]John H. Gage to A. N. Richards, 12 December 1938, box 31, "Merck and Co., 1930-1939," Richards Papers.

[115][J. K. Lilly,] "Eli Lilly and Company: A History," 75, Lilly Archives.

[116]Ibid., 91-92.

[117]Minutes of the meeting of the Research Committee, Eli Lilly and Company, 1 July 1942, "Research Committee, 1942," +XRDj, Lilly Archives, and "Outline of 1943 Research Plan," sec. 6, p. 1, "Research Plans, 1942-1944," ibid.

organizing themselves to promote or at least facilitate cooperative research. For example, pharmaceutical scientists organized the National Conference on Pharmaceutical Research in 1922 to encourage and coordinate pharmaceutical research. Academic and industrial scientists served side-by-side on the Conference's Executive Committee and various scientific committees, which reviewed research of the previous year in medicinal chemistry, bacteriology and biologicals, pharmacology and bioassays, and other areas. The Conference lasted through the 1920s and 1930s.[118] Academic and industrial scientists also worked together on the Subcommittee on Bioassays of the United States Pharmacopoeial Committee. Representatives from Squibb, Parke-Davis, and Mulford served with five university workers and one government scientist on the Subcommittee appointed for the 10th revision of the Pharmacopoeia, beginning in 1920.[119] The National Research Council established a Committee on Chemical Research on Medicinal Substances to promote contacts between industry and academe. Among the members of this Committee were industrial researchers Frederick Heyl of Upjohn and Arthur Dox of Parke-Davis, and university chemists who were seasoned collaborators with

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[118]See the Proceedings of the National Conference on Pharmaceutical Research, which began publication in 1928, and the Annual Survey of Research in Pharmacy, which replaced the Conference's Proceedings and continued to be published until 1940.

[119]Peter Stechl, "Biological Standardization of Drugs before 1928," Ph.D. diss., University of Wisconsin, 1969, 223-229. Industry scientists had played a prominent role in a similar committee, the Committee on Physiological Testing of the Scientific Section of the American Pharmaceutical Association, since its inception in 1910; see M. G. Allmark et al., "A History of the Committee on Physiological Testing, Scientific Section, American Pharmaceutical Association," Drug Standards 24 (1956):200-205.

the pharmaceutical industry, such as Roger Adams of Illinois, Frank Whitmore of Northwestern (and later Pennsylvania State), and Treat Johnson of Yale.[120]

Later in the period between the two World Wars, an abortive but nonetheless notable attempt to organize cooperation unfolded among a few prominent biomedical scientists. In 1939 a group of distinguished researchers from academe, including Newton Richards, George Whipple of the University of Rochester, pharmacologist E. K. Marshall of Johns Hopkins, and Wilder Penfield of McGill University--headed by Frederick Banting and later William P. Murphy of Harvard--organized the Committee on Cooperation between Industrial and Medical Research.[121] The Committee hoped "that the large industrial groups might be interested in making available for medical research data or products developed in their laboratories, and that they might help to organize and subsidize mass attacks, according to the industrial method, against certain diseases or problems."[122] The planning stage of the Committee lasted over a year, but it never came to fruition. In the first place, both sides gradually lost interest. Also, the United States government

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[120]Haynes, American Chemical Industry, 4:251-252.

[121]William P. Murphy to A. N. Richards, 6 September 1939, 13 September 1939, and 9 October 1939, box 14, "Murphy's Committee," Richards Papers; A. N. Richards to William P. Murphy, 11 September 1939, ibid.; and Alfred N. Richards to Ross G. Harrison, 11 June 1940, ibid. According to Richards (ibid.), the idea for this committee originated with the du Ponts' personal physician-psychiatrists, who were interested in medical research and "wanted to get some of the du Pont money but [they] decided that their claims were scarcely convincing enough to bring home the bacon, and so they conceived the plan of drawing in the medical [researchers]."

[122]Murphy to Richards, 9 October 1939.

already had begun coordinating (under Richards' direction) industry, academe, private research institutions, and government laboratories on a mass scale on the eve of America's entrance into the war.

I have suggested some ways by which we can gauge the growth of university-industry interactions in the 1920s and 1930s. Another way we can estimate this growth is by looking at the process of interaction as it emerged at the end of this period. In Eli Lilly and Company, certainly one of the most active firms in the pharmaceutical industry in terms of research, we can see that a very elaborate system of contacts with the community of academic biomedical scientists emerged by the early 1940s. First, fellowships were Lilly's primary source of contact with university researchers. As mentioned above, the firm's support of university work through fellowships and grants approached $100,000 annually by 1942. In that year, Lilly began classifying fellowships according to the following scheme: A) new products, B) establishment or improvement of a product, C) fundamental work, and D) good will (to remain on intimate terms with a research group). After determining the distribution of total fellowship funds in this scheme for the previous year, the firm decided to award future fellowships with the following distribution in mind: A) 40 percent (30 percent the previous year), B) 10 percent (3.7 percent), C) 30 percent (30.3 percent), and D) 20 percent (36 percent). The firm also elected to dispense with the requirement of regular research reports from fellows (unless the fellow sought a renewal). Instead, Lilly chose to gather information on a fellow's research through contact trips by Lilly representatives to the fellow's laboratory, or through meetings of

scientific and professional societies.[123]

Second, Lilly tapped the scientific resources of universities by engaging consultants--trouble-shooters for specific problems and advisors on general problems:

> Consultants on our problems will for the most part be confined to university professors who, by their own endeavors and those of their students, have acquired specialized knowledge in one particular field. Their potential value to us will depend on the assumption that their highly specialized knowledge--
> a. will save time on specific important research projects;
> b. will suggest new methods of approach on existing problems;
> c. will give us suggestions from their own experience which may lead directly or indirectly to new fields of research and the possibility of developing new products.
> In a practical sense these functions resolve into two types of consultants--special, per diem consultants brought in for help on specific problems, and long-term, general consultants who virtually act as advisers to an entire research department.[124]

To what extent Lilly took advantage of "special" consultantships is not clear, but the firm used these as needed, and paid them a maximum of $100 per day, plus expenses. Lilly appears to have engaged four general consultants by 1943: an organic chemist from the University of Chicago, at $2000 annually; a chemical engineer from Purdue, at $600 per year; a biochemist from the University of Illinois, at $600

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[123]Minutes of Lilly Research Committee meetings, 20 May 1942 and 10 July 1942, "Research Committee, 1942," Lilly Archives, and Report of the Fellowship Committee of the Lilly Research Committee, 1 July 1942, ibid.

[124]"Outline of 1943 Research Plan," sec. 4, pp. 2-3. Lilly's "special" and "general" consultants both fall under the rubric of "specialist-consultant," as I have defined it in Part III. Note also that a firm could glean such information as stated in a., b., and c. from its fellows. The general consultant, as I define the term in Part II, was more an advisor to the company overall, than an advisor to a single research department.

per year; and an organic chemist from the University of Indiana, at $2400 annually.[125]

Third, Lilly publicized its interest in academic research through awards to several scientific societies. While these awards carried no obligation whatsoever to Lilly, they benefited the company indirectly by elevating its image among the scientific community. Lilly offered annual awards worth $1000 each to the American Chemical Society, the American Association for the Advancement of Science, and the Society of American Bacteriologists; the firm added the American Society of Tropical medicine to this group in 1941. The societies administered these awards.[126] In 1942, Lilly even arranged a $1000 award for the American Society for Pharmacology and Experimental Therapeutics, the society that only a year earlier had overturned its membership ban on pharmacologists employed by industry.[127]

Fourth, the company launched a plan by the early 1940s whereby

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[125]J. P. Scott to [K. K.] Chen and [H. A.] Shonle, 6 April 1942, "Research Committee, 1942," Lilly Archives; Minutes of Lilly Research Committee meetings, 20 May 1942, 10 July 1942, and 12 November 1942, ibid.; "Outline of 1943 Research Plan," sec. 4, pp. 2-3; Minutes of the Executive Committee of the Lilly Research Committee meeting, 8 February 1943, "Research Committee, 1943," +XRDj, Lilly Archives; and Minutes of the Lilly Research Committee meeting, 13 May 1943, ibid.

[126]Report of the Committee on Scientific Awards of the Lilly Research Committee, 11 June 1942, "Research Committee, 1942," Lilly Archives. On the typical terms of these awards see, e.g., "The Eli Lilly and Company Award in Biological Chemistry," Industrial and Engineering Chemistry 26 (1934):425-426.

[127]Minutes of the Lilly Research Committee meeting, 10 July 1942; Minutes of the Executive Committee of the Lilly Research Committee meeting, 13 August 1942, "Research Committee, 1942," Lilly Archives; Minutes of the Executive Committee of the Lilly Research Committee meeting, 1 April 1943, "Research Committee, 1943," Lilly Archives.

research staff annually visited scores of academic research centers across the United States and in Canada. This system of contacts helped keep Lilly apprised of research in universities, even if the contact were unable to spend more than one or two days at each institution. Every division within the company took part in this program: the Medical Department sent six representatives to visit 75 universities and independent medical colleges; seven representatives of the Biological Division contacted 19 universities; two representatives from the Pharmacology Department visited 18 medical schools; the Organic Chemistry Department put six representatives in contact with 31 academic institutions; and the Biochemistry Department sent four representatives to 12 universities.[128] It is not clear how cooperative the academic workers were with the Lilly representatives, but the firm built up many valuable research contacts with this program.

Fifth, Lilly established quotas of delegates to attend scientific and medical meetings. This gave the firm an opportunity to learn of the progress of its fellows, to keep abreast of the latest developments in various fields, to publicize the firm's own research achievements, and to encourage quality research among its staff. The Lilly Research Committee determined the quotas, and the department heads selected the delegates. The firm decided to send about 100 delegates to 38 different meetings and symposia from July 1942 to January 1944, including 18

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[128]Report of the Committee on Contact Visits to Research Centers of the Lilly Research Committee, 6 July 1942, "Research Committee, 1942," Lilly Archives, and Minutes of the Lilly Research Committee meeting, 10 July 1942. The proposal for such a contact program was first made in 1939; see M. M. Weaver to Eli Lilly, 7 June 1939, "Myron M. Weaver, Suggestions for New Research Contact Plan, 7 June 1939," XRDc, ibid.

delegates for the joint meetings of the Federation of American Societies for Experimental Biology, nine delegates for the American Chemical Society meetings, and six to seven delegates for annual meetings of the American Medical Association and the American Pharmaceutical Association.[129] Sixth, Lilly initiated a series of monthly lectures at the firm, often by distinguished scientists, such as Cornell biochemist Vincent du Vigneaud. This gave at least some Lilly researchers the opportunity to interact with stars in biochemistry, pharmacology, organic chemistry, and other fields, plus it allowed the firm to put its research programs on display--and perhaps plant the seed for future collaborations with leaders in their fields.[130]

Finally, the Indianapolis firm assembled a so-called "cream list" of researchers and physicians. The company sent the cream list three or four "carefully chosen reprints" of Lilly research publications each month, "as a means for acquainting outside research investigators and those interested in research with the scope of our activities in our laboratories . . ." Lilly's cream list numbered about 1300 individuals by about 1942.[131] Lilly clearly had developed an involved network of contacts with the scientific community by the end of the

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[129]Report of the Committee on Delegates to Society Meetings of the Lilly Research Committee, 6 July 1942, "Research Committee, 1942," Lilly Archives, and Minutes of the Lilly Research Committee meeting, 10 July 1942.

[130]Minutes of the Lilly Research Committee meetings, 20 May 1942 and 10 July 1942. Some of these distinguished speakers, however, already had established connections with Lilly. Vincent du Vigneaud, for example, held a Lilly fellowship since 1938.

[131]"Outline of 1943 Research Plan," sec. 3, pp. 1-2

period under study. The details of contact programs probably varied from company to company, but firms had to evolve some means of contact with academe to remain competitive with Lilly. By this time, discoveries in the pharmaceutical industry rapidly became obsolete, and the only way to avoid obsolescence was by staying on top of the latest research in biomedical fields. A well-established in-house research program was a big step in this direction, but in itself was insufficient; firms also had to keep in close contact with work in universities. The growing frequency and complexity of interactions between universities and industry reflected the needs of a competitive, research-based, rapidly changing enterprise like the prescription-drug industry.

Conclusion

As the period between the wars drew to a close, university workers were more receptive to collaborative research with industry, as documented above, less censorious in their view of industrial work, and were themselves pursuing certain commercial practices with respect to medical discoveries which formerly were commonly decried in academe. Members of ASPET, for example, began challenging the Society's policy of banning industrial pharmacologists from membership. As early as 1915, John J. Abel had begun collecting opinions from members about removing the ban. His personal opinions of cooperative work notwithstanding, Abel began wondering if interactions between academe and industry might improve the latter; membership for the better industrial

workers would indicate to firms that pharmacologists were willing to help elevate the pharmaceutical industry.[132] Four years later Abel, Arthur Loevenhart (President of the Society), and five other members proposed an amendment to the ASPET Constitution to eliminate the ban. They felt the Constitution already amply provided for cases of unethical conduct, and that ASPET should consider membership eligibility on individual merit alone. When the amendment came up for a vote at the 1920 meeting, the members present unanimously defeated the proposal.[133]

The issue of the ban arose again from time to time in the 1920s and 1930s; while proponents of the proposed amendment of 1919 could not secure the necessary four-fifths of the vote, they sometimes won a simple majority. The movement against the ban grew stronger during this period. Abel, among others, revealed his opinions in no uncertain terms. For example, he informed one colleague that "I do not approve of our exclusion from membership in the Society of highly trained men like Chen, John Anderson, Clowes, and others just because they happen to be making their living by working in the research laboratories of

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[132]John Parascandola, "Academic Pharmacologists and the Pharmaceutical Industry in the United States, 1900-1940," unpublished paper presented at the Johns Hopkins Institute of the History of Medicine, Baltimore, Maryland, 1 December 1983.

[133]Minutes of the American Society for Pharmacology and Experimental Therapeutics 11th Annual Meeting, Cincinnati, Ohio, 29 December 1919, box 3, "Personal Correspondence, P-Q," Loevenhart Papers; A. S. Loevenhart to S. J. Meltzer, 19 January 1920, ibid.; Arthur S. Loevenhart et al., circular regarding proposed amendment to the Constitution of the American Society for Pharmacology and Experimental Therapeutics, n.d., ibid.; and Parascandola, "Academic Pharmacologists and the Pharmaceutical Industry."

some of our large firms."[134] In 1937, ASPET amended its Constitution to exclude paid consultants formally from the ban, in part because several members (such as Newton Richards, Arthur Tatum, and Chauncey Leake) were collaborating with firms. In April, 1941, the Society finally voted to remove the ban.[135]

Companies made frequent use of the patent system to protect their research investments, once they established research programs. Squibb held only one patent as of 1920. Ten years later the firm held 21 domestic and 33 foreign patents, and by 1940 these numbers increased to 164 domestic and 39 foreign patents. In 1937 alone, Merck filed 27 domestic and 19 foreign patent applications. Ernest Volwiler had a hand in 27 domestic patents awarded to Abbott between 1920 and 1940.[136] A rising number of universities, too, were using the patent system by the early 1920s. Schools ostensibly administered patents on discoveries by their faculty for the public interest--to prevent pharmaceutical companies from monopolizing these discoveries, and to maintain quality standards among firms they licensed to market the discoveries. That royalties derived from these licenses padded a university's research coffers also entered into the decision to secure patents. President

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[134]John J. Abel to William deB. McNider, 3 June 1931, Abel Papers; see also Abel to MacNider, 5 April 1935.

[135]Parascandola, "Academic Pharmacologists and the Pharmaceutical Industry," and Chen, American Society for Pharmacology and Experimental Therapeutics, 178-179.

[136]Nitardy, "Long Range Comparative Report," 43; Randolph T. Major, "Report of Research and Development, Merck and Co., Inc., Year of 1937," 27-page typescript, 25 March 1938, 17-20, box 31, "Merck and Co., 1930-1939," Richards Papers; and "Testimonial Dinner to Volwiler," [10].

Nicholas Murray Butler of Columbia admitted that one of the reasons his university pursued patents was "to enable the University itself to share in the benefits of the patents, to the end that the funds at its disposal for the promotion of research may be increased."[137]

Thus, by the mid-1920s several universities established early precedents for the patenting of medical discoveries: Columbia, which administered the patent on T. F. Zucker's concentrated preparation of cod liver oil; Minnesota, to which Edward Calvin Kendall of the Mayo Clinic assigned his patent on thyroxin; Toronto, which administered the patent on insulin, stemming from the work of Frederick Banting, Charles Best, J. J. R. Macleod, and J. B. Collip at that institution; and Wisconsin, which benefited from Harry Steenbock's vitamin D patent, as administered by the Wisconsin Alumni Research Foundation.[138] By the mid-1930s, at least a dozen universities administered patents on medical discoveries by faculty.[139] This movement did not proceed without resistance. Pennsylvania, Johns Hopkins, and Harvard, for example, instituted policies in the early 1930s forbidding faculty to take out

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[137]Quoted in H. Steenbock, "The Relations of the Writer to the Wisconsin Research Foundation and the Events Which Led to Its Organization," 9-page typescript, January 1926, box 1, "Relation of Writer to Foundation, 1," Harry Steenbock Papers, University of Wisconsin Archives, Madison, Wisconsin (I am indebted to Jonathan Liebenau for this and other material cited from the Steenbock Papers); see also Shryock, American Medical Research, 141.

[138]Ibid.; [Harry Steenbock,], "The Administration of the Results of Research," 7-page typescript, n.d., ibid.; and Michael Bliss, The Discovery of Insulin (Chicago: University of Chicago Press; Toronto: McClelland and Stewart, 1982), 131-133.

[139]Morris Fishbein, "Medical patents," Journal of the American Medical Association 109 (1937):1539-1540.

patents for the purpose of profiting the discoverer or university. But in general the process of academic scientists patenting their discoveries, a process sanctioned and even encouraged by many universities, was fairly well-established by the 1930s. What was once an impediment to cooperation between pharmaceutical firms and universities was now an important interest of academic researchers.

Industry support of medical research in universities was growing at a good time. Over the period between the wars, the massive support of private foundations (Rockefeller, Carnegie, Macy, etc.) was slowly declining, particularly during the Depression, and the federal government had not yet launched its mega-support of research in academe.[140] The contact with universities helped industry, too; first, because the former offered companies their valuable experience in research; and second, because no matter how far developed, an industrial laboratory alone could not possibly attend to all research needs in every field. Finally, collaborations between the two sides yielded important hormones, anticonvulsants, sedatives and hypnotics, chemotherapeutic agents, and other drugs between 1920 and 1940. Therapeutics and public health thus profited from cooperative research as well.

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[140]Shryock, American Medical Research, 88-174, and George Rosen, "Patterns of Health Research in the United States, 1900-1906," Bulletin of the History of Medicine 39 (1965):211-216.

PART II

THE SCIENTIST AS A GENERAL CONSULTANT

American pharmaceutical companies did not begin to cultivate research until the period between the two World Wars, as mentioned in the previous two chapters. Firms such as Squibb, Abbott, Lilly, and Merck, with their newly formed interest in developing in-house research programs, faced several problems in transforming themselves to research-based industrial organizations. For example, how would they organize, house, and staff their research programs in the various medical and pharmaceutical sciences? Once they established such programs, what research policies would they formulate to direct these new programs? They would have to decide to what extent their research personnel would be permitted to contribute to the general advance of science, which called for policy statements on attendance at scientific meetings, publications in scientific journals, and so on. More importantly, these companies would have to decide which drugs or drug groups they would explore and develop. As a final example, how would these firms--if they were to take this course--establish outside contacts to supplement their own research programs? Company executives, research directors, and research staff solved some of these problems. But occasionally some companies turned outside, to university scientists, for counsel on such problems. But occasionally some companies turned outside, to university scientists for counsel on such problems.

The type of academic researcher that a company would contact for advice on its internal affairs was a well-rounded, well-informed

individual. He was a first-rate scientist, well-respected by his peers. But he was not the type of worker who spent his life in the laboratory, like a Max Gottlieb. Rather, he formed and maintained outside contacts in his field, and he developed some contacts outside of his field. If he was not aware of some recent development within or outside of his sphere of expertise, he probably knew people who did. He was persuasive, analytical, and usually had some business sense. He typically had some experience in establishing a new research program at a university. His energy level was usually in overdrive; it would not be unusual for him to direct a major research program, head a professional society, and edit a major scholarly journal--simultaneously. His experience in the planning and execution of research, his broad knowledge of research and researchers, and the universal respect and admiration that he commanded among his colleagues, served the fledgling industrial research programs of the 1920s and 1930s well.

This type of scientist influenced, not only company affairs dealing directly with his narrow sphere of expertise, but many facets of the company's operations. Thus, I call this interaction between a university scientist and a pharmaceutical company a general consultantship, as opposed to the specialist-consultant (see Part III) and the project collaborator (Part IV). The cases I have investigated suggest that the general consultant provided a wide range of services for the company. Moreover, he primarily served only one pharmaceutical firm in this capacity (although he could serve companies in other industries), for many years; one consultantship cited in this Part spanned six decades. The following exemplify some of the ways in which a

general consultant interacted with a pharmaceutical company, although the extent to which each of these services was emphasized varied with the individual.

First, the consultant[1] helped the company develop its research program, in one or more fields. This could consist of recommending or recruiting research scientists to fill new or vacated positions, suggesting designs for the laboratory facilities, or even inculcating the necessity of having industrial research programs for certain fields in the company. Second, the consultant acted as a liaison between the company and the academic community. This was an especially important service for some companies, if they could not call upon their own reputation to engage a university scientist or group for some type of research collaboration. It meant a lot to a prospective collaborator for a consultant to tell them of his long and close relationship with a company, and his confidence in the company's commitment to high scientific ideals. Third, the consultant helped foster particularly close connections between his university and the company. These connections could extend to other departments in the university, and to the clinical units.

Fourth, the consultant served as a sort of character reference for the company in any disputes with the government, in a somewhat analogous way to number two above. In the case of the university liaison, however, the consultant could help bring the two parties together and assist in the cooperative research plan. The consultant's role in the

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[1]When referring to a consultant or consultantship in this Part, I mean a general consultant or consultantship, unless indicated otherwise.

case of industry-government affairs was more of a public relations activity. Fifth, the consultant kept the company abreast of the latest trends in pharmacology, chemistry, therapeutics, etc. It was vital for a company in a competitive, research-oriented business like the pharmaceutical industry to know what researchers were working on, so that it could be among the first to develop or apply therapeutic advances. Sixth, the consultant shared with the company practical developments emanating from his own work or from the research in his department. This arrangement potentially benefitted both sides. The scientist could have channelled his consultantship fees or any royalties from practical discoveries back into departmental research funds.[2] Finally, often the consultant served on the company's board of directors (the only academic scientist in such a position at the company). This gave the consultant an intimate view of the company's operations, and it afforded him the opportunity to impact directly on the firm's research policies.

I have only been able to identify two bona fide examples of what I call general consultants. Perhaps this is to be expected, given the extraordinary type of person that is characterized above. Two points should be mentioned before proceeding. First, that I have not found more examples of a general consultantship by no means indicates no other examples exist. Second, although I based my generalizations

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[2]Here I must speculate on how a consultant disbursed his fees and royalties--whether he put these back into research, pocketed them, or both. This kind of information is extremely difficult to locate. My point is that the general consultant had these fees available to put into his or the department's research programs.

above on a rather substantial body of evidence, this evidence nonetheless pertains to only two consultants. Appropriate caution therefore should be used when considering these broad statements about the general consultantship.

Few twentieth-century scientists, in any field, have had careers as distinguished as that of Roger Adams (1889-1971), an organic chemist at the University of Illinois. During the period that he served as a consultant to Abbott Laboratories in North Chicago, from 1917 to the late 1960s, Adams built an impressive personal research program, headed the premier chemistry department in the United States, and served on many professional, private, and governmental organizations. All of the above figured significantly in Adams' service to Abbott.

His personal interest in devising commercially useful syntheses of some therapeutic agents that had grown scarce in this country, during World War One, led to his initial connections with Abbott. "As Chairman of the Illinois chemistry department from 1926 to 1956," according to historian Arnold Thackray, "Adams was responsible for building the largest single-discipline Ph.D. machine in the world. . . .Through his Ph.D.s Adams created an ever-growing network of links with industrialists and industrial concerns . . ."[3] Most of his Ph.D.s

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[3]Arnold Thackray, "An Academic Genius with Links to Industrial Science," review of Roger Adams: Scientist and Statesman, by D. Stanley Tarbell and Ann Tracy Tarbell, Chemical and Engineering News 60, no. 23 (1982):41-42. Adams' department produced 544 Ph.D.s from 1922 to 1941, and over half of these went into industry; see Roger Adams, "Universities and Industry in Science," Perkin Medal Address to the Society of Chemical Industry, New York, 15 January 1954, Industrial and Engineering Chemistry 46 (1954):506.

Figure 9. Roger Adams (1889-1971), Professor and Head of the Department of Chemistry at the University of Illinois who was a consultant to Abbott Laboratories from 1917 to the late 1960s (from D. Stanley Tarbell and Ann Tracy Tarbell, Roger Adams: Scientist and Statesman, frontispiece; UW neg. no. 10266 C-3).



that went into industry entered the chemical industry, although Adams supplied 18 students to drug companies (including three who went to work for Abbott).[4] Adams' outside activities brought him into close contact with the national and international scientific communities. He was an active member--often occupying powerful positions--in many organizations throughout his career. Among these organizations were the American Chemical Society, the National Academy of Sciences, and the American Association for the Advancement of Science; the Battelle Memorial Institute and the Sloan Foundation; and the National Science Board of the National Science Foundation and the wartime National Defense Research Committee. Despite the time that these various commitments consumed, Adams maintained his consultantship with Abbott, even during World War Two.[5]

The connections between Adams and Abbott originated as a project type of collaboration, which shortly changed to a specialist-consultantship. Gradually, Adams' relationship with the company began taking on more and more character of a general consultantship. At the time Abbott first contacted Adams, in the late Summer of 1917, the United States was suffering through a drought of many synthetic chemicals and drugs. German firms had ruled the world-wide trade in crude materials and intermediates necessary for synthetic drugs and chemicals, as well as the finished products themselves, for many years before World War

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[4]D. Stanley Tarbell and Ann Tracy Tarbell, Roger Adams: Scientist and Statesman (Washington, D.C.: American Chemical Society, 1981), 99, 221-228. Also, eight of Adams' postdoctoral fellows went into the pharmaceutical industry; see ibid., 229-231.

[5]Ibid., 103-114, 137-148, 183-195.

One. As the war grew, European industries began shifting their focus to the war effort. Moreover, those companies still producing synthetic drugs faced closed or restricted shipping routes to the United States. American industry was unprepared to meet the consequent shortages right away. However, by the time the United States declared war, in April of 1917, pharmaceutical and chemical firms had begun to pick up some of the slack in synthetic crudes, intermediates, and finished products.[6] It was around this time that Adams began looking for a pharmaceutical firm to apply some small scale methods he devised to produce a few synthetic drugs, and Abbott was searching for a chemist to assist it in manufacturing the same drugs.

Both parties had developed recent interests in synthetic drugs and chemicals. Around 1916 or 1917, Abbott introduced several synthetic germicidal agents, chloramines, which a British researcher had developed. This was the result of the company's recent policy to deemphasize alkaloidal drugs and stress synthetics.[7]

Adams' interest in the manufacture of synthetic chemicals and drugs stemmed from the organic "preps" laboratory at Illinois. In the

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[6]See L. F. Haber, The Chemical Industry, 1900-1930: International Growth and Technological Change (Oxford: Oxford University Press, Clarendon Press, 1971); Williams Haynes, American Chemical Industry, 6 vols. (New York: D. Van Nostrand, 1945-1954), vols. 1 and 3; and John Swann, "The Rise of American Synthetic Drug Industry before 1920," 15-page typescript, 1980, C(38)a, Kremers Reference Files, F. B. Power Pharmaceutical Library, University of Wisconsin, Madison, Wisconsin.

[7]Herman Kogan, The Long White Line (New York: Random House, 1963), 85-89, and Louis Goodman and Alfred Gilman, The Pharmacological Basis of Therapeutics (New York: Macmillan, 1941), 847-849. The company introduced, for example, the antiseptic Chlorazene, and Halazone, a sterilizing agent for drinking water.

Summer of 1914, C. G. Derick, the organic chemist whom Adams replaced in 1916, started a program at Illinois to prepare some key organic compounds that researchers around the country needed but could not find. The program continued for many Summers thereafter, and it grew rapidly after Adams took charge. What began with a few students preparing ten to fifteen chemicals emerged, by 1917, as an $8000-9000 business that employed ten students full-time during the Summer. By this date, the preps laboratory was manufacturing about 125 chemicals--albeit in quantities generally less than one pound each--for 30 universities, 18 government laboratories, twelve chemical distributors, and over 50 companies. Adams thought the preps laboratory was a useful program. In the first place, it saved researchers the time and trouble of synthesizing these chemicals. Also, the laboratory provided the students with valuable training that otherwise would be unavailable to them in a university, as well as paying them enough to cover their living expenses.[8]

Adams first tried to convince G. Mallinckrodt and Company of St. Louis to collaborate with him on some synthetic drugs, but the company was not interested. Not long after this, in the Summer of 1917, an Abbott representative contacted the Illinois chemistry department for

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[8]Tarbell and Tarbell, Roger Adams, 52-57; Roger Adams, "The Manufacture of Organic Chemicals at the University of Illinois," Science 47 (1918): 225-228; and Transactions of the Board of Trustees of the University of Illinois, 21 July 1916 to 11 June 1918, 717-718, University of Illinois Archives, Urbana, Illinois.

a possible collaborator on synthetic drugs.[9] Adams and Abbott soon were negotiating an agreement for the company to produce barbital, a barbiturate which German researchers introduced in the early 20th century as Veronal. Adams and Abbott agreed that, for the former's services in helping the firm manufacture barbital, Abbott would pay Adams a royalty of 2.5 percent of the net sales of barbital. The royalty arrangement would continue until 1922, when the United States patent on Veronal expired.[10] Adams improved the patented process somewhat, although it is not clear what specifically he changed in the process. Neither he nor Abbott appear to have discussed patenting any of the improvements.[11]

The Illinois chemist kept in close touch with Abbott's progress,

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[9]Ernest H. Volwiler, interview by John P. Swann, Abbott Laboratories, North Chicago, Illinois, 18 April 1984, transcript, A(2) "Volwiler, Ernest H.," Kremers Reference Files, 1; Kogan, Long White Line, 93; and Elmer Vliet to Walter Southern, 24 March 1984, Archives, Abbott Laboratories, North Chicago, Illinois (hereafter Abbott Archives; Abbott hired Vliet as a chemist in 1919).

[10]Roger Adams to Abbott Alkaloidal Co., 17 September 1917, box 4, "Procaine, 1917-1918," Roger Adams Papers, University of Illinois Archives, Urbana, Illinois (hereafter Adams Papers); Alfred S. Burdick to Roger Adams, 25 October 1917, ibid.; Roger Adams to A. S. Burdick, 3 December 1917, ibid.; Roger Adams to J. Stieglitz, 22 June 1918, box 4, "1918-1919," Adams Papers; and Emil Fischer, "C-C-Dialkyl-barbituric Acid and Process of making Same," United States Patent 782,739, patented 14 February 1905. Abbott was able to produce this patented drug, without seeking the permission of the patentee (who assigned his patent to a German firm), under the Trading With the Enemy Act, which Congress passed in September, 1917. The Federal Trade Commission issued licenses to American firms which were qualified to produce vital and depleted drugs that had been patented in this country by members of enemy states.

[11]Roger Adams to A. S. Burdick, 6 November 1917, box 4, "Procaine, 1917-1918," Adams Papers; Adams to Stieglitz, 22 June 1918; and Alfred S. Burdick to Roger Adams, 6 December 1917, box 4, "Procaine, 1917-1918," Adams Papers.

and he visited the company intermittently. Even after he began spending much of his time in Washington with the Chemical Warfare Service, in early 1918, Adams planned to make regular visits to Abbott, monthly or semimonthly. In addition, he had a student or fellow faculty member working on the project while he was away.[12] Abbott produced its first lot of barbital in November, 1917. Although the yield was less than satisfactory, Adams helped the company make the necessary adjustments so that, by about the Spring of 1918, Abbott was producing barbital on a large scale. It was the first American firm to accomplish this.[13]

About two weeks after Adams and Abbott began negotiating a collaboration on barbital, the company solicited Adams' assistance to prepare procain, a local anesthetic which a German researcher introduced in 1905 as Veronal. By November, 1917, Adams perfected the German worker's patented process, which enabled Abbott to produce the anesthetic more inexpensively than other companies theretofore.[14] Adams, for unknown reasons, preferred to keep his new process a secret rather

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[12]Roger Adams to A. S. Burdick, 2 February 1918, box 4, "Procaine, 1917-1918," Adams papers.

[13]Adams to Burdick, 6 November 1917, 3 December 1917, and 2 February 1918; Alfred S. Burdick to Roger Adams, 8 November 1917 and 20 November 1917, box 4, "Procaine, 1917-1918," Adams Papers; and "Testimonial Dinner Tendered by His Friends and Associates in the Scientific Divisions to Dr. Ernest H. Volwiler," c. 1959, mimeographed, Abbott Archives, 2.

[14]Alfred S. Burdick to Roger Adams, 4 October 1917, box 4, "Procaine, 1917-1918," Adams Papers; Adams to Burdick, 6 November 1917; Burdick to Adams, 8 November 1917; Adams to Burdick, 3 December 1917; Roger Adams to A. S. Burdick, [21] January 1918, box 4, "Procaine, 1917-1918," Adams Papers; and Alfred Einhorn, "Alkamin Esters of Para-aminobenzoic Acid," United States Patent 812,554, patented 13 February 1906. Abbott undertook the production of procaine, another drug patented by a member of an enemy state, on the same basis as the case with barbital; cf. n. 10.

than seek a patent. Abbott urged Adams to take the latter course. The company recently had learned that a chemist at Yale, Treat Johnson, who was working with the Calco Company in New Jersey, also was on the verge of finding a new, improved process for manufacturing the anesthetic.[15] Two weeks later the Illinois chemist submitted a patent application. Adams received letters patent on his discovery in March of the following year, and he assigned his rights to Abbott. In return, the company tentatively agreed to give Adams and a colleague a 2.5 percent royalty through most of the life of the patent (I have not been able to locate any final agreement between the parties).[16]

Adams continued to patent and assign to Abbott several synthetic drugs and potential therapeutic agents from the early 1920s on. For example, he helped prepare Butyn, and later Butesin, both of which were valuable additions to Abbott's growing roster of local anesthetics.[17] Among the other numerous compounds he submitted to Abbott were antiseptic iodine preparations, antisyphilitic arsenicals, and cyclic organic acids as possible bactericides.[18]

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[15]Adams to Burdick, 3 December 1917, and Alfred S. Burdick to Roger Adams, 10 December 1917, box 4, "Procaine, 1917-1918," Adams Papers.

[16]Roger Adams and Oliver Kamm, "Beta-bromoethyl Para-nitro-benzoate," United States Patent 1,260,289, patented 26 March 1918, and Adams to Burdick, 3 December 1917.

[17]Volwiler, interview by Swann, 18 April 1984, 5; Kogan, Long White Line, 104-105; Oliver Kamm, R. Adams and E. H. Volwiler, "Anesthetic Compound," United States Patent 1,358,751, patented 16 November 1920; and Roger Adams and E. H. Volwiler, "N-Butyl Esters of Para-amino Benzoic Acid," United States Patent 1,440,652, patented 2 January 1923.

[18]Adams to Burdick, 6 November 1917; Roger Adams to A. S. Burdick, 26 October 1923, "Roger Adams," Abbott Archives; Roger Adams, "Cyclopentenyl Compound and Process of Making Same," United States Patent

Late in 1917, when Adams was involved in the work on barbital and procaine for Abbott, Wallace Abbott (founder of the company) offered Adams $50 per month to ". . . act as a consulting chemist to them, particularly in regard to the various synthetic drugs that they were starting to produce and others that they intended to produce later."[19] Dr. Abbott even went a step farther by early 1918, and invited Adams to join the company on a full-time basis. The Illinois chemist was sufficiently impressed by the company to give the offer serious consideration. However, he turned down the job offer, probably because he felt it might appear to his colleagues that he was selling out.[20] His refusal was fortunate for Abbott, because he accomplished much more for the company on the outside than he would have been able to as an Abbott employee. Adams served the company well as a specialist-consultant on strictly chemical matters. Typically, he sent compounds from his laboratory to North Chicago (see above), and he advised the company

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1,715,052, patented 28 May 1929; and idem and Charles W. Rodewald, "Arsonophenyl Amino Alcohols and the Process of Making the Same," United States Patent 1,801,535, patented 21 April 1931.

[19]Adams to Stieglitz, 22 June 1918. Adams' reimbursement as a consultant to Abbott ($600 per annum) was a significant addition to his yearly income as an assistant professor at Illinois. Illinois hired Adams in 1916 at a salary of $2800. Toward the end of Adams' consultantship with Abbott, in the late 1960s, the company paid him $4000 annually for his services. He probably also received a salary during his years on the Abbott Board (discussed below). See Roger Adams to Paul Gerden, 10 March 1967, box 27, "Abbott Laboratories, 1962-1971," Adams Papers, and Tarbell and Tarbell, Roger Adams, 45.

[20]Alfred S. Burdick to Roger Adams, 5 February 1918 and 20 February 1918, box 4, "Procaine, 1917-1918," Adams Papers, and Roger Adams, interview by John B. Mellecker, New York, 20 November 1964, 12 February 1965, and 15 March 1965, tape, University of Illinois Archives, Urbana, Illinois.

on the practicality of manufacturing other drugs.[21]

Adams' services to the company had already begun to transcend the responsibilities that we would expect of a specialist-consultant before Dr. Abbott offered him the consultantship. For example, Adams helped the company establish contact with the Federal Trade Commission, so that the latter would license Abbott to produce barbital, procaine, cincophen (an antipyretic and analgesic), and other drugs from abrogated patents (see note 10).[22] That a solid chemist like Adams was assisting Abbott probably enhanced the company's standing as a candidate for licenses. Abbott was among the first companies to receive licenses, and used this advantage to take an early lead in the markets for barbital, procaine, and other synthetic pharmaceuticals after the war. Adams also served the general needs of the company by supplying some of his own students as research chemists. Ernest Volwiler, Adams' first doctoral student, was the most notable Adams-trained chemist at Abbott. Knowing the company's wish to have more in-house scientific personnel, Adams suggested that Volwiler join the firm--which he did, in April, 1918. By 1930, Volwiler became the firm's Director of Research; eventually he served over a decade as President and Chairman

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[21]For example, see Alfred S. Burdick to Roger Adams, 27 February 1918, box 4, "Procaine, 1917-1918," Adams Papers, and Roger Adams to A. S. Burdick, 28 February 1918, ibid. The company felt that another drug depleted by wartime conditions, the antipyretic and analgesic aminopyrine, had a promising demand. Adams advised the company against producing this drug, because of the complex, multi-step process involved, and because some of the necessary intermediates were unobtainable at the time.

[22]Alfred S. Burdick to Roger Adams, 16 October 1917, ibid.; Alfred S. Burdick to Federal Trade Commission, ibid.; Burdick to Adams, 25 October 1917; and Burdick to Adams, 20 November 1917.

of the Board of Directors.[23]

Adams consulted with all levels of the Abbott organization, from the bench scientists to the executives. It was important to him that the scientific workers and the officers understood each other. Thus, during his monthly or so visits to North Chicago, Adams typically discussed both technical problems and issues concerning general business methods with the Abbott scientists. His meetings with executive officers, such as Alfred Burdick (elected President of the firm in 1921), likewise covered a range of topics on the company's affairs: new products that Abbott might wish to consider, development of the research program, marketing and other business issues, and possible candidates--at Illinois or elsewhere--to fill new or vacated positions.[24] A postdoctoral fellow and later biographer of Adams, Dean Stanley Tarbell, characterized Adams the consultant:

> . . . Adams furnished solid benefits to his consultees. He had an encyclopedic knowledge of synthetic and structural organic chemistry, including recent developments that had not yet reached the scientific journals, such as the availability of new compounds from industrial exploratory research, and he was unusually well informed about economic and political trends that might affect a potential industrial process.[25]

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[23]Volwiler, interview by Swann, 18 April 1984, 1, and Kogan, Long White Line, 95-96. "Testimonial Dinner to Volwiler" contains a biography of Volwiler, and lists his publications, patents, and outside professional activities.

[24]E. H. Volwiler to Walter A. Southern, January 1984, Abbott Archives; Volwiler, interview by Swann, 18 April 1984, 6-7; and Ernest H. Volwiler, "Remarks at a Symposium Honoring Roger Adams," 16-page typescript, c. 3 September 1954, Abbott Archives, 7-8.

[25]Tarbell and Tarbell, Roger Adams, 112. Adams also consulted with DuPont, the A. E. Staley Company, Coca-Cola, the M. W. Kellogg Company, and Johnson and Johnson.

Adams' involvement with Abbott as a general consultant increased considerably in the 1940s, 1950s, and 1960s, particularly as his research career declined. Here I will only summarize his general contributions to the company. Adams, alone or with the help of his many contacts in the drug and chemical industries, occasionally came to Abbott's aid by solving problems in ongoing research projects at the company. He also could tap into his intelligence network to notify Abbott about the latest research of its competitors.[26] Adams used his experience as a member of official scientific delegations to post-war Germany and Japan to help broaden Abbott's research and business connections in these two countries.[27] For example, he notified the company of many German chemists who would be valuable potential consultants for Abbott. In the late 1950s, when the firm was considering branching out into Japanese markets and establishing research connections there, Adams played a vital role. He used his contacts to identify potential collaborating companies and universities for Abbott, he escorted two Abbott research directors on a reconnoitering trip to Japan, and he provided the firm with a detailed, insightful analysis of Abbott's possibilities for future joint ventures with Japanese

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[26]For example, see Roger Adams to Arthur W. Weston, 18 April 1960, box 15, "Abbott Laboratories, Correspondence, 1959-1960," Adams Papers; Roger Adams to A. W. Weston, 6 February 1961, box 16, "Abbott Laboratories, Correspondence, 1960-1962," ibid.; L. E. Miller to Roger Adams, 15 June 1961, ibid.; and Roger Adams to A. W. Weston, 19 June 1961, ibid.

[27]Tarbell and Tarbell, Roger Adams, 151-167, 199.

businesses and researchers.[28]

In April, 1952, Adams was elected to the Abbott Board of Directors; he was the only university scientist on the Board until he retired as a Director, seven years later.[29] This Directorship gave Adams the unique opportunity, as an outsider, to help formulate business and research policies at Abbott. His election to the Board also gives us some indication of the company's impressions of Adams' past contributions to the firm. He maintained intimate connections with the company even after leaving the Board. For example, the close contacts he had with both the bench scientists and upper level Abbott management, coupled with his vantage point as someone not in the permanent employ of Abbott, put him in a position as mediator when conflicts arose between the two. Consider one occasion when George Cain, President and General Manager of Abbott, sought Adams' advice to rectify an internal problem at the company:

> Certainly, everything that I have done personally, as well as with the cooperation of my associates, has been to strengthen by both word and deed our research setup. . . . the next time you are at North Chicago I would appreciate it if you would take the time to come into the office and explore this matter

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[28]For example, see Roger Adams to G. R. Cain, 3 July 1958, box 15, "Abbott Laboratories, Correspondence, 1957-1958," Adams Papers; Roger Adams to E. Biekert, 29 June 1959, box 15, "Abbott Laboratories, Correspondence, 1959-1960," Adams Papers; Roger Adams to Toru Iwadare, 8 July 1959, ibid.; and Roger Adams, "Report on Japanese Trip," 10-page typescript, attached to Roger Adams to George R. Cain, 24 November 1959, ibid. For another example of Adams' efforts to help Abbott establish research connections with foreign scientists, see Robert L. Jones to Roger Adams, 15 February 1963, box 27, "Abbott Laboratories, 1962-1971," Adams Papers, and Roger Adams to Robert L. Jones, 22 February 1963, ibid.

[29]E. H. Volwiler to Roger Adams, 28 January 1952, "Roger Adams," Abbott Archives, and Abbott Laboratories Annual Report, 1952-1958.

> of the feeling on the part of some individuals in the research group that they are being used as "whipping boys." Since that is simply not true I am anxious to get to the root of the matter and correct it.[30]

It should not be surprising, given his long and close associations with Abbott and other companies (see note 25), that Adams was a strong advocate of the development of ties between universities and companies. Cooperative ties, he believed, would strengthen research programs of both academe and industry. First, in an address he delivered in the mid-1930s, Adams reflected on the growing emphasis in this country on applied research at the expense of basic research in universities. University workers did not have the time, personnel, or equipment to carry out their fundamental investigations. Industry, he argued, could help solve this problem in American universities by reinvesting in basic research at these institutions, especially since it would amount to an investment in industry's own future:

> The chemical companies in the United States, progressive, efficient, well-managed, have now reached that level of success where they must consider not merely the building of powerful research and production units, but must give equal consideration to the conditions of those organizations in which the technical leaders of the future are to be trained; they must take their equitable share of the responsibility for the proper progress of pure science, which is the foundation of applied science.[31]

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[30]George R. Cain to Roger Adams, 3 August 1959, box 15, "Abbott Laboratories, Correspondence, 1959-1960," Adams Papers. See also George R. Cain to Roger Adams, 10 August 1959, ibid.; Roger Adams to A. W. Weston, 14 October 1966, box 27, "Abbott Laboratories, 1962-1971," Adams Papers; and Roger Adams to Lowell T. Coggeshall, 1 December 1966, ibid.

[31]Roger Adams, "The Relation of the University Scientist to the Chemical Industries," Industrial and Engineering Chemistry 13 (1935):365-367 (quotation from p. 367).

Adams must have been pleased when he noted, about fifteen years later, that industry had begun to assume much more of its responsibility for the welfare of science departments in universities.[32]

Second, universities had much to offer industry (in addition to manpower), a good example being consultantships. With his broad knowledge, the consultant could provide a fresh perspective on an industrial problem. Yet, Adams believed the consultant could contribute much more to a company:

> His presence convinces the industrial chemist that the company has a real interest in science per se. He is usually a stimulus to the men in the laboratory. A teacher-student relationship often exists between consultant and chemist and provides a means for discussion of personal problems whether they be private or professional. Chemists will often mention to the consultant minor or more serious complaints about the laboratory or its management when he would not do so to his official superior. Consultants can keep the higher level executives informed of any lowering of morale so that it may promptly be corrected. An opinion by consultants of the qualifications of its employees may at times be sought. Executives may acquire information of scientific trends in this country and abroad.[33]

As we saw in the preceding pages, Adams contributed in all these ways as a consultant to Abbott. In the next chapter we see how a pharmacologist served another company as a general consultant. Like Adams at Abbott, he impinged on numerous affairs at his company.

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[32][Roger Adams], "Introductory Remarks," 12-page typescript, c. 1950, box 54, "Speeches, 1947-1950," Adams Papers. See also Adams, "Universities and Industry in Science," 510, and idem, interview by Mellecker, 20 November 1964, 12 February 1965, and 15 March 1965.

[33]Adams, "Universities and Industry in Science," 510.

CHAPTER 4

A. N. RICHARDS AND MERCK AND COMPANY

Alfred Newton Richards (1876-1966), a pharmacologist at the School of Medicine of the University of Pennsylvania, served as a general consultant to Merck and Company in Rahway, New Jersey, for over thirty years, beginning in the early 1930s. Richards was a respected researcher, teacher, editor, and administrator, and all of these roles came into play during his association with Merck. Although the company first approached him to help it establish a pharmacological research laboratory, it soon became apparent to the people at Merck that Richards had much more to offer to the company. Richards was an expert in kidney physiology, but his overall value to Merck as a general consultant rested more in his perspicacious approach to the organization and administration of scientific research, his effectiveness as a diplomat in a variety of scientific matters, and his willingness to commit his strong opinions about the value of university-industry cooperative research to action. His progress in the worlds of scientific research and administration, both before and after he began his association with Merck, bears witness to these qualities.

Richards' training was in physiological chemistry rather than pharmacology, first under the renowned physiological chemist Russell Chittenden in the Sheffield Scientific School at Yale, and later under William Gies in the College of Physicians and Surgeons at Columbia, where Richards received his Ph.D. in 1901. He developed a course in pharmacology at P and S over the following years, in part by

familiarizing himself with the literature in the field, and also by assisting in a pharmacology course at a neighboring institution. In 1908, he accepted an offer to establish a pharmacology department at the Medical School of Northwestern University. Two years later, Richards moved to the University of Pennsylvania School of Medicine to head a similar department.

The research that earned Richards such a high reputation among his peers, on renal physiology, began shortly after he arrived at Pennsylvania. His studies on the kidney continued until the late 1930s, when his administrative duties for the university and for the United States government began to occupy more of his time. Richards and his associates in the Department of Pharmacology, through years of painstaking research, provided compelling evidence to support a hypothesis dating back to the mid-19th century: that the kidney filters and reabsorbs vital substances, such as glucose, amino acids, and salts, and then passes on various waste products as urine. Richards' laboratory used several pioneering techniques (for example, kidney micropuncture and ultramicrochemical analysis of the kidney contents) to localize these functions of filtration and reabsorption within specific parts of the nephron.[1]

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[1]See A. N. Richards, "Processes of Urine Formation," Croonian Lecture, delivered on 30 June 1938 to the Royal Society of London, Proceedings of the Royal Society of London, Series B--Biological Sciences, 126 (1938):398-432; cf. Carl W. Gottschalk, "Dr. A. N. Richards and Kidney Micropuncture," in Isaac Starr, ed., "Alfred Newton Richards: Scientist and Man," Supplement 8, Annals of Internal Medicine 71, no. 5 part 2 (1969):28-37, and Carl F. Schmidt, "Alfred Newton Richards," Biographical Memoirs of the National Academy of Sciences 42 (1971):287-290, 292-296, 298-300.

During the period that he served as a consultant to Merck, most of Richards' duties at Pennsylvania shifted away from research and teaching, and towards administration. The Dean of the Medical School had already begun seeking Richards' advice on administrative issues by the mid-1920s.[2] His influence among the medical faculty at Pennsylvania grew quickly, and in 1939 Richards became Vice President in Charge of Medical Affairs at Pennsylvania. He took this opportunity to ensure that medical research continued to have a solid foothold at the University of Pennsylvania. However, he also was a strong advocate of clinical utility of the medical sciences; Richards' clinical pharmacology program was one of the earliest of its kind.[3]

In 1941, President Roosevelt appointed Richards Chairman of the Committee on Medical Research. This organization was created to meet the country's wartime medical needs by advising its parent body, the Office of Scientific Research and Development, on medical research and development vital to the war effort. As part of its duties, the CMR mobilized medical researchers from universities, industry, government, and private foundations, and it recommended projects to the OSRD that merited the highest priority from the standpoint of national defense.[4]

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[2]Schmidt, "Richards," 297.

[3]Isaac Starr, "Other Activities of Dr. Richards' Department: 'Clinical Pharmacology'," in idem, ed., "Alfred Newton Richards," 41-42.

[4]For a summary of CMR-sponsored research during the war, see E. C. Andrus et al., eds., Advances in Military Medicine, 2 vols. (Boston: Little, Brown, 1948), especially Richards' Foreword to this work on pp. xli-liv; see also Chester S. Keefer, "Dr. Richards as Chairman of the Committee on Medical Research," in Starr, ed., "Alfred Newton Richards," 61-70.

Figure 10. Alfred Newton Richards (1876-1966), Professor of Pharmacology and Vice-President in Charge of Medical Affairs at the University of Pennsylvania who was a consultant to Merck and Company from 1930 to 1959 (from John Francis Marion, The Fine Old House, p. 123; UW neg. no. 10277 C-3).



The government terminated the CMR in January, 1947, but in the same year Richards was elected to the presidency of another major scientific organization, the National Academy of Sciences. He remained in that position until 1950. These appointments brought Richards into contact with many researchers from academe, industry, and government, and he became familiar with many different research projects over a wide range of fields.[5] Considering his background as a skilled and successful researcher by itself, Richards was a valuable connection for Merck to have. But far more valuable to Merck was his rich experience in dealing with research and researchers on a national, and even an international, level. Some of the ways that Merck tapped this resource are discussed in the following pages.

Merck began to assemble a chemical research staff by the early 1930s, headed by the former Princeton chemist, Randolph Major (see Chapter 3). Merck wished to establish a pharmacological laboratory as well, partially to evaluate products from the chemical group, but also to generate its own fundamental contributions to pharmacological science. So, George W. Merck (President of the firm), George Perkins (Executive Vice President), and Major met and decided to seek the

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[5]Other notable administrative positions that Richards held included Vice President of the American Philosophical Society, from 1944-1947, and member of the Medical Section of the First Hoover Commission on the Organization of the Executive Branch of the United States Government. John Parascandola and Elizabeth Keeney, Sources in the History of American Pharmacology (Madison: American Institute of the History of Pharmacy, 1983), 17, 47-50, summarizes additional biographical information, and lists other sources for further material on Richards.

counsel of Richards on the establishment of a pharmacological laboratory.[6] There are several reasons why the company approached Richards, although it is not clear who specifically suggested his name to Merck. First, as mentioned, he was a well-known and well-respected person in his field. Second, he had experience in organizing pharmacology departments at Northwestern and Pennsylvania, and he introduced the subject into the curriculum at the College of Physicians and Surgeons of Columbia University. Third, Merck had established indirect connections with the University of Pennsylvania when it merged with the Philadelphia firm, Powers-Weightman-Rosengarten, in 1927. Frederic Rosengarten, whose family had supported the University of Pennsylvania for a long time, became Chairman of the Board of Merck after the merger. The Rosengarten connection favorably impressed Richards when he was considering the Merck offer.[7]

Finally, Richards was a pharmacologist who favored strong ties between industry and universities--at a time when the American Society

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[6]"Dr. Alfred Newton Richards: Some Observations" (remarks made at a dinner in honor of Alfred Newton Richards in Philadelphia, 25 May 1959, mimeographed), 5, "Alfred Newton Richards," Biographical Files, University of Pennsylvania Archives, Philadelphia, Pennsylvania.

[7]A. N. Richards to [John J.] Abel, 30 August 1930, John Jacob Abel Papers, Alan Mason Chesney Archives, Johns Hopkins University, Baltimore, Maryland (hereafter Abel Papers). I am indebted to John Parascandola for this and all other letters that I have used from the Abel Papers. See also Tom Mahoney, The Merchants of Life: An Account of the American Pharmaceutical Industry (New York: Harper, 1959), 195. On the role of one of the Rosengartens, Joseph G., as a steady benefactor to the University of Pennsylvania, see Martin Meyerson and Dilys Pegler Winegrad, Gladly Learn and Gladly Teach: Franklin and His Heirs at the University of Pennsylvania, 1740-1976 ([Philadelphia:] University of Pennsylvania Press, 1978), 185, and Edward Potts Cheyney, History of the University of Pennsylvania, 1740-1940 (Philadelphia: University of Pennsylvania Press, 1940), 374 and 378.

for Pharmacology and Experimental Therapeutics banned from membership any pharmacologist employed by industry on a full time basis (see Chapter 3). For example, at the time he was considering the offer from Merck, Richards expressed his opinions about academic and industrial connections:

> I have long thought that the sentiment--so strong in this country--that university people should have nothing to do with commercial firms engaged in the manufacture of drugs was overdone. [Such a sentiment] works an injustice to businessmen who may have just as high ideals as do educators and research men, [and when] carried to extreme, defeats the aim of a university to be useful to its community.[8]

A grant that a Philadelphia pharmaceutical firm, Smith Kline and French, awarded to one of Richards' colleagues around 1929 may have strengthened his views about the importance of university-industry links. "Certainly the liberality of the terms with which that grant was made," according to Richards, "and the spirit with which it was made gave me a changed idea of the attitude of industrial administrators to academic investigations."[9]

Merck approached Richards in the late Summer of 1930, with an offer of a pharmacology consultantship. Richards' responsibilities would be "to prepare opinions on various pharmacological problems which confront the company;" for the immediate future, this meant that he would help Merck establish and staff a laboratory of pharmacology. While it is not clear how much total time Richards was expected to

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[8]Richards to Abel, 30 August 1930.

[9]Quoted in John Francis Marion, The Fine Old House (Philadelphia: SmithKline, 1980), 120. I have not been able to determine the subject of this grant, or the scientist that received it.

devote to the consultantship, the company felt he would have to spend one day per month in Rahway.[10] Richards received a yearly honorarium for his services[11], although I have not been able to determine the actual amount. The company proposed to pay him $5000 annually, but Richards was unsure--at least during the initial negotiations--if he would be able to devote the time and attention to this arrangement commensurate with such a payment.[12] He was also unsure, notwithstanding his strong feelings about the potential value of university-industry research connections, of what his peers would think of the consultantship. Thus, he wrote to John J. Abel, the dean of American pharmacology, to see if the Johns Hopkins pharmacologist would share his opinions of the consultantship. Richards explained to Abel that he was confident of the scientific integrity of Merck and its officers, and that the company was considering the consultantship as a way to improve its products, although he felt that "it would be idle to think that the element of prospective profit does not enter in." He also informed Abel that he had to consider the feelings of the President of the University, Thomas S. Gates, and the Dean of the Medical School, William Pepper III, both of whom recommended that he accept the consultantship,

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[10]Richards to Abel, 30 August 1930.

[11]A. N. Richards to Council of the American Society for Pharmacology and Experimental Therapeutics, 4 April 1935, box 10, "American Society for Pharmacology and Experimental Therapeutics," Alfred Newton Richards Papers, University of Pennsylvania Archives, Philadelphia, Pennsylvania (hereafter Richards Papers).

[12]George W. Perkins to A. N. Richards, 3 September 1930, box 31, "Merck and Co., 1930-1939," Richards Papers, and A. N. Richards to George W. Perkins, 23 September 1930, box 32, "A. N. R., Merck and Co.," Richards Papers.

and the feelings of his wife, who felt they needed the extra income.[13]

Abel was understanding. He agreed that the Merck firm maintained high standards; that the time had come for the American Society for Pharmacology and Experimental Therapeutics to admit the good pharmacologists from the better firms; that the pharmaceutical industry should develop research laboratories; and that the better firms had learned to understand the special concerns of the academic medical researcher over the past four decades. Abel avoided making any personal evaluations of industrial consultants. He merely said that some university scientists were compelled not to serve as consultants, because they simply could not take part in a project that did not originate in their own laboratories. Other academics, such as many German pharmacologists, did not share this approach to research. But the former group, according to Abel, should not look upon consultants disparagingly, because good work could come out of consultantships.[14] While this was not exactly a blessing from the father of American pharmacology (not that Richards was seeking such from Abel), Richards knew that Abel's high opinion of him would not change, whatever he decided to do. The opportunity to influence, in a major way, the development of a pharmacology laboratory in an institution altogether different from what he was accustomed to was too much for Richards to pass up. So, Richards agreed to serve as a consultant to Merck, beginning in 1931.

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[13]Richards to Abel, 30 August 1930; see also Richards to ASPET Council, 4 April 1935.

[14]John J. Abel to A. N. Richards, 5 September 1930, Abel Papers.

Richards as Liaison between Merck and the Academic Community

Richards served Merck in a number of ways as a general consultant, but the company relied more on Richards' service as a mediator in its transactions with the academic world than on any other service he provided for Merck. For example, he helped to identify and recruit candidates, especially those from universities, for research positions at the firm. He also established contacts for the company among (sometimes distinguished) university researchers, for purposes ranging from research associations to speaking engagements. Finally, Richards attracted scientific and medical advisors from universities, who played an important part in the company's operations. Following are specific examples of how Richards acted as a liaison between Merck and academe.

The first order of business for Merck's new consultant was to lay the groundwork for the company's pharmacology laboratory; Merck's most immediate need was a well-trained experimental pharmacologist. By 1930, America possessed a small but growing pool of experimental pharmacologists. As one indication of this growth, membership in the American Society for Pharmacology and Experimental Therapeutics increased from the charter membership of 18 to over 140, from 1908 to 1930.[15] Also, some excellent pharmacologists, such as K. K. Chen of Eli Lilly and Company and David Macht of the Baltimore drug firm Hynson, Westcott and Dunning, had recently departed universities for permanent industrial positions. The ASPET promulgation on industrial pharmacologists,

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[15]K. K. Chen, ed., The American Society for Pharmacology and Experimental Therapeutics, Incorporated: The First Sixty Years, 1908-1969 (n.p.: [American Society for Pharmacology and Experimental Therapeutics], 1969), 158-159.

while not preventing any academic pharmacologist from working full-time for industry, certainly did not create the kind of atmosphere that John Abel encouraged, in which ". . . our great firms should establish extensive research laboratories of their own and preach this doctrine at every possible opportunity."[16] Richards turned to Europe to fill Merck's position because of this situation in America, but also because 1) pharmacology was a more established discipline there, which meant he had a larger pool of good experimental pharmacologists to choose from, and 2) at least in Germany, pharmacologists working in industry did not suffer the same stricture that the ASPET ban posed to industrial pharmacologists in America. Unlike the case in America at this time, academic pharmacologists in Germany simply did not have an inbred negative reaction to the thought of working full-time for a company.[17]

The evidence is insufficient to say how energetically Richards tried to recruit pharmacologists for the Merck position. But in December of 1931 he wrote to a colleague in the Pharmakologischer Institut of the University of Vienna, to see if he could recommend anyone for the position at Merck. The colleague suggested that Hans Molitor, an Assistant Professor in the Institut, was the best candidate, ". . . an experienced researcher and a self-reliant critical

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[16]Abel to Richards, 5 September 1930. Abel went on to say, ". . . I also encourage my own men to take positions as pharmacologists with good firms when the conditions are favorable to scientific research, promotion et cetera." Both Chen and Macht worked with Abel.

[17]On the development of cooperative research between industry and universities in Germany, see Chapter 3.

scholar who has an understanding for the pharmacological problems of such a firm [as Merck]."[18] Richards had met Molitor in 1927, and the latter had impressed Richards as much as he had impressed Richards' colleague at the Institut. So, Richards recommended Molitor to Merck.[19]

Merck was not enthusiastic about hiring Molitor. The company anticipated immigration problems in bringing Molitor to the United States. While Molitor would have no problem entering this country under the Austrian quota, the pharmaceutical firm feared that, ". . . if we engage him this would involve some subterfuge on his and also on our part."[20] Merck was under the assumption that Molitor could not come to this country for the sole purpose of accepting a specific job that had been offered to him. Actually, the legislation that prohibited the immigration of contract labor, the Foran Act of 1885, primarily applied to unskilled labor. "Skilled labor needed for new

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[18]A. N. Richards to E. P. Pick, 18 December 1931, box 32, "Hans Molitor, 1932-1933," Richards Papers, and E. P. Pick to A. N. Richards, 20 January 1932, ibid.

[19]A. N. Richards to Randolph T. Major, 3 February 1932, ibid.

[20]Randolph T. Major to A. N. Richards, 12 February 1932, ibid. The quota system of immigration restriction in the United States stemmed from provisional legislature developed in Congress in 1921, which became the Johnson-Reed Act of 1924. The government imposed a ceiling on total annual immigration (150,000), and placed quotas on the maximum number permitted to emigrate from any one country to the United States--two to three percent of the American population born in that country, on the basis of the 1890 census. Clearly, this Act particularly limited those groups who emigrated mostly after 1890, such as the eastern and southern Europeans. See Maldwyn Allen Jones, American Immigration, Chicago History of American Civilization, ed. Daniel J. Boorstin (Chicago: University of Chicago Press, 1960), 276-279.

industries" was exempt.[21] Another reason why Merck was not interested in Molitor was that they were planning to hire--at least on a part-time basis--Peter Knoefel, a postdoctoral research fellow in pharmacology at the University of California, in addition to using the facilities and personnel in Richards' department.[22]

It took Merck only two weeks to change its mind about Molitor. Although I have not seen any correspondence between Richards and Merck during this two-week period, Richards very likely was responsible for the company's shift in opinion. Aside from the questions concerning the feasibility of Molitor's immigration (which were probably secondary in importance, at most), the bottom line concern was whether the company should establish the foundations for an in-house pharmacological research program, or to emphasize the farming out of their research needs. When he wrote to Abel a year and a half earlier, Richards preferred to see the company rely on university connections.[23] But this was before he knew that a pharmacologist of the high caliber of Molitor might be available for Merck. Also, the thought may have occurred to Richards that Merck might want to saddle its university connections, including the Department of Pharmacology at Pennsylvania, with routine work, such as bioassays on different compounds that the Merck chemical staff produced. Richards would have recognized the necessity of such work, but he also would have realized that the bulk of this kind of

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[21]Jones, American Immigration, 251-252.

[22]Major to Richards, 12 February 1932.

[23]Richards to Abel, 30 August 1930.

work was the province of a company laboratory rather than a university pharmacology department.

In late February of 1932, Richards contacted Molitor, through his colleague at the Pharmakologischer Institut, to let Molitor know that Merck was interested in hiring the Viennese pharmacologist. Richards related some general information about the company and the pharmacology position.[24] Merck's decision to have Richards make the initial contact paid off. Considering that Molitor was happy with his position in Vienna, and that he was sought for a position in a foreign country with a company he was not familiar with (although Molitor must have known of the highly respected firm, E. Merck-Darmstadt, formerly the parent firm of Merck and Company), it is difficult to believe that this was a job that could sell itself. Richards' role as the initial contact person was important; Molitor himself indicated that ". . . one of the first arguments which led me to a 'yes' was the fact that the offer came from you."[25] Richards' part in the Molitor affair did not cease when he finally put Molitor in touch with Merck.[26] Indeed, he maintained an active interest in negotiating the conditions on which Molitor would accept the industrial position, and he helped Molitor establish himself as a new member of the American pharmacological community.

Molitor and Richards discussed many details of the Merck position,

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[24]A. N. Richards to E. P. Pick, 26 February 1932, box 32, "Hans Molitor, 1932-1933," Richards Papers.

[25]Hans Molitor to A. N. Richards, 7 March 1932, ibid.

[26]George W. Perkins to Hans Molitor, 31 March 1932, ibid.

such as the type of job security that the firm would be willing to concede to Molitor, the layout of the new pharmacological laboratory, and the assignment to Molitor of research and development problems. Typically, Richards discussed Molitor's concerns with Merck executives, and then presented Merck's counterproposals to the Viennese pharmacologist. For example, Molitor wanted a five year contract upon the expiration of a mutually satisfactory trial year, plus a guaranteed annual salary for the full five years if the agreement had to be terminated through no fault of Molitor. Richards suggested that Molitor accept Merck's counterproposal--that the guaranteed compensation, if Molitor departed the company, be one half of the annual salary for each of the remaining five years. The consultant reminded Molitor how one half of his Merck salary would compare with his present and future salary at Vienna. This arrangement apparently satisfied Molitor.[27]

The latter also discussed with Richards his questions and preferences about the make-up of the laboratory (e.g., sterile surgical facilities, sufficient space for animals, and an adequately stocked library), and the process used for the selection of research and development assignments. Molitor felt that only a fellow researcher like Richards, rather than the businessmen at Merck, could fully appreciate such concerns.[28] Richards reiterated his confidence in Merck's willingness to accommodate the new pharmacologist in every way possible,

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[27]Molitor to Richards, 7 March 1932; Perkins to Molitor, 31 March 1932; and A. N. Richards to Hans Molitor, 31 March 1932, box 32, "Hans Molitor, 1932-1933," Richards Papers.

[28]Hans Molitor to [A. N. Richards], 15 April 1932, ibid.

and additional facilities at the University of Pennsylvania Medical School (such as sterile operating rooms) would be available to Molitor if needed. Richards' assurance that Molitor himself would play a large role in the selection of research problems, and that the company would consult the Pennsylvania pharmacologist on difficult research decisions, must have helped quell Molitor's fear[29] of becoming a slave to the commercial interests of the firm.[30]

The details above show Richards' strong personal involvement in recruiting Molitor for the pharmacology post at Merck.[31] Even after Molitor arrived in America, in the late Summer of 1932, Richards helped smooth the way. For example, he introduced Molitor to several major figures in pharmacology, physiology, and medicine in this country, such as Abel, Torald Sollmann, and Cecil Drinker.[32] This was an especially valuable service by Richards for Merck, since the latter felt that "the time spent in renewing and widening your [i.e., Molitor's] acquaintance

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[29]For example, see ibid.:

> I have just now heard very active complaints of gentlemen of the Höchster Laboratory of I. G. [i.e., I. G. Farbenindustrie, the cartel of the German chemical industry]--[the kind of complaints that] appear when purely commercial or chemical interest directs pharmacological work and, if possible, the desired results! As you will understand, I have not the least desire to expose myself to such things and thus to bring my good scientific reputation and name into danger.

[30]Ibid.; A. N. Richards to R. T. Major, 4 May 1932, ibid.; and A. N. Richards to Hans Molitor, 6 May 1932, ibid.

[31]Additional examples of Richards' involvement in the negotiations with Molitor can be seen in Hans Molitor to [A. N. Richards], 26 May 1932 and 12 July 1932, ibid.

[32]A. N. Richards to Joseph Wearn, 26 September 1932, ibid., and A. N. Richards to Hans Molitor, ibid.

with the pharmacologists in this country we believe to be most important, and we should wish you to spend this time in this way even though our building were fully finished and ready to receive you when you reached this country."[33] Richards also saw that Molitor received most reasonable assistance he required from academics.[34] As a charter member of the American Society for Pharmacology and Experimental Therapeutics, Richards also acted as an introducer (as required by the Society) when Molitor wished to present some of the results of his research to that Society. Molitor was not permitted to join that organization until 1941, when ASPET removed its ban on industrial pharmacologists.[35]

Under Molitor's leadership, Merck's pharmacological laboratory--which the company christened as the Merck Institute for Therapeutic Research--became one of the leading industrial research centers for pharmacology (see Chapter 3). The company again called upon the

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[33]Perkins to Molitor, 31 March 1932.

[34]For example, see A. N. Richards to H. S. Gasser (of the Cornell University Medical College), 6 June 1934, box 30, "Merck Institute, 1931-1940," Richards Papers:

> [Molitor] talked to me a couple of weeks ago about certain plans for experiments which should involve the sort of technique with which you are particularly familiar. I suggested to him that there would be no impropriety in his writing to you to ask for an opportunity of getting some advice. He sends me now a rather pathetic message to the effect that you have not answered his letter and [he wants me to] write to you to commend him to your good graces . . . . I feel certain that you will not regard it as a waste of time to make Molitor's acquaintance.

[35]A. N. Richards to E. M. K. Geiling, 1 February 1936, ibid. For the abstract of the paper that Richards referred to in this letter, see Hans Molitor, "Some Undescribed Pharmacological Properties of Bulbocapnine," Journal of Pharmacology and Experimental Therapeutics 57 (1936):135-136.

services of Richards early in 1933, when it was planning a dedication for its new research laboratories (of which the Institute would be a vital part) before a distinguished assembly of physicians and scientists from academe, government, and industry. As in the case of his recruiting Molitor, Richards played an important part in attracting the eminent pharmacologist, Sir Henry Hallet Dale (see Chapter 6), to Rahway to address the notables at the dedication. The hiring of Molitor, of course, had a much greater impact on the development of research at Merck than Dale's appearance, but the latter was also of great value to the company.

Richards apparently conceived the idea of inviting Dale after learning that the British pharmacologist planned to be in the United States in April, 1933, to present a series of lectures at Johns Hopkins. Richards knew Dale well, having spent time working with him in London in 1917 (on wound shock) and from 1926-1927 (on the action of adrenaline).[36] President George W. Merck liked his consultant's idea and sent an invitation to Dale early in February, suggesting that Dale consider presenting a lecture on the relationship between academic and industrial research at the opening of the new research laboratories.[37] Richards sent a letter to Dale at the same time, expressing his attachment to and high regard for the company, and urging Dale to accept

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[36]R. T. M[ajor] to G. W. Merck, 21 January 1933, Merck and Company Archives, Rahway, New Jersey (hereafter Merck Archives), and A. N. Richards to Henry Dale, 3 February 1933, box 32, "Merck, Dedication of Research Laboratory, 1933," Richards Papers. On Richards' collaboration with Dale, see Schmidt, "Richards," 289, 297-8.

[37]George W. Merck to Henry H. Dale, 2 February 1933, box 32, "Merck, Dedication of Research Laboratory, 1933," Richards Papers.

Merck's invitation:

> I am convinced as a result of close acquaintance for two years past with the fashion in which Merck and Company have been managing their pharmacological research projects that the standards--scientific and ethical--which they have adopted are quite as idealistic, if not more so, than those which obtain in most of our universities . . . . I should not be writing this if I did not think this projected extension of Merck and Company's plans was worthy of the help which you could give.[38]

Dale accepted Merck's offer,[39] probably for several reasons: the opportunity to take part, at least in an honorary way, in a company's effort to develop a university-grade research program; Richards' personal recommendation of the company; and certainly to some extent, he had already planned to be in this country, and Merck offered him the then rather generous honorarium of $600. Richards kept in contact with Johns Hopkins and Dale about the address. For example, he found out that Hopkins would not object if Merck invited Dale to speak at the dedication ceremony.[40] Dale's address per se was not nearly as important to Merck as his physical presence at the opening of its research laboratories.[41] His appearance lent considerable credibility

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[38]Richards to Dale, 3 February 1933.

[39]H. H. Dale to [George W.] Merck, 20 February 1933, box 32, "Merck, Dedication of Research Laboratory, 1933," Richards Papers.

[40]Major to Merck, 21 January 1933. For other examples of Richards' service to Merck in bringing Dale to Rahway, see A. N. Richards to George W. Merck, 11 February 1933, Merck Archives; G. W. Merck to Henry Dale, 2 March 1933, ibid.; A. N. Richards to E. K. Marshall, Jr., 6 March 1933, box 32, "Merck, Dedication of Research Laboratory, 1933," Richards Papers; A. N. Richards to [R. T.] Major, 12 March 1933, Merck Archives; and A. N. Richards to Randolph T. Major, 31 March 1933, ibid.

[41]See Henry H. Dale, "Academic and Industrial Research in the Field of Therapeutics," address delivered at the opening ceremony of the Research Laboratories of Merck and Company, Inc., Rahway, New Jersey,

to Merck's efforts to cast itself as a research-oriented company in the eyes of the medical and scientific communities--particularly among those physicians and scientists in universities.

Another way Richards used his contacts in the academic world for Merck was in trying to find a chief of medical affairs. The chief, as outlined by Merck personnel and Richards, would have several responsibilities: 1) to apprise the executive officers of developments in the general area of medicine which Merck could have an impact on; 2) to organize clinical trials of promising drugs which the company research laboratories produced; 3) to analyze the clinical results on new drugs and counsel Merck on how to present these to the medical community; 4) to submit research proposals to Merck chemists and pharmacologists; and 5) to conduct his own research in the Merck laboratories (if the chief had the proper training and the desire).[42] Although the type of person Merck was interested in would have a medical rather than a pharmacological or physiological background, the company's consultant had a more than adequate familiarity with the clinical community. Richards knew of physicians who would be good candidates for this posi-

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25 April 1933, box 32, "Merck, Dedication of Research Laboratory, 1933," Richards Papers, and "Merck Research Laboratory Dedicated," Merck's Report 42 (1933):82-85. This address was published as Henry H. Dale, "Academic and Industrial Research in the Field of Therapeutics," Science 77 (1933):521-527. H. H. Dale to [A. N.] Richards, 6 April 1933, box 32, "Merck, Dedication of Research Laboratory, 1933," Richards Papers, explains why the British pharmacologist chose not to speak more frankly on American academic and industrial research policies in his address. Dale did not feel entitled, as a guest in another country, to take a "critical and superior" attitude in his lecture.

[42]A. N. Richards to Joseph T. Wearn, 7 February 1934, box 31, "Medical Advisor, 1933-1934," Richards Papers.

tion, and he knew others who could recommend strong candidates.

In early February, 1934, Richards asked a former Pennsylvania colleague--then at Case Western University School of Medicine--if an associate professor at Case Western, Gerald Shibley, would be interested in the medical affairs position. Shibley met with several Merck executives, employees, and with Richards, but he decided to withdraw his name from consideration.[43] Richards soon found another candidate for the position, a physician at the Rockefeller Institute; he, too, eventually decided he was not interested in the job.[44] The consultant persevered in his search for a chief of medical affairs for Merck; he continued to suggest some candidates on his own, and he approached his medical acquaintances for possible candidates on their staffs.[45] Dickinson W. Richards, an associate professor at Columbia's College of Physicians and Surgeons, accepted the medical affairs post--on a part-time basis, around 1935.[46] It is not clear if Newton Richards

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[43]Ibid.; Joseph T. Wearn to A. N. Richards, 16 February 1934, ibid.; Gerald L. Shibley to [A. N.] Richards, ibid.; Gerald L. Shibley to [A. N.] Richards, 20 March 1934, ibid.; and Gerald Shibley to [George] Perkins, ibid.

[44]A. N. Richards to George W. Perkins, 2 April 1934, ibid.; Harold L. Amoss to George Perkins, 23 April 1934, ibid.; and A. N. Richards to Harold L. Amoss, 27 April 1934, ibid.

[45]For example, see A. N. Richards to Randolph T. Major, 9 May 1934, box 31, "Merck and Co., 1930-1939," Richards Papers, and George R. Minot to A. N. Richards, 31 May 1934, ibid.

[46]See André F. Cournand, "Dickinson Woodruff Richards, 1895-1973: A Survey of His Contributions to the Physiology and Physiopathology of Respiration in Man," American Journal of Medicine 57 (1974):318, and "Fifty Years of Merck Research," Merck Sharp and Dohme International Review 21, no. 2 (1983):65. Dickinson Richards remained a medical advisor to Merck for nearly forty years.

played a significant role in the hiring of Dickinson Richards, but his earlier involvement with this post would suggest that the consultant probably contributed much to his namesake's employment. Here we see again how Richards had a major hand in staffing a position--a position outside of the field of pharmacology--of great importance to the company. This and the other examples I have cited of Richards' role as a liaison between Merck and the academic community illustrate his vital contributions to the company's research program, and to the establishment of Merck's strong ties with scientists and clinicians. Richards' services for the pharmaceutical firm, however, did not end here. In many other ways, the company's consultant helped to propagate both in-house and collaborative research.

Richards and Pennsylvania-Merck Research Connections

The University of Pennsylvania was a logical site for Merck to establish connections for biomedical research and clinical investigation of its drugs. Pennsylvania was a major research institution, with access to extensive clinical facilities; the university was conveniently located not far from Rahway; and most important, Merck had close contact with one of the faculty whom the university community esteemed--Newton Richards. Following are a few examples in which Richards linked Pennsylvania and Merck in therapeutic research and development during the early years of his consultantship. Some of these examples also will illustrate one of the points I made in Chapter 3, that types of collaboration were not pure or ideal. Here we will see cases of a general consultant who was part of specific project

collaborations between a university and a company.

Richards began working with Merck before the latter hired him as a consultant. Beginning around late 1930, Merck sponsored a fellowship in Richards' department. André Simonart, of the University of Louvain, came to Pennsylvania to work on a problem of mutual interest to him,[47] Merck, and Richards. Before proceeding, some background information is necessary. Simonart's research at Pennsylvania involved a pharmacological study of compounds, synthesized at Merck, similar to acetylcholine. A German chemist synthesized acetylcholine (for unknown reasons) in the mid-nineteenth century, and researchers decades later discovered that this chemical occurred naturally in the plant and animal kingdoms. Reid Hunt, of the Hygienic Laboratory of the United States Public Health Service, and especially Henry Dale, among others, shed much light on the pharmacological properties of acetylcholine in the early twentieth century. They found that it elicited pronounced cardiovascular, respiratory, glandular, and gastrointestinal responses. However, acetylcholine's pharmacological action was variable and, more importantly, evanescent--because an enzyme in the body deactivated the chemical. Hence, acetylcholine had little therapeutic potential. Researchers then began synthesizing many compounds, similar to

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[47]For examples of Simonart's prior interest in the research for which he came to Pennsylvania to work under a Merck fellowship, see André Simonart, "Etude physiologique de quelques dérivés d'homocholine: L'Ether methylique de la gamma-phenylhomocholine," Archives internationales de pharmacodynamie et de thérapie 34 (1928):15-32, and idem, "Etude physiologique de quelques dérivés d'homocholine: II, L'Ether méthylé d'homocholine, III, Rapports avec les cholines," ibid., 375-390.

acetylcholine but with a more promising clinical future.[48]

Merck chemists were among those searching for a useful acetylcholine homologue. They probably began their work on such compounds shortly before Simonart arrived at Pennsylvania, sometime in 1930. They developed a unique and commercially applicable synthesis for a variety of chemicals similar to acetylcholine,[49] but the company did not yet possess the pharmacological facilities to test these products. Thus, they contacted Richards, who arranged for Simonart to work on the Merck products in his department, under his direction. The company established a fellowship at Pennsylvania to support Simonart's work, totalling $4000 per academic year. Simonart's research at Pennsylvania lasted from 1930 to 1932, but Merck continued the fellowship until 1934, so that Richards and his colleagues could conduct more extensive pharmacological and clinical tests on the more promising Merck products.[50]

Simonart tested several compounds for Merck. Two of these were

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[48]Louis Goodman and Alfred Gilman, The Pharmacological Basis of Therapeutics (New York: Macmillan, 1941), 349-356.

[49]See Randolph T. Major and Joseph K. Cline, "Preparation and Properties of Alpha- and Beta-methylcholine and Gamma-homocholine," Journal of the American Chemical Society 54 (1932):242-249; idem, "Beta-methylcholine Derivatives and Salts and Processes for their Preparation," United States Patent 2,040,146, patented 12 May 1936; and Goodman and Gilman, Pharmacological Basis of Therapeutics, 356.

[50]George W. Perkins to A. N. Richards, 11 September 1930, box 31, "Merck and Co., 1930-1939," Richards Papers; George W. Perkins to Trustees of the University of Pennsylvania, 26 September 1930, box 33, "Merck Fellowship Fund, 1930-1934," ibid.; A. N. Richards to William Pepper, 18 December 1931 and 6 June 1932, ibid.; and Isaac Starr et al., "Acetyl-beta-methylcholin: I. The Action on Normal Persons, with a Note on the Action of the Ethyl Ether of Beta-methylcholin," American Journal of the Medical Sciences 186 (1933):315.

far better than the rest, and one of the two was particularly valuable when compared to acetylcholine:

> Of all the compounds investigated, the acetyl ester of beta-methyl choline appears actually to offer the greatest possibility of clinical usefulness, since it is approximately as potent as acetyl choline in lowering blood pressure when given intravenously; it has no demonstrable nicotinic action on the circulation, and it is so much more stable than acetyl choline that it is effectively absorbed from the intestinal tract and is much more potent than acetyl choline when injected subcutaneously.51

Workers at Pennsylvania conducted an in-depth pharmacological study of acetyl-beta-methylcholine, and they carried out the first clinical evaluations of the compound. The latter revealed the methylcholine's "spectacular action" in attacks of paroxysmal tachycardia (a condition of excessive heart action that begins and ends abruptly), its "striking relief" in some cases of abdominal distention, and its superior vasodilating power relative to acetylcholine.52

On the basis of the generally successful results with Mecholyl Chloride (Merck's trade name for this chemical) at Pennsylvania, the company arranged for about fifteen clinicians to evaluate Mecholyl on a large scale early in 1933. Richards helped Merck considerably

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51André Simonart, "On the Action of Certain Derivatives of Choline," Journal of Pharmacology and Experimental Therapeutics 46 (1932):192-193. The "nicotinic action on the circulation" refers to the slowing and then the increasing of the heart rate, elevation of blood pressure, and the occurrence of various kinds of cardiac arrhythmia.

52Starr et al., "Acety-beta-methylcholin, I," 313-323; W. Osler Abbott, "Acetyl-beta-methylcholin: II, The Action on the Gastro-Intestinal Tract of Normal Persons, in Abdominal Distention, and in Certain Other Conditions," American Journal of the Medical Sciences 186 (1933):323-330; and Isaac Starr, Jr., "Acetyl-beta-methylcholin: III, Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease, with a Discussion of Its Action in Other Conditions," ibid., 330-345.

in these arrangements. He probably suggested the clinics that the firm attempted to engage, and he certainly wrote the letter of proposal--signed by President Merck--that the company sent to each of the clinicians. In those cases where the company did not receive replies from a few clinicians, it turned to Richards for advice on how to deal with these physicians. Richards also helped Merck prepare the informational booklets on Mecholyl that the company sent to clinicians.[53] These were the types of services that Merck's chief of medical affairs was responsible for, but Dickinson Richards did not assume this position until 1935. Until then, it apparently was another of the services that Richards provided as a general consultant. We can see, then, that Richards maintained a close personal involvement in the development of Mecholyl. A visiting scholar, medical student assistants, and others carried out the initial pharmacological tests on Mecholyl Chloride in Richards' department, and Pennsylvania medical faculty that were jointly appointed in the pharmacology department conducted the early clinical investigations of this drug. Later, Richards had a key role in the organization of the expanded clinical testing of Mecholyl.[54]

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[53]A. N. Richards to Randolph T. Major, 23 March 1933, and enclosed draft of a letter from George W. Merck to [Warfield] Longcope, undated, box 31, "Merck and Co., Mecholin Correspondence, 1930-1934," Richards Papers; P. C. Ackerman to A. N. Richards, 11 May 1933, ibid.; A. N. Richards to P. C. Ackerman, 15 May 1933, ibid.; and Anna M. H. Josephson to A. N. Richards, 12 April 1935, ibid.

[54]Merck was granted a patent on their process for preparing Mecholyl Chloride in 1936--about four years after applying; see Major and Cline, "Beta-methylcholine Derivatives." The company had a much longer delay--over eight years--in trying to have the Council on Pharmacy and Chemistry include Mecholyl in New and Nonofficial Remedies; the Council

At the same time that the Mecholyl work was in progress, Richards had a hand in another joint Merck-Pennsylvania project. In this case, the collaborators investigated an anesthetic called Vinethene (divinyl ether). Again some brief background information is necessary. The credit for postulating that divinyl ether might be a useful anesthetic must go to Chauncey Leake, a pharmacologist at the University of California Medical School. Leake believed that compounds combining the chemical characteristics of two useful anesthetics, ethylene ($CH_2=CH_2$) and diethyl ether ($CH_3CH_2OCH_2CH_3$), would be worth studying. So he asked chemists at Princeton--including Randolph Major--to synthesize several possible anesthetics; among these, Leake had listed divinyl ether ($CH_2=CHOCH=CH_2$). His preliminary tests (on mice, using diethyl ether as a standard for comparison) revealed that divinyl ether was superior to the other compounds, including the standard, with respect to the time required to induce anesthesia, the time for recovery, and toxicity.[55]

Major left Princeton to work at Merck in 1930, and soon thereafter he and his colleagues developed a manufacturing process that yielded

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finally listed Mecholyl in 1941. On this, see Paul Nicholas Leech to R. E. Gruber, 15 August 1934, box 31, "Merck and Co., Mecholin Correspondence, 1930-1934," Richards Papers; Council on Pharmacy and Chemistry of the American Medical Association, "Preliminary Report of the Council," Journal of the American Medical Association 105 (1935):281-283; and idem, "New and Nonofficial Remedies," ibid., 860-861.

[55]Chauncey D. Leake and Mei-Yü Chen, "The Anesthetic Properties of Certain Unsaturated Ethers," Proceedings of the Society for Experimental Biology and Medicine 28 (1930):151-154, and C. D. Leake, P. K. Knoefel, and A. E. Guedel, "The Anesthetic Action of Divinyl Oxide in Animals," Journal of Pharmacology and Experimental Therapeutics 47 (1933):5.

Vinethene virtually free of impurities.[56] (Leake's promising results notwithstanding, the samples Major had sent to California were quite impure.) For further pharmacological tests and preliminary clinical evaluations of Vinethene, Merck turned, not to Leake and the University of California Medical School, but to Richards and Pennsylvania. In February, 1932, Leake notified Merck that he and his associates would be unable to spend any time on Vinethene for several months, because of the heavy teaching load and their lack of funds to purchase the animals and equipment necessary for the Vinethene work. Whether or not Leake intended the latter to be an informal request for some financial support, the company "did not feel that it would be advantageous to spend a great deal of money for the pharmacological study of vinyl ether in California. The distance was so great that a true cooperation could not be obtained."[57]

Around this time, Richards and Samuel Goldschmidt, a Professor of Physiology at the University of Pennsylvania Medical School, arranged with Merck to conduct further pharmacological work on Vinethene at Pennsylvania. Later, some of the clinical faculty entered the

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[56]On the discovery by Merck chemists of a process to produce pure divinyl ether, see William L. Ruigh and Randolph T. Major, "The Preparation and Properties of Pure Divinyl Ether," Journal of the American Chemical Society 53 (1931):2662-2671; Randolph T. Major and William L. Ruigh, "Divinyl Ether and Processes for Its Production," United States Patent 2,021,872, patented 19 November 1935; idem, "Means and Composition for the Stabilization of Divinyl Ether," United States Patent 2,044,800, patented 23 June 1936; and idem, "Production of Stabilized Divinyl Ether Suitable for General Anesthesia," United States Patent 2,044,801, patented 23 June 1936.

[57]Randolph T. Major to A. N. Richards, 9 June 1933, box 33, "Vinethene, 1933-1936," Richards Papers.

Vinethene project;[58] they were the first to test Merck's new anesthetic. While Richards probably was not personally involved in the Vinethene research, he did help mediate some of the arrangements between the university and company. The latter did not arbitrarily engage Pennsylvania for the follow-up pharmacological research and the initial clinical work. As in the case with Mecholyl, Merck had a very useful contact at Pennsylvania in Richards. Vinethene was not among Richards' personal research interests, but he kept abreast of the progress on both the experimental and clinical work on this anesthetic. Among his mediations connected with this project, he helped Goldschmidt negotiate a suitable reimbursement from Merck for the physiologist's contributions to the project. Also, Richards assisted in the arrangements for a Merck-sponsored anesthesia research fellowship (worth $4500, for the academic year 1934-1935) in Pennsylvania's Physiology and Research Surgery Departments.[59]

Within a few years, the Pennsylvania clinicians collected substantial evidence--more, in fact, than any of the other two dozen or so clinics involved in the testing program had assembled--of Vinethene's

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[58] Ibid.

[59] A. N. Richards to Randolph T. Major, 31 May 1933, ibid.; Randolph T. Major to A. N. Richards, 7 June 1933, ibid.; S. Goldschmidt to George W. Perkins, 16 April 1934, box 33, "Merck Fellowship Fund, 1930-1934," Richards Papers; A. N. Richards to H. I. MacLean, 23 April 1934, ibid. That Richards received copies of correspondence and reports dealing with different issues of the Vinethene project, e.g., the expansion of clinical evaluations of Vinethene and AMA Council on Pharmacy and Chemistry actions on Vinethene, also indicates his (indirect) involvement. See, e.g., Randolph T. Major to Wesley Bourne, 2 May 1933, box 33, "Vinethene, 1933-1936," Richards Papers; Randolph T. Major to I. S. Ravdin, 12 April 1934, ibid.; and Paul Nicholas Leech to R. E. Gruber, 26 December 1935, ibid.

value in most short-term surgical procedures and in dental use. Their results were instrumental in the establishment of Vinethene as a most useful anesthetic.[60]

Around the time that Pennsylvania was concluding its work on Mecholyl Chloride and Vinethene for Merck, Richards, in conjunction with the Vice President in Charge of Medical Affairs at Pennsylvania and Merck, drew up a guideline for future Pennsylvania-Merck collaborations. Although couched without reference to any specific firm, this nine-point policy statement definitely intended to address Pennsylvania's connections with the Rahway firm. Richards acted as an intermediary between the representatives of Merck and Pennsylvania during negotiations over the few disputed clauses of this plan. The plan covered three areas: Pennsylvania's wish to collaborate with industry on medical research, and the university personnel who authorized such collaborations; policies on publication of the results of cooperative research, and the company's right to publicize research which Pennsylvania took part in; and Pennsylvania's right to accept or reject any outsiders that the company wanted to include in the cooperative project.

First, the plan explicitly stated that "authorities of the University of Pennsylvania regard it as desirable that members of the faculty

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[60]Samuel Goldschmidt et al., "Divinyl Ether: Experimental and Clinical Studies," Journal of The American Medical Association 102 (1934):21-27; I. S. Ravdin et al., "Divinyl Ether: A Report of Its Further Use as a General Anesthetic," ibid., 108 (1937):1163-1167; Council on Pharmacy and Chemistry of the American Medical Association, "New and Nonofficial Remedies," ibid. 102 (1934):44; and idem, "Report of the Council," ibid. 109 (1937):656-658.

of the Medical School should on occasion collaborate with reputable commercial firms" on therapeutic investigations. The head of the relevant department and the Dean of the Medical School, or the Vice President in Charge of Medical Affairs, had the power to approve of such work, and thereby they determined which firms were "reputable." The reference to occasional collaboration was important, because the university did not wish to see so much work of this type undertaken that it might "give a commercial aspect to the activities of [its] departments."[61] Pennsylvania, like some of its peer institutions (e.g., Johns Hopkins and Harvard), had recently instituted an official ban on the patenting of health related discoveries for the purpose of garnering profit for the faculty member or the university (see Chapter 3). The Executive Committee of the university made an exception to this ban if it believed patenting were the only way to protect a discovery from monopolization by others.[62] The point is that the environment at Pennsylvania in the early 1930s was very unreceptive to any blatantly commercial activities within its medical school, and the guideline on cooperative research reflects this environment.

Second, the research guideline defended the university's right to publish any research it deemed fit for publication. Also, with the

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[61]Untitled, undated, one-page typescript on the University of Pennsylvania's connections with companies on medical research, c. 12 March 1934 [hereafter Penn-Merck Agreement], box 33, "Merck Fellowship Fund, 1930-1934," Richards Papers; cf. George W. Perkins to A. N. Richards, 12 March 1934, Merck Archives.

[62]On the policy of the University of Pennsylvania regarding medical patents, see A. N. Richards to George W. Perkins, 9 March 1934, Merck Archives, and Morris Fishbein, "Medical Patents," Journal of the American Medical Association 109 (1937):1540.

exception of literature references, the guideline prohibited Merck from using the names of Pennsylvania researchers or the university in any advertising. The company had no apparent objections to these stipulations, but others led to some complaints from Merck personnel. Pennsylvania's wish to avoid having the company distribute reprints of university scientists prompted Hans Molitor to lament the university's failure to appreciate the needs of the company. This was just another indication, according to Molitor, of how the university had been safeguarded, while "not the slightest intention is given to the interests of the commercial concern; . . . [the agreement] should protect both parties."[63] Molitor was right; not once did the agreement refer to the rights of the company. The Merck pharmacologist also objected to a clause that gave Pennsylvania the right to approve "all advertising or publicity matter based on an investigation at the University of Pennsylvania . . . insofar as the advertising or publicity material refers to or is an interpretation of the work done at the University." Molitor felt this was too restrictive, because it was the company's duty to relate as much information as possible about therapeutic products in the informational circulars it sent to health professionals.[64]

Finally, the research agreement gave Pennsylvania at least some

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[63]Hans Molitor to [George W.] Merck, 3 January 1934, Merck Archives. I have no evidence that the company executive officers, such as George Merck and George Perkins, shared Molitor's concerns about the agreement. But Molitor was a respected and distinguished member of Merck's research staff, and the Director of the Merck Institute for Therapeutic Research; as such, the Merck executives most likely carefully considered his comments and suggestions.

[64]Penn-Merck Agreement, c. 12 March 1934, and Hans Molitor to [George] Perkins, 5 March 1934, Merck Archives.

control over Merck's selection of other groups it wished to invite to work on the collaborative project.[65] There were probably two reasons why Pennsylvania wanted to maintain such control. First, in the case of a group joining the collaboration to work on a different aspect of the project than Pennsylvania (e.g., if Pennsylvania pharmacologists were working with Merck, and the latter sought outside chemists for assistance), Pennsylvania wanted to be sure that its researchers could work with the outsiders. The university's motive here could be for professional or even personal reasons. Second, and more importantly, this clause was a source of security for the academic workers. Merck, no matter how good its intentions, was a business that had to stay close to the cutting edge of research to maintain its position in the pharmaceuticals market. The firm could find itself in a position where it had to crowd out the collaborating Pennsylvania pharmacologists, say, with another group that could produce results. With this stipulation in the agreement, Pennsylvania medical researchers guaranteed themselves a quasi-monopoly on any collaboration they entered into with Merck. The firm probably did not realize how it was potentially shackling itself; if it did occur to the company, it probably did not pay much heed to this clause. Certainly, I have not seen any evidence suggesting that Merck put up much if any resistance to this clause. A similar issue came up several years later between Parke-Davis and Arthur Tatum, a pharmacologist at Wisconsin who had been collaborating with the Detroit firm for over fifteen years on organic arsenicals

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[65]Molitor to Perkins, 5 March 1934.

(see Chapter 5). Parke-Davis wanted to support a scientist who seemed on the verge of a useful discovery in the arsenical field. However, its contract with Tatum gave the Wisconsin pharmacologist the power to veto any outside involvement. But Tatum agreed to allow the company to subsidize outside workers in the arsenical field.[66]

In this section, I have tried to convey some sense of how Newton Richards stimulated research connections between his university and Merck. He offered the company a site where it could have some of its products tested, at a time when Merck did not yet possess the pharmacological facilities and personnel, much less the clinical capacity, to evaluate these products itself. More significantly, Richards engineered a formal agreement between Pennsylvania and Merck. Despite its slant towards the rights of the university, this agreement essentially granted Merck access to one of the leading research institutions in the United States. This was particularly important to Merck in the light of the firm's still fledgling research programs in the early 1930s.

Richards' Later Services for Merck

Beginning in the mid-1930s, Richards occupied various posts within

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[66]See A. W. Lescohier to A. L. Tatum and C. S. Hamilton, 10 September 1943, box 5, folder 5, Arthur Lawrie Tatum Papers, University of Wisconsin Archives, Madison, Wisconsin; C. S. Hamilton and A. L. Tatum to A. W. Lescohier, 23 September 1943, ibid.; A. W. Lescohier to C. S. Hamilton and A. L. Tatum, 11 October 1943 and 17 November 1943, ibid. I should mention that Tatum could afford to relinquish the security that this contractual clause gave him, because he was collecting considerable royalties from Parke-Davis on a discovery he made earlier in the collaboration; see John Patrick Swann, "Arthur Tatum, Parke-Davis, and the Discovery of Mapharsen as an Antisyphilitic Agent," Journal of the History of Medicine and Allied Sciences, in press (1985).

Merck, which gave the outsider a close look at the operations of the company and an opportunity to directly influence Merck's research policies. Richards served on the Scientific Advisory Board of the Merck Institute of Therapeutic Research, the Merck Fellowship Committee (as Chairman), the Merck Board of Directors, the Scientific Committee of the Board (as Chairman), and the company's Scientific Policy Council. While all but the first of these positions came after World War Two, I feel they too merit some mention, as logical extensions of Richards' growing influence on the pharmaceutical firm during the 1930s. No academic scientist was as extensively and intensively involved in Merck's affairs as Richards.

Hans Molitor, the Director of the Merck Institute of Therapeutic Research, complained about the original scientific advisors to the Institute, two of the three advisors being Merck employees. Molitor preferred to have at least one clinician and one biomedical scientist from different universities as his advisors, most likely because they would facilitate outside contacts for the Institute. Molitor received his wish the next year, 1936, when the company engaged Richards, William Castle (a Professor of Medicine at Harvard Medical School), and Henry Dakin (a biochemist in a private New York laboratory) to serve as the Institute's scientific advisors.[67] Richards not only

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[67][Hans Molitor], "Merck Institute of Therapeutic Research: Its Organization at Present and in the Future," 18-page typescript, c. January, 1935, 11-12, attached to idem to [A. N.] Richards, 18 January 1935, box 30, "Merck Institute, 1931-1940," Richards Papers; Hans Molitor, "Merck Institute of Therapeutic Research: Fourth Annual Report," 13-page typescript, [1937], 1, ibid. See also A. N. Richards to William B. Castle, 8 June 1936, box 30, "Business and Research," Richards Papers.

agreed to serve on the Advisory Board, but recruited at least one of the other members.[68]

Richards and the other advisors discussed "all principal problems of current or contemplated research" of the Merck Institute. The advisors met with Molitor, other Institute staff, and Merck executive officers and researchers about three times a year. In addition, Molitor occasionally visited and corresponded with the advisors about different research projects at the Merck Institute. It was an arrangement that called upon the "experience, judgement, and wisdom" of Richards and the others without taxing their other responsibilities. Merck paid each of them $1000 for their services.[69] The Advisory Board counseled Molitor, and other Merck personnel with an interest in the Institute, on various research-related issues, often dealing with drug research and development: new directions for research on old drugs, new drugs or classes of drugs for the Institute to investigate, diseases for which no useful drug existed, and so on. Richards, Castle, and Dakin also discussed less research oriented issues concerning the Merck Institute. For example, they evaluated ways to publicize the Institute to the medical and scientific communities, and how the Merck Institute could arrange with local universities to train some of the Institute employees for higher degrees--while working

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[68]See Richards to Castle, 8 June 1936; W. B. Castle to A. N. Richards, 13 June 1936, box 30, "Business and Research," Richards Papers; A. N. Richards to W. B. Castle, 16 June 1936, ibid.; and G. W. Merck to William B. Castle, 23 June 1936, ibid.

[69]Molitor, "Merck Institute: Organization," 12; Richards to Castle, 8 and 16 June 1936; Merck to Castle, 23 June 1936; and A. N. Richards to [George W.] Merck, 27 December 1939, Merck Archives.

on Institute-related projects.[70]

Richards served on the Scientific Advisory Board of the Merck Institute into the 1950s, with a brief hiatus during the war, when he headed the Committee on Medical Research. Despite the tripartite (and later, quadripartite) nature of the Advisory Board, Richards usually had his way on policy decisions. His way, according to John T. Connor, President of Merck whose career at the pharmaceutical firm overlapped that of Richards for several years, translated into "tremendous research progress" for the Institute and the firm:

> . . . Dr. A. N. became the keystone of the Institute's Board of Advisors. In that capacity he always pressed for emphasis on basic research, insisting on adequate facilities for it which meant, inevitably, an adequate budget. He was a minority of one on more than one occasion, but his persistence usually brought the rest of the Board around to his way of thinking. Merck's tremendous progress through research is more than adequate testimony for the validity of his farsighted proposals.[71]

Richards also provided a useful service for Merck by helping to plan and administer the Merck Fellowships in Natural Sciences, which began in 1947 and lasted many years thereafter. Merck, of course, had supported numerous outside studies through fellowships and grants for

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[70]Hans Molitor to George W. Merck et al., 13 December 1937, Merck Archives; Hans Molitor to A. N. Richards, 7 November 1939, ibid.; and Hans Molitor to [William B.] Castle et al., 10 May 1940, ibid.

[71]"Richards: Some Observations," 7 (quotation); "The Merck Institute for Therapeutic Research" (1942, mimeographed), 2, 4, Merch Archives; and Hans Molitor to [Randolph] Major, 6 February 1951, box 30, "Consultants, Grants, Fellowships as of Feb., 1951," Richards Papers. Richards, in addition to his Institute duties as a scientific advisor, became a member of the Board of Trustees of the Merck Institute (as did Castle) in 1950. The three Trustees oversaw the financial operations of the Institute; see ibid., and "Merck Institute for Therapeutic Research," 1942, 4.

many years prior to this. The Merck Fellowships in Natural Sciences, however, were more benevolent than directly strategic in character (that is, they did not have a direct bearing on Merck's own research and development programs, although they surely had at least some value for public relations). A request late in 1945 from the Committee on the Chemistry of Proteins of the National Research Council, for Merck to fund a few $4000-$5000 fellowships in protein chemistry, prompted the firm to devise an alternative fellowship plan. Merck appropriated $100,000 for the awards, which would range from $1500-$5000 annually each. An independent Merck Fellowship Board, chosen by Frank B. Jewett (then President of the National Academy of Sciences), selected the graduate and postdoctoral fellows. Rather than focusing on protein chemistry, Merck opened the awards to all fields of chemistry and biology.[72]

Richards contributed to the Merck Fellowships in two ways. First, he helped the company design the fellowships program. President Merck's early draft of the fellowship plan incorporated some of the ideas he and Richards had discussed in earlier years, on how industry could support fundamental work in outside institutions. The final fellowship arrangements included several of Richards' recommendations, such as restricting awards to United States citizens, suitably

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[72]H. B. Vickery to George W. Merck, 5 December 1945, box 13, "Merck Award Committee, 1946-1948," Richards Papers; George W. Merck to H. B. Vickery, 25 January 1946, ibid.; George W. Merck to A. N. Richards, with attached memorandum, ibid.; George W. Merck, memorandum to Committee of Awards, 16 July 1946, ibid.; and "Merck Fellowships in Natural Sciences Administered by the National Research Council" (4-page mimeograph, c. 1947), ibid.

reimbursing the members of the Merck Award Committee ($500) for their work, and establishing policies on the distribution of patent rights in the event the fellow made a patentable discovery.[73] Second, Richards served as the Chairman of the Merck Award Committee.[74] In itself, this position was not a great burden. However, recall some of his other Merck activities at this time; he was a Scientific Advisor for the Merck Institute and a general consultant to the company at large. In addition, he had positions as Vice President in Charge of Medical Affairs at Pennsylvania (until 1948) and President of the National Academy of Sciences (1947-1950). Richards had good reason to turn down the invitation to serve on this committee. Instead, he accepted the Chairmanship. This, I believe, is a very good example of Richards' willingness to assist the company, in whatever way he could.

Richards developed a particularly intimate contact with the company after 1948, the year he was elected to the Merck Board of Directors; he remained on the Board for ten years. During that period, Richards was the only academic medical researcher (albeit retired) among the Merck Directors.[75] His unanimous election to the Board, a

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[73]Merck to Richards, 25 January 1936; A. N. Richards to George Merck, 12 June 1946, box 13, "Merck Award Committee, 1946-1948," Richards Papers; and George W. Merck to A. N. Richards, A. Baird Hastings, and Frank B. Jewett, 16 July 1946, ibid.

[74]Alfred N. Richards to D. W. Bronk, 17 October 1946, box 13, "Merck Award Committee, 1946-1948," Richards Papers, and Alfred N. Richards to George W. Merck, 14 April 1947, ibid.

[75]*Henry D. Dakin, a biochemist in a private New York laboratory who did* not have an academic appointment, served on the Merck Board from 1938 through 1949. Vannevar Bush, the former head of the wartime Office

position which paid Richards $10,000 a year, reflected what George Merck called Richards' ". . . broad experience in and knowledge of the problems in medical research and its related sciences that are common to our educational institutions, the government, and industry."[76]

Soon after becoming a Director, President Merck appointed Richards Chairman of the new Scientific Committee of the Board, a post he held for the duration of the Committee (1948-1956). The functions of this Committee are not clear, but the available evidence indicates one incident in which Richards--probably as Chairman of the Scientific Committee--was thrown into a battle between the legal division and the research and development division over Merck's scientific publication policy. The former preferred that publication of patentable research be delayed from two to five years after applying for the patent, whereas the research personnel wanted to preserve the established policy of publishing soon after filing letters patent.[77] Richards,

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of Scientific Research and Development, became a Board member in 1949 and served throughout Richards' stay; eventually he became Chairman of the Board. Bush was a former professor of electrical engineering at the Massachusetts Institute of Technology, and the President of the Carnegie Institution (since 1939) at the time he joined the Merck Directors. See Merck and Co., Inc.: Report to Stockholders, 1938-1958; Percival Hartley, "Henry Drysdale Dakin," Obituary Notices of Fellows of the Royal Society of London 8 (1952):129-148; and American Men of Science, 8th ed., s.v. "Bush, Dr. V(annevar)."

[76]Merck and Co., Inc.: Report to Stockholders, 1948, p. 7 (quotation), and Minutes of the meeting of the Board of Directors of Merck and Co., Inc., New York, New York, 20 July 1984, box 32, "ANR--Appt.--Bd. of Directors," Richards Papers.

[77]E. H. O'Brien to J. T. Connor, 2 May 1949, box 32, "Publication Policy," Richards Papers; Karl Folkers to H. D. Dakin, 9 June 1949, ibid.; R. T. Major to A. N. Richards, 23 June 1949, ibid.; and "Richards: Some Observations," 18.

Figure 11. A. N. Richards with Merck and Company personnel at a ground-breaking ceremony in 1951 for a new Merck Institute. Participants are (left to right) Randolph Major, Vice-President and Scientific Director; Richards; Hans Molitor, Director of the Merck Institute for Therapeutic Research; George W. Merck, Chairman of the Board; and James J. Kerrigan, President (from Merck Review 19, no. 5 (1958):9; UW neg. no. 10272 C-3).

of course, favored a liberal publication policy:

> I believe that any substantial change from the present policy would work harm to the Company to a degree which would not be balanced by the advantages over competitors which could possibly be obtained by long-postponed disclosure. In my opinion the research staff of Merck and Co. have a unique position among those of other chemical manufacturing companies in the country. The members of our staff are looked upon as participating in the general advance of chemical and medical science on equal footing with their colleagues in academic institutions and they are held in correspondingly high respect. I regard this fact as responsible in large degree for the morale of the scientific staff and for the pride which they take in the achievements of the organization.[78]

Since the outcome of this fight within the company is unknown, we cannot precisely tell how much influence Richards had on the issue. But it is difficult to imagine that anyone else involved in this dispute could have argued the problem so authoritatively, from the standpoint of universities' impressions of the Merck research programs.

After the company disbanded the Scientific Committee of the Board, Richards still had the opportunity to influence Merck's research policies, as a member of the Scientific Policy Council. This group, which began meeting in 1953, evaluated all aspects of research policies at Merck. The Council focused primarily on the exploration and development of specific drugs and classes of drugs, for example, whether to concentrate on a microbial or synthetic means of producing a certain drug. Yet, it also addressed such topics as leaves of absence for Merck scientists to study elsewhere, fellowship programs, and

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[78]A. N. Richards to R. T. Major, 4 July 1949, box 32, "Publication Policy," Richards Papers.

scientific publication policies.[79]

I have deliberately given short shrift to Richards' later roles in the company, because they extend well beyond the period under investigation. But the examples in this section are important, because they show that his close contact with Merck during the 1930s grew even closer later on. I believe two basic reasons explain his burst of activities at Merck by the late 1940s. First, despite his commitment to the National Academy of Sciences in the late 1940s, Richards had more time to devote to the pharmaceutical firm after the war. Second, and more significantly, Richards was able to rise to the highest echelons at Merck because of his great breadth of understanding of medical research and medical researchers, which he readily shared with the company since the early years of his consultantship.

Conclusion

I have tried to convey in this chapter a sense of Newton Richards' service to Merck as a general consultant. He functioned in a variety of fashions as a liaison, both between the company and the academic world, and between the former and the University of Pennsylvania. Also, the various positions he occupied within the company, from the mid-1930s to 1959 (when his association with Merck formally ended), afforded Richards the opportunity to directly influence the research

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[79]The folders, "Scientific Policy Council" and "Policy of Merck, Corporate and Scientific," in box 33, Richards Papers, illustrate the Council's activities. For example, see Minutes of the meeting of the Merck Scientific Policy Council, [Rahway, New Jersey], 14 June 1954, box 33, "Policy of Merck, Corporate and Scientific," Richards Papers.

policies at Merck. This is not to say that the pharmacologist had to be on the inside to have an impact, for "during the difficult early years," John T. Connor reflected, "Dr. Richards participated in the formulation of Merck's whole new research plan. Even more important, *he helped to attract to Rahway some of the finest research men, either as consultants or as regular staff members."*[80]

The company called on Richards for many services other than those I have already discussed. For example, it sought his advice on directions it should take in the research and development of different drugs and drug groups. In the mid-1930s, the Pennsylvania pharmacologist urged Merck to make at least a modest investment in hormone research. The company did just that, by developing a hormone research program at Rahway and linking up with chemists at Princeton. The investment eventually paid off, as Merck became one of the early industrial leaders in the synthetic hormone field.[81] Around the same time, Richards also counseled Merck on the development of the first of its litany of vitamin successes, vitamin B_1. George Merck set out to "lay the whole matter before Dr. Richards and get his wise head to work on this difficult snarl." The snarl involved, among other things, a dispute between the Carnegie Institution and Robert Williams, a chemist at Bell

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[80]"Richards: Some Observations," 7 (quotation), and Detlev W. Bronk, "Alfred Newton Richards (1876-1966)," Perspectives in Biology and Medicine 19 (1976):420.

[81]George W. Merck to [George W.] Perkins et al. (memorandum of meeting with Dr. Richards), 25 January 1935, Merck Archives; Molitor to Richards, 7 November 1939; Mahoney, Merchants of Life, 198-201; and Gary L. Nelson, ed., Pharmaceutical Company Histories, vol. 1 (Mandan, N.D.: Woodbine, 1983), 83-86.

Laboratories, over the patenting of Williams' discovery of a method to produce B_1 from rice polishings. The Carnegie Institution, which had supported much of Williams' work, opted to dedicate the patent to the public, whereas Williams disagreed, hoping to maintain some control over B_1 production. Merck supplied the vitamin in bulk to Williams for his chemical studies, and the company hoped to be one of the first licensees to produce B_1.[82] The various parties gradually worked out their differences, and Merck became an early leader in the B_1 market. Whatever Richards contributed to the solution of these problems is unknown to me, but the point is that Merck valued and frequently tapped Richards' keen analytical sense and his broad familiarity with biomedical research and researchers.

In the late 1930s, the consultant helped connect Merck with another drug discovery. René Dubos, of the Rockefeller Institute, isolated an antibiotic from a soil microorganism, called tyrothricin (later identified as a mixture of two microorganisms), in 1939. Dubos was willing to accede to Merck's request for a sample of the antibiotic, but the Rockefeller Institute was not as cooperative. After the company approached him for advice, Richards recommended that the company frame a proposal that would complement the Rockefeller Institute's own plan for tyrothricin; for example, how Merck chemists could

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[82]George W. Merck to [George W.] Perkins et al. (memorandum of interview with R. R. Williams), 25 January 1935, Merck Archives (quotation); George W. Merck to A. N. Richards, 29 January 1935, box 31, "Merck and Co., 1930-1939," Richards Papers; J. S. Zinsser to [George] Merck, 28 January 1935, ibid.; R. E. Gruber to [George] Merck, ibid.; H. Molitor to [George] Merck et al., 28 January 1935, Merck Archives; and W. L. Sampson to [Hans] Molitor, ibid.

assist the Institute in developing this drug. Richards even wrote a letter of introduction for Merck to Herbert Spencer Gasser, the Director of the Institute with whom Richards was well-acquainted.[83] The company not only received tyrothricin, but brought in Dubos as a consultant.[84]

Richards' assistance was not always directly related to Merck research programs or specific research projects. For example, when President George Merck agreed to address the Medicinal Chemistry Division at the April, 1935 meeting of the American Chemical Society, Richards lent his hand in outlining and writing the speech. Not that George Merck did not agree with the ideas, but the topic and the tone of this address--on the relationship between industry and universities in medical research--was vintage Richards.[85] After the New Jersey State Department of Health refused to grant Merck a permit to conduct vivisection experiments (see Chapter 3), Richards petitioned the

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[83]A. N. Richards to Herbert S. Gasser, 3 October 1939, Merck Archives: "I write this note, not with the thought of supporting Major's request [i.e., Randolph Major's request for a sample of tyrothricin], but only to say that as the result of eight years of association I am confident that you can have complete faith in any engagements into which you may see fit to enter with the officers of [Merck]."

[84]Hubert A. Lechevalier and Morris Solotorovsky, Three Centuries of Microbiology (1965; reprint, New York: Dover, 1974), 478; H. W. Florey et al., Antibiotics, vol. 1 (London: Oxford University Press, 1949), 422-442; Randolph T. Major to A. N. Richards, 14 August 1939, Merck Archives; A. N. Richards to [Randolph] Major, 26 August 1939, ibid.; W. H. Engels to A. N. Richards, 3 October 1939, ibid.; H. Molitor to [George] Merck, 8 October 1939, ibid.; and A. N. Richards to R. T. Major, 28 November 1939, ibid.

[85]Merck to Perkins et al., memorandum of meeting with Richards, 25 January 1935, and George W. Merck, "An Essential Partnership: The Chemical Industry and Medicine," Industrial and Engineering Chemistry 25 (1935):739-741.

President of the Department of Health to reverse this decision. He emphasized both the necessity of animal experiments for therapeutic advances, and his conviction that the Merck pharmacology laboratory could become one of the great centers in this country to further scientific medicine. Richards' arguments no doubt helped convince the Department to reconsider its earlier action, and issue Merck a permit.[86]

Newton Richards' value to Merck was simply inestimable. The pharmacologist from the University of Pennsylvania impacted on so many aspects of the company's affairs, so frequently, that it is impossible here even to survey his contributions to the drug firm comprehensively. What I have done is illustrate his connections with Merck. Richards was closely associated with Merck during the years when the firm became one of the research giants in the pharmaceutical industry. Merck's research personnel and expenditures for research grew tremendously from 1930 to 1940. The company had only a handful of chemists in 1930, but over 70 chemists, pharmacologists, bacteriologists, and other researchers by 1940. Merck's research budget grew nearly tenfold during the 1930s.[87] Richards was not necessarily the driving force behind

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[86]A. N. Richards to Hans Molitor, 29 September 1932, box 32, "Hans Molitor, 1932-1933," Richards Papers; Randolph T. Major to A. N. Richards, 29 December 1932, box 30, "Merck Institute, 1931-1940," Richards Papers; A. N. Richards to Charles I. Lafferty, 30 December 1932, ibid.; and A. N. Richards to A. Haines Lippincott, ibid.

[87]Clarence J. West and Ervye Risher, "Industrial Research Laboratories of the United States, Including Consulting Research Laboratories," 3d ed., Bulletin of the National Research Council, no. 60 (1927); Clarence J. West and Callie Hull, "Industrial Research Laboratories of the United States, Including Consulting Research Laboratories," 5th ed., ibid., no. 91 (1933); Callie Hull, "Industrial Research Labora-

this growth, but he was certainly one of the gears that helped propel Merck research in this era of initial growth. Merck research staff, consultants, advisors, general in-house and collaborative research policies, research and development of numerous drugs, Merck prestige in the eyes of academic scientists and others--Richards influenced all of these in one way or another. He is the example par excellence of a general consultant. President Merck's future plans for Richards, from a 1935 memorandum to executive officers and research heads in the company, clearly expressed Richards' value to Merck and Company:

> [Richards and I] spent considerable time discussing various contacts [that] members and divisions of our organization have with him. I shall insist that a definite program be laid down to provide informal and leisurely talks with Dr. Richards by Mr. Perkins, Dr. Major, Dr. Molitor--each at least four times this year, without reference to whatever number of other conversations they may have with him accompanied by others of the organization. It is my firm belief, confirmed by experience, that in this way we will get the most from Dr. Richards, and it is essential that we get all we can.[88]

The consultantship, I think, meant just as much to Richards as it did to the company. The pay was substantial; he received $1000 a year as a Scientific Advisor to the Merck Institute for Therapeutic Research, perhaps around $5000 annually for his general consulting work, and $10,000 yearly as a Merck Director. How often he received

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tories of the United States, Including Consulting Research Laboratories," 7th ed., ibid., no. 104 (1940); Merck Corporation, Annual Report, 1931; and "Merck and Co., Inc. and Consolidated Domestic Subsidiaries: Analysis of Research and Development Expenses," 1-page typescript, 15 November 1951, box 29, "Budget, 1953," Richards Papers. Also, see Chapter 3.

[88]Merck to Perkins et al., memorandum of meeting with Richards, 25 January 1935.

these payments is unknown. As considerable as these sums may have been, I do not believe they meant nearly as much to Richards as did the opportunity to take part in and help shape the evolution of the research programs at Merck. Few academic scientists had such an opportunity at other pharmaceutical companies. Here, he had a chance to apply his conviction that industry had the potential of fostering biomedical science on an equal footing with universities. Richards personally contributed a great deal towards effecting this goal at Merck.

PART III

THE SCIENTIST AS A SPECIALIST-CONSULTANT

During the early era of cooperative research, pharmaceutical companies engaged two types of consultants: the general consultant, who had a rather broad impact on a firm's research program, and what I call the specialist-consultant. The latter had a much more intensive than extensive influence on industrial research, because companies engaged these researchers for their expertise in a particular field of pharmacology, chemistry, microbiology, and so on. The specialist-consultant served the pharmaceutical firm in two ways. First, he was a research source who filled deficiencies in the company's own research organization. For example, in a discipline like pharmacology, in which the American labor pool was fairly low compared to other more established scientific disciplines, and which fostered a generally disparaging if not hostile attitude toward the drug industry in the early twentieth century, industry suffered a manpower shortage. Thus, until companies could rely on in-house personnel, they had to search outside for trained pharmacologists to evaluate their drugs. Second, the specialist consultant, regardless of the manpower situation within a firm, was always useful as a well-informed source for and an active participant in the latest developments in a field. A firm could not possibly hire experts in all fields of all scientific disciplines. It had to maintain contact with experts on certain chemical compounds, or classes of drugs, or types of drug-yielding microorganisms, to remain competitive in an increasingly research-based enterprise like the

pharmaceutical industry.

This type of consultantship was a valuable source of continuing support for the university scientist of the 1920s and 1930s. It was not unusual for a scientist to consult with several firms on many topics, over a number of years. The compensation he derived from these connections, in the form of graduate fellowships, consulting fees, or whatever form of compensation the collaborators agreed on, was a vital source of support for his research program. Consultants fortunate enough to take part in a practical therapeutic discovery in the course of the collaboration enjoyed--if they made prior arrangements for such an event--the additional benefit of royalties from the sale of a drug. Depending upon the significance of the discovery, these royalties could support a major laboratory for years, or significantly supplement a scientist's personal income, or both. Clearly, the specialist-consultantship benefitted research programs in both industry and universities.

The specialist-consultantship could contain some elements of the general consultantship (Part II) and the specific project collaboration (Part IV). For example, companies turned to specialist-consultants for recommendations to fill research positions in the consultant's field, and possibly for assistance in dealing with the United States Patent Office or the Council on Pharmacy and Chemistry of the American Medical Association. Also, these consultantships quite often yielded specific therapeutic agents, which the consultant helped develop as part of his responsibilities as an advisor on the chemistry or pharmacology of that class of therapeutic agents. From the standpoint of the company, of course, a specific drug was the ideal product of a

specialist-consultantship. While the specialist-consultantship could bear some characteristics of the other two types of collaboration, this type of university-industry interaction generally did not trespass beyond the academic scientist's sphere of expertise, and the collaborators typically initiated the specialist-consultantship to investigate a group or class of drugs, rather than an individual therapeutic agent.

Examples of the specialist-consultant abound. Chapter 5 relates the consulting experiences of two pharmacologists at the University of Wisconsin. Consider some other cases of consultants in pharmacology and other disciplines. Chauncey Leake, a pharmacologist who held positions at four universities during his career, worked with several drug companies between the two World Wars. Leake evaluated barbiturates in cooperation with Abbott beginning about 1929. He investigated arsenicals in amebic dysentery and infections involving the Trichomonas parasite for Parke-Davis during the 1930s.[1] Leake also worked with Lilly on the chemotherapy of amebiosis, and on antileprotic agents. He collaborated with Merck on a study of derivatives of prostigmine, a synthetic drug similar in structure and action to the Calabar bean alkaloid, physostigmine.[2]

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[1]J. F. Biehn to A. L. Tatum, 19 October 1929, box 1, "Abbott Laboratories, 1929-1931," Arthur Lawrie Tatum Papers, University of Wisconsin Archives, Madison, Wisconsin; Arthur L. Tatum to J. F. Biehn, 21 October 1929, ibid.; Oliver Kamm to A. L. Tatum, 25 September 1933, box 4, folder 11, ibid.; and O. M. Gruhzit to [Oliver] Kamm, 15 December 1936, box 4, folder 5, ibid.

[2]Chauncey D. Leake to H. W. Rhodehamel, 24 January 1940, box 44, "Lilly Research Laboratories, 1933-1940," Chauncey D. Leake Papers, National Library of Medicine, Bethesda, Maryland; Randolph T. Major to Chauncey D. Leake, 20 November 1942, box 47, "Merck and Co. (G. W. Merck, R. T. Major), 1941-1945," ibid.; and Chauncey D. Leake to Randolph T. Major,

The consultantship between microbiologist Selman Waksman and Merck on industrial fermentations and antibiotics demonstrates the impact this type of collaboration could have on an entire university's research program, as well as the consultant's own laboratory. Merck established a fellowship for an investigation of industrial fermentations in Waksman's laboratory at the College of Agriculture at Rutgers in 1938. Among his other contributions to the firm in this field, Waksman helped launch submerged fermentation production of lactic, citric, and fumaric acids at Merck.[3] Merck established another fellowship in Waksman's laboratory, for the investigation of antibiotics, in 1939--shortly after a former student of Waksman, René Dubos, had discovered an antibiotic-producing soil microorganism. Waksman and Merck drew up an agreement at this time whereby the firm supplied chemical, pharmacological, and mass production assistance for any promising antibiotics the Rutgers microbiologist developed. Waksman agreed to assign Merck exclusively any patentable discoveries in his laboratory, for a royalty of 2.5 percent of the sales of these discoveries, to be paid to Rutgers.[4]

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24 November 1942, ibid.

[3]Selman A. Waksman, My Life with the Microbes (London: Robert Hale, 1958), 184; H. Boyd Woodruff, "A Soil Microbiologist's Odyssey," Annual Review of Microbiology 35 (1981):8; Selman A. Waksman to Timothy Atkeson, 18 November 1950, box 1, Selman A. Waksman Papers, Division of Manuscripts, Library of Congress, Washington, D.C. [hereafter Waksman Papers]; and R. T. Major, "The Research Program of Merck and Co., Inc.," 15-page typescript, 3 December 1938, 7, box 31, "Merck and Co., 1930-1939," Alfred Newton Richards Papers, University of Pennsylvania Archives, Philadelphia, Pennsylvania [hereafter Richards Papers].

[4]Waksman, My Life with the Microbes, 184, and Waksman to Atkeson, 18 November 1950.

Beginning with actinomycetes, Waksman isolated a litany of antibiotics from soil microorganisms, such as actinomycin (1940), clavacin (1941), and streptothricin (1942). Typically, once Waksman and his co-workers isolated and conducted preliminary tests on a new antibiotic, Merck chemists tried to purify the drug and solve its chemical structure, Merck pharmacologists investigated its toxicity and therapeutic value in animals, and Merck bacteriologists and engineers developed methods to produce the antibiotic on a large scale.[5] All of the above antibiotics were too toxic to receive serious consideration for clinical tests. But Waksman isolated an antibiotic from Streptomyces griseus in 1943, streptomycin, which was much less toxic than its predecessors and active against some bacteria that neither the sulfonamides nor penicillin could touch, most notably Mycobacterium tuberculosis.[6]

Fearful of criticism that they had permitted the monopolization of a very promising therapeutic agent, and suspecting that Merck alone could not fill the demand for streptomycin, Waksman and Rutgers petitioned Merck in 1945 to rescind part of their earlier agreement, so

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[5]Waksman, My Life with the Microbes, 200, and Selman A. Waksman to A. N. Richards, 26 July 1940, box 4, Waksman Papers. Waksman himself inoculated the flasks with microorganisms, which Merck workers then incubated at the Rahway plant; see Woodruff, "Soil Microbiologist's Odyssey," 7. Hubert A. Lechevalier, "The Search for Antibiotics at Rutgers University," in The History of Antibiotics: A Symposium, ed. John Parascandola (Madison: American Institute of the History of Pharmacy, 1980), 115, presents a list of the antibiotics that Waksman and his associates isolated.

[6]Waksman, My Life with the Microbes, 200-201, 251, and Harry F. Dowling, Fighting Infection: Conquests of the Twentieth Century (Cambridge, Mass.: Harvard University Press, 1977), 158-172. While streptomycin was less toxic than actinomycin and the other antibiotics from soil, it was by no means non-toxic; see Dowling above.

that other companies would be able to produce streptomycin and any other useful drugs developed in Waksman's laboratory. According to Waksman, "The response was magnanimous; the company accepted all our recommendations, thus saving me personally and the university in particular considerable embarrassment and possible ill will on the part of the public as a whole for trying to establish absolute control of a process that was to save human lives."[7] Subsequently, Merck assigned its patents on Waksman's discoveries to the Rutgers Research and Endowment Foundation around 1946, and within two years eight companies were producing streptomycin in the United States.[8]

The royalties from sales of any Waksman antibiotics, according to the 1938 agreement, went entirely to Rutgers. After the Foundation assumed control of the patents, Waksman eventually received ten percent of the royalties, half of which he applied to the establishment of a Foundation for Microbiology, "to promote microbiology throughout the world." In a settlement out of court, three percent of the royalties, plus $125,000, went to Albert Schatz, Waksman's graduate student who had brought suit against Waksman and Rutgers to achieve recognition of his part in the discovery of streptomycin. A small part of the royalties went to others who shared in the antibiotic work in Waksman's

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[7]Waksman, My Life with the Microbes, 185. Merck released the patents with the provision that it could withhold part of the royalties until its investment in the development of streptomycin was partially reimbursed (Lechevalier, "Antibiotics at Rutgers," 118), but this almost certainly was a pittance compared to what the firm would have made if it retained the patents.

[8]Lechevalier, "Antibiotics at Rutgers," 118-119; Dowling, Fighting Infection, 163; and Waksman, My Life with the Microbes, 185, 252.

laboratory. The Foundation applied the remaining 80 percent of the royalties towards the construction and endowment of the Waksman Institute of Microbiology at Rutgers. What began in 1938 as a modest specialist-consultantship on antibiotics yielded, in the next 40 years, twelve million dollars, the bulk of which supported research and related activities in microbiology at Rutgers and around the world.[9]

Waksman stressed the importance of the consultantship with Merck for the success of his antibiotics research program. He received "meager" assistance from Rutgers, and "limited" support from two philanthropic sources, the Commonwealth Fund and the Lasker Foundation. His work received "no support whatsoever" from governmental sources. But the Merck connection, he felt, was responsible for the practical turn his research took: "Without the help, however, of an industrial organization that took over a major part of the pharmacological evaluation of the antibiotic [streptomycin] and large-scale production our contribution would have never attained its goal."[10] That Waksman's products would have been little more than "bibliographic curiosities" without the cooperation of Merck seems doubtful to me, particularly in the light of the swelling interest in antibiotics in the 1940s and afterwards. But it is likely that the introduction of streptomycin to

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[9]Lechevalier, "Antibiotics at Rutgers," 119; Woodruff, "Soil Microbiologist's Odyssey," 11; Dowling, Fighting Infection, 161-162; and Waksman, My Life with the Microbes, 250-254.

[10]Selman A. Waksman, "Support of Research," comments to be made at a banquet of the American College of Chest Physicians, Atlantic City, New Jersey, 4 June 1955, pp. 3-4, box 6, "Speech and Article File," Waksman Papers. See also idem, My Life with the Microbes, 184-185, 246.

therapeutics would have been considerably delayed without this university-industry interaction.

Despite the change in the exclusive nature of their agreement, Merck maintained close contact with Waksman's group. The company established a Waksman-Merck Fellowship in Natural Science at Rutgers in 1949, worth $3600 annually; Merck soon increased the value of the Fellowship to $4500. The Fellowship lasted until the mid-1950s, and probably beyond, because "the grant is very valuable since it assures us [Merck] contact with Waksman's laboratory and early information on new developments there." Waksman also worked with Ciba Pharmaceutical Products, the New Jersey branch of the Swiss pharmaceutical firm, as a "classification consultant," but the records are too sparse to characterize his relationship with this company.[11]

During the 1930s, Lyndon Small, an organic chemist at the University of Virginia, engaged in specialist-consultantships with three pharmaceutical firms--Merck, Squibb, and Mallinckrodt of St. Louis--on the preparation of morphine derivatives and synthetic homologues of this drug. These consultantships were part of a broader program on the study of drug addiction, involving representatives from federal and state governments and private foundations in addition to universities and the pharmaceutical industry. Beginning in 1929, the Bureau of

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[11]Randolph T. Major to Robert Clothier, 22 April 1949, box 3, Waksman Papers; "Outside Research Analysis: Research and Development Division," 8-page (unpaginated) typescript, 10 October 1952, 5, box 29, "Budget Proposals, 1953," Richards Papers (quotation); Scientific Administration Division, Merck, "[Grants and Fellowships]," memorandum to Clarke et al., 29 May 1953, ibid.; C. R. Scholz to S. A. Waksman, 20 June 1946, box 4, Waksman Papers; and Selman A. Waksman to C. R. Scholz, 9 July 1946, ibid.

Social Hygiene--and later the Rockefeller Foundation--offered to subsidize an investigation to alleviate drug addiction, under the direction of the National Research Council. The Council appointed a Committee on Drug Addiction within its Division of Medical Sciences to organize this program.

The Committee decided to approach the project by focusing on non-narcotic substitutes for addictive drugs. It established a chemical unit at Virginia in 1929 under the direction of Small, for analytical work on opium alkaloids and preparation of synthetic compounds similar to these alkaloids. The Committee set up a unit for the study of the pharmacology of these compounds under Nathan Eddy at the University of Michigan, in the following year. The Division of Mental Health of the United States Public Health Service conducted clinical investigations of Small's compounds at two locations: the Federal Penitentiary in Leavenworth, Kansas, and the United States Public Health Service Hospital in Lexington, Kentucky (also known as one of the Service's Narcotic Farms). The Department of Health of the State of Massachusetts, and the Departments of Medicine and Surgery at the University of Michigan, also tested drugs in the clinic for the Committee. While drug companies had connections with all phases of this program, I will focus on their interactions with Small.[12]

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[12]William Charles White, "Committee on Drug Addiction of the National Research Council," Science 73 (1931):97-98; Nathan B. Eddy, "Studies of Morphine, Codeine and their Derivatives. I. General Methods," Journal of Pharmacology and Experimental Therapeutics 45 (1932):339; Lyndon F. Small et al., Studies on Drug Addiction, with Special Reference to Chemical Structure of Opium Derivatives and Allied Synthetic Substances and their Physiological Action, Supp. 138 to the Public Health Reports of the Public Health Service, United States

Small and his group of chemists concentrated on modifications of the host of alkaloids in opium. They were especially interested in synthesizing derivatives of phenanthrene, the compound of which morphine and other opium alkaloids are derivatives. Some of the compounds produced in Small's laboratory were unrelated to opium alkaloids, and others were already known. Most of the compounds he submitted to Michigan were derivatives of phenanthrene and modifications of morphine. Eddy and his group at Michigan used mice, rabbits, and cats to conduct several pharmacological tests on Small's drugs: toxicity, analgesia, respiratory effect, general depression, and effect on the gastro-intestinal tract. On the basis of these tests, using morphine as a standard of reference, the more promising drugs entered the next phase, evaluation in humans. Out of several hundred compounds prepared at Virginia, by the late 1930s physicians tested 16 in clinics, all of which were morphine derivatives.[13]

Small's earliest contact with a drug company came early in 1930, when Merck offered to supply him with about a half dozen alkaloids, mostly from opium. Merck and other firms were an important source of alkaloids for Small. While he had nearly an "unlimited supply" of morphine through his connections with the Public Health Service, Small

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Treasury Department (Washington, D.C.: Government Printing Office, 1938), iii-vi; and William Charles White, "Report of the Committee on Drug Addiction," 9-page typescript plus appendices, October, 1934, box 3, "NA, 1934-35," Lyndon Frederick Small Papers, National Library of Medicine, Bethesda, Maryland [hereafter Small Papers].

[13]White, "Report of the Committee on Drug Addiction," 5; Eddy, "Studies of Morphine," 340-359; and Small et al., Studies on Drug Addiction, iv.

had to depend on firms for most other opium alkaloids.[14] A year later, Merck initiated the Merck Fellowship in Alkaloid Chemistry to support Small's research on opium alkaloids at a rate of $700 each year, which the firm maintained through the 1930s. The Rahway company assisted Small's group in another way, by purifying crude alkaloids and other compounds in bulk, and processing these to intermediates for further elaboration at Virginia.[15] The Virginia group prepared a particularly promising derivative of morphine (dihydrodesoxy-morphine-D) around 1933; Eddy and his associates at Michigan found that it was lower in some manifestations of toxicity (e.g., lack of emesis) relative to morphine, and about ten times more effective than the latter as an analgesic. The Committee on Drug Addiction arranged for Merck to begin production of this on a large scale, and this derivative was one of the earliest compounds tested clinically. Tests in humans demonstrated that it was addictive.[16] Harry J. Anslinger, Commissioner of Narcotics in the Treasury Department and a member of the Committee, urged that

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[14]Lyndon F. Small to Joseph Rosin, 22 April 1930, box 3, "ME, 1932," Small Papers, and Lyndon F. Small to A. C. Boylston, 27 April 1931, box 2, "MA," ibid.

[15]George W. Merck to E. A. Alderman, 17 April 1931, box 3, "ME, 1932," ibid.; Committee on Drug Addiction of the National Research Council, "Preliminary Annual Report, 1933-1934," 4, box 1, "DO-DR," ibid.; Lyndon F. Small to Joseph Rosin, 28 June 1932, box 3, "ME, 1932," ibid.; and Lyndon F. Small to Joseph Rosin, 8 June 1933, box 3, "ME, 1932-1934," ibid.

[16]Lyndon F. Small to Joseph Rosin, 21 June 1933, ibid.; White, "Report of the Committee on Drug Addiction," 2; Lyndon F. Small to Edward Mallinckrodt, 12 February 1935, box 2, "MA-MC," Small Papers; and Lyndon F. Small, Kechee C. Yuen, and Louis K. Eilers, "The Catalytic Hydrogenation of the Halogenmorphides: Dihydroesoxymorphine-D," Journal of the American Chemical Society 55 (1933):3863-3870 (reports the preparation of the morphine derivative).

Small's derivative be patented, "in the interest of control of narcotics." Small received a patent on this compound in 1934, and assigned it to the Treasury Department.[17]

Squibb also supported Small's research on morphine derivatives, with a $700 annual fellowship that had been in effect at least since 1933. The firm subsidized a similar fellowship for pharmacological work at Michigan, the only pharmaceutical firm to extend such support there. In 1936, Squibb offered to fund a special fellowship at Virginia under Small's direction on derivatives of phenanthrene, with the provision that the firm could retain exclusive rights to any patentable developments. Neither the President of the University of Virginia nor the Chairman of the Committee on Drug Addiction objected, so the Squibb Fellowship in Phenanthrene Chemistry, worth $2500 annually, began in 1936. Thus, by the late 1930s Squibb was investing $3900 each year towards the support of research related to phenanthrene derivatives and modified opiate and other alkaloids.[18]

Small's laboratory obtained support in the form of alkaloids and a fellowship from another firm, Mallinckrodt, in the 1930s. Like Merck, Mallinckrodt supplied Small with several alkaloids, and the St. Louis

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[17]White, "Report of the Committee on Drug Addiction," 3 (quotation); Lyndon F. Small to George Merck, 4 September 1934, box 3, "ME, 1934-35," Small Papers; and Lyndon Frederick Small, "Morphine Derivative and Processes for Its Preparation," United States Patent 1,980,972, patented 13 November 1934.

[18]"Memorandum concerning the appointment of Alkaloid Research Fellows in the Drug Addiction Laboratory at the University of Virginia," n.d., box 1, "DO-DR," Small Papers; John F. Anderson to J. L. Newcomb, 7 February 1936, box 1, "AM-AR," ibid.; Lyndon F. Small to John F. Anderson, 21 March 1936, ibid.; and Lyndon F. Small to John F. Anderson, 6 June 1936, ibid.

firm assisted him by converting bulk morphine into codeine. In 1933, Mallinckrodt instituted a $1000 fellowship at Virginia, under the direction of Small, to assist the chemist in his work for the Committee on Drug Addiction. Mallinckrodt also mass-produced a codeine derivative Small synthesized (and later patented, in 1939), a derivative with which clinicians had promising results in the relief of tubercular cough.[19]

Sharp and Dohme and the Barrett Company of New York did not offer fellowships, but they did contribute phenanthrene and other raw materials to the Committee's investigation. For example, Barrett donated over 100 kilograms of phenanthrene to Small, worth several hundred dollars, from about 1929 to 1932.[20] In all, five firms supported research in Small's laboratory on substitutes for addictive drugs between the two World Wars. By the late 1930s, Small and his group of chemists were receiving almost $5000 each year in fellowships from industry for this work. In addition, the companies contributed many bulk chemicals, and they processed these compounds to intermediates

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[19]R. Norris Shreve to L. F. Small, 7 April 1931 and 4 August 1931, box 2, "MA," Small Papers; R. Norris Shreve to Lyndon F. Small, 23 May 1933, box 4, "SH-SM," ibid.; A. C. Boylston to William Charles White, 7 August 1933, box 1, "BL-BR," ibid.; L. F. Small to V. H. Wallingford, 19 December 1934, box 2, "MA-MC," ibid.; and Lyndon F. Small to Edward Mallinckrodt, 12 February 1935, ibid. R. Norris Shreve, a professor of chemical engineering at Purdue and a consultant to Mallinckrodt and several other chemical firms, mediated much of Small's interactions with Mallinckrodt; see American Men of Science, 8th ed., s.v. "Shreve, R. Norris."

[20]White, "Committee on Drug Addiction," 98; Lyndon F. Small to Barrett Co., 28 June 1930, box 1, "BA-BL," Small Papers; A. G. Stern to Lyndon F. Small, 11 July 1930, ibid.; F. H. Johnson to Lyndon F. Small, 15 February 1932, ibid.; and R. C. Quortrup to Lyndon F. Small, 19 September 1932, ibid.

for the Virginia group. The Bureau of Social Hygiene and the Rockefeller Foundation provided a majority of the funds for the work at Virginia,[21] but the Committee on Drug Addiction would have been forced to reduce the scale of its project considerably without the support of industry.

The following chapter discusses the impact of industrial support through specialist-consultantships on research in a major biomedical department, from the late 1920s to the late 1940s.

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[21]See, e.g., "[Report of the Committee on Drug Addiction,"] c. November, 1936, app. B (budget), box 1, "CO," ibid. The budget for the project did not include the Squibb phenanthrene fellowship, but this clearly was relevant to the Committee's project.

CHAPTER 5

WISCONSIN PHARMACOLOGISTS AND THE DRUG INDUSTRY: A. S. LOEVENHART AND A. L. TATUM

Arthur Salomon Loevenhart (1878-1929) and Arthur Lawrie Tatum (1884-1955) collaborated with seven companies on a variety of pharmacological and toxicological problems from the mid-1920s to the late 1940s. The two pharmacologists were interested in a rather wide array of drug groups, all of which entered into their collaborations. It will be useful, then, to summarize their research interests, since these were the bases of their specialist-consultantships with industry. Arthur Loevenhart received his baccalaureate (1898) and master's (1899) degrees from Kentucky State College, and spent the next decade at Johns Hopkins. After graduating from the medical school in 1903, he began working in John J. Abel's Department of Pharmacology and Physiological Chemistry. Loevenhart left Hopkins in 1908 to establish a pharmacology department at the University of Wisconsin Medical School, where he remained until his death. One of Loevenhart's earliest interests, beginning as an undergraduate at Kentucky, concerned biological oxidations. His investigation of the effects of different compounds on biological oxidations led Loevenhart to identify benzoyl peroxide and salts of iodoxy-benzoic acid as useful therapeutic agents. The latter remained in therapeutic favor as an anti-arthritic drug for several years, and the former is

still a widely used antibacterial agent.[1]

Loevenhart's research experience in antisyphilitic organic arsenicals led to his association with two companies, separately, on this topic. Eventually, his colleague in the Department of Pharmacology and Toxicology at Wisconsin inherited the arsenical collaboration with one of the drug companies. Loevenhart developed an interest in this field during his work for the Chemical Warfare Service from 1917 to 1918, as head of the Pharmacological and Toxicological Section. This section evaluated a number of war gases developed by chemists, including several arsenicals (e.g., Adamsite and Lewisite).[2] Soon after the war, Loevenhart organized a cooperative study of arsenicals and mercurials for the treatment of neurosyphilis, a form of the disease in which arsphenamine and neoarsphenamine had little or no efficacy. The chemistry department at Northwestern prepared the compounds, Loevenhart's Department of Pharmacology and Toxicology conducted the experimental evaluations of the drugs, and the Wisconsin Psychiatric Institute of the Mendota State Hospital in Madison carried out the clinical tests. This project, which lasted from 1919 to the mid-1920s,

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[1]See H. S. Gasser, "Arthur S. Loevenhart," Science 70 (1929):317-319; Russell Chittenden, The Development of Physiological Chemistry in the United States, American Chemical Society Monograph Series (New York: Chemical Catalog, 1930), 293-297; and A. S. Loevenhart, "Certain Aspects of Biological Oxidation," lecture to the Harvey Society, New York, 8 November 1914, Archives of Internal Medicine 15 (1915):1059-1071.

[2]Daniel Patrick Jones, "The Role of Chemists in Research on War Gases in the United States during World War I," Ph.D. diss., University of Wisconsin, 1969, 113-114, 156-164, 216-222, and H. C. Bradley, "Dr. Loevenhart's War Work," in "The Loevenhart Memorial Meeting: University of Wisconsin Medical School, May 3, 1929," Quarterly of the Phi Beta Pi Medical Fraternity 26 (1929):283-287.

received most of its funds from the United States Interdepartmental Social Hygiene Board and the Public Health Institute of Chicago.[3]

The most successful drug the Wisconsin workers tested came, not from Northwestern, but from the Rockefeller Institute for Medical Research. Tryparsamide, an organic arsenical which researchers at the Rockefeller Institute had prepared in 1915, was one of the first drugs Loevenhart and his colleagues in Madison investigated. At Loevenhart's request, the Institute sent tryparsamide and some other drugs to Madison in 1919, for possible applications in neurosyphilis, along with the data they compiled on these antisyphilitics. The Rockefeller Institute had tested tryparsamide in experimental syphilis and in some clinical forms of the disease, but the Wisconsin group was the first to establish

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[3]Chauncey D. Leake, "Arthur S. Loevenhart," Journal of Pharmacology and Experimental Therapeutics 36 (1929):497; idem, "Cooperative Research: A Case Report," Science 62 (1925):251-255; and M. E. McCaffrey to A. S. Loevenhart, 9 March 1922, box 11, "A. S. Loevenhart," General Files, Dean's Office, Papers of the University of Wisconsin Medical School Administration, University of Wisconsin Archives, Madison, Wisconsin. On the United States Interdepartmental Social Hygiene Board (est. 1918), see William F. Snow, "Contributions to Medical Science Developed Under the Auspices of the United States Interdepartmental Social Hygiene Board," American Journal of Tropical Medicine 1 (1921):97-108, and T. A. Storey, "A Summary of the Work of the United States Interdepartmental Social Hygiene Board," Social Hygiene 7 (1921):59-76. Congress instituted the Board to organize and subsidize investigations on the treatment and prophylaxis for venereal diseases. On the Public Health Institute of Chicago, which a former army medical officer and a sociologist organized in 1920 to manage venereal diseases in that Midwestern city, see Leake, "Cooperative Research," 253. In addition to Loevenhart, the principal workers involved in the neurosyphilis project were Winford Lee Lewis and Frank C. Whitmore at Northwestern, and W. F. Lorenz at the Wisconsin Psychiatric Institute.

the value of tryparsamide in neurosyphilis.[4] This major success, coupled with their efforts to organize a systematic cooperative study of a large group of drugs, targeted the Wisconsin group as a desirable potential collaborator in the eyes of some pharmaceutical firms.

Another research interest of Loevenhart that had a significant impact on his collaborations with industry concerned local anesthetics. Loevenhart had a solid background in chemistry before he began focusing on pharmacology (his graduate degree from Kentucky State College was in chemistry). This facilitated his work on the relationship between chemical structure and pharmacological activity of drugs, such as antisyphilitic arsenicals and anesthetics. In the early 1920s, for example, Loevenhart and a graduate student reported their results on an extensive study of the structure-activity relationships of several local anesthetics.[5]

Like Loevenhart, Arthur Tatum was well-trained in chemistry before he began formal work in pharmacology. He received his undergraduate degree in 1905 at a small college in Iowa, and a master's degree in chemistry two years later at the University of Iowa. After a three-

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[4]W. F. Lorenz et al., "The Therapeutic Use of Tryparsamid in Neurosyphilis," Journal of the American Medical Association 80 (1923):1497-1502; Leake, "Cooperative Research," 255-256; and A. S. Loevenhart, "Tryparsamide," Science 62 (1925):587-588. Cf. Wade H. Brown, "Tryparsamide," ibid., 350-351.

[5]H. L. Schmitz and A. S. Loevenhart, "A Study of Two Series of Procaine Derivatives with Reference to the Relationship between Their Pharmacological Action and Chemical Constitution," Journal of Pharmacology and Experimental Therapeutics 24 (1924):159-166; idem, "A Comparative Study of the Local Anesthetic Properties of Para-amino Benzoyl Di-iso-propyl Amino Ethanol Hydrochloride ('Isocaine'), Cocaine, Procaine and Butyn," ibid., 167-177; and Leake, "Arthur S. Loevenhart," 498.

year stay at the University of Colorado as a chemistry instructor, Tatum spent four years in Chicago. During this first stay in Chicago, when he earned a Ph.D. in the Department of Physiology and Pharmacology at the University of Chicago (1913) and an M.D. from Rush Medical College, Tatum found time to work as an instructor in Loevenhart's department. Following brief appointments in two physiology departments, Tatum joined the Department of Pharmacology at the University of Chicago in 1918. Ten years later, he accepted Loevenhart's invitation to come to Wisconsin's Pharmacology and Toxicology Department. Tatum was Chairman of that department from 1929 until his retirement, in 1954.[6]

Tatum's research interests, prior to the period when he began collaborating with pharmaceutical firms (in the mid-1920s), focused on the physiology of the thyroid gland and acute and chronic intoxication involving opium alkaloids, barbiturates, and local anesthetics. He did not incorporate thyroid research in any of his collaborations. Tatum emerged as an expert on the pharmacology of morphine, barbiturates, and other central nervous system depressants fairly early in his career. This, not surprisingly, led to some important collaborations with industry. For example, Tatum contributed much to our understanding of the physiological aspects of morphine addiction. His results with several species of animals suggested that morphine simultaneously stimulated and depressed different parts of the central nervous system. Recovery

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[6]"Profile of a Research Scientist," Bulletin for Medical Research of the National Society for Medical Research 8, no. 6 (1954):7-8; F. E. Shideman, "A. L. Tatum, Practical Pharmacologist," Science 123 (1956): 449; and John Parascandola and Elizabeth Keeney, Sources in the History of American Pharmacology (Madison: American Institute of the History of Pharmacy, 1983), 52-53.

from the latter, according to Tatum, came much faster than recovery from the manifestations of morphine's stimulation of the nervous system.[7] On the basis of his work on drug intoxication, Tatum discovered that barbiturates were an effective antidote for cocaine overdosage. A few years later, he found that picrotoxin, a central nervous system stimulant derived from a plant, was an antidote for barbiturate overdosage.[8]

In one sense, Tatum is quite atypical among the examples of specialist-consultants presented in this Part. Companies usually engaged a consultant for a particular series of researches because the consultant was a specialist--if not an authority--on that subject. Tatum consulted with several companies, for many years, on the chemotherapy of syphilis and malaria. However, his publications do not indicate any interest in this topic until after he began collaborating with companies on antisyphilitic and antimalarial drugs. Thus, in the case of Tatum, cooperative work with drug companies fostered a new research interest, to which he devoted a majority of his time in the latter half of his career. The reasons behind this extraordinary case of a specialist-consultantship will be addressed later in the chapter.

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[7]A. L. Tatum, M. H. Seevers, and K. H. Collins, "Morphine Addiction and Its Physiological Interpretation Based on Experimental Evidences," Journal of Pharmacology and Experimental Therapeutics 36 (1929):447-475.

[8]A. L. Tatum, A. J. Atkinson, and K. H. Collins, "Acute Cocaine Poisoning, Its Prophylaxis and Treatment in Laboratory Animals," ibid. 26 (1925):325-335; A. H. Maloney, R. Fitch, and A. L. Tatum, "Picrotoxin as an Antidote in Acute Poisoning by the Shorter Acting Barbiturates," ibid. 41 (1931):465-482; and Shideman, "A. L. Tatum," 449.

Loevenhart's Connections with Abbott, Commercial Solvents, and Parke-Davis

There is relatively little information documenting the interactions between Loevenhart and Abbott Laboratories. Moreover, the extant sources on this consultantship document only the negotiations between the Wisconsin pharmacologist and the firm on two different projects; it is not clear how, or even if, Loevenhart and Abbott worked together on these research problems. However, this consultantship merits at least a summary. In the first place, it is the earliest known contact between Loevenhart and a pharmaceutical company for the purpose of cooperative research. Second, the proposed organization of one of the two cooperative projects between the academic researcher and Abbott appears to be the basis upon which Loevenhart organized a later, similar project with another company. Late in 1926, Loevenhart learned through a former student then at Abbott that the company was planning to market the ammonium salt of iodoxy benzoate. Loevenhart informed the company that he had been working on this compound for over fifteen years, and that he was prepared to share with the firm a new, efficient method of producing the benzoate that a Wisconsin colleague developed. At the same time, he asked if the company would be willing to supply his department with the compound, for Loevenhart's continuing pharmacological studies of iodoxy benzoate. Although Abbott felt its own process was more economical than Loevenhart's, it promised to supply Loevenhart

Figure 12. Arthur Salomon Loevenhart (1878-1929), Professor of Pharmacology and Toxicology at the University of Wisconsin Medical School from 1908 to 1929 (from Journal of Pharmacology and Experimental Therapeutics 36 (1929):493; UW neg. no. 10269 C-3).



with some of the drug.[9]

Abbott was much more interested in a collaborative project with Loevenhart on antisyphilitic organic arsenicals. Loevenhart had not only an established track record with arsenicals (tryparsamide), but a well-organized, cooperative research program between Northwestern, his own department, and the Wisconsin Psychiatric Institute. Abbott wanted to plug into this program because it was a likely source of future therapeutic discoveries. Loevenhart, Abbott, and Frank C. Whitmore, a chemist at Northwestern, began drafting an agreement for collaborative research on antisyphilitic arsenicals around the Fall of 1926. The three parties drew up a fairly complete contract for cooperation, but they did not sign it. The available evidence is too sparse to suggest why the agreement never came to fruition. However, Wisconsin and Northwestern came to terms on a similar agreement with a different pharmaceutical company, Parke-Davis, in 1927.[10]

Not all of Loevenhart's consulting work dealt with drugs. He spent a year directing toxicological work in his laboratory on a series of solvents for a chemical company. Commercial Solvents Corporation, of

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[9]A. S. Loevenhart to A. S. Burdick, 4 October 1926, box 1, "Abbott Laboratories, 1926-1927," Arthur Salomon Loevenhart Papers, University of Wisconsin Archives, Madison, Wisconsin (hereafter Loevenhart Papers), and Alfred S. Burdick to A. S. Loevenhart, 13 October 1926, ibid. See also Council on Pharmacy and Chemistry of the American Medical Association, New and Nonofficial Remedies, 1928 (Chicago: American Medical Association, 1928), 219-221.

[10]Agreement between Abbott Laboratories, Frank C. Whitmore, and A. S. Loevenhart on therapeutic arsenicals [hereafter Abbott-Whitmore-Loevenhart Agreement], c. October 1926, box 1, "Abbott Laboratories, 1926-1927," Loevenhart Papers, and A. S. Loevenhart to Alfred S. Burdick, 4 November 1926, ibid.

Terre Haute, Indiana, approached Loevenhart in February, 1928, to study the toxicity of two of its products--butyl alcohol and butyl acetate--in relation to the toxicity of some competing compounds--Cellosolve, butyl Cellosolve, and Cellosolve acetate.[11] Shortly after World War One, a du Pont chemist developed a durable, quick-drying lacquer that required solvents such as those above. With almost immediate industry-wide application of this discovery among auto manufacturers, the lacquer industry grew enormously during the 1920s. Commercial Solvents had been producing butyl alcohol since World War One, based on a discovery by Chaim Weizmann, a Russian-born chemist at the University of Manchester, that certain microorganisms fermented foodstuff starch to yield butyl alcohol. Carbide and Carbon Chemicals Corporation, following methods worked out by the Mellon Institute chemist George O. Curme, Jr., introduced the synthetically-produced Cellosolve group of lacquer solvents in the 1920s.[12]

Commercial Solvents agreed to pay Loevenhart $500 to conduct as many acute and chronic toxicity tests as possible with this sum. If the project proceeded satisfactorily to both parties, the company would extend its support, because Commercial Solvents eventually wanted toxicological evaluations of 19 products. The two parties agreed that the Wisconsin workers would investigate the toxicity of these solvents for several routes of administration--orally, intravenously, by skin

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[11]A. S. Loevenhart to Arthur Orr, 16 February 1928, box 1, "Commercial Solvents Corp.," Loevenhart Papers.

[12]Williams Haynes, American Chemical Industry, 6 vols. (New York: D. Van Nostrand, 1945-1954), 4:187-201, 6:85-89, 436.

absorption, and via inhalation of solvent vapors. The latter two routes were particularly relevant, since these were the routes by which workers in the lacquer solvent industry came into contact with the compounds.[13] The chemical company intended the results to be strictly internal, and thus asked Loevenhart not to publish any of this work. The Wisconsin pharmacologist petitioned the company to allow one of his students to do this work as part of his degree work, since "a thesis gets very little publicity; it is simply filed away in the University library." The company, however, would not permit this as well.[14] Loevenhart probably did not raise more of an issue about this publication policy because of the nature of the work. Basically, this was routine work--not the kind of high-level research that Loevenhart was accustomed to publishing, and not the kind of work he was accustomed to directing as the basis for a graduate degree.

Loevenhart and his colleagues conducted the acute and chronic toxicity tests by gassing rats with several concentrations of solvent vapors, over varying durations. By January, 1929, the preliminary results on acute toxicity suggested that Commercial Solvents' own butyl alcohol was the least toxic of the five solvents, whereas the firm's butyl acetate was the most toxic. The Wisconsin scientists were able to test only the Cellosolve solvents for chronic toxicity by January,

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[13]C. L. Gabriel to Arthur S. Loevenhart, 28 February 1928, box 1, "Commercial Solvents Corp.," Loevenhart Papers; A. S. Loevenhart to C. L. Gabriel, 1 March 1928, ibid.; J. C. Woodruff to A. S. Loevenhart, 6 March 1928, ibid.; A. S. Loevenhart to J. C. Woodruff, 3 April 1928, ibid.; and J. C. Woodruff to A. S. Loevenhart, 7 April 1928, ibid.

[14]Gabriel to Loevenhart, 28 February 1928; Loevenhart to Gabriel, 1 March 1928 (quotation); and Woodruff to Loevenhart, 6 March 1928.

1929. They gassed rats six hours per day, six days a week, for a month. When exposed to air saturated 25 percent with these solvents over this period, only a few of the animals were affected, and they experienced only occasional blood discharge into the urine. When the concentration was doubled, most of the rats died within three days.[15]

Loevenhart met with representatives of Commercial Solvents the next month to discuss the work thus far, and the two parties had some sharp differences of opinion on what they could conclude from Loevenhart's results; on the possibility of future problems created by these solvents; and on the persons responsible for the toxicity of the solvents. The company personnel believed the Wisconsin results indicated there was not a significant difference between the toxicities of their solvents and the toxicities of the Cellosolve compounds. Loevenhart, however, emphasized that this was not an informed generalization, since his experiments still were too few and too narrow in scope to make such a judgement. One of the Commercial Solvents representatives claimed that, on the basis of recent improvements in ventilation in lacquer factories and the lack of cases of poisoning in the past, he did not expect complaints in the future. Loevenhart objected to this line of reasoning, because by the nature of chronic cases of industrial poisoning, the symptoms could be obscured and defy detection for years. Loevenhart felt this was a particularly dangerous line of

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[15]C. W. Muehlberger to J. C. Woodruff, 23 August 1928, box 1, "Commercial Solvents Corp.," Loevenhart Papers; A. S. Loevenhart and C. W. Muehlberger, "Exposure of Albino Rats to Vapors of Cellosolve and Butyl Cellosolve," 15-page typescript, 23 August 1928, ibid.; and idem, "Report of Experiments on the Toxicity of Cellosolve and Butyl Cellosolve Vapors," 4 January 1929, three-page typescript, ibid.

reasoning, especially if applied to new compounds.

Finally, the personnel from the chemical firm voiced their belief that the responsibility for the toxicity of the solvents rested with the paint and lacquer manufacturers, who actually mixed the solvents, not solvent manufacturers like Commerical Solvents. Loevenhart again disagreed, because he believed it was the responsibility of the company producing the solvent, regardless of who handled it thereafter, to provide instructions for the proper use of the solvent to avoid injury or accidents.[16] Loevenhart's work for Commercial Solvents ended after this meeting. While it might be tempting to speculate that the differences between the university scientist and the company were too sharp to effect a reconciliation, I do not think this was the case. Commercial Solvents seemed to want to continue with the toxicology work at Wisconsin at the end of the meeting with Loevenhart, and it might have except for the rapid deterioration of Loevenhart's health.

Loevenhart's interactions with Commercial Solvents illustrate the fact that a company could call upon the general technical knowledge and skills of a specialist-consultant, whether or not he was familiar with a specific subject. Loevenhart certainly had no special training in the pharmacology and toxicology of lacquer solvents, nor did Arthur Tatum have any particular background in the dye he tested toxicologically for another chemical firm (see below). Loevenhart and Tatum were fundamentally solid pharmacologists, and once they established

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[16]Minutes of a meeting between Mr. Woodruff, Mr. Orr, Dr. Blumfield, and members of their staffs [at Commercial Solvents Corporation] and Arthur S. Loevenhart, at Commercial Solvents Corporation, Terre Haute, Indiana, 20 February 1929, ibid.

themselves as pharmacologists willing to work with companies, it was logical for a company like Commercial Solvents to turn to Loevenhart for assistance. Therefore, this was a case where a company did not approach a specialist-consultant primarily for his expertise in an area the company was interested in. Rather, the firm was interested in him as a sound and dependable scientist.

Loevenhart had more extensive contact with Parke, Davis and Company of Detroit than with any other company. He collaborated with this company on local anesthetics, ephedrine preparations, and arsenicals. The latter collaboration was the beginning of an alliance between Parke-Davis and Wisconsin that continued for twenty years after Loevenhart's death. All of these projects began around 1927. Early in 1926, the company assured Loevenhart that "if at any time we can cooperate with you in the matter of supplying special material, or carrying out any work for which you do not have the time or facilities, we shall be very glad indeed to be of any possible service."[17] I have not seen any evidence, however, suggesting that Loevenhart and Parke-Davis cooperated on any projects until the following year.

Their collaboration on local anesthetics stemmed from promising results Loevenhart found in his study of isocaine, which the discoverer of procaine had prepared early in the 20th century.[18] Researchers had paid little attention to isocaine up to the time of Loevenhart's work.

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[17]A. W. Lescohier to A. S. Loevenhart, 12 February 1926, box 1, "Parke, Davis and Co.: Lescohier, A. W., 1926-1929," Loevenhart Papers.

[18]Schmitz and Loevenhart, "Study of Two Series of Procaine Derivatives," and idem, "Study of Isocaine, Cocaine, Procaine and Butyn."

He found that isocaine was as effective as cocaine for ophthalmic uses, with only a third the toxicity of cocaine. Late in 1927--about three years after publishing his isocaine work--Loevenhart asked Parke-Davis to consider manufacturing this anesthetic. He told the company that clinicians he knew (and possibly Loevenhart himself) had been using isocaine for urethral catheterization and in many "tonsil cases." Loevenhart did not mention their source for the drug, but he was "terribly anxious to have somebody put it on the market." He also offered to perform toxicity tests on the Parke-Davis product before it was distributed for clinical trials. The firm agreed to produce enough isocaine for more clinical trials.[19]

Around this time, William L. Ruigh, a chemist at Princeton, developed an entirely new type of local anesthetic. He combined certain parts of the structure common to the procaine series of anesthetics with carbazole, a tricyclic, amino-substituted hydrocarbon that occurred naturally in coal tar. Although Ruigh's carbazole derivatives apparently were untested, Parke-Davis was hopeful enough--on the basis of structure-activity considerations--to postpone the work on isocaine indefinitely. Loevenhart began testing these derivatives in late December of 1927, and by the Spring of 1928 he, Ruigh, and Parke-Davis concluded a contract for the development and testing of carbazole

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[19]A. S. Loevenhart to Oliver Kamm, 30 November 1927, box 1, "Parke, Davis and Co.: Kamm, O., 1927-1929," Loevenhart Papers; Oliver Kamm to A. S. Loevenhart, 17 December 1927, ibid.; and A. S. Loevenhart to Oliver Kamm, 28 December 1927, ibid.

derivatives.[20] The collaborators made little progress in the following year. Ruigh's laboratory at Princeton burned down sometime during this period, which obviously slowed the anesthetic project from the Princeton end. Also, Loevenhart began devoting more and more of his time during 1928 to the ephedrine and arsenical projects with Parke-Davis. As his health deteriorated through the early months of 1929, Loevenhart became less of a factor in the local anesthetic collaboration. It is not clear if Parke-Davis and Ruigh continued to work together through the remainder of 1929 and thereafter, but Ruigh's carbazole derivatives never found a niche in the armamentarium of local anesthetics.[21]

Loevenhart also collaborated with Parke-Davis on preparations of ephedrine, an alkaloid isolated from an ancient Chinese medicinal herb in the 1880s and investigated pharmacologically--principally by K. K. Chen--from the 1920s on. Among its many other actions on the heart, lungs, gastrointestinal tract, etc., ephedrine constricts the blood vessels that serve the mucous membranes of the nose. Thus, it is (and was known in Loevenhart's time to be) a useful drug in cases such as

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[20]C. W. Muehlberger to A. W. Lescohier, 3 January 1928, box 1, "Parke, Davis and Co.: Lescohier, A. W. 1926-1929," Loevenhart Papers; O. Kamm to [A. W.] Lescohier, 14 May 1928, box 1, "Parke, Davis and Co.: Kamm, O., 1927-1929," ibid; A. W. Lescohier to A. S. Loevenhart, 31 May 1928, box 1, "Parke, Davis and Co.: Lescohier, A. W., 1926-1929," ibid. The terms of the agreement are unknown, since I have not been able to locate a copy of the contract.

[21]A. W. Lescohier to A. S. Loevenhart, 31 December 1928, ibid.; A. S. Loevenhart to A. W. Lescohier, 15 February 1929, ibid.; and William L. Ruigh, "Acid Halides of Carbazole-N-carboxylic Acids and Process for Their Production," United States Patent 2,089,095, patented 17 August 1937.

head colds and minor infections that cause nasal congestion. In 1927, Loevenhart began helping Parke-Davis formulate a compound ephedrine spray. Also around this time, he urged the company to market another dosage form, an ephedrine snuff, that he had recently developed.

In the Fall of 1927, Loevenhart sent Parke-Davis a sample of his ephedrine snuff; in addition to ephedrine (one percent), it contained menthol (one percent) and camphor (one percent), with a lactose base. Over the next half-year, the Wisconsin pharmacologist changed the proportions of each component several times. Eventually, he settled on a snuff of 3 percent ephedrine, 0.1 percent menthol, 0.25 percent camphor, and a base of lactose and urea (four parts to one part, respectively). The aromatic components made the powder more pleasant to the patient, helped prevent the mucous membrane from drying out, and as irritants, would help shrink the mucosa. While lactose was inert, urea was a keralytic stripping) agent; it helped clear congestion by shedding part of the membrane wall. Today, most ephedrine decongestants have a maximum of one percent ephedrine, a sufficient strength to effect the desired result. Loevenhart's three-percent preparation, then, must have had a forceful action against the patient's congestion. In all, the snuff had a well-conceived formulation. The physicians who tried the snuff on some of their patients, according to Loevenhart, reported excellent results. The snuff was convenient as well as effective. It did not require an atomizer, unlike ephedrine sprays, so the patient could easily carry a small vial in a pocket for unexpected

needs (for example, while travelling).[22]

The company was not as enthusiastic as Loevenhart about the ephedrine snuff, primarily because it already had a new ephedrine spray and ointment in the works. Yet Parke-Davis agreed to manufacture enough of the powder to test it among twenty to forty physicians. In the meantime, Loevenhart continued to experiment with new formulations, sometimes on himself.[23] He also decided to work on a small inhalation tube to deliver the powder. Applying the powder this way, he felt, would be more socially acceptable than "taking [the powder] in the fingers and snuffing it into the nose." One must wonder, too, how easily it would have been for patients with very congested nasal passages to actually sniff the medicine into the nostril, without the aid of some blowing device. The company was not receptive to Loevenhart's idea of supplying a mechanical blower with the powder, because it was the convenience of the snuff that appealed to the firm.[24]

Through 1928, Loevenhart kept adjusting the formulation of the ephedrine powder, and improving the blowing apparatus. He was confident

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[22]A. S. Loevenhart to Oliver Kamm, 25 October 1927 and 11 November 1927, box 1, "Parke, Davis and Co.: Kamm, O., 1927-1929," Loevenhart Papers, and A. S. Loevenhart to A. W. Lescohier, 6 July 1928, box 1, "Parke, Davis and Co.: Lescohier, A. W., 1926-1929," ibid.

[23]Oliver Kamm to A. S. Loevenhart, 27 January 1928 and 6 March 1928, box 1, "Parke, Davis and Co.: Kamm, O., 1927-1929," Loevenhart Papers; A. S. Loevenhart to Oliver Kamm, 12 March 1928, ibid.; and A. W. Lescohier to A. S. Loevenhart, 15 February 1929, box 1, "Parke, Davis and Co.: Lescohier, A. W., 1926-1929," ibid.

[24]A. S. Loevenhart to Oliver Kamm, 15 March 1928 (quotation) and 20 March 1928, box 1, "Parke, Davis and Co.: Kamm, O., 1927-1929," *Loevenhart Papers; Oliver Kamm to A. S. Loevenhart, 31 March 1928,* ibid.; and A. W. Lescohier to C. W. Muehlberger, 9 August 1928, box 1, "Parke, Davis and Co.: Lescohier, A. W., 1926-1929," ibid.

enough in his snuff to make tentative patent arrangements, whereby he would license Parke-Davis exclusively, in exchange for a nominal royalty. But in February, 1929, Parke-Davis informed Loevenhart that it was no longer interested in his ephedrine snuff. The benefits the snuff offered, according to the company, did not warrant the additional merchandising investment that would be required to market this preparation, particularly since the snuff sales probably would come at the expense of the company's other ephedrine preparations.[25]

By the time Loevenhart and Parke-Davis started working on an ephedrine spray for the company, Lilly was already marketing an ephedrine inhalant, and Abbott and Swan-Meyers were not far behind.[26] The Wisconsin pharmacologist and the company investigated several possible formulations for the spray. Parke-Davis, for example, wanted to market a spray containing ephedrine and epinephrine, an adrenal gland hormone that was somewhat similar, pharmacologically, to ephedrine. Ostensibly, the company hoped to capitalize on the synergistic activity of these two drugs, and produce an inhalant superior to its competitors' preparations. However, Parke-Davis already had an epinephrine spray on the

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[25]Loevenhart to Lescohier, 6 July 1928; C. W. Muehlberger to A. W. Lescohier, 7 August 1928 and 14 August 1928, box 1, "Parke, Davis and Co.: Lescohier, A. W., 1926-1929," Loevenhart Papers; and Lescohier to Loevenhart, 15 February 1929.

[26]"The Red Book Price List," 67th ed., November, 1927, Druggists Circular 71, no. 11, pt. 2 (1927):78; Eli Lilly and Company, A Complete Priced List: Products of the Lilly Laboratories, January, 1927, 199, Kremers Reference Files, F. B. Power Pharmaceutical Library, University of Wisconsin, Madison, Wisconsin [hereafter Kremers Reference Files]; and Abbott Laboratories, Price List of Pharmaceutical and Biologic Products and Fine Medicinal Chemicals, 1928, 31, "Abbott," Manufacturers' Price Lists and Promotional Material, Kremers Reference Files.

market. The company might have felt that, by combining epinephrine with ephedrine, the firm could preserve some of the old epinephrine business as well as attract new business with ephedrine. Loevenhart suggested that Parke-Davis consider marketing a compound, aromatic ephedrine inhalant, similar to Lilly's preparation but with less menthol and camphor, which could be irritating.[27]

Loevenhart and his associates in the Wisconsin pharmacology department continued to test all the various ephedrine inhalants for Parke-Davis in late 1927 and 1928. Precisely what tests he conducted are unknown--as in the case of ephedrine snuff. The inhalant that the collaborators finally decided to market was a simple preparation of ephedrine and methyl salicylate in an oily base, which Parke-Davis introduced by November, 1928. Although the ingredients were stronger and the base different, Parke-Davis' ephedrine preparation was basically similar to the formulation that first appeared in the National Formulary, eight years later.[28]

The work on ephedrine preparations between Loevenhart and Parke-

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[27]Loevenhart to Kamm, 25 October 1927; Oliver Kamm to A. S. Loevenhart, 4 November 1927 and 10 November 1927, box 1, "Parke, Davis and Co.: Kamm, O., 1927-1929," Loevenhart Papers; A. S. Loevenhart to Oliver Kamm, 7 November 1927 and 22 November 1927, ibid.; and Parke, Davis and Co., Complete Catalogue of the Products of the Laboratories of Parke, Davis and Co., 2 March 1925, 133, Kremers Reference Files.

[28]Oliver Kamm to A. S. Loevenhart, 9 January 1928, box 1, "Parke, Davis and Co.: Kamm, O., 1927-1929," Loevenhart Papers; A. W. Lescohier to A. S. Loevenhart, 13 February 1928, box 1, "Parke, Davis and Co.: Lescohier, A. W., 1926-1929," ibid.; Loevenhart to Kamm, 12 March 1928; "The Red Book Price List," 69th ed., November, 1928, Druggists Circular 72, no. 11, pt. 2 (1928):79; and American Pharmaceutical Association, The National Formulary, 6th ed. (Washington, D.C.: American Pharmaceutical Association, 1935), 264.

Davis typified a project type of academic-industrial research collaboration more than a specialist-consultantship, inasmuch as it focused on a specific therapeutic agent for a disease or symptom. It was not a joint study, after all, of vasoconstricting drugs useful as nasal decongestants. Loevenhart, Tatum, and the other specialist-consultants examined in this Part engaged in an occasional project type of research collaboration with industry, although the bulk of their services to companies was as specialist-consultants. As noted previously, the three categories of collaboration defined in this dissertation rarely, if ever, existed in a pure form in the case of any given individual. The arsenical collaboration between Loevenhart and Parke-Davis was much more representative of his relationship with industry than the ephedrine projects.

Loevenhart, Parke-Davis, and Frank Whitmore and C. S. Hamilton of the Northwestern University Chemistry Department concluded an agreement on 30 September 1927 for research on organic arsenicals for the treatment of syphilis and trypanosomiasis.[29] I have already mentioned Loevenhart's interest in arsenicals. Parke Davis, which initiated in-house arsenical research in August, 1910--shortly after Paul Ehrlich reported his success with Salvarsan (arsphenamine)--wished to

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[29]Contract between Parke, Davis and Company, Frank C. Whitmore, Cliff S. Hamilton, and Arthur S. Loevenhart on arsenicals for syphilis and trypanosomiasis [hereafter Parke, Davis-Whitmore-Hamilton-Loevenhart agreement], 30 September 1927, box 1, "Parke, Davis and Co.: Lescohier, A. W., 1926-1929," Loevenhart Papers. Trypanosomes (such as the one that causes African sleeping sickness) and the spirochete responsible for syphilis are similar--so much that the Wisconsin investigators typically investigated arsenicals in trypanosome-infected animals before testing them in syphilitic animals, to get an indication of the value of the compounds under study in syphilis.

collaborate with the two university groups for the same reasons as Abbott had. Among the Northwestern chemists involved in the collaboration, C. S. Hamilton had a much greater interest in the chemistry of arsenicals than Whitmore. Hamilton's first systematic exposure to arsenical research probably occurred during World War One, when he was part of the Army Chemical Warfare Service at Edgewood Arsenal. Also, an expert on organic arsenicals, Winford Lee Lewis (who left Northwestern in 1924), supervised Hamilton's doctoral work at Northwestern in the early 1920s. Whitmore did not have such a strong interest in arsenicals. His name appeared in this contract (and in the earlier Abbott-Wisconsin-Northwestern proposed agreement) probably as a formality, since he headed the Northwestern Chemistry Department. Moreover, when Hamilton moved to the University of Nebraska Chemistry Department in 1929--the same year Whitmore left Northwestern for Pennsylvania State--Northwestern was no longer involved in the collaboration.[30]

Parke-Davis agreed to support the arsenical research at Wisconsin and Northwestern with payments of $3000 and $4000 per year, respectively. However, the company raised its support for the Wisconsin work to $4000 annually in 1928, and to $5000 in 1929. Loevenhart and Hamilton would disclose the complete details of their research whenever the company requested, and Parke-Davis had the right to observe and

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[30]Oliver Kamm to A. L. Tatum, 29 December 1930, box 4, folder 10, Arthur Lawrie Tatum Papers, University of Wisconsin Archives, Madison, Wisconsin [hereafter Tatum papers, UW]; "Colleges Pay Industry Dividends," Chemical and Engineering News 33 (1955):5038; and American Men of Science 4th ed., s. v. "Whitmore, Frank C."

study the ongoing work at Wisconsin and Northwestern. The university workers, moreover, were prohibited from sharing their arsenical work with any other individual not involved in the arsenical program. In the event that Loevenhart or Hamilton made any patentable discoveries, Parke-Davis would have the exclusive right to apply these discoveries commercially. In return, the firm agreed to pay Loevenhart and Hamilton each a royalty of 2.5 percent of the net sales of all patented products derived from the collaboration (the selling price to be determined by Parke-Davis). The university researchers had the right to inspect records of the company's sales of the relevant drugs. Any royalties due the Wisconsin and Northwestern groups first would be applied to Parke-Davis' earlier support of the academic workers, until its subsidies were reimbursed in full. Thereafter, Loevenhart and Hamilton had to apply their royalties to future arsenical research. If the royalties failed to meet the necessary support for arsenical research at the universities, Parke-Davis would make up the difference. If the royalties exceeded the necessary support, Loevenhart and Hamilton would receive the surplus funds.[31]

The contract failed to address some key issues. For example, it did not mention any procedure by which some or all of the collaborators could terminate the agreement, and it left unclear the rights of the academic workers if company scientists discovered and developed a patentable drug. But overall, the contract was fair to both the company

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[31]Parke, Davis-Whitmore-Hamilton-Loevenhart agreement, 30 September 1927, and A. W. Lescohier to A. L. Tatum, 3 July 1929 and 26 September 1929, box 5, folder 3, Tatum Papers, UW.

and the university scientists. In the late 1920s, $3000 went a long way towards the support of a professor's graduate students. Thus, the agreement helped support the research programs of Loevenhart and Hamilton. Also, while the agreement restricted the sharing of information with outsiders, the collaboration served as the basis for several publications and theses by the academic workers.[32] From the standpoint of Parke-Davis, it managed to hook up with some very talented drug researchers, and the contract ensured that it would be the only firm to capitalize on arsenical discoveries emanating from the laboratories of Loevenhart and Hamilton.

The contract also did not address expected functions of each party, even in a rudimentary way. The collaborators nonetheless established a fairly well-defined division of labor early in the arsenical program. Loevenhart and his associates designed compounds, according to chemical structure and expected pharmacological activity.[33] They also were responsible for toxicological and therapeutic evaluations of the

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[32]See, e.g., Garrett Arthur Cooper, "The Present Status of Arsenicals in the Treatment of Syphilis," M.D. thesis, University of Wisconsin, 1935, and Phyllis Magdalene Nelson, "I. A Comparative Study of Various Agents in the Chemotherapy of Rat Trichomoniasis; II. Trichomonas Foetus: Infection, Immunity, and Chemotherapy," Ph.D. diss., University of Wisconsin, 1938. Various publications are cited in the notes to this chapter.

[33]Loevenhart was quite familiar with structure-activity considerations with respect to arsenicals. For example, a few years earlier he and a graduate student discovered why, in terms of the structure of the compound, tryparsamide occasionally had deleterious effects on the optic nerve. The problem was due to an amino group situated in a certain position in the drug molecule. See A. G. Young and A. S. Loevenhart, "The Relation of the Chemical Constitution of Certain Organic Arsenical Compounds to Their Action on the Optic Tract," Journal of Pharmacology and Experimental Therapeutics 23 (1924):107-126.

arsenicals, in which they employed both in vitro and in vivo tests. Typically, the Wisconsin group determined: 1) the toxicity of an arsenical, 2) the therapeutic value of a product in rats or mice infected with various trypanosomes, and 3) the therapeutic value of the product in syphilitic rabbits. The Wisconsin pharmacologists carried out some chemical investigations as well, such as analyses of arsenical excretion products. The Wisconsin Psychiatric Institute and the University of Wisconsin Hospital conducted preliminary clinical tests on the more promising drugs. If an arsenical continued to show promise, the collaborators would engage other physicians around the country for expanded clinical tests.

Much less is known about the activities of the Northwestern group and the scientists at Parke-Davis. Generally, Hamilton and his colleagues worked out practical syntheses of the compounds Loevenhart proposed. Also, Hamilton developed some arsenicals of his own design. Parke-Davis conducted both pharmacological and chemical work on the products, and supplied arsenicals in bulk for the toxicological and therapeutic tests in animals, and for clinical tests.

The collaborators achieved little practical therapeutic success during the year and a half that Loevenhart took part in the tripartite arsenical program. The academic and industrial workers investigated many organic arsenicals, but only one compound--the so-called arsenical 115--showed any significant promise. The preliminary results convinced Loevenhart that this drug could be useful in both trypanosomiasis and neurosyphilis, perhaps superior even to tryparsamide in the latter disease. In 1928, a colleague of Loevenhart applied his Guggenheim

Fellowship to a field study of 115 and some other arsenicals in African sleeping sickness in the Belgian Congo. To evaluate 115 in neurosyphilis, Loevenhart proposed an investigation involving fourteen clinics across the country, or as many as Parke-Davis could supply. The company could not supply many, though, because manufacturing 115 on a large scale turned out to be impossible. Thus the collaborators had to abandon 115.[34]

Loevenhart's sudden death in April, 1929, ordinarily would have terminated the arsenical program--at least as far as Wisconsin was concerned. No one else in the Wisconsin pharmacology department was nearly as experienced as Loevenhart in the chemotherapy of syphilis or other infectious diseases. But the department recently had acquired another person who, like Loevenhart, put into practice his conviction that universities and the pharmaceutical industry had much to offer one another, in the way of research support for academic scientists; expert consultation for companies; and possibly advances in therapeutics. Arthur Tatum picked up where Loevenhart left off, inexperienced in the subject or not, and soon discovered an antisyphilitic arsenical that superseded the arsphenamines. His arsenical work with Parke-Davis, however, was by no means Tatum's first or only collaboration with a company.

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[34]A. S. Loevenhart to A. W. Lescohier, 20 March 1928 and 20 November 1928, box 1, "Parke, Davis and Co.: Lescohier, A. W., 1926-1929," Loevenhart Papers; A. W. Lescohier to A. S. Loevenhart, 9 November 1928 and 22 November 1928, ibid.; and A. W. Lescohier to Warren Stratman-Thomas, 22 February 1929, ibid.

Tatum's Early Collaborations with Industry

The earliest known research contacts between Tatum and a pharmaceutical firm began in 1925, when he was still in the Pharmacology Department at the University of Chicago. Cook Laboratories, a small Chicago firm, contacted Tatum in the Summer to have him conduct biological assays of some of its biological, botanical, and synthetic drugs, twice a year at most. Tatum agreed, on the conditions that this work would not interfere with his research, and that the firm would be willing to pay a fair amount for these services--which he estimated would cost about $2.00 per hour. Tatum was not an expert on any of the drugs that Cook wanted him to test, but that was not necessary, since anyone skilled in the art would be able to test these drugs. Cook probably engaged Tatum simply because of his proximity to the firm. He occasionally tested drugs for Cook over the following three years, until he moved to Wisconsin. The total charges for his work amounted to about $500--very little compared to the compensation that his future collaborations involved.[35]

Another company hired Tatum to conduct pharmacological and toxicological tests on one of its products in 1927, and his work for the firm continued through his first year at Wisconsin. The National Aniline

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[35]F. C. Koch to P. G. Heinemann, 13 June 1925, box 1, "Correspondence, 13 Jan. 1922-21 Oct. 1927," Arthur Lawrie Tatum Papers, State Historical Society of Wisconsin, Madison, Wisconsin [hereafter Tatum Papers, SHSW]; P. G. Heinemann to F. C. Koch, 16 June 1925, ibid.; A. L. Tatum to P. G. Heinemann, 2 July 1925, 29 July 1925, 28 July 1926, and 30 June 1927, ibid.; and A. L. Tatum to P. G. Heinemann, 23 May 1928, box 1, "Correspondence, 13 Jan. 1928-5 Oct. 1928," ibid.

Figure 13. Arthur Lawrie Tatum (1884-1955), Professor of Pharmacology at the University of Wisconsin Medical School from 1928 to 1955 (courtesy of the National Library of Medicine; UW neg. no. 10267 C-3).



and Chemical Company of Buffalo submitted a coal tar dye to the Food, Drug, and Insecticide Administration of the United States Department of Agriculture in 1927, for inclusion in the Administration's list of permitted synthetic food colors. In the early 1920s, the Administration had developed a procedure for the pharmacological and toxicological testing of submitted dyes--employing the latest techniques in these fields--without seriously affecting the Administration's tight budget. First, the company's method of producing the dye had to be well known, so that other manufacturers could produce it if they wished. Also, the dye had to be chemically certifiable, that is, of a constant and pure composition. Finally, the dye had to be biologically certifiable. The latter involved both external and internal testing. The company had to file with the Administration a "full report made by a reputable pharmacologist of the pharmacological and toxic properties of the dyes," consisting of acute and chronic toxicity tests, using approved food colors as standards. If these tests were promising, the company sent a pharmacologist to Washington to check and extend these results in cooperation with the Administration's pharmacologists.[36]

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[36]Charles Browne [chief of the FDIA's predecessor, the Bureau of Chemistry] to the Warner-Jenkinson Company, 6 August 1924 (quotation), "General Correspondence, 1919-1937," Food and Drug Administration Papers, Record Group 88, National Archives, General Archives Division, Suitland, Maryland [hereafter FDA Papers], quoted in Sheldon Hochheiser, "Synthetic Food Colors in the United States: A History under Regulation," Ph.D. diss., University of Wisconsin, 1982, p. 88 n. 59; memorandum of interview of L. H. Cone by [C. W.] Crawford, [H. T.] Herrick, and [J. C.] Munch, 15 June 1927, "General Correspondence, 1919-1937," FDA Papers; C. W. Crawford to Walter E. Ralph, 9 January 1928, ibid.; and Hochheiser, "Synthetic Food Colors," 84-90. On National Aniline, see Haynes, American Chemical Industry, 6:292-296. I am indebted to Sheldon Hochheiser for the above and other letters from the Papers of the Food and Drug Administration.

Tatum served National Aniline as the "reputable pharmacologist" who conducted the preliminary tests on the firm's dye, alphazurine FG. National Aniline forwarded Tatum's results on the acute toxicity of the dye to the FDIA late in 1927, which so impressed the latter that the Administration suggested the firm begin tests on the chronic toxicity of alphazurine, first on animals and later on humans. Although National Aniline arranged for Tatum to continue testing alphazurine early in 1928, the pharmacologist did not start this work until later in the Summer of that year, probably because Tatum was busy tying up matters in Chicago. The terms of his earlier work are unknown, but for his research on the chronic toxicity of the dye, National Aniline paid Tatum $500 monthly--the total remuneration he received from Cook Laboratories for his periodic work over three years.[37]

Tatum's results with animals were so promising that, by November of 1928, National Aniline planned "to go ahead with manufacture in the plant on the basis that results thus far indicate that the color cannot possibly be denied admission as a permitted color."[38] National Aniline could have proceeded with the manufacture and distribution of alphazurine regardless of the FDIA's decision about including its dye on the permitted list. Color certification was a voluntary enterprise, despite the widespread apprehension in the food industry that certification had legal backing. The Administration occasionally prosecuted

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[37]Crawford to Ralph, 9 January 1928, and Walter M. Ralph to Arthur L. Tatum, 14 September 1928, box 1, "Correspondence, 13 Jan. 1928-5 Oct. 1928," Tatum Papers, SHSW.

[38]Walter M. Ralph to Arthur L. Tatum, 7 November 1928, box 1, "Correspondence, 7 Nov. 1928-28 March 1929," Tatum Papers, SHSW.

flagrant violators of its certification regulations, but it could pursue legal action only within the confines of the 1906 Food and Drug Act--for example, if a manufacturer adulterated or mislabelled a food color.[39]

Walter Ralph, the Manager of Research and Development at National Aniline, assisted Tatum in the final external phase of the tests, on the toxicity of alphazurine in humans. In February, 1929, they began ingesting increasing amounts of the dye about twice a week, starting with 20 milligrams. They monitored their progress with frequent physical examinations and detailed visual descriptions of their urine and feces. Tatum and Ralph planned to work up to a dosage exceeding the total amount of dye a person would consume in a day if all food and water were colored with alphazurine--300 milligrams.[40] Over the following weeks, neither of the two experienced any adverse reactions to the dye. Two developments in mid-March, "not of a physiological sort," forced Ralph temporarily to terminate his side of the feeding experiments:

> On Tuesday 3/12 as I was preparing to take the 333 mg. dose, we received a prohibitory wire from the General Manager in New York who apparently had just learned of our experiments. He is not a technical man and your experiments are all very mysterious to him. He has some foolish idea as to the value of my own personal services to the company and seems to feel I am taking a risk unjustified from a company point of view. I was all prepared to argue the point, when on Wednesday, March 13th, we had a tremendous explosion here at the plant

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[39]See Hochheiser, "Synthetic Food Colors," 71-81.

[40]According to workers in the Dye Laboratory at National Aniline, the maximum concentration of alphazurine FG in food would be 0.02 percent. Ralph arrived at 300 mg. of dye consumed daily by assuming that an average adult took in about three pounds of food and water each day (Walter M. Ralph to Arthur L. Tatum, 15 February 1929, box 1, "Correspondence, 7 Nov. 1928-28 March 1929," Tatum Papers, SHSW).

> which destroyed one building and disrupted things pretty generally. There are so many major and pressing matters no[w] before the executives of the company that I do not feel justified in raising an argument just now.[41]

Ralph tried to change the General Manager's mind, but failed. In the meantime, Tatum worked his way up to a dosage of 500 milligrams by late March, a dose that Ralph apparently duplicated surreptitiously. At Ralph's suggestion, the human experiments ended at this point.[42]

Tatum's work for National Aniline ended in early May, 1929, when the company sent his final report on the pharmacology and toxicology of alphazurine FG to the FDIA. The Administration's Color Certification Laboratory and Pharmacological laboratory issued their final approval of the dye within two months. Later in the year, the FDIA admitted alphazurine FG to its list of permitted synthetic food colors as brilliant blue FCF (For Coloring Food), and it remains on the list today, as FD & C Blue #1.[43] Cook Laboratories and National Aniline called upon Tatum more as a solid, reputable pharmacologist than as an expert in a particular field of pharmacology--much like the case of Loevenhart's work for Commercial Solvents. But Tatum's expertise came much more actively

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[41]Walter M. Ralph to A. L. Tatum, 15 March 1929, ibid.

[42]Walter M. Ralph to Arthur L. Tatum, 25 February 1929, 1 March 1929, 6 March 1929, 15 March 1929, 22 March 1929, and 27 March 1929, ibid.

[43]Walter M. Ralph to Arthur L. Tatum, 3 May 1929, box 2, "Correspondence, 2 April 1929-17 September 1929," Tatum Papers, SHSW; H. T. Herrick to [Paul B.] Dunbar, 24 May 1929, "General Correspondence, 1919-1937," FDA Papers; Nicholas G. Barbella and William T. McClosky to [Paul B.] Dunbar, 24 June 1929, ibid.; Haynes, American Chemical Industry, 4:231; and Walter G. Campbell, "1930 Report of Food and Drug Administration," in Federal Food, Drug and Cosmetic Law Administrative Reports, 1907-1949, Food Law Institute Series (Chicago: Commerce Clearing House, 1951), 728.

into play in his collaboration with Abbott on barbiturates. Elements of the project collaboration (Part IV) and the general consultantship (Part II) entered into Tatum's interactions with Abbott. For example, two important hypnotics blossomed from the Tatum-Abbott collaboration, and Abbott occasionally drew a willing Tatum into its frays with the AMA Council on Pharmacy and Chemistry. We will see, however, that the overall relationship between Tatum and Abbott was clearly a case of a specialist-consultantship, as characterized earlier.

Tatum and Abbott

In his first year at Wisconsin, Tatum launched an investigation of the relative merits of the rather extensive series of barbiturates. Tatum approached Abbott in February, 1929, to see if the company would subsidize some of this work. Abbott had developed an interest in barbiturates during the 1920s; by 1929, the company was marketing barbital and Neonal (n-butylethylbarbituric acid), and it had several other barbiturates in the experimental stage. Moreover, Abbott already had formed a contact with at Wisconsin through Arthur Loevenhart, who spent a year earlier in the decade testing Butesin (n-butyl-p-aminobenzoate), a synthetic local anesthetic, for Abbott. The company offered to supply Tatum with various established and experimental barbiturates for his work, and to subsidize a fellowship for this research. Abbott provided $1200 each year for the next decade for this fellowship, which paid the salary of the assistant who conducted the research under Tatum's

direction, as well as paying for animals, food, and equipment.[44] Tatum eventually hoped to find

> . . . a substance with a wide margin of safety between the effectively depressant and the toxic or lethal dosage, one that is stable in solution (which amytal [a Lilly barbiturate] is not), whose depression period is not too long (as is barbital), and that does not produce serious late effects as does chloral hydrate. This is asking for an ideal but that is what we want.[45]

Abbott did its best to help Tatum find the ideal compound. Over the following several years, the Wisconsin group received over 150 hypnotics from the company, most of which were barbiturates.[46]

Tatum and his colleagues spent most of their time during 1929 comparing several established barbiturates, including Abbott's Neonal and barbital. They compared these hypnotics in a variety of tests, such as the impact of different routes of administration on hypnotic

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[44]Abbott increased the research fellowship to $2500 in 1930, to meet an offer that the assistant, Richard H. Fitch, had received for another job. The fellowship returned to $1200 the next year. See Arthur L. Tatum to E. H. Volwiler, 17 April 1930, box 1, "Abbott Laboratories, 1929-1931," Tatum Papers, UW, and Alfred S. Burdick to M. E. McCaffrey, 1 May 1930, ibid.

[45]A. L. Tatum to A. S. Burdick, 7 March 1929, ibid.

[46]Arthur L. Tatum to P. N. Leech, 23 February 1934, box 1, "Abbott Laboratories, 1934," Tatum Papers, UW; Carl Nielsen to A. L. Tatum, 21 February 1929, box 1, "Correspondence, 7 Nov. 1928-28 March 1929," Tatum Papers, SHSW; A. S. Burdick to Arthur L. Tatum, 28 February 1929, box 1, "Abbott Laboratories, 1929-1931," Tatum Papers, UW; Abbott Laboratories, Price List, 8, 38; Herman Kogan, The Long White Line (New York: Random House, 1963), 105-106; Tatum to Burdick, 7 March 1929; and Alfred S. Burdick to Arthur L. Tatum, 26 March 1929, box 1, "Abbott Laboratories, 1929-1931," Tatum Papers, UW. A compilation of Abbott hypnotics sent to Tatum is in an unlabelled notebook in box 1, General Subject Files, Papers of the Department of Pharmacology and Toxicology of the University of Wisconsin Medical School, University of Wisconsin Archives, Madison, Wisconsin [hereafter Pharmacology Department Papers].

activity, the acquisition of tolerance to lethal doses of barbiturates, and the excretion of these drugs. By the end of 1929, the Wisconsin group had studied only a handful of Abbott's experimental hypnotics, but Tatum felt this approach was prudent, so that they could have a solid idea of the standards of reference when they began working on the firm's new series of barbiturates.[47]

The Wisconsin researchers made a surprising observation during their work with hypnotics early in 1930. One of the barbiturates they were testing, manufactured by a German firm, produced local anesthesia upon subcutaneous administration on a par with highly regarded procaine (i.e., short duration of action, lack of irritation, and absence of aftereffects). This suggested to Tatum an entirely new line of research, because local anesthetics theretofore had chemical structures very different than the structure of barbiturates.[48] Tatum was confi*dent enough in the possibilities of modified barbiturates for local* anesthesia to draw up a tentative contract between the Wisconsin group and Abbott for the preparation and pharmacological investigation of barbiturates as local anesthetics. Abbott would be given the exclusive right to patent any discoveries issuing from this project, and Tatum

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[47]Richard H. Fitch, "An Experimental Study of Tolerance to Barbiturates," Journal of Pharmacology and Experimental Therapeutics 39 (1930): 266-267; R. P. Herwick, "A Study of Barbiturate Excretion," ibid., 267-268; A. L. Tatum to Carl Nielsen, 19 September 1929, 27 September 1929, and 12 October 1929, box 1, "Abbott Laboratories, 1929-1931," Tatum Papers, UW; E. H. Volwiler to A. L. Tatum, 16 December 1929, ibid.; and A. L. Tatum to E. H. Volwiler, 18 December 1929 and 30 December 1929, ibid.

[48]Arthur L. Tatum to E. H. Volwiler, 6 February 1930 and 12 February 1930, ibid.

would receive a 2.5 percent royalty from any barbituric local anesthetics the firm marketed.[49] Nothing ever came of Tatum's proposal, however, probably because Wisconsin and Abbott soon became involved with some very promising hypnotic barbiturates.

Abbott sent Tatum three of its more promising experimental barbiturates around April, 1929, for the Wisconsin group to compare to established barbiturates, but Tatum and his colleagues did not begin tests on these until the following September.[50] At that time, Abbott workers reported their own preliminary pharmacological results with some barbiturates. One of the compounds, ethyl-(1-methyl butyl)barbituric acid--better known later as Nembutal--was the "most efficient" drug among barbital and other well-known barbiturates.[51] This was a rather vague assessment of the value of Nembutal, albeit of a preliminary nature. Tatum and his co-workers, on the other hand, were able to show that Nembutal offered several advantages relative to established barbiturates. Nembutal, they found, was more toxic, on a weight for

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[49]Tentative contract between Abbott Laboratories and A. L. Tatum for development of local anesthetics as a substitute for cocaine, procaine, butyn, etc., attached to Arthur L. Tatum to E. H. Volwiler, 4 April 1930, ibid.

[50]Burdick to Tatum, 26 March 1929, and Tatum to Nielsen, 19 September 1929 and 27 September 1929.

[51]E. H. Volwiler and D. L. Tabern, "5,5-Substituted Barbituric Acids," Journal of the American Chemical Society 52 (1930):1676-1679 (presented to the Medicinal Products Division at the 78th meeting of the American Chemical Society, Minneapolis, Minnesota, 10 September 1929). Carl Nielsen and Henry Spruth, neither of whom were formally trained in pharmacology, conducted the pharmacological investigations at Abbott; see Kogan, Long White Line, 127, and Ernest H. Volwiler, interview by John P. Swann, Abbott Laboratories, North Chicago, Illinois, 18 April 1984, transcript, 12, A(2): "Volwiler, E. H.," Kremers Reference Files.

weight basis, than other barbiturates. In reality this was a benefit, since a comparatively smaller quantity of the drug could induce anesthesia. Consequently, the body was faced with less drug to break down or eliminate. In the laboratory animal, this amounted to a quicker onset of anesthesia, a deeper and briefer duration of anesthesia, and a faster post-anesthetic recovery.[52] Physicians at the University of Wisconsin and the Mayo Clinic carried out the earliest clinical tests with Nembutal beginning in 1930, and confirmed the laboratory results with this barbiturate.[53]

Abbott attempted to patent Nembutal, but the patent office rejected its application, most likely because German researchers had discovered this barbituric acid derivative several years earlier.[54] Abbott's

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[52]Tatum to Nielsen, 27 September 1929 and 12 October 1929; Tatum to Volwiler, 30 December 1929; T. W. Pratt, "A Comparison of the Action of Pentobarbital (Nembutal) and Sodium Barbital in Rabbits as Related to the Detoxicating Power of the Liver," Journal of Pharmacology and Experimental Therapeutics 48 (1933):285; R. H. Fitch and E. E. McCandless, "A Comparison of the Intraperitoneal and Oral Effects of the Barbituric Acid Derivatives," ibid. 42 (1931):266-267; and Richard H. Fitch, Ralph M. Waters, and Arthur L. Tatum, "The Intravenous Use of the Barbituric Acid Hypnotics in Surgery," American Journal of Survery, n.s. 9 (1930):110-114.

[53]Fitch and McCandless, "Barbituric Acid Derivatives," 267; Fitch, Waters, and Tatum, "Barbituric Acid Hypnotics;" and John S. Lundy, "Experience with Sodium Ethyl (1-Methylbutyl) Barbiturate (Nembutal) in More than 2,300 Cases," Surgical Clinics of North America 11 (1931):909-915.

[54]Volwiler and Tabern, "Barbituric Acids," 1677. Lilly workers reported their results with the sodium salt of this barbituric acid soon after Volwiler and Tabern's publication (see below), and the patent office turned down their application as well. In the light of the earlier discovery of this compound, and considering that neither Abbott nor Lilly received a patent, I feel that the patent interference on ethyl(1-methyl butyl)barbituric acid between Abbott and Lilly did not have much impact on the decision of the United States Patent Office. See E. H. Volwiler to A. L. Tatum, 4 February 1933, box 1, "Abbott Labora-

effort to have the Council on Pharmacy and Chemistry of the American Medical Association include Nembutal in New and Nonofficial Remedies did not fare any better. By January, 1931, Abbott requested the Council to approve its proprietary name for ethyl(1-methyl butyl)barbituric acid. The Council was not convinced that Abbott's product offered anything substantially new, even though the hypnotic action of Nembutal was shorter than other barbiturates. Even so, the Council was willing to seriously consider approving the trade name, "Nembutal," since they felt the drug filled a therapeutic need. Yet there was another problem. Lilly had been working with a similar barbituric acid at the same time and independently of Abbott, and within two months of Abbott's first publication on Nembutal, Lilly researchers also reported that this barbiturate was far more "active" than barbital and other well-known barbiturates.[55] The publications from each company appeared too close together, according to the Council, to establish priority (and thereby the right to a proprietary name) for one over the other.[56]

The Council felt that if any party had priority, it was Tatum's group at Wisconsin, who clearly were the first to recognize the

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tories, 1933," Tatum Papers, UW; Arthur L. Tatum to E. H. Volwiler, 6 February 1933, ibid.; and Carl Nielsen to Arthur L. Tatum, 7 February 1933, ibid.

[55]H. A. Shonle, Anna K. Keltch, and E. E. Swanson, "Dialkyl Barbituric Acids," Journal of the American Chemical Society 52 (1930):2440-2451; cf. Volwiler and Tabern, "Barbituric Acids."

[56]E. H. Volwiler to W. A. Puckner, 2 February 1931, box 1, "Abbott Laboratories, 1929-1931," Tatum Papers, UW, and Council on Pharmacy and Chemistry of the American Medical Association, "Preliminary Report of the Council," Journal of the American Medical Association 109 (1937): 504-505.

therapeutic contribution of Nembutal--its brief duration of action--in their publication of July, 1930.[57] Abbott and Lilly had reported merely that this barbiturate was comparatively "efficient" and "active." Since the Wisconsin article did not acknowledge any support from Abbott, the Council would not consider it a basis for the priority of the North Chicago firm, even if one could argue that a fellowship transferred a discovery from the university workers to Abbott.[58] Ironically, two opportunities arose prior to the Wisconsin publication that could have established such priority for Abbott. First, in November, 1929, Abbott sought Tatum's permission to include its pharmacology fellowship at Wisconsin in the list of industrial grants and fellowships to universities that the National Research Council compiled and periodically published. Tatum preferred not to have their support publicized:

> My idea is this, that since we are finding your own preparation [Nembutal] to rate very high by the means of testing we are employing, it might look better if it did not appear to come from your immediate support. . . . I am inclined to think that it might be more convincing to our readers subsequently if they did not know the support you people were giving us. You know, of course, as well as others who know us personally, that we are not for sale to anyone, but those who do not know us might see in your sponsorship or subsidy, a personal interest in the matter and, consequently, a somewhat biased report.[59]

Second, Tatum composed a tentative agreement with Abbott, in April of

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[57]Fitch, Waters, and Tatum, "Barbituric Acid Hypnotics," and Council on Pharmacy and Chemistry, "Preliminary Report," 505.

[58]Council on Pharmacy and Chemistry, "Preliminary Report," 505 n. 1.

[59]Arthur L. Tatum to E. H. Volwiler, 2 December 1929, box 1, "Abbott Laboratories, 1929-1931," Tatum Papers, UW; cf. E. H. Volwiler to A. L. Tatum, 29 November 1929 and 5 December 1929, ibid. Abbott agreed not to publicize the fellowship.

1930, whereby the company would pay him a 2.5 percent royalty on all Nembutal sales for his role in the elucidation of the therapeutic value of the barbiturate. If Abbott had agreed to this contract, the firm could have contended that there was indeed "a definite previous agreement to . . . transfer the discovery to the manufacturers," which the Council claimed was not the case in Abbott's support of Tatum's Nembutal research. However, I have not found any evidence indicating Abbott came to such an agreement with Tatum.[60]

Abbott tried to convince the Council that through its early funding of Tatum's work, it established priority on Nembutal. Tatum also sent a letter to the Council, at the request of the firm, which confirmed Abbott's financial assistance. The Council did not reconsider. When they established an approved name for the barbiturate, "pentobarbital," Lilly promptly agreed to market its product under that name. "In order to allow the Abbott Laboratories ample time for adjustment," the Council allowed the firm to label its pentobarbital with "Nembutal" as a subtitle for a year and a half (à la "Insulin (Iletin-Lilly)" of a few years earlier; see Chapter 6).[61] Since Abbott refused to sell its barbiturate under the Council-approved name at the end of that period,

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[60]Tentative contract between Abbott Laboratories and A. L. Tatum for compensation for the development of ethyl(1-methyl butyl)barbituric acid as a hypnotic, attached to Tatum to Volwiler, 4 April 1930, and Council on Pharmacy and Chemistry, "Preliminary Report," 505 n. 1.

[61]E. H. Volwiler to A. L. Tatum, 26 March 1931, box 1, "Abbott Laboratories, 1929-1931," Tatum Papers, UW; E. H. Volwiler to A. L. Tatum, 19 February 1934 and 22 February 1934, box 1, "Abbott Laboratories, 1934," Tatum Papers, UW; Paul Nicholas Leech to E. H. Volwiler, 16 February 1934, ibid.; E. H. Volwiler to Council on Pharmacy and Chemistry, 19 February 1934, ibid.; Tatum to Leech, 23 February 1934; and Council on Pharmacy and Chemistry, "Preliminary Report," 505 (quotation).

the Council omitted Nembutal from New and Nonofficial Remedies. This precluded Abbott from advertising Nembutal in many major medical journals (cf. Chapter 6), although the firm continued to market the drug.

Despite the difficulties with the Council, and the failure to patent Nembutal, Abbott did not let Tatum's contributions to the development of this drug go unrewarded. The firm began paying Tatum $500 each year in 1933 as a "token of our appreciation of your pharmacological work on Nembutal." These "tokens of appreciation" continued until 1940 (two years after the collaboration on hypnotics had formally ended), when Abbott began sending Tatum payments for "consulting services." Whether or not Tatum actually was consulting for Abbott after the late 1930s is not clear from the Wisconsin pharmacologist's personal papers, but the consulting fees grew to $1000 yearly around 1946, and continued until Tatum's death in 1955. If we assume that all of these payments were de facto rewards for Tatum's work on Nembutal, they amounted to about $17,000. This was clearly a significant sum, although most likely much less than what a 2.5 percent royalty on Abbott's Nembutal sales would have amounted to, if the company had agreed to Tatum's tentative contract of 1930.[62]

Tatum and Abbott collaborated on an even shorter-acting barbiturate beginning late in 1933. Ernest Volwiler, a chemist and Director of Research at Abbott, and Donalee Tabern, also an Abbott chemist, prepared

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[62]This information comes from various letters between Abbott personnel and Tatum, most of which are in boxes 2 and 3 in Tatum Papers, SHSW, and box 2, "Abbott Laboratories, Dr. Volwiler, 1941-1953," Tatum Papers, UW. See especially E. H. Volwiler to A. L. Tatum, 5 October 1933, box 2, "Correspondence, 3 Jan. 1933-21 Dec. 1933," Tatum Papers, SHSW, which explains the purpose of the payments.

a slightly modified version of Nembutal, in which they substituted sulfur for one of the oxygens in the barbituric acid moiety of Nembutal. Abbott conducted some preliminary pharmacological tests on this and several other so-called "thiobarbiturates" it had prepared, and sent them to Tatum for pharmacological evaluations in depth. It is difficult to say precisely why the Abbott chemists prepared sulfur-substituted barbiturates, although both Abbott and Tatum agreed by October, 1933, that they needed a new direction in their research on hypnotics, because "the ordinary barbituric acid series has been pretty well worked over. It may be that if unusual substituents become available so that they may be used, there is a possibility of developing barbituric acid derivatives which might have somewhat different properties."[63]

In one account, Volwiler claimed that he and Tabern conceived the idea of preparing thiobarbiturates after hearing a paper at the meeting of the American Chemical Society in Chicago, in September of 1933. This paper dealt with the substitution of sulfur for oxygen in a series of compounds entirely different than barbiturates. It is also possible that Volwiler and Tabern realized that German workers had prepared a series of thiobarbiturates over twenty-five years earlier. Even though the pharmacological results with these compounds had not impressed the earlier researchers, the latter did not prepare a sulfur-substituted Nembutal, or "thionembutal." The Abbott workers might have reasoned that sulfur substitution could improve its star barbiturate; if so, the firm would have a reasonably good chance of putting a superior,

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[63]E. H. Volwiler to A. L. Tatum, 11 October 1933, box 1, "Abbott Laboratories, 1933," Tatum Papers, UW.

patented, Council-approved hypnotic of ultrashort duration on the market.[64]

Tatum reported his earliest findings on thionembutal to Abbott in November, 1933. Although his results were sparse, the barbiturate produced an even briefer duration of anesthesia in a laboratory animal--about ten to fifteen minutes--than an equivalent dose of Nembutal. In comparative tests at Wisconsin with several established barbiturates and experimental thiobarbiturates, thionembutal produced the shortest duration of anesthesia, while it was among the best in terms of post-anesthetic untoward reactions to the drugs.[65] The earliest clinical results with thionembutal, collected in March of 1934 at the University of Wisconsin Hospital and the Mayo Clinic, seemed to support the pharmacological findings at Wisconsin. According to Tatum,

> Dr. [Ralph] Waters [Professor of Anesthesia at the University of Wisconsin] is intensely interested in this drug and states that the most extraordinary feature of it is the very prompt recovery from what appears to be a satisfactory depth of anesthesia. One of the last two patients was walking around the room and walked back to his ward somewhere between ten and fifteen minutes after the operation. This is something

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[64]E. H. Volwiler to C. S. Downs, 4 May 1959, Archives, Abbott Laboratories, North Chicago, Illinois; Kogan, Long White Line, 166-167; Volwiler, interview by Swann, 18 April 1984, 12; D. L. Tabern and E. H. Volwiler, "Sulfur-Containing Barbiturate Hypnotics," Journal of the American Chemical Society 57 (1935):1961; and Alfred Einhorn, "Ueber neue Arzneimittel," Annalen der Chimie 359 (1908):145-187.

[65]A. L. Tatum to [E. H.] Volwiler, 13 November 1933 and 13 December 1933, box 1, "Abbott Laboratories, 1933," Tatum Papers, UW; T. W. Pratt et al., "Sodium Ethyl(1-Methyl Butyl)Thiobarbiturate: Preliminary Experimental and Clinical Study," American Journal of Surgery n.s. 31 (1936):464-465; and H. W. Werner, T. W. Pratt, and A. L. Tatum, "A Comparative Study of Ultrashort-Acting Barbiturates, Nembutal, and Tribromethanol," Journal of Pharmacology and Experimental Therapeutics 60 (1937):189-197.

they are not heretofore familiar with.[66]

Despite the positive reports from Wisconsin, Abbott soon urged Tatum and his associates to devote more time to another of its experimental thiobarbiturates, thiosebutal (allyl secondary-butyl thiobarbituric acid). In the first place, Abbott's in-house pharmacological research on comparative toxicities and duration of anesthesia indicated that thiosebutal was slightly better than thionembutal. Second, the former was much easier to prepare than the latter. Thus, Tabern emphasized Abbott's belief that a study of thiosebutal "may prove to be just as interesting and perhaps more important commercially" than an investigation of thionembutal.[67] That the hypnotic project continued to focus on thionembutal, despite Abbott's petitions on behalf of thiosebutal, is due in large part to Tatum, who knew they had something good in the sulfur analogue of Nembutal: "In regard to the virtues of #8064 [thionembutal] vs. 'Thiosebutal' we are prepared to argue the point with you . . . we feel that our own deductions are more nearly correct

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[66]Arthur L. Tatum to D. L. Tabern, 3 April 1934, box 1, "Abbott Laboratories, 1934," Tatum Papers, UW. The operation referred to here was a tooth extraction. Tatum reported on Waters' earliest clinical experiences with thionembutal in Arthur L. Tatum to E. H. Volwiler, 16 March 1934 and 23 March 1934, ibid. The first extensive reports from Wisconsin and the Mayo Clinic on clinical experiences with thionembutal are Pratt et al., "Sodium Ethyl(1-Methyl Butyl)Thiobarbiturate," 465-466, and J. S. Lundy, "Intravenous Anesthesia: Preliminary Report of the Use of Two New Thiobarbiturates," Proceedings of the Staff Meetings of the Mayo Clinic 10 (1935):536-543; see also J. W. Dundee, "Editorial: Fifty Years of Thiopentone," British Journal of Anaesthesia 56 (1984): 211-213.

[67]D. L. Tabern to A. L. Tatum, 28 December 1933, box 1, "Abbott Laboratories, 1933," Tatum papers, UW; D. L. Tabern to A. L. Tatum, 20 April 1934, box 1, "Abbott Laboratories, 1934," Tatum Papers, UW (quotation); E. H. Volwiler to A. L. Tatum, 27 April 1934 and 4 June 1934, ibid.; and Tabern and Volwiler, "Barbiturate Hypnotics," 1963.

because of the wider spread of dosage range, which we feel gives us a better viewpoint of the comparisons."[68] Abbott, curiously, was challenging the barbiturate expert whom the company hired for detailed investigations of its products, on the basis of preliminary data of its own pharmacological workers who lacked any formal training. This obviously was defeating the purpose of hiring a specialist-consultant. Abbott eventually accepted Tatum's counsel, and Pentothal--the firm's trade name for thiobarbital--became a successful drug for Abbott.

The North Chicago firm had much better luck selling Pentothal to the patent office and the Council on Pharmacy and Chemistry than was the case with Nembutal. Abbott received both a patent and Council approval of Pentothal in 1939.[69] I have not found any records of royalties or more informal compensation (as in the case with Nembutal) that Abbott might have paid to Tatum for his role in the development of Pentothal. It would be most ironic if the firm did not compensate Tatum, since he championed Pentothal at a time when Abbott was pushing another thiobarbiturate.

Abbott, having produced two successful products between 1929 and

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[68]A. L. Tatum to E. H. Volwiler, 10 May 1934, box 1, "Abbott Laboratories, 1934," Tatum Papers, UW.

[69]Ernest H. Volwiler and Donalee L. Tabern, "Thiobarbituric Acid Derivatives," United States Patent 2,153,729, patented 11 April 1939, and Council on Pharmacy and Chemistry of the American Medical Association, New and Nonofficial Remedies, 1940 (Chicago: American Medical Association, 1940), 130-132. With respect to the delay in receiving a patent (which Abbott applied for five years earlier), an interference on this patent with Parke-Davis and Sharp and Dohme, and the fact that thiobarbiturates (although not thionembutal specifically--unlike the case with Nembutal) were prepared many years earlier, probably contributed to this delay. See E. H. Volwiler to A. L. Tatum, 18 June 1935, box 1, "Abbott Laboratories, 1935," Tatum Papers, UW.

1933, gradually lost interest in the field of hypnotics. In 1938, the firm informed Tatum that it would no longer be submitting experimental compounds to Wisconsin for testing. Volwiler suggested toward the end of the collaboration that Abbott was considering projects with Tatum on local anesthetics and analgesics, but these projects never materialized.[70] As mentioned above, Abbott paid Tatum for consulting services long after 1938, but it is not clear how (or even if) he served the company as a consultant. During the ten-year collaboration, Abbott provided over $13,000 in support of research fellows under Tatum's direction, and this research served as the basis for a number of publications that came out of Tatum's laboratory. The company also paid Tatum personally over $15,000, which the Wisconsin pharmacologist could have disbursed as he pleased. If Tatum and Abbott had agreed to some type of royalty settlement at the start of the collaboration, the compensation almost certainly would have exceeded $15,000, perhaps by several fold. But in the depressed economy of America in the 1930s, Tatum probably was satisfied to secure whatever support he could for his laboratory. Also, Tatum found an even greater source of support during these years in a collaboration with another company, on an entirely different research project.

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[70]E. H. Volwiler to A. L. Tatum, 13 July 1938, box 3, "Correspondence, 11 Jan. 1937-27 Dec. 1939," Tatum Papers, SHSW; E. H. Volwiler to A. L. Tatum, 27 July 1938 and 13 October 1938, box 2, "Abbott Laboratories, 1938-1939," Tatum Papers, UW; and E. H. Volwiler to A. L. Tatum, 9 December 1940, box 2, "Abbott Laboratories, 1940-1942," Tatum Papers, UW.

Tatum and Parke-Davis: Antisyphilitics and Antimalarials

After Arthur Loevenhart died in April, 1929, neither Parke-Davis nor Cliff Hamilton appeared to question Tatum's move to supervise the Wisconsin side of the tripartite collaboration on antisyphilitic organic arsenicals, even though he had never published a single paper on the chemotherapy of infectious diseases up to that time.[71] However, within about a year he independently discovered the therapeutic value of an arsenical that superseded all other arsenicals in the treatment of syphilis, including the hallowed Ehrlichian arsphenamines.

Several researchers before Tatum investigated this arsenical--arsenoxide, which Parke-Davis introduced as Mapharsen[72]--but all rejected it because of its high toxicity. Paul Ehrlich was the first to discard arsenoxide. His search for chemotherapeutic agents against syphilis led Ehrlich to test various organic arsenicals, especially trivalent arsenicals, which he believed were the active forms of arsenicals in the body (as opposed to pentavalent arsenicals). Ehrlich introduced arsphenamine (also known as Salvarsan, or 606), an arsenobenzene compound, in 1910, as a tailor-made cure for syphilis. A few years later he introduced neoarsphenamine (also known as Neosalvarsan, or 914), a slight modification of arsphenamine to correct some of the

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[71]"Original Contributions by or under the Direction of Arthur L. Tatum," 16-page typescript, A(2) "Tatum, Arthur L.," Kremers Reference Files.

[72]"Mapharsen" was an abbreviation for the drug's chemical name, meta-amino para-hydroxy phenyl arsine oxide. The following account of Mapharsen summarizes John Patrick Swann, "Arthur Tatum, Parke-Davis, and the Discovery of Mapharsen as an Antisyphilitic Agent," Journal of the History of Medicine and Allied Sciences (in press, April 1985).

latter's undesirable features.[73] Mapharsen, the partially oxidized product from the cleavage of the double-bonded arsenic atoms in arsphenamine, was one of the trivalent arsenicals Ehrlich and his colleagues investigated. They determined that Mapharsen had a superior therapeutic index (the ratio of the minimum therapeutic dose to the maximum tolerated dose) compared to several useful arsenicals, but its index was only one-third that of arsphenamine. However, Mapharsen's extremely high toxicity--twenty times the toxicity of arsphenamine according to Ehrlich and his co-workers--convinced Ehrlich to abandon Mapharsen as a chemotherapeutic agent.[74]

In the early 1920s, Carl Voegtlin, a pharmacologist at the United States Public Health Service Hygienic Laboratory, investigated the comparative rate at which a series of pentavalent arsenicals, arsphenamine and related trivalent arsenicals, and Mapharsen and other oxidized trivalent arsenicals similar to it, eliminated trypanosomes from the blood of infected animals. Voegtlin found that Mapharsen worked immediately on the trypanosomes, whereas arsenicals from the other groups required hours to begin reducing the number of pathogens. He concluded that arsenicals were transformed in the body to the oxidized trivalent form, that is, arsphenamine underwent in vivo conversion to Mapharsen,

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[73]John Parascandola, "The Theoretical Basis of Paul Ehrlich's Chemotherapy," ibid. 36 (1981):19-43, addresses the ideological framework of Ehrlich's research.

[74]Paul Ehrlich and S. Hata, Die experimentelle Chemotherapie der Spirillosen (Berlin: Julius Springer, 1910), 42, 57, 81, 84, 121-122, and P. Ehrlich and A. Bertheim, "Über das salzsaure 3.3'-Diamino-4.4'-dioxyarsenobenzol und seine nächsten Verwandten," Berichte der Deutschen Chemischen Gesselschaft 45 (1912):764.

which was the active form of arsphenamine.[75] Voegtlin nonetheless did not recommend Mapharsen in syphilotherapy, in part because of its inferior therapeutic index relative to arsphenamine, and also because Mapharsen remained in the body for a prohibitively long time. Arsphenamine, however, was slowly converted to Mapharsen in the body without exposing the organism to a high concentration at one instant, as with direct administration of Mapharsen.[76]

Tatum began working with Mapharsen in January, 1930, as part of a theoretical investigation into the role of the host in arsenotherapy. He soon noticed that Mapharsen, the toxic oxidation product of arsphenamine, itself oxidized to a much less toxic product. This was a revelation of immense potential. The oxidation of arsphenamine and neoarsphenamine was a vital concern for physicians. They had to be extremely careful to protect both of these drugs from exposure to the atmosphere, because of the possibility of conversion to the toxic oxidation product--Mapharsen. If enough of a normal dose of an arsphenamine were oxidized accidentally to Mapharsen and then administered, it could kill the patient. However, this would not be a concern if one administered Mapharsen, the toxic, active agent; since it was much more toxic

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[75]Carl Voegtlin and Homer Smith, "Quantitative Studies in Chemotherapy. II. The Trypanocidal Action of Arsenic Compounds," Journal of Pharmacology and Experimental Therapeutics 15 (1920):475-493; Carl Voegtlin, "Arsphenamine and Related Arsenicals," Physiological Reviews 5 (1925):79-81; and John Parascandola, "Carl Voegtlin and the 'Arsenic Receptor' in Chemotherapy," Journal of the History of Medicine and Allied Sciences 32 (1977):158-159.

[76]Voegtlin and Smith, "Studies in Chemotherapy," 479; Voegtlin, "Arsphenamine and Related Arsenicals," 84; and Parascandola, "Carl Voegtlin," 159-160.

than arsphenamine, much less drug could accomplish what a larger amount of arsphenamine could.[77]

The Wisconsin group and the pharmacological laboratory of Parke-Davis launched an intensive comparison of Mapharsen, arsphenamine, and neoarsphenamine in the Summer of 1930. By March of the following year Tatum concluded that Mapharsen was as effective as arsphenamine and neoarsphenamine in experimental syphilis.[78] Clinical tests, which began at the University of Wisconsin Hospital and the Wisconsin Psychiatric Institute in August, 1931, and included nearly a dozen clinics by the mid-1930s, confirmed the laboratory results. The consensus of clinicians was that results achieved with Mapharsen were equal to the best results obtained with the arsphenamines in primary, secondary,

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[77]A. L. Tatum to C. S. Hamilton, 24 June 1930, box 2, folder 17, Tatum Papers, UW, and Arthur L. Tatum, untitled three-page typescript, 23 April 1940, box 6, folder 10, ibid. On Tatum's investigations of Mapharsen and the role of the host in arsenotherapy, see A. L. Tatum to Oliver Kamm and A. W. Lescohier, 2 October 1929, box 4, folder 10, ibid., and A. L. Tatum to C. S. Hamilton, 18 October 1929, box 1, folder 17, ibid. He maintained an interest in the interplay of the host, arsenical, and pathogen after he discovered Mapharsen's therapeutic value; see Carl C. Pfeiffer and Arthur L. Tatum, "A New Experimental Approach to the Study of the Role of the Reticulo-Endothelial System in the Cure of Trypanosomiasis," Journal of Pharmacology and Experimental Therapeutics 53 (1935):358-376, and Arthur Tatum, "Specific Chemotherapy," lecture delivered at the Chaos Club, Chicago, Illinois, 16 March 1935, nine-page typescript, box 5, "Lectures," Tatum Papers, SHSW.

[78]A. L. Tatum to A. W. Lescohier, 25 March 1931, box 5, folder 3, Tatum Papers, UW. The Wisconsin and Parke-Davis groups published extensive pharmacological results with Mapharsen in A. L. Tatum and G. A. Cooper, "An Experimental Study of Mapharsen (Meta-Amino Para-Hydroxy Phenyl Arsine Oxide) as an Antisyphilitic Agent," Journal of Pharmacology and Experimental Therapeutics 50 (1934):198-215, and O. M. Gruhzit, "Mapharsen ('Arsenoxide') in the Therapy of Experimental Syphilis and Trypanosomiasis," Archives of Dermatology and Syphilology 32 (1935): 848-867.

and congenital syphilis.[79] It was not only efficacious, but safer than the arsphenamines--a great irony, considering that researchers before Tatum ignored Mapharsen as a therapeutic agent, primarily because of its toxicity.[80]

Mapharsen by no means was the only arsenical the collaborators investigated. Tatum's group examined scores of drugs for Parke-Davis after the Mapharsen work began, two of which attracted considerable attention. Parke-Davis pharmacologist O. M. Gruhzit, who had been searching since 1924 for an oral arsenical, believed he found such a drug in so-called arsenical 142, on the basis of chemical structure and expected pharmacological action. After the first year of tests in 1931, mostly at Parke-Davis, arsenical 142 was considered as effective orally as neoarsphenamine given by injection. Clinically, however, 142 could not eliminate syphilis treponema from the body, and after years of trying to find a form of syphilis that would respond to 142,

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[79]A. L. Tatum to Oliver Kamm, 1 September 1931 and 21 September 1931, box 4, folder 10, Tatum Papers, UW; A. L. Tatum to Albert B. Scott, 25 November 1931, box 6, folder 1, ibid.; E. A. Sharp to A. L. Tatum, 15 March 1933 and 31 March 1933, box 6, folder 2, ibid.; A. L. Tatum to E. A. Sharp, 3 November 1934, ibid.; Arthur L. Tatum and Garrett A. Cooper, "Meta-Amino Para-Hydroxy Phenyl Arsine Oxide as an Antisyphilitic Agent," Science 75 (1932):541-542; O. H. Foerster et al., "Mapharsen in the Treatment of Syphilis: A Preliminary Report," Archives of Dermatology and Syphilology 32 (1935):868-892; O. M. Gruhzit and R. S. Dixon, "Mapharsen in Mass Treatment of Syphilis in a Clinic for Venereal Diseases," ibid. 34 (1936):432-458; and L. M. Wieder et al., "Mapharsen in the Treatment of Syphilis: Further Experiences," ibid. 35 (1937):402-413.

[80]Louis Goodman and Alfred Gilman, The Pharmacological Basis of Therapeutics (New York: Macmillan, 1941), 947-950, 956-958, addresses the advantages of Mapharsen and disadvantages of the arsphenamines. See also Patricia Spain Ward, "The American Reception of Salvarsan," Journal of the History of Medicine and Allied Sciences 36 (1981):47-48.

the collaborators discarded this arsenical in 1936.[81] Tatum's group had especially high aspirations for an arsenical structurally somewhat similar to tryparsamide, and like the latter designed as a specific for neurosyphilis. Tatum's initial results in 1933 with this arsenical, called "phemarsenol," indicated that it had a much higher therapeutic index than tryparsamide in experimental syphilis. The early clinical work with phemarsenol in 1934 and 1935 supported Tatum's findings, but later work established phemarsenol's toxic side effects on vision.[82]

Like arsenical 142, phemarsenol never found a place in arsenotherapy, yet the collaborators persisted--in the case of phemarsenol for over ten years[83]--in trying to find some molecular modification, dosage form, or disease in which these and other arsenicals might be useful.

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[81]C. S. Hamilton to A. S. Loevenhart, 20 November 1928, box 1, "Hamilton, C. S.," Loevenhart Papers; A. S. Loevenhart to C. S. Hamilton, 14 February 1929, ibid.; O. Kamm to C. S. Hamilton, 15 September 1930, box 4, folder 10, Tatum Papers, UW; O. M. Gruhzit to A. L. Tatum, 8 February 1932, 23 June 1932, and 15 April 1932, box 4, folder 5, ibid.; Oliver Kamm to A. L. Tatum, 28 January 1932 and 22 June 1932, box 4, folder 11, ibid.; Oliver Kamm to A. L. Tatum, 18 December 1934, box 5, folder 1, ibid.; "Conferences in Detroit, June 19-20, 1936 with Professors Hamilton and Tatum on Arsenicals and Other Cooperative Research Work," ibid.; and O. M. Gruhzit to [Oliver] Kamm, 15 December 1936, box 4, folder 5, ibid.

[82]C. S. Hamilton to A. L. Tatum, 2 February 1933, box 2, folder 18, Tatum Papers, UW; A. L. Tatum to A. B. Scott, 20 April 1933, box 6, folder 1, ibid.; A. L. Tatum to Oliver Kamm, 16 February 1934 and 7 April 1934, box 5, folder 1, ibid.; A. L. Tatum to A. W. Lescohier, 12 November 1935, box 5, folder 4, ibid.; and A. L. Tatum et al., "A Study of the Sodium Salt of 3-Amino-4-beta-hydroxyethoxyphenylarsonic Acid in Experimental Trypanosomiasis and Syphilis and in Clinical Syphilis and Neurosyphilis," Journal of Pharmacology and Experimental Therapeutics 59 (1937):241-248.

[83]As late as 1943, Tatum was still trying to find an effective route of administration for phemarsenol; see A. L. Tatum to E. A. Sharp, 8 September 1943, box 6, folder 3, Tatum Papers, UW.

This is not surprising, since the collaborators wanted a return on their intellectual and economic investments. Giving up on drugs like arsenical 142 and phemarsenol was difficult for both the academic and industrial collaborators.

The specialist-consultantship, as I have defined it, did not originate for the study of a particular therapeutic agent; that was more the province of the project collaboration (see Part IV). But specific projects could, and often did, emerge from the specialist-consultantship. Tatum's consultantships, for example, helped produce such drugs as Nembutal and Pentothal. From the standpoint of the company a strike, such as one of these drugs, was a fulfillment of the consultantship, since the aim was to find therapeutic agents. From the standpoint of the academic researcher, a therapeutic strike could be a source of additional financial support for his research program and/or himself. Mapharsen illustrates the impact a therapeutic discovery could have on a specialist-consultant.

Tatum received a patent on Mapharsen in 1937. In accordance with the original agreement dating back to 1927, Parke-Davis had an exclusive license to manufacture the drug, and Tatum and Hamilton each received a royalty of 2.5 percent of the net sales of the drug. Parke-Davis withheld 60 percent of each royalty payment until the firm was fully reimbursed for its past investment in arsenical research at Wisconsin and Nebraska. Once the company was fully compensated, Wisconsin and

Nebraska fully subsidized their arsenical research with the royalties.[84]

Tatum collected royalties from 1937 until the Mapharsen patent expired, in 1954. The initial payments were fairly modest, but they grew tremendously in the 1940s, especially during the war. The royalties fully compensated Parke-Davis' past support by mid-1942; thereafter, Tatum received his full complement of royalties, part of which he applied to cover the arsenical research at Wisconsin.[85] Consider the period from 1937 to 1947, for which we have fairly complete financial data. Parke-Davis estimated the total cost of the research at Wisconsin, from mid-1942 through 1947, at $4800 per year, or about $26,000.[86] Tatum's royalties through 1947, consisting of the 40 percent payments up to 1942 and the full payments from then through 1947, amounted to about $240,000, exceeding the expenses of the arsenical research at Wisconsin by $215,000.[87] I have not been able to determine

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[84]Arthur L. Tatum, "Therapeutic Agent," United States Patent 2,092,036, patented 7 September 1937; Parke, Davis-Whitmore-Hamilton-Loevenhart agreement, 30 September 1927; A. W. Lescohier to A. L. Tatum, 4 November 1937, box 5, folder 5, Tatum Papers, UW; Oliver Kamm to A. L. Tatum, 10 May 1939, box 5, folder 2, ibid.; and A. L. Tatum and C. S. Hamilton to A. W. Lescohier, 23 September 1943, box 5, folder 5, ibid.

[85]My information on royalties comes from statements which accompanied Parke-Davis' checks to Tatum, in box 5, "Professional Financial Matter," Tatum Papers, SHSW.

[86]Kamm to Tatum, 10 May 1939.

[87]This figure must be regarded as approximate, although it is probably underestimated if anything. In the first place, four quarterly statements during the period 1937-1947 are missing from Tatum's papers. Rather than estimate what these might have amounted to, I have simply omitted them from the total royalties. Second, the sale of Mapharsen to the government yielded additional royalties of $19,600. It appears that the government might have pressured Tatum and Hamilton to relinquish these royalties (see A. L. Tatum to C. S. Hamilton, 8 August 1943, box 2, folder 22, Tatum Papers, UW), so I have omitted this sum

whether Tatum channelled these surplus royalties back into the Department of Pharmacology, pocketed them, or both. The Department of Pharmacology's records do not shed any light on this. It is also possible that Tatum used the Mapharsen money for research without going through the departmental research fund. But my point is that Tatum, whose salary did not exceed $6000 until 1942,[88] had these available to him an average of over $21,000 a year, from 1937 to 1947, to spend as he pleased.

Late in 1947, twenty years after the original agreement, Parke-Davis informed Tatum of its intention to terminate the Wisconsin side of the arsenical collaboration. The company felt it had sufficient pharmacological facilities and personnel to carry out this work on its own.[89] In one sense, this was a surprising decision, since the connection with Wisconsin was basically gratis; the Mapharsen royalties fully subsidized Wisconsin's research expenses at this time. However, with the rise of penicillin after the war, the organic arsenicals were rapidly approaching obsolescence. In this respect, the dissolution of the collaboration was not such a surprise.

Tatum, Hamilton, and representatives of Parke-Davis held a conference in June, 1936, to discuss the arsenical work and new lines of

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from my results as well.

[88]University of Wisconsin Budgets, University of Wisconsin Archives, Madison, Wisconsin.

[89]A. W. Lescohier to A. L. Tatum, 2 December 1947, box 5, folder 5, Tatum Papers, UW; A. L. Tatum to C. S. Hamilton, 8 January 1948, box 2, folder 22, ibid.; and C. S. Hamilton to A. L. Tatum, 27 October 1948, ibid.

collaborative research. E. A. Sharp, the Director of Clinical Investigation at Parke-Davis, raised the issue that a project on therapy for malaria would be a worthwhile endeavor, given the prevalence of the disease and the strong possibility of finding a useful antimalarial drug. The company General Manager, A. W. Lescohier, disagreed. He felt a long-term study of antimalarials would be impractical; requiring too much time to produce any tangible results. Tatum sided with Sharp.

> Dr. Tatum argued strongly against limiting our cooperative work to one or two problems. He feels that we should not risk having all our eggs in one basket. He is quite enthusiastic about the malaria problem because he feels that it fits in well with our cooperative arsenical work, that methods of testing are already available and that the hope of some practical outcome is reasonable.[90]

Others argued that, notwithstanding available therapeutic and public health procedures, the incidence of and mortality from malaria remained shockingly high.[91] As late as 1930, India alone annually suffered 100 million cases of malaria, of which two to three million died.[92] According to Macfarlane Burnet, "If we take as our standard of importance the greatest harm to the greatest number, then there is no question that malaria is the most important of all infectious diseases."[93] Lescohier

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[90]"Conferences in Detroit, June 19-20, 1936," 4.

[91]Ibid. The major antimalarials at this time, which were useful only for certain phases of the plasmodia life cycle in the human, were quinine, pamaquine (prepared by chemists at Bayer, and introduced in 1926 as Plasmochin), and quinacrine (introduced as Atabrine in 1930, and also synthesized by Bayer chemists).

[92]Macfarlane Burnet, Natural History of Infectious Disease, 3d ed. (Cambridge: Cambridge University Press, 1962), 341, and Erwin H. Ackerknecht, History and Geography of the Most Important Diseases (New York: Hafner, 1965), 88.

[93]Burnet, History of Infectious Disease, 341.

decided that it would be advisable to enter the malaria field. The collaborators, he felt, could plan the pharmacological work at a later date, after they established a chemical program.[94]

Tatum began testing some old arsenicals and new compounds as antimalarials in 1937, but Parke-Davis did not start subsidizing the malaria work at Wisconsin until 1940. Perhaps, as Lescohier urged (see n. 94), Tatum spent most of his time during this period "cleaning up" and catching up on the antisyphilitic arsenical research. Also, Tatum wanted to set up his laboratory for the malaria work before taking on research assistants for the program.[95] Parke-Davis supported both Hamilton's group at Nebraska, and Tatum and his associates. The firm funded the pharmacological work under Tatum at a rate of $2000 per year from 1940 to 1944, $3000 from 1944 to 1946, and $4000 from 1946 until the termination of the project, in 1948.[96]

Tatum's procedure for testing the antimalarials prepared by Parke-Davis and Hamilton was somewhat similar to his method of testing antisyphilitic arsenicals. He established a rudimentary measure of toxicity

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[94]Lescohier was quite concerned, however, "that we should concentrate in cleaning up any unfinished work on the general arsenical problem before doing much chemically in the malaria field . . . [and] checking up pharmacologically the arsenical compounds already available." See A. W. Lescohier to A. L. Tatum, 13 July 1936, box 5, folder 4, Tatum papers, UW, and "Conference in Detroit, June 19-20, 1936," 5.

[95]A. L. Tatum to Albert B. Scott, 4 February 1937, box 6, "Parke, Davis and Co., A. B. Scott, 1931-1937," Tatum Papers, UW.

[96]See folder "Parke, Davis and Co., Grant-in-aid," box 5, Gifts and Grants, Pharmacology Department Papers, especially Agreement between Parke, Davis and Company and the University of Wisconsin for research on the chemotherapy of malaria, n.d., attached to A. L. Tatum to C. A. Dykstra, 20 July 1940, ibid.

for each antimalarial, so he could estimate a suitable dose for the therapeutic tests. Only those compounds showing appreciable therapeutic activity, relative to known antimalarials, received a more rigorous toxicological analysis. Tatum used the canary, as did many other laboratories, to determine the toxicity and therapeutic value of the experimental compounds. A few days after inoculating test and control birds with a predetermined number of one of the various malaria plasmodia, he administered the antimalarial twice a day to the test group, until the external symptoms of the infection subsided in both groups. He measured efficiency of the compound by the comparative parasite count in the treated and untreated groups. Tatum tested drugs that passed this suppressive test as prophylactic agents against a plasmodium, alongside quinine or another established antimalarial.[97]

Knowing that some investigators had some success with neoarsphenamine in malaria, Tatum started with Mapharsen and a few other arsenicals. These, however, did not have any effect on avian malaria, so Parke-Davis, Hamilton, and Tatum abandoned arsenicals, and focused instead on derivatives of the bicyclic compound, quinoline.[98] This approach made sense, since quinoline made up half of the molecule of quinine. One of the two major synthetic antimalarials known at this

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[97]A. L. Tatum, "Pharmacological Test," three-page typescript, 26 October 1942, box 6, "Parke, Davis and Co., L. A. Sweet and O. Kamm, 1942-1943," Tatum Papers, UW.

[98]Tatum to Scott, 4 February 1937; A. L. Tatum to Oliver Kamm, 3 March 1937, box 5, "Parke, Davis and Co., O. Kamm, 1937-1941," Tatum Papers, UW; W. F. Holcomb to [Oliver] Kamm, 27 March 1937, box 1, "Synthetic Anitmalarials," Manuscripts and Publications, Pharmacology Department Papers; and L. A. Sweet to A. L. Tatum, box 6, "Parke, Davis and Co., L. A. Sweet and O. Kamm, 1937-1941," Tatum Papers, UW.

time, pamaquine (Plasmochin), was a derivative of quinoline (the other synthetic drug, quinacrine (Atabrine), was an alkyl amino derivative of acridine, a tricyclic molecule; see n. 91). By 1941, Tatum's group had tested about 50 compounds from Parke-Davis and Nebraska; less than ten of these had any appreciable activity. The collaborating chemists thus decided to concentrate on different series of compounds, including sulfonamides.[99]

The complexion of the collaboration on antimalarials changed significantly in 1942. Then, a seemingly myriad of panels, conferences, committees, subcommittees, and surveys of the National Research Council, in association with the Committee on Medical Research of the Office of Scientific Research and Development, consolidated all phases of antimalarial research in the United States. Over a dozen nations contributed to this wartime work as well.[100] The planning for this project had begun two years earlier, in anticipation of quinine shortages during the

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[99]W. F. H[olcomb], "Antimalarial Conference, April 11-12-14, 1941, Detroit, Michigan," box 3, "Conferences (Antimalarial)," Professional Organizations, Pharmacology Department Papers, and idem to A. L. Tatum, 18 December 1942, box 4, "Parke, Davis and Co., W. F. Holcomb, 1942, Antimalarials," Tatum Papers, UW (attached is a summary of the pharmacological results with antimalarials 101-200).

[100]George A. Carden, Jr., "Introduction," in Advances in Military Medicine, eds. E. C. Andrus et al., 2 vols. (Boston: Little Brown, 1948), 2:665-666. On the various phases of the antimalarial research program, see Robert C. Elderfield, "The Synthesis of Antimalarial Drugs," ibid., 671-677; William H. Taliaferro, "The Biology and Biochemistry of the Malarial Parasites," ibid., 678-690; George A. Carden, Jr., "The Screening Program," ibid., 691-697; James A. Shannon, "The Clinical Testing of Antimalarial Drugs," ibid., 698-716; and Frederick Y. Wiselogle, ed., A Survey of Antimalarial Drugs, 1941-1945, 2 vols. in 3 (Ann Arbor, Mich.: J. W. Edwards, 1946; for a list of the participating individuals, organizations, institutions, and nations, see pp. 29-48).

war. After Pearl Harbor, the needs of American troops in the Pacific and Mediterranean for treatment and protection against malaria became especially urgent. Participants in the national malaria program sent chemical, pharmacological, and other data on antimalarials to a central CMR-NRC clearing-house, for circulation among other participants, although contributors had the right to restrict whatever information they wished, thereby preventing its circulation. The clearing-house also arranged for pharmacological and clinical testing on all submitted products.[101]

Strategically, Parke-Davis could not avoid taking part in the program, according to Director of Research Oliver Kamm:

> Presumably the research divisions of practically all competing pharmaceutical houses have been asked to collaborate and so it turns out that, although we have expended more effort in the past than others in the direction of antimalarial research, our competitors may be securing a real advantage unless we also take part in the work sponsored by the Government through the National Research Council.[102]

The company joined the national program, but it also developed its own scaled down version of a crash antimalarial program. It engaged an additional six outside chemists and three researchers for pharmacological investigations, and Parke-Davis communicated the results of this group to the CMR-NRC clearing-house.[103] Meanwhile, Tatum's laboratory

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[101]Oliver Kamm to Those Cooperating with Parke, Davis and Company on Antimalarial Research, 10 August 1942, box 3, "Corres., 5 Aug. 1942-7 Sept. 1943," Tatum Papers, SHSW.

[102]Oliver Kamm to A. L. Tatum, 20 June 1940, box 6, "Parke, Davis and Co., L. A. Sweet and O. Kamm, 1937-1941," Tatum Papers, UW.

[103]"Antimalarial Conference, April 11-12-14, 1941," 5; L. A. Sweet to A. L. Tatum, 14 July 1942, box 6, "Parke, Davis and Co., L. A. Sweet and O. Kamm, 1942-1943," Tatum Papers, UW; Oliver Kamm to A. L. Tatum,

streamlined their work such that by early 1943, they alone were prepared to evaluate thirty antimalarials per month, while the chemical group was planning to produce 100 compounds monthly.[104] Within just a few years, the Parke-Davis cooperative group processed hundreds of antimalarials, for many of which the national clearing-house arranged further pharmacological evaluations and clinical tests.

So-called antimalarial 184 was probably the most promising--and ultimately the most disappointing--compound the group developed. Parke-Davis obviously had impressive preliminary results with 184. When a company chemist sent the drug to Tatum in May, 1942, he predicted, "I think, when you have finished your experiments on [184], you will say it is unnecessary to look further for 'The Antimalarial'--or should I say I hope so?"[105] Structurally, the drug made a lot of sense. It was comprised of molecular parts from Plasmochin (quinoline) and Atabrine (acridine), connected by an alkyl amino group. Since Plasmochin had greater activity against the sexual forms of the malaria parasites in the body (gametocytes), and Atabrine was specific against the asexual

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23 July 1942, ibid.; Kamm to Those Cooperating, 10 August 1942;" Antimalarial Conference, September 11, 1942," box 3, "Conferences (Antimalarial)," Professional Organizations, Meetings, and Conferences, Pharmacology Department Papers; Oliver Kamm to A. L. Tatum, 2 March 1943, box 6, "Parke, Davis and Company, L. A. Sweet and O. Kamm, 1942-1943," Tatum Papers, UW; W. F. Holcomb to A. L. Tatum, 27 January 1944, box 4, "Parke, Davis and Co., W. F. Holcomb, 1944-1945," ibid.; and A. L. Tatum to F. Y. Wiselogle, 20 August 1942, box 3, "Corres., 5 Aug. 1942-7 Sept. 1943," Tatum Papers, SHSW.

[104]"Antimalarial Conference, Chicago, February 1, 1943," box 3, "Conferences (Antimalarial)," Organizations, Meetings and Conferences, Pharmacology Department Papers, and Kamm to Tatum, 2 March 1943.

[105]W. F. Holcomb to A. L. Tatum, 8 May 1942, box 4, "Parke, Davis and Co., W. F. Holcomb, 1942, Antimalarials," Tatum Papers, UW.

forms (schizonts), 184 apparently had the life cycle of the plasmodia in the human covered.[106]

Tatum's early results, which compared 184 and Atabrine, supported Parke-Davis' hopes for the new drug. Antimalarial 184 was much better tolerated, and four to five times more active, compared to Atabrine. Even though pharmacological results on chicks by another collaborator indicated 184 was inferior to Atabrine, Parke-Davis submitted this antimalarial to the National Research Council in October, 1942, for further pharmacological evaluations and possibly clinical tests.[107] The results on 184, from pharmacological laboratories cooperating with Parke-Davis (Michigan, the Rockefeller Institute, and Wisconsin) and from some other groups in the national malaria program (the National Institute of Health, Johns Hopkins, Chicago, and Texas), confirmed Tatum's findings on the relatively low toxicity of 184 and the value of 184 in canary malaria. However, the drug did not fare as well as established antimalarials in malaria of other birds, when used as a suppressive drug and a prophylactic agent. Also, the drug compared poorly to Atabrine

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[106]J. H. Burckhalter et al., "N-Substituted 2-Methoxy-6-chloro-9-aminoacridines," Journal of the American Chemical Society 65 (1943):2013. The chemical name of antimalarial 184 was 2-methoxy-6-chloro-9-[gamma-(6'-methoxy-8'-quinolylamino)-propylamino]-acridine.

[107]A. L. Tatum to W. F. Holcomb, 15 July 1942, box 4, "Parke, Davis and Co., W. F. Holcomb, 1942, Antimalarials," Tatum Papers, UW; Oliver Kamm to National Malaria Conference of the National Research Council, 21 August 1942, box 3, "Corres., 5 Aug. 1942-7 Sept. 1943," Tatum Papers, SHSW; L. A. Sweet to E. K. Marshall, 29 October 1942, box 6, "Parke, Davis and Co., L. A. Sweet and O. Kamm, 1942-1943," Tatum Papers, UW; and W. F. Holcomb to A. L. Tatum, 5 November 1942, box 4, "Parke, Davis and Co., W. F. Holcomb, 1942, Antimalarials," ibid.

in clinical tests.[108] Parke-Davis and its collaborators decided to end work on 184 in February, 1943, although they created and tested many variations of this drug.

While antimalarial 184 failed to live up to the early expectations of Parke-Davis and Tatum, the company produced a compound later during the national malaria project that was as much as thirty times more active than quinine in pharmacological tests. The company introduced the drug in 1950 as Camoquine (amodiaquine).[109] After twelve years collaborating on a project that started out as a modest tripartite arrangement and eventually plugged into an international research network, Parke-Davis broke off the cooperative antimalarial research program with Tatum in 1948. Just a year earlier, the company had terminated the syphilis project with Wisconsin. Even if the company had not lost interest in malaria,[110] it probably would have ended the connections with Wisconsin, for the same reason it ended the arsenical project: Its own pharmacology department was far enough advanced to carry out most of the company's needs in that area. Yet the university scientist and pharmaceutical firm did not part empty-handed. Parke-Davis at

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[108]W. F. Holcomb to A. L. Tatum, 15 January 1943, box 4, "Parke, Davis and Co., W. F. Holcomb, 1942, Antimalarials," Tatum Papers, UW; W. F. Holcomb to [L. A.] Sweet and [Oliver] Kamm, 24 May 1944, box 4, "Parke, Davis and Co., W. F. Holcomb, 1944-1945," ibid.; Wiselogle, Survey of Antimalarial Drugs, 1:366-368, 2:1375.

[109]Wiselogle, Survey of Antimalarial Drugs, 1:398-400, 2:1165, and J. H. Burckhalter et al., "Aminoalkylphenols as Antimalarials. II. (Heterocyclic-amino)-alpha-amino-orthocresols. The Synthesis of Camoquin," Journal of the American Chemical Society 70 (1948):1363-1373.

[110]W. F. Holcomb to A. L. Tatum, 22 June 1948, box 4, "Parke, Davis and Co., W. F. Holcomb, 1944-1945," Tatum Papers, UW.

least could point to Camoquine to justify its investments in the program, and Tatum had found an additional $22,000 to support his research program at Wisconsin during the 1940s.

Tatum's Work with Other Firms

Tatum collaborated with two other companies, Charles Pfizer and Company and Upjohn, on the chemotherapy of syphilis during his arsenical work with Parke-Davis. Tatum's work with Pfizer and Upjohn concerned bismuth compounds, which physicians employed in syphilotherapy since the late 19th century. Bismuth grew in popularity during the first quarter of the 20th century, and it soon replaced the long-esteemed mercury as the heavy metal of choice in the treatment of syphilis. Bismuth was especially useful when administered with arsenicals, although physicians used bismuth alone as well. The bismuth research with these two companies illustrates how Tatum, sometimes to the frustration of the company, incorporated company-sponsored projects into his own research program.

In October, 1931, Pfizer engaged Tatum to investige the clinical suitability of its bismuth preparation, bismuth mannonate. Apparently Hugh L. Templeton, a chemist and a Pfizer fellow in dairy industry at the University of Wisconsin College of Agriculture from 1926 to 1937, represented the New York firm in its negotiations with Tatum, and occasionally relayed Tatum's progress back to Pfizer. Tatum agreed to test Pfizer's product for toxicity (acute and chronic), distribution and fate in the body, and therapeutic value in experimental and clinical

syphilis. Pfizer agreed to pay Tatum $250 per month, for six months, with the possibility of continuing the support beyond that time.[111] Two months later, Tatum was able to report on the toxicity of bismuth mannonate. His next step, however, was a comparison of the toxicities of other bismuth preparations with mannonate, rather than focusing on the latter and its possible role as an antisyphilitic agent. Thus, "in order to get a basis of comparison for the mannonate," Tatum launched an investigation of the toxicities of bismuth citrate, tartrate, and iodide.[112]

By the end of the six-month period, Tatum admitted to Pfizer that bismuth mannonate did not seem sufficiently promising as a therapeutic agent, on the basis of comparative studies of its toxicity and absorption characteristics, to extend the collaboration. Bismuth citrate, on the other hand, impressed Tatum enough that he recommended extending the collaboration to study this preparation in depth. The company was not enthused, because "there are now citrates and tartrates of various makes on the market and our prime interest was in the mannonate."[113] Still, Tatum reminded the firm that the therapeutic proof was in the pudding, and since he had not yet administered bismuth mannonate to a

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[111]Arthur L. Tatum to H. L. Templeton, 6 October 1931, box 3, "Chas. Pfizer and Co., Inc., J. L. Smith, Vice Pres.," ibid.; John L. Smith to Arthur L. Tatum, 19 October 1931, ibid.; and American Men of Science, 8th ed., s.v. "Templeton, Hugh L."

[112]Arthur L. Tatum to John L. Smith, 31 December 1931 and 11 March 1932, box 3, "Chas. Pfizer and Co., Inc., J. L. Smith, Vice Pres.," Tatum Papers, UW.

[113]Arthur L. Tatum to John L. Smith, 29 March 1932, ibid., and John L. Smith to Arthur L. Tatum, 7 April 1932, ibid. (quotation).

syphilitic rabbit,[114] he could not yet pass a final judgement on the preparation. Pfizer then seemed interested in extending the bismuth work. But the Wisconsin pharmacologist informed the company that he would need another six to eight months to form a definite idea of the value of the bismuth preparations in experimental syphilis. Also, his arsenical collaboration took priority for whatever clinical cases of syphilis that became available for the next several months. Faced with the strong possibility of another long investigation that might still fail to produce any solid idea about "the suitability for clinical purposes of our sodium bismuthyl mannonate," Pfizer finally terminated its support of Tatum's bismuth research in the Summer of 1932.[115]

Tatum did not have to wait very long to find support for his bismuth research. The Upjohn Company of Kalamazoo, Michigan, who learned about Tatum's interest in bismuth compounds "through our good friends The Chas. Pfizer Company," approached Tatum in December of 1932 for pharmacological and toxicological work on bismuth mannonate and other bismuth preparations. The firm was considering marketing the mannonate, and perhaps other compounds, but it needed more pharmacological data to take this step. Upjohn had no one to spare on its research staff to assign this problem, much less anyone familiar with the pharmacology of

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[114]Ostensibly, Tatum argued that six months was not enough time to gain an impression of the therapeutic efficacy of bismuth mannonate, since it required three to four months to establish the disease in the rabbit and begin collecting therapeutic data. However, Tatum already had syphilitic rabbits on hand for his arsenical work with Parke-Davis. If he made use of these, he would have been able to cut the waiting time at least in half. See Arthur L. Tatum to John L. Smith, 7 May 1932, ibid.

[115]Ibid.; John L. Smith to Arthur L. Tatum, 18 May 1932 and 29 June 1932, ibid.; and Arthur L. Tatum to John L. Smith, 6 June 1932, ibid.

bismuth preparations. In accordance with Tatum's wishes, Upjohn paid the Wisconsin pharmacologist $3000 per year for this investigation.[116]

Walter W. Enz, who studied under Edward Kremers at Wisconsin and joined Upjohn as a pharmaceutical chemist in 1932, prepared new bismuth compounds for Tatum, as well as a few well-known preparations that Tatum was not able to acquire from other firms. (Parke-Davis and G. D. Searle and Company of Chicago supplied Tatum with some bismuth preparations, although they did not provide financial support for his bismuth research.)[117] Herbert A. Braun, another recent Wisconsin graduate whom Upjohn hired in 1933, conducted preliminary pharmacological evaluations on the experimental bismuths before sending these to Wisconsin. Despite his assurance to Pfizer in June of 1932 that he was ready to begin testing bismuths in experimental syphilis, Tatum continued to focus on the chronic toxicity of these compounds during the early collaboration with Upjohn. He reported his first therapeutic results two years after the collaboration began--on a Searles product. Upjohn issued a subtle yet pungent reply, which acknowledged Tatum's familiarity with its competitor's product, and expressed disappointment that the Wisconsin worker

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[116]H. S. Adams to Arthur L. Tatum, 8 December 1932, box 3, "Upjohn Co., Dr. H. S. Adams, 1932-1937," Tatum Papers, UW, and F. W. Heyl to Arthur L. Tatum, 27 January 1933, ibid.

[117]A. L. Tatum to Milton L. Kuhs, 21 July 1942, box 1, "Upjohn Company, Grant-in-aid, 1942-1943," Gifts and Grants, Pharmacology Department Papers, and N. M. Clausen et al., "A Study of the Similarities of Several Representative Types of Bismuth Preparations Used in the Therapy of Experimental Syphilis," Journal of Pharmacology and Experimental Therapeutics 76 (1942):338 n. 1.

had to "exclude our bismuth preparations from similar considerations."[118]

Upjohn recently had prepared a new bismuth compound, bismuth ethyl camphorate, that Upjohn and Wisconsin researchers found very promising, on the basis of toxicity tests. It was much less toxic than other bismuth preparations, so much so that Tatum's laboratory animals tolerated several times more bismuth ethyl camphorate than other popular bismuths. The comparative therapeutic evidence Tatum accumulated from 1935 to 1938, combined with clinical tests of bismuth ethyl camphorate on over 200 patients at the Boston Dispensary, were promising enough for Upjohn to submit this drug to the Council on Pharmacy and Chemistry.[119] The latter, however, felt the data were insufficient to distinguish the camphorate from the plethora of bismuth compounds already on the market: ". . . the Council has already gone on record as being opposed to development of further bismuth preparations for the treatment of syphilis unless they represent something new and of an unusual type. Bismuth ethyl camphorate can hardly be called a new or unusual type of preparation."[120]

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[118]Arthur L. Tatum to George F. Cartland, 23 November 1933, 3 February 1934, 8 December 1934, and 7 February 1935, box 3, "Upjohn Co., Dr. H. S. Adams, 1932-1937," Tatum Papers, UW, and George Cartland to Arthur L. Tatum, 21 December 1934, ibid.

[119]Tatum to Cartland, 8 December 1934 and 7 February 1935; Cartland to Tatum, 21 December 1934; E. Gifford Upjohn to Arthur L. Tatum, 6 May 1938, box 3, "Upjohn Co.," Tatum Papers, UW; A. L. Tatum to E. Gifford Upjohn, 11 May 1938 and 19 May 1938, ibid.; Clausen et al., "Bismuth Preparations in Experimental Syphilis," 338-342; and Council on Pharmacy and Chemistry of the American Medical Association, "Reports of the Council," Journal of the American Medical Association 113 (1939):1569.

[120]Council on Pharmacy and Chemistry, "Reports of the Council," 1569.

Upjohn ended its support of bismuth research at Wisconsin in 1938, probably because 1) the firm by then was interested primarily in bismuth ethyl camphorate alone, whereas Tatum still emphasized the rigorous, comparative approach to the investigation of bismuth compounds, and 2) the Council aimed its criticisms at the paucity of clinical data on the camphorate. Thus, Upjohn focused on the expansion of clinical work in the following years. The Council finally admitted bismuth ethyl camphorate to New and Nonofficial Remedies early in 1942.[121] Shortly thereafter, Upjohn renewed its research fellowship under Tatum, for "more extensive and complete studies" on camphorate and other bismuth compounds, at a lesser rate ($2000 annually) than earlier. The Wisconsin pharmacologist apparently applied this fellowship to extend his earlier research, on the quantitative synergy of bismuth and arsenical compounds in experimental syphilis, to human cases. He also investigated the elimination of bismuth in clinical syphilis. The pharmaceutical firm renewed the support for at least one year, but records of the Tatum-Upjohn collaboration cease after 1943.[122]

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[121]Idem, "Report of the Council," Journal of the American Medical Association 118 (1942):896-897; E. Gifford Upjohn to A. L. Tatum, 27 October 1938, box 3, "Correspondence, 11 Jan. 1937-27 Dec. 1939," Tatum Papers, SHSW; and Tatum to Kuhs, 21 July 1942.

[122]Milton L. Kuhs to A. L. Tatum, 22 May 1942, box 1, "Upjohn Company, Grants-in-aid, 1942-1943," Gifts and Grants, Pharmacology Department Papers; Agreement between the Upjohn Company and the University of Wisconsin for research on bismuth in the chemotherapy of syphilis, c. July, 1942, ibid.; A. L. Tatum to Milton L. Kuhs, 4 June 1942 and 20 April 1943, ibid.; E. Girrord Upjohn to A. L. Tatum, 24 May 1943, ibid.;A. L. Tatum to E. Gifford Upjohn, 15 October 1943, ibid.; and N. M. Clausen, B. J. Longley, and A. L. Tatum, "The Quantitative Nature of the Coaction of Bismuth and Arsenical Compounds in the Therapy of Experimental Syphilis," Journal of Pharmacology and Experimental Therapeutics 74 (1942):324-333.

The bismuth research programs with Pfizer and Upjohn were a logical extension of Tatum's established collaboration with Parke-Davis on the chemotherapy of syphilis. The two programs complemented each other nicely, much the same way that bismuth compounds and arsenicals complemented each other in the treatment of syphilis. Tatum did not enjoy the same kind of success in his bismuth research as he had in the arsenical work, but he did help Upjohn develop a new bismuth preparation that filled a therapeutic niche in an armamentarium replete with such compounds. The Wisconsin pharmacology department was able to supplement its research funds with over $25,000 from bismuth fellowships--most of this support coming during the Depression. Thus, the bismuth collaborations yielded many benefits to the principals in this consultantship, benefits to the company (in the form of a marketable drug), to the consultant (in the form of long-term support of his research program), and to therapeutics as well (in the form of an enhanced understanding of the pharmacology of a group of drugs, with the added benefit of a useful drug for the treatment of disease).

Conclusion

Both Loevenhart and Tatum are examples of very active consultants to industry. In the late 1920s, Loevenhart was consulting with three companies on six different research topics; he may have been consulting prior to this, but the records are insufficient to venture more than a guess. Tatum was a virtual consulting machine, at least prior to World War Two. He worked with a total of six companies, on a variety of

topics. At one point in the late 1930s, he was consulting simultaneously with Abbott on barbiturates, with Parke-Davis on arsenicals and antimalarials, and with Upjohn on bismuth compounds. By this time he even had developed standardized contracts for projects undertaken with companies. Both Loevenhart and Tatum fostered these many industrial contacts without any noticeable drain on their university duties.

Loevenhart and Tatum were valuable resources for companies. While a few firms had solid pharmacologists on their staffs in the 1920s and 1930s (see Chapter 3), the majority of companies did not. Thus, Abbott, Parke-Davis, and the other companies turned to Loevenhart and Tatum to sift and winnow arsenicals, antimalarials, barbiturates, bismuths, and other groups of drugs. The litany of successful pharmaceuticals they helped develop is testament to their value to these companies. In turn, the consulting arrangements provided a valuable resource for the Wisconsin pharmacologists. They derived hundreds of thousands of dollars from associations with industry, which helped support many of their students, and thereby supported their own research programs.

PART IV

THE SCIENTIST AS A PROJECT RESEARCHER: INSULIN AND LIVER EXTRACTS

The interactions between academic scientists and the pharmaceutical industry in the formative era of collaborative research involved a variety of typologies, two of which I have already discussed. The general consultant's contact with a company touched many aspects of the company's affairs. The general consultant counseled the firm on narrow scientific problems, acted as a liaison between the company and the academic community, advised the firm on general research policy, and served the company in other ways. The thrust of the specialist-consultantship was considerably narrower in scope, although the specialist-consultant often dealt with more than one firm. The subjects of Chapter 5, for example, linked with over a half-dozen firms in several research areas. The specialist-consultantship could lead to a study of one particular drug (Mapharsen, for example), but this type of collaboration typically began for a broader purpose--an investigation of a wide class of compounds, depending on the specialty of the academic scientist.

The specific project collaboration had the narrowest scope of all three typologies discussed in this dissertation. It is not unusual to find elements of the specific project collaboration in the other two typologies (for example, Adams' work with Abbott on barbital, Tatum's Nembutal research for Abbott, and the joint development of streptomycin by Merck and Waksman), but we see very little suggestion of the vice

versa case. The object of scientists represented by the specific project collaboration was to develop a specific therapeutic agent, usually to such a point of safety, efficacy, and economy that the product was fit for general distribution. The following two chapters describe exemplary specific task-oriented collaborations between 1920 and 1940. Chapter 6 deals with the development of insulin, and Chapter 7 discusses the work on two liver extracts for the treatment of anemias. While there was no such thing as a standard formula by which collaborations like these operated, certain common characteristics of the project type of arrangement will become clear during the next two chapters. The following pattern is based primarily on the detailed cases in Chapters 6 and 7, and on the little that is known about the other cases mentioned below. The generalizations below should be weighed accordingly, pending further research on this typology.

First, researchers from either academe or industry discovered the therapeutic agent prior to the collaboration. This contrasts markedly with the case of the scientist who (if lucky) would discover an agent, like Mapharsen, after the start of the academic-industrial agreement. Second, it was often (but not always) the case that a company would approach the university scientist, who made some therapeutic discovery, with an offer of collaboration. It was a fact of corporate life that the firm needed to keep up with or surpass its competition, thus the company's need to be among the first to capitalize on therapeutic discoveries. While economic interests took priority, at least some companies (such as the one mentioned in Chapters 6 and 7) were

partially driven by humanitarian interests as well. On the other side, university scientists who hoped to apply their discoveries to practical therapeutics needed assistance too. If not already known, a suitable method of preparing the product, capable of being scaled up, had to be worked out. Also, the product had to be made available to the thousands or millions who needed this therapy. Universities did not have the facilities to manufacture drugs, so some academic scientists turned to companies, at least to mass produce their drugs, and possibly to help in the experimental development of the drug. The company and the university scientist, then, required assistance from each other.

Third, at the conclusion of their negotiations, a company and university usually came to some formal agreement, which was not necessarily unique to this typology. This agreement typically addressed such topics as the tasks of each party, possible commercial arrangements, the sharing of research information (including publication policies) with outsiders, quality control for the drug, and advertising. Fourth, the collaborators laid out plans for testing the item in the laboratory and/or in the clinic. In the case of clinical evaluations, a few outside testing centers were needed to get a sufficient number of cases so that the collaborators could make a reliable estimation of the value of the drug.

Fifth, if the company could adequately manufacture the drug (without it being prohibitively expensive for the patient), and if the preliminary clinical tests were promising, the collaborators invited additional clinics to test the drug. Sixth, providing the expanded

clinical testing program was satisfactory, the collaborators decided that the company could throw the product into general distribution across the country. Finally, the pharmaceutical firm and university usually terminated their active interchange of research data at this point, although the two could remain in contact for many years thereafter. For example, the academic party could have arranged to receive patent royalties from the university, or it could have maintained a supervisory role over the manufacture of the product. Also, the company could give the university unsolicited support for a research program unrelated to the collaborative project, as a reward for the decision of the university scientists to collaborate with their firm.

While the cooperative developments of insulin and liver extracts may have been two of the more celebrated project collaborations during the era between the World Wars, these were certainly not the only joint university-industry research projects. Sharp and Dohme of Baltimore, for example, worked with Johns Hopkins University scientists to introduce the bactericidal chemical hexylresorcinol (Caprokol) in the mid-1920s. Also, William Murphy of the Harvard Medical School helped Lederle Laboratories develop a liver extract and an extract solution for the treatment of pernicious anemia, at the same time that his colleagues at Harvard were working on a similar problem with Eli Lilly and Company. Lilly developed its popular mercurial antiseptic, Merthiolate (thimerosal), in cooperation with chemist Morris S. Kharasch of the University of Chicago. The firm introduced this drug in 1928.

In the 1930s, scientists at the Harvard Medical School collaborated with Parke, Davis and Company of Detroit on a drug for epilepsy,

Dilantin, which is still widely used today. A German chemist synthesized Dilantin (diphenyl hydantoin) in 1908, for unknown reasons.[1] Parke-Davis workers investigated Dilantin as a potential hypnotic agent in the early 1920s,[2] most likely because chemically it was very similar to an established hypnotic, Nirvanol, but they rejected Dilantin. Two neurologists at the Harvard Medical School, Tracy J. Putnam and H. Houston Merritt, as part of their program to screen various potential anticonvulsant drugs, contacted the Detroit firm for samples of any drugs that the company thought might be useful. Putnam and Merritt particularly were interested in anticonvulsants without the inconvenient sedative action of phenobarbital, a drug used in epilepsy since 1912. Dilantin was among the first lot of drugs that Parke-Davis sent to Harvard.[3]

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[1]Heinrich Biltz, "Uber die Konstitution der Einwirkungsprodukte von substitutierten Harnstoffen auf Benzil und über einige neue Methoden zur Darstellung der 5,5-Diphenyl-hydantoine," Berichte der Deutschen Chemischen Gesselschaft 41 (1908):1391-1392. See also Heinrich Biltz and Karl Seydel, "Eine neue Darstellung von Diphenyl-amido-methan (Benzhydryl-amin)," ibid. 44 (1911):411-413.

[2]Arthur W. Dox and Adrian Thomas, "5,5-Diarylbarbituric Acids," Journal of the American Chemical Society 45 (1923):1815.

[3]According to Merritt,

> We asked the pharmaceutical houses to send us some drugs which had been devised as hypnotics but had not been useful in that capacity. Parke-Davis was one of the first drug companies we asked, because the Director of Research there [Oliver Kamm] was a friend of Tracy Putnam. Parke-Davis sent about twenty-five drugs that had not worked as hypnotics. The first drug which they sent was diphenylhydantoin, and, by God it worked. We tried about a thousand drugs after that. We found one or two which were more effective anticonsulvants than diphenylhydantoin, but they were too toxic to use

(quoted in Benjamin V. White, Stanley Cobb: A Builder of the Modern Neurosciences (Boston: Francis A. Countway Library of Medicine, 1984),

On the basis of preliminary experiments in which they tested the ability of various compounds to extend a cat's convulsive threshold (in the presence of electric shocks), Putnam and Merritt concluded that Dilantin was one of the best drugs they had investigated. Moreover, it did not manifest any soporific effect on the animals.[4] These results, coupled with the similarly promising results which Parke-Davis scientists had found,[5] convinced Putnam and Merritt to launch a clinical study of the drug. Their results with hundreds of patients from about 1938 to 1940 indicated that, while Dilantin produced mixed results with grand mal epilepsy patients (the more severe of the two forms), the drug gave 85% of the petit mal patients complete or near-complete relief from their seizures.[6] A comparative study in the late 1930s of Dilantin and phenobarbital in about 250 patients with grand or petit mal epilepsy, conducted at over a dozen medical centers, revealed that

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[4]Tracy J. Putnam and H. Houston Merritt, "Experimental Determination of the Anticonvulsant Properties of Some Phenyl Derivatives," Science 85 (1937):525-526; H. Houston Merritt and Tracy J. Putnam, "A New Series of Anticonvulsant Drugs Tested by Experiments on Animals," Archives of Neurology and Psychiatry 39 (1938):1003-1015.

[5]O. M. Gruhzit, "Sodium Diphenyl Hydantoinate: Pharmacologic and Histopathologic Studies," Archives of Pathology 28 (1939):761-762.

[6]H. Houston Merritt and Tracy J. Putnam "Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders," Journal of the American Medical Association 111 (1938):1068-1073; idem, "Sodium Diphenyl Hydantoinate in Treatment of Convulsive Seizures," Archives of Neurology and Psychiatry 42 (1939):1053-1058; idem, "Further Experiences with the Use of Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders," American Journal of Psychiatry 96 (1940):1023-1027.

over half of the patients responded better with Dilantin.[7] Not surprisingly, Dilantin was a great strike for Parke-Davis.

Shortly before World War Two, workers at the University of California and Lilly joined efforts to develop a new sulfa drug, nicotinyl sulfanilamide. Troy C. Daniels of the College of Pharmacy of the University of California prepared this drug (4-nicotinyl-amino-benzene-sulfonamide) in 1937, to see if the product of a reaction between sulfanilamide and nicotinic acid would combine the pharmacological properties of each reactant. The preliminary pharmacological work, carried out by Chauncey Leake and his associates at California, indeed suggested that nicotinyl sulfanilamide was as effective as sulfanilamide in protecting laboratory animals against meningococcal infections, and superior to sulfanilamide in clearing some streptococcal infections.[8]

Scientists at Lilly were working with nicotinyl sulfanilamide at the same time and independently of the California group. A patent interference resulted late in 1939 when both sides attempted to file letters patent on this drug. However, Lilly and the Research Corporation, a private organization established in 1911 to administer patents, issue licenses, and distribute profits from patents in the form of

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[7]Council on Pharmacy and Chemistry, "Reports of the Council," Journal of the American Medical Association 113 (1939):1734.

[8]T. C. Daniels and Harry Iwamoto, "N^1,N^4-Nicotinyl Derivatives of Sulfanilamide," Journal of the American Chemical Society 62 (1940):741-742, and Norman Karr et al., "Chemotherapeutic Activity of 4-Nicotinyl-Amino-Benzene-Sulfonamide," Scientific Proceedings of the American Society for Pharmacology and Experimental Therapeutics, 31st Annual Meeting, New Orleans, Louisiana, 13-16 March 1940, Journal of Pharmacology and Experimental Therapeutics 69 (1940):291.

grants throughout the United States (the Research Corporation managed Daniels' patent application),[9] soon reached an agreement whereby Lilly withdrew its patent application.[10] By January, 1940, Leake began organizing clinical evaluations of nicotinyl sulfanilamide, first among clinics in the San Francisco area, and later among selected clinics elsewhere in the United States. Lilly supplied the drug in bulk for these clinical tests. Leake's occasional progress reports to the company on results in San Francisco area clinics suggested that nicotinyl sulfanilamide might find a therapeutic niche. For example, it was considerably less toxic than sulfanilamide, and yet at least as effective as the latter in some infections. But Lilly apparently was not convinced that the results with nicotinyl sulfanilamide justified marketing this sulfa drug, and the firm soon lost interest in the drug.[11]

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[9]Richard H. Shryock, American Medical Research: Past and Present (New York: Commonwealth Fund, 1947), 143.

[10]Chauncey D. Leake to A. H. Fiske, 10 November 1939, box 44, "Lilly Research Laboratories, 1933-1940," Chauncey D. Leake Papers, National Library of Medicine, Bethesda, Maryland [hereafter Leake Papers]; A. H. Fiske to Chauncey D. Leake, 15 November 1939, ibid.; H. W. Rhodehamel to Chauncey D. Leake, 21 November 1939, ibid.; Chauncey D. Leake to [H. W.] Rhodehamel, 25 November 1939, ibid.; and Troy C. Daniels, "Therapeutic Agent," United States Patent 2,192,828, patented 5 March 1940 [assigned to the Research Corporation]. It is not clear what, if anything, Lilly received in return for withdrawing its application; perhaps the promise of a (limited-term) exclusive license if the drug were marketable.

[11]Eli Lilly to Chauncey D. Leake, 15 January 1940, box 44, "Lilly Research Laboratories, 1933-1940," Leake Papers; Chauncey D. Leake to H. W. Rhodehamel, 15 January 1940, 29 January 1940, 10 April 1940, and 13 August 1940, ibid.; and H. W. Rhodehamel to Chauncey D. Leake, 5 February 1940 and 2 July 1940, ibid.

In the cases above, we know very little about the actual interactions between the companies and the academic scientists, although enough is known to consider these as examples of the specific project collaboration. The following chapters will present a sufficiently detailed picture to illustrate how, and why, universities and pharmaceutical firms carried out project collaborations.

CHAPTER 6

THE UNIVERSITY OF TORONTO, ELI LILLY AND COMPANY, AND INSULIN

The search for the internal secretion of the pancreas to treat diabetes mellitus began three decades before Frederick Banting initiated his work at the University of Toronto. Endocrinology itself was a comparatively recent field at that time.[1] The modern era of endocrinology dates from 1855, with the publication of Thomas Addison's On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules. Although physicians and scientists knew little of the physiology of these capsules, i.e., the adrenal glands, Addison was the first to identify a disease syndrome and associate it with pathological changes in the suprerenal capsules. His announcement stimulated others to investigate the physiology of the adrenal glands, including the French-American physiologist, Charles Edouard Brown-Séquard. Brown-Séquard's more significant work concerned rejuvenation studies with testicular extracts, which he reported in 1889. Based on this research, he postulated the existence of various internal secretions in animals, a lack of which produced diseases. He suggested that extracts could be prepared from certain animal tissues to capture these

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[1]The following summary of endocrinology up to the turn of the century is based on Merriley Borell, "Organotherapy, British Physiology, and Discovery of the Internal Secretions," Journal of the History of Biology 9 (1976):235-268; idem, "Brown-Séquard's Organotherapy and Its Appearance in America at the End of the Nineteenth Century," Bulletin of the History of Medicine 50 (1976):309-320; and F. G. Young, "The Evolution of Ideas About Animal Hormones," in The Chemistry of Life: Eight Lectures on the History of Biochemistry, ed. Joseph Needham (Cambridge: Cambridge University Press, 1971), pp. 125-155.

internal secretions. The physician then could employ these extracts for diseases connected with those particular tissues.

Brown-Séquard's work was much more readily applied in medical quackery than scientific medicine.[2] Some discoveries during the 1890s, however, lent credibility to Brown-Séquard's theories and accelerated investigations of internal secretions. In 1891 George Redmayne Murray, of the Hospital for Sick Children in Newcastle, reported his successful treatment of myxedema, a thyroid disorder, by injecting an extract of the thyroid. Three years later, an English physician from Harrogate, George Oliver, and Edward Schäfer, a physiologist from University College, London, published their discovery of an adrenal gland extract that elicited a pressor reaction. They later collaborated on the discovery of another pressor substance, vasopressin, located in the posterior pituitary gland.

William Maddock Bayliss and Ernest Henry Starling of University College demonstrated the nature of the mechanism involved in internal secretions. In 1902 they published their results on the triggering of pancreatic juice. They found that the pancreas secreted this juice after the stomach contents passed into the duodenum, even when they cut all nerves connecting the pancreas and intestine. Next, they prepared an extract from the duodenal mucous membrane, and injected this into the animal's bloodstream. This triggered secretion of pancreatic juice, thus establishing the chemical--rather than neurological--nature

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[2]See, for example, Gerald Carson, The Roguish World of Doctor Brinkley (New York: Holt, Rinehart and Winston, 1960), which relates how one quack made millions from studies on rejuvenation.

of the mechanism. They named this internal secretion from the duodenum, secretin. In 1905, Starling proposed the term "hormone" (from the Greek, "I arouse") for such substances as secretin that form in one organ and pass through the circulation to another organ to produce a response.

When scientists discovered which organ was most likely responsible for diabetes, it was thus a logical step for them to attempt to extract the active ingredient, i.e., the internal secretion, from that organ.[3] Joseph von Mering and Oscar Minkowski at the University of Strasbourg provided a solid link between the pancreas and diabetes in 1889. Much to their surprise, when they removed the pancreas to observe its effect on digestion, diabetes resulted. Eugene Opie, a pathologist at Johns Hopkins, localized the connection between the pancreas and diabetes even further. In 1901 he demonstrated a link between diabetes and impaired islets of Langerhans--pancreatic cells smaller than the others in this organ, discovered in the late 1860s.

Minkowski was the first of many who tried to treat diabetes with pancreatic extracts. Their results, on the whole, were uneven. Attempting to isolate the internal secretion was a very difficult maneuver, because the proteolytic enzymes in the pancreatic external (digestive) secretion rapidly inactivated the internal secretion. From 1911-1912, a graduate student at the University of Chicago, Ernest Lyman Scott, tried to bypass this problem by tying off the pancreatic

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[3]On attempts to isolate the internal secretion of the pancreas prior to the research at Toronto, see Michael Bliss, The Discovery of Insulin (Chicago and Toronto: University of Chicago Press and McClelland and Stewart, 1982), pp. 20-44.

ducts. This, he believed, would force the pancreatic juice-secreting cells to atrophy, leaving the islets of Langerhans intact. But Scott failed to induce atrophy of any part of the pancreas. Next, he prepared extracts of whole pancreas with alcohol, achieving good results with a few of his diabetic dogs. But Scott abandoned this research. For one thing, the alcoholic extracts actually elevated the blood sugar in some of his animals. Also, Scott was aware that a growing number of physiologists--including his advisor--doubted that the internal secretion of the pancreas could be isolated.

Between 1915 and 1920, Israel Kleiner at the Rockefeller Institute and Nicolas Paulesco in Bucharest compiled perhaps the best results with pancreatic extracts prior to the Toronto work. Using water as an extractive agent, and making use of recent advances in the technology of blood sugar determinations, they reported impressive reductions in sugar and ketones in the blood and urine. Moreover, toxic side effects from these extracts were comparatively minor. Such untoward effects as kidney failure, vomiting, and convulsions invalidated whatever positive results earlier researchers had managed with their extracts. Unfortunately, Kleiner ceased diabetes research after leaving the Rockefeller Institute, probably because of a lack of funding, and while Paulesco continued his investigations, his results failed to generate much interest among researchers in the field.

The person responsible for initiating the research at the University of Toronto which eventually led to the discovery of insulin, Frederick Grant Banting (1891-1941), was hardly a mainstream

investigator in diabetes research.[4] In fact, his laboratory experience in general was limited at most. Banting was a practicing physician in London, Ontario, when he devised an experiment, late in October, 1920, to ligate the pancreatic ducts of dogs, wait for the pancreatic juice-secreting cells to atrophy, and finally isolate the internal secretion from the islets. (Although this was similar to Scott's experiment several years earlier, Banting was not aware of Scott's work at the time.) Banting approached John James Rickard Macleod (1876-1935), a physiologist at the University of Toronto with a special interest in carbohydrate metabolism, about the feasibility of pursuing his research in Macleod's laboratory. Macleod was understandably hesitant at first, but eventually the determined Banting convinced Macleod. With Charles Herbert Best (1899-1978), a medical student and research assistant to Macleod at his side, Banting began his search for the internal secretion of the pancreas on 17 May 1921.

The experimental procedure Banting and Macleod mapped out was straightforward. In one group of dogs, Banting would ligate the pancreatic ducts, wait several weeks for degeneration to occur, and then remove what was left of the pancreas. In another group he would extirpate the pancreas, and upon the onset of diabetes either graft pieces of the atrophied pancreas into the diabetic dog or inject an extract. Best had charge of the blood sugar and glycosuria determinations. It required many dogs before Banting mastered the operations, but between

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[4]The synopsis below of the work at Toronto through the Spring of 1922 relies on ibid., 45-153. Bliss' study is not only the definitive piece on insulin, but also stands as a model for future drug histories.

30 July and 7 August the pair managed to perform their first series of therapeutic tests. Their extracts lowered the blood sugar in each of three diabetic dogs; they even revived one dog from a diabetic coma. However, their data were far from complete or satisfactory. In another test, carried out through August, Banting and Best compared two diabetic dogs, only one of which received pancreatic extracts. The blood sugar of the dog receiving "Isletin" (which Banting and Best called their extracts) remained well below the control dog's blood sugar. The latter survived only four days, whereas the Isletin dog lasted over two weeks.

The lack of a steady supply of extracts was a bottleneck in these experiments; it took about five to seven weeks for the pancreas to sufficiently atrophy before removal. Hence the importance of Banting and Best's observation early in December that alcoholic extracts of fresh, whole adult pancreases could significantly lower blood sugar. Earlier, Scott had made the same observation, which he could have passed along to Macleod. However, it is not clear if Macleod later informed Banting and Best of Scott's observation.

Soon afterwards Macleod invited a biochemist on sabbatical at the University of Toronto, James Bertram Collip (1892-1965), to join Banting and Best. Banting had long been needling Macleod for more manpower, Collip had told Macleod earlier of his desire to take part in the research, and most of all, the preliminary results were promising and warranted an expansion of personnel. Collip soon made his presence felt. For example, he significantly improved the purity of extracts by preparing each batch of whole beef pancreases with

Figure 14. The principal workers who discovered insulin (1921-1922) at the University of Toronto. Banting was a general practitioner from London, Ontario; Macleod was Professor of Physiology at Toronto; Collip was Professor of Biochemistry at the University of Alberta, on sabbatical leave at Toronto; and Best was a medical student at Toronto and assistant in Macleod's laboratory (from Michael Bliss, The Discovery of Insulin; UW neg. no. 10265 C-3).



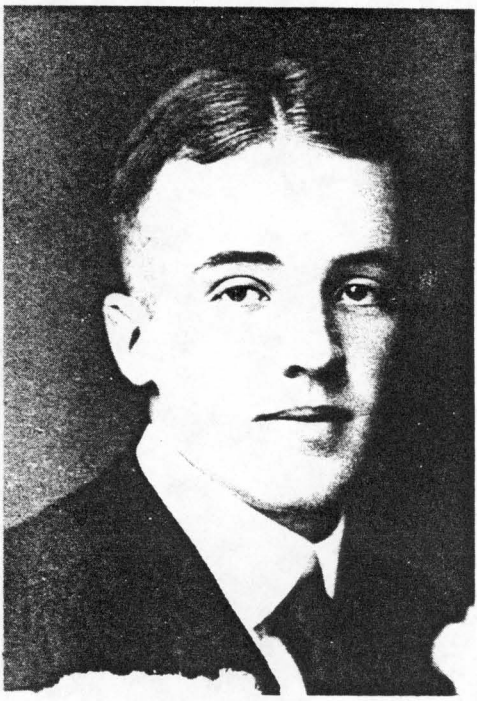
Frederick Grant Banting (1891-1941).



John James Rickard Macleod (1876-1935).



James Bertram Collip (1892-1965).



Charles Herbert Best (1899-1978).

increasingly concentrated alcohol. Also, he discovered that the extracts could lower the blood sugar of normal rabbits. This provided the group with a means of standardizing their preparations. Collip provided the first experimental evidence at Toronto that the pancreas extracts could eliminate ketones as well as sugar from the urine, and he compiled incontrovertible evidence that the preparations restored the liver's glycogenetic function. Both results were solid indications of the extract's antidiabetic value.

The Toronto group tested their insulin clinically in late December and early January; it had little or no benefit to the patient. But later in January of 1922, an extract Collip prepared drastically reduced the patient's blood sugar and glycosuria, and eliminated his ketonuria. The group soon planned an expansion of the clinical testing program in Toronto. To accommodate this, the University of Toronto's Connaught Anti-Toxin Laboratories, established in 1914, set up facilities in the basement of the medical building for large scale production of insulin, which Best directed. For unknown reasons, the ability to produce insulin escaped the Toronto researchers through March and April. But they modified their process, and in May production was on again. The publicity which their initial reports and publications[5]

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[5]Banting and Best, with Macleod present, announced their results through early November, 1921, at the meeting of the American Physiological Society at Yale University, on 30 December 1921. On 3 May 1922, Macleod reported to the Association of American Physicians, at a meeting in Washington, D.C., the present status of the group's work (including the preliminary clinical findings). The first publication of their work, by Banting and Best, appeared in February, 1922: "The Internal Secretion of the Pancreas," Journal of Laboratory and Clinical Medicine 7 (1922):256-271. A handy compilation of the Toronto group's earliest publications through September of 1922 (including summaries

generated resulted in a rising number of requests for the treatment in May. This, coupled with recurrent problems in scaling up insulin production, led the group to seek outside assistance.

Negotiating an Agreement for Collaboration

The Toronto group hoped to produce as much insulin as inexpensively as possible. Their attempts to produce insulin on a large scale, however, resulted in zero yield.[6] Even if Toronto succeeded in scaling up production, the University (including its Connaught Laboratories) simply lacked the resources necessary to satisfy the demand for this drug. What Toronto needed was a reliable pharmaceutical firm with the facilities, know-how, and desire to help them fulfill their aspirations for insulin. They found such an organization in Eli Lilly and Company of Indianapolis.

Toronto had good reason to select Lilly as a collaborator. In the first place, Lilly recently had added several gland products to its inventory when Banting and Best started their insulin research. The company listed many different preparations of eleven glands and gland products in its 1922 price list. The experience Lilly gained in manufacturing and physiologically standardizing such items as pituitary extract played no small part in Toronto's decision to work with the

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of each article), is F. M. Allen, "Summary of Publications on Insulin to Date," Journal of Metabolic Research 2 (1922):125-140.

[6]J. J. R. Macleod, "Insulin and the Steps Taken to Secure an Effective Preparation," Canadian Medical Association Journal 12 (1922):899.

Indianapolis firm.[7] Even more important to Toronto was the company's Director of Research, G. H. A. Clowes (see Chapter 3), who represented Lilly in the negotiations with the University. Clowes' scientific stature, and Lilly's support of his ongoing fundamental research in Indianapolis and at the Marine Biological Laboratory in Woods Hole, Massachusetts, convinced the Toronto group that this was the kind of company they wanted to work with.[8]

Clowes first heard of Toronto's insulin work in October of 1921, possibly from Lewellys Barker, a Professor of Medicine at Johns Hopkins and alumnus of the University of Toronto.[9] However, Clowes did not approach any of the Toronto researchers to volunteer his company as a collaborator until late December of 1921. He met with Banting, Best, and Macleod immediately following their presentation at the meeting of the American Physiological Society in New Haven, Connecticut (see note

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[7]Eli Lilly and Company, A Complete Priced List of the Products of the Lilly Laboratories, no. 41 (Indianapolis: Eli Lilly, 1922), pp. 181-184 (in Kremers Reference Files, F. B. Power Pharmaceutical Library, University of Wisconsin, Madison, Wisconsin). See also Gene E. McCormick, "Insulin: A Hope for Life," Tile and Till 57, no. 2 (1971): 33.

[8]["Contract between the Board of Governors of the University of Toronto and Eli Lilly and Company for the Production of Insulin"], 30 May 1922, "Insulin--Section 5," Eli Lilly and Company Archives, Indianapolis, Indiana (hereafter Lilly Archives; this document, as well as some of the others cited in this chapter, would appear to be photocopies of documents from the Insulin Committee Papers in the University of Toronto Archives); F. G. Banting, "The History of Insulin," Edinburgh Medical Journal, n.s. 36 (1929):10; G. H. A. Clowes to J. K. Lilly, 7 July 1945, "J. K. Lilly, 1861-1948--Letters to and from Dr. G. H. A. Clowes, 1920-1945," XBLk, Lilly Archives; and Charles H. Best, interview by Gene E. McCormick, Best Institute, University of Toronto, 24 September 1968, transcript, Lilly Archives, p. 6.

[9]G. H. A. Clowes, "The Banting Memorial Address," Proceedings of the American Diabetes Association 7 (1947):53, and Bliss, Insulin, 96.

5). Even though the group had no clinical results and had not even attempted to scale up production yet, Clowes informed them that the company wanted to help in any way possible to advance the research and mass production of insulin.[10] Lilly's offer of assistance, as mentioned in Chapter 3, was a logical extension of both the company's recent policy emphasizing the development of specialties and Clowes' personal belief in the importance of industry-university collaborations. In addition, getting in early on a treatment for a disease for which no satisfactory treatment existed made enormous commercial sense, given the prevalence of diabetes. It was the kind of opportunity that could elevate a company to the upper echelon of the pharmaceutical industry. Thus, even though Toronto's work by late December, 1921, was still inconclusive, Lilly was eager to collaborate.

Macleod informed Clowes that Toronto was not far enough along on insulin research for industrial production of the drug, but he promised to consider the offer from Lilly.[11] Clowes again contacted Macleod three months later, reminding him of Lilly's interest in the insulin work. If Toronto would share the details of the method to produce insulin with Lilly, according to Clowes, the company could supply the University with the hormone for experimental and clinical

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[10]Clowes, "Banting Address," 53; McCormick, "Insulin," 33; and Frederick Banting, "The Early Story of Insulin," in Lilly Research Laboratories: Dedication (Indianapolis: Lilly, 1934), p. 19. For a discussion of the Toronto group's presentation at Yale University, see Bliss, Insulin, 104-106.

[11]J. J. R. Macleod, "History of the Researches Leading to the Discovery of Insulin, with an Introduction by Lloyd G. Stevenson," Bulletin of the History of Medicine 52 (1978):306.

investigations. Moreover, the company would not market insulin until the University of Toronto believed the drug was ready for mass distribution. If Lilly could arrange with Toronto to market insulin, Clowes said, the University could expect to receive royalties. The company was prepared to begin its own research on insulin with or without Toronto's assistance, although Clowes assured Macleod that Lilly preferred the former.[12] Macleod's position had not changed since his meeting in New Haven with Clowes. His laboratory was still working feverishly, in the hopes of publishing a detailed method so that insulin production could begin "elsewhere." If Toronto's failures persisted, they would possibly engage Lilly to help find a solution.[13]

The Toronto group was not incognizant of parties that might and probably would profit from their discovery by taking unfair advantage of the public. Indeed, the history of medicine is replete with examples of medical fraudulence.[14] Macleod and his colleagues took the rather naive approach that publishing a detailed process for making non-toxic insulin preparations would sufficiently protect the public. But such a procedure did not appear in any journals, because the

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[12]G. H. A. Clowes to J. J. R. Macleod, 30 March 1922, "Insulin--Section 5," Lilly Archives.

[13]J. J. R. Macleod to G. H. A. Clowes, 3 April 1922, "Insulin--Section 5," Lilly Archives. By this time the question was not with whom Toronto would collaborate, but whether they would collaborate: ". . . if the time comes for collaboration your firm will receive first consideration" (ibid.).

[14]For example, see James Harvey Young, The Toadstool Millionaires: A Social History of Patent Medicines in America before Federal Regulation (Princeton: Princeton University Press, 1961), and idem, The Medical Messiahs: A Social History of Health Quackery in Twentieth Century America (Princeton: Princeton University Press, 1967).

Toronto scientists never found a reliable method of production to report prior to the collaboration with Lilly. Also, in April, 1922, they began to move towards another means of protection, protection for both the public health and their own research--the patent. As patentees, the Toronto group could control licenses to pharmaceutical firms for the manufacture of insulin. While this would not (and in fact, did not)[15] prevent unlicensed firms from producing pancreatic extracts, it at least would enable the scientists to see that there were safe, effective, and perhaps reasonably priced preparations of insulin on the market.[16] A patent would give Toronto, rather than a commercial interest, a monopoly on insulin, and thereby effect a de facto demonopolized insulin industry: "The patent would not be used for any other purpose than to prevent the taking out of a patent by other persons. When the details of the method of preparation are published anyone would be free to prepare the extract, but no one could secure a profitable monopoly."[17]

Toronto applied for a United States Patent on insulin and a method of preparing it in May of 1922, shortly before representatives from the University and Lilly met to arrange terms for a collaboration. The patent had a profound bearing on the interactions between the University and company, which I will discuss later in the chapter.

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[15]Bliss, Insulin, 175.

[16]Cf. Macleod, "Insulin Preparation," 899.

[17]F. G. Banting, C. H. Best, J. B. Collip, J. J. R. Macleod, and J. G. Fitzgerald (of the Connaught Laboratories) to Robert Falconer (President of the University of Toronto), 12 April 1922, quoted in Bliss, Insulin, 133.

Lilly encouraged Toronto to patent insulin, and offered them counsel on the United States patent application.[18] This advice, combined with Clowes' continuing inquiries about both the status of the Toronto work and the possibility of cooperative research,[19] and Toronto's continuing problems with large-scale production, led the Toronto group to invite Lilly representatives to Toronto for a conference in late May. Clowes, company Vice-President Eli Lilly (1885-1977), a chemist (probably George Walden), and a patent attorney from the Lilly Company[20] forged, with personnel from the University of Toronto, a contract for cooperative research on insulin that was the source of more than a few disputes between the two parties over the next year.

Around the time when the University of Toronto was considering the issues of the insulin patent and collaborative research, the Board of Governors created the Insulin Committee. The Committee, composed of representatives from the Governors, the Connaught Laboratories, and the University faculty,[21] had several functions. For example, it was responsible for licensing companies to produce insulin. The chief responsibility of the Insulin Committee was to oversee quality

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[18]G. H. A. Clowes to J. J. R. Macleod, 30 March 1922 and 11 May 1922, "Insulin--Section 5," Lilly Archives.

[19]G. H. A. Clowes to J. J. R. Macleod, 24 April 1922 and 11 May 1922, ibid.

[20]Bliss, Insulin, 137.

[21]A. E.Gooderham (the Chairman), Robert Falconer, T. A. Russell, and Joseph Flavelle represented the University of Toronto Board of Governors on the Insulin Committee. J. G. Fitzgerald and R. D. Defries were the delegates from the Connaught Laboratories, and the Toronto faculty on the Insulin Committee were Macleod, Banting, Best, and Duncan Graham. The Committee also had a legal advisor.

control for North American insulin producers. As part of this function, the Insulin Committee Laboratory was established early in 1923 to provide the necessary checks for proper standardization and uniformity on commercial products. The Committee also screened advertising by Lilly and other companies producing insulin. In all dealings with the Lilly Company, the Insulin Committee represented the interests of the University of Toronto.[22]

The bulk of the agreement between Toronto and Lilly, dated 30 May 1922,[23] addressed strategies in the exchange of information between the university and company, and how the former would license the latter. Toronto would divulge all they knew about insulin, and send representatives (usually Best and one other scientist) to Lilly to demonstrate personally how to produce and physiologically standardize insulin. A virtual hormonal highway was beaten between Toronto and Indianapolis during 1922; Best claimed that he visited Lilly nine times in that year, and Clowes made as many as 25 trips to Toronto.[24] Lilly could not share information obtained from Toronto with anyone else, although it is difficult to believe that the company would even want to divulge

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[22]"From Sea to Sea and Beyond: Insulin and the University of Toronto, 1921-1948," n.d., 19-page typescript, "Insulin--Section 5," Lilly Archives, pp. 8-12; Best, interview by McCormick, 24 September 1968, p. 23; McCormick, "Insulin," p. 33; and Insulin Committee of the University of Toronto, "Insulin: Its Action, Its Therapeutic Value in Diabetes, and Its Manufacture," Canadian Medical Association Journal 13 (1923):484.

[23]["Contract between Toronto and Lilly"], 30 May 1922.

[24]Best, interview by McCormick, 24 September 1968, p. 6; Clowes, "Banting Address," p. 51; and E. J. Kahn, All in a Century: The First 100 Years of Eli Lilly and Company ([Indianapolis: Lilly, c. 1976]), p. 97.

any of Toronto's data. Lilly was also obligated, as long as it was a licensee, to inform Toronto of any improvements it made in producing insulin. If any of these improvements were patentable, the company had to assign their patents to Toronto, with the exception of patent applications in the United States.[25]

The Lilly Company would have an appreciable head start over its competitors in the nascent insulin industry as the sole collaborator with Toronto. The latter considered it inefficient to collaborate with more than one company. But despite Lilly's retention of rights in the United States, it ceded considerable ground to Toronto--not that it was in a position to offer much opposition; Toronto certainly needed assistance, but there were several capable firms the University could have approached. Toronto had the upper hand. The fact that they were under no obligation to keep their own or Lilly's research secret attests to this. If sensitive information fell into the hands of one of Lilly's competitors, the Indianapolis firm could find itself embattled in a United States patent interference.

Toronto took steps against such a possibility by circulating production details among only a minimum of outsiders. Macleod issued warnings to the few diabetes specialists who received insulin data, to keep this information away from commercial organizations.[26] Clowes,

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[25]["Contract between Toronto and Lilly"], 30 May 1922, pp. 3-4.

[26]J. J. R. Macleod to W. D. Sansum, 21 June 1922, "Potter," Insulin Committee Papers, University of Toronto Archives, Toronto, Canada (hereafter Insulin Committee, Toronto Archives); J. J. R. Macleod to R. T. Woodyatt, 21 June 1922, "Woodyatt," ibid.; and Bliss, Insulin, 270 n. 37.

however, was more concerned with the fact that the Toronto workers were releasing production information to outsiders before Lilly had a chance to supply them:

> . . . information regarding the mode of preparation of [insulin] was given by members of the Toronto group to a few individuals with the result that the procedure was widely known some months earlier than we had anticipated would be the case. . . . . Information about such matters spreads rapidly and most of the men to whom we are now supplying the product have indicated their intention of making it if we could not supply them at once.[27]

The licensure stipulations of the contract established a limited-term exclusive license for Lilly. During a so-called "experimental period," Lilly would have the sole right to produce and sell insulin. The experimental period would last one year, which Toronto could extend if they so desired.[28] Lilly would sell insulin at cost or distribute it gratis, at its own discretion, to a select group of clinicians. Toronto was guaranteed a proportion of Lilly's output, 12-28 percent, depending on whether the company charged for insulin or not.[29] This last clause was probably included because 1) production at the University of Toronto's Connaught Laboratories', which was mostly earmarked for Canadian distribution, was still uneven at best, 2) it assured the Toronto group of avoiding a potentially embarrassing situation--an

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[27]G. H. A. Clowes to J. J. R. Macleod, 5 September 1922, "Lilly and Co.," Insulin Committee, Toronto Archives.

[28]Toronto earlier rejected Lilly's proposal for a two-year experimental period; see J. J. R. Macleod to G. H. A. Clowes, 25 May 1922, "Macleod, Telegram to Clowes, 25 May 1922," XRDzf, Lilly Archives.

[29]["Contract between Toronto and Lilly"], 30 May 1922, pp. 2-3.

insulin drought in Canada while Americans would be receiving the drug,[30] and 3) insulin was, after all, the Toronto group's discovery, and they probably felt this warranted them certain proprietary rights in the development of the discovery.

The terms of licensure also covered the years following the experimental period, when Toronto planned to institute a program of general licensing for the pharmaceutical industry. The University guaranteed Lilly an insulin license for the life of the patent, in exchange for which Lilly (and other licensees) would pay the University of Toronto a 5 percent royalty. Later, I will show that Lilly actually supported insulin research at Toronto decades after the insulin patents expired.[31]

Finally, the Toronto-Lilly contract included somewhat ambiguous statements regarding advertising and publicity of insulin. The University and company would collaborate on how Lilly advertised the drug. Also, Toronto would decide in what way Lilly could use the names of the Toronto scientists in publicizing insulin. The University of

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[30]For example, see J. J. R. Macleod to G. H. A. Clowes, 12 December 1922, "Insulin--Section 7," Lilly Archives: "The [Insulin] Committee feels strongly that it would be important in the next few months to increase considerably the quota of [insulin] distributed in Canada. It feels that otherwise the University of Toronto is open to criticism that this material discovered in Canada is never-the-less much more readily available on your side of the border."

[31]["Contract between Toronto and Lilly"], 30 May 1922, p. 4. The Toronto group planned to use the royalties to support the Insulin Committee Laboratory, and surplus funds would be applied to insulin-related research. None of the workers in Macleod's laboratory personally profited from the royalties, although some did receive compensation from Lilly during the post-patient era. See Macleod, "Insulin Preparation," 899-900, and "Sea to Sea and Beyond," p. 10.

Toronto already had transgressed traditional medical ethics, at least in the eyes of some,[32] by applying for a patent on a medicinal agent. So, Toronto wished to play down their own role in the marketing of insulin, and thereby hopefully avoid any misconceptions that the group was personally profiting from the sale of insulin. Another advertising-related issue concerned Lilly's use of a trade name for insulin, "Iletin". The relevant clause in the contract did not explicitly state that Lilly had the right to use a trade name, but suggested that ". . . upon the termination of this agreement [if Lilly cannot profitably produce insulin] the Trade Name or Names used by [Lilly] in connection with the said extracts [i.e., insulin], shall thereupon become the property of [Toronto]."[33]

Research, Production, and Distribution

The Lilly Company organized its insulin research team, and even produced its first successful lot of the hormone, before signing the contract. The company heads, Josiah K. Lilly, Sr. (1861-1948) and his son Eli, were prepared to invest a quarter of a million dollars to get large scale production rolling. George Walden headed insulin research at Lilly, and Harley W. Rhodehamel, Jasper P. Scott, and

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[32]Even Banting, who went to great lengths to ensure that he received credit for the discovery of insulin, wanted no part in the patent application. Only after considerable persuasion did Banting allow his name to appear on the application; see Bliss, Insulin, 132-133, 177-178. Chapter 3 discusses biomedical scientists and medical patents.

[33]["Contract between Toronto and Lilly"], 30 May 1922, p. 5.

Walden's wife, Eda Bachman, all chemists, assisted in the project.[34]

The clinical evaluation of this scarce and dangerous drug required some thoughtful planning. The collaborators decided that distribution would be limited to jointly selected diabetes specialists during the experimental period. Furthermore, only the most severe cases could receive insulin, because of the uncertainty in production.[35] Clowes organized a clinical advisory committee--the first to use insulin in the United States and Canada--who evaluated questions about the posology, forms of administration, and overall value of the hormone. They also processed all clinical data--a considerable task after 1922, with the rapid expansion of the clinical program. The clinical advisory committee maintained a discreet existence, to avoid both popularizing insulin in the press and offending clinicians not invited to join the committee.[36]

Lilly's strategy was to maintain small-scale (i.e., experimental)

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[34]Kahn, All in a Century, 96-97; McCormick, "Insulin," 34; and J. K. Lilly to G. H. A. Clowes, 4 August 1922, "J. K. Lilly, 1861-1948--Letters to and from Dr. G. H. A. Clowes, 1920-1945," KBLk, Lilly Archives.

[35]["Contract between Toronto and Lilly"], 30 May 1922, p. 2, and Banting, "History of Insulin," 10.

[36]G. H. A. Clowes to J. J. R. Macleod, 12 August 1922, "Insulin--Section 7," Lilly Archives; Clowes to Macleod, 5 September 1922; and [F. M. Allen?] Preface to Journal of Metabolic Research 2, nos. 5 and 6 (1922). The clinical advisory committee consisted of representatives from Toronto and Lilly, and several of the leading American specialists: Elliott Joslin (Harvard Medical School and the New England Deaconess Hospital, Boston), Frederick Allen (Psychiatric Institute, Morristown, New Jersey), Rollin Woodyatt (Otho Sprague Memorial Institute Laboratory for Clinical Research, and the Presbyterian Hospital, Chicago), H. Rawle Geyelin (College of Physicians and Surgeons, and Presbyterian Hospital, New York), John Williams (Highland Hospital, Rochester, New York), and Russell Wilder (Mayo Clinic, Rochester, Minnesota).

projects and mass-production projects simultaneously in Indianapolis. The company also supported insulin research at Woods Hole under Clowes' direction, during his Summers away from Indianapolis. The pharmaceutical firm took quick advantage of Toronto's results, and started a laboratory scale run of insulin on 2 June 1922. Best, probably accompanied by Collip, arrived in Indianapolis five days later to demonstrate personally how to make insulin, as stipulated in the contract. The Lilly researchers learned fast. They successfully produced their first lot of the drug by 17 June. Within a month they were able to devise several useful innovations in the extraction process. For example, Lilly workers used 5 percent of the amount of solvent (alcohol or acetone) Toronto employed in part of their method. The company also improved the procedure by extracting insulin under refrigeration. This helped to inhibit the catalytic deterioration of the active ingredient of the pancreas.[37]

Another problem with producing insulin, which Lilly solved from the start, involved eliminating the solvent used to capture insulin from the pancreas. Too much heat to evaporate the solvent could destroy the active ingredient. The Toronto researchers alleviated the problem by placing shallow pans containing the insulin extract

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[37]On Clowes' insulin work at Woods Hole, see, e.g., G. H. A. Clowes to J. J. R. Macleod, 17 September 1922, "Insulin--Section 7," Lilly Archives. McCormick, "Insulin," 34, Eli Lilly to J. J. R. Macleod, 17 June 1922, "Insulin--Section 6," Lilly Archives, and Clowes, "Banting Address," 55, refer to Lilly's insulin work in early June and to the first visit of the Toronto scientists. On Lilly's initial improvements on Toronto's method of making insulin, see Eli Lilly to Macleod, 17 June 1922, and G. H. A. Clowes to J. J. R. Macleod, 20 June 1922, "Insulin--Section 6," Lilly Archives.

beneath hot coils in a wind tunnel. The process worked, but it was inefficient and dangerous. Lilly was never satisfied with the wind tunnel method, and instead concentrated extracts in vacuum stills. These lowered pressure sufficiently to evaporate the solvent at a low temperature, thus avoiding the possibility of destroying the hormone. Vacuum stills were expensive, however, and the University of Toronto was unable to purchase a still until late in the Summer of 1922.[38]

Lilly's insulin production, maintained on a small scale until the Autumn of 1922, still increased enormously through June, July, and August. Virtually all Lilly insulin not earmarked for experimental studies went to Banting during June and July. In fact, Toronto received nearly 60% of Lilly's output from June through August, far above the amount the company was contractually obligated to provide to the Canadians. Lilly's success came at a very good time, because Toronto's production--which had been struggling for some time--apparently broke down completely in July.[39] Lilly essentially was the sole supplier of insulin during the late Summer and early Autumn of 1922, with the exception of W. D. Sansum of the Potter Metabolic Clinic in Santa Barbara, California, and Woodyatt. Both of these physicians prepared insulin for their own patients, according to Toronto's

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[38]G. H. A. Clowes to F. G. Banting, 18 July 1922, F. G. Banting Papers, Thomas Fisher Rare Book Library, University of Toronto (hereafter Banting Papers, Fisher Library); Best, interview by McCormick, 24 September 1968, pp. 7, 13; and Bliss, Insulin, 133-134. On the events surrounding Toronto's purchase of their vacuum still, see ibid., 147-149.

[39]Clowes to Macleod, 12 August 1922.

publications and directions provided by Macleod.[40] The collaborators expanded the clinical testing program in August, to include the American members of the clinical advisory committee and four other medical centers. Thus, by the end of August a total of twelve groups representing eight states and one Canadian province were involved in the clinical side of the insulin project. Banting, the least experienced in diabetes treatment of all the participating physicians, received the most insulin from Lilly, an average of over 550 units[41] per week from late July through August. The leading diabetes specialists, Joslin and Allen, received much more insulin from Lilly during August than any other American physicians--more than 150 units per week each--although this was still well below Banting's complement.[42]

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[40]Clowes to Macleod, 5 September 1922. On the background and purpose of Sansum and Woodyatt's interest in insulin manufacture, see n. 26, and R. T. Woodyatt to J. J. Macleod, 10 May 1922, "Woodyatt," Insulin Committee, Toronto Archives; J. J. R. Macleod to R. T. Woodyatt, 15 May 1922, ibid.; W. D. Sansum to J. J. R. Macleod, 15 June 1922 and 16 February 1923, "Potter," Insulin Committee, Toronto Archives.

[41]The insulin unit was an arbitrary measure of the potency of the hormone, derived from physiological assays on rabbits. It was based on the amount of sample required to produce convulsions (i.e., lowering the blood sugar to such a point of convulsions) in a non-diabetic rabbit within a certain time.

[42]The data on Lilly's production are from G. H. A. Clowes, "Report on Iletin," n.d., three-page typescript, "Insulin--Section 6," Lilly Archives; see also McCormick, "Insulin," 34. On the early planning of the clinical program by Toronto and Lilly, i.e., who would be involved and how much insulin each would receive, see, e.g., Eli Lilly to Macleod, 17 June 1922, J. J. R. Macleod to [R. D. Defries], 14 July 1922, J. J. R. Macleod Papers, Thomas Fisher Rare Book Library, University of Toronto, Toronto, Canada (hereafter Macleod Papers, Fisher Library); Clowes to Banting, 18 July 1922; J. K. Lilly to J. J. R. Macleod, 22 July 1922, "Insulin--Section 6," Lilly Archives; J. K. Lilly to G. H. A. Clowes, 8 August 1922, "J. K. Lilly, 1861-1948--Letters to and from Dr. G. H. A. Clowes, 1920-1945," XBLk, Lilly Archives; and Clowes to Macleod, 12 August and 5 September 1922.

Assembling clinical personnel to evaluate insulin led to some disagreements between Toronto and Lilly. The contract stipulated that Lilly and Toronto together would choose the clinicians to receive insulin during the experimental period. Clowes interpreted the agreement differently. Of the first one to two dozen physicians who took part in the clinical program, Clowes sought the Insulin Committee's permission to supply only those who received an appreciable amount of insulin (100 units or more weekly). The Insulin Committee was unaware that Lilly was supplying about a half-dozen fairly inexperienced physicians with 50 to 100 units of insulin. When Macleod voiced his disapproval of this procedure, Clowes retorted in characteristic fashion. In the first place, he explained that knowing the kinds of problems that confronted an inexperienced doctor using insulin therapy would be helpful later, when insulin became available to the general medical public.

Second, Clowes assumed that, as long as the collaborators had a solid group of investigators working on insulin (Joslin, Allen et al.), a few more physicians in the testing program need not warrant approval from Toronto. Third, he believed the contract should not be interpreted rigidly anyway; it should "be handled as a sort of gentlemen's agreement." Finally, Clowes admitted that Lilly feared physicians would start manufacturing their own insulin, or would collaborate with other firms to produce the drug, if Lilly could not supply them. The company's motivation here, to inundate the market during the experimental period, will be discussed in detail in a later section. Clowes' arguments may have explained the company's procedure, but after September of 1922, Lilly made sure to obtain the Insulin Committee's

approval before adding new names to the list of clinical investigators.[43]

Lilly continued to increase its insulin output during September, almost doubling their production from June through July.[44] Qualitatively, however, Lilly already had begun to experience difficulties. By mid-September, clinical results revealed that Lilly's insulin lots produced in late August were less than half as strong as earlier lots. Clowes attributed the loss in potency to errors in standardization, since Lilly workers diluted the extract to the desired strength, on the basis of bioassay results. Impurities began to creep into the Lilly product at the same time. Clowes believed this was due to a reagent too weak to precipitate unwanted proteins and other substances out of the insulin solution. He could not settle the problems unequivocally until he returned to Indianapolis from Woods Hole, but Clowes was confident enough in September to inform Toronto that his company was ready to swing into mass production around 1 October: "You may rest assured that the industrial problem has virtually been solved and that we shall be able to produce [insulin] in very large amounts in the near future."[45]

The problem was far from solved. Although Clowes felt the manufacturing process was not the source of the loss in potency, he really

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[43]Clowes to Macleod, 5 and 17 September 1922.

[44]Clowes, "Report on Iletin," and McCormick, "Insulin," 34.

[45]G. H. A. Clowes to J. J. R. Macleod, 17 (quotation) and 23 September 1922, "Insulin--Section 7," Lilly Archives, and Clowes, "Report on Iletin."

had little on which to base this assumption. The company ceased performing stability tests on insulin lots in August, according to Clowes. First, he argued that the clinical demand for insulin was too great to withhold samples for experimental work or to pull employees off production work, especially after the breakdown in production at the Connaught Laboratories. Second, even if there were a chance of deterioration, physicians would use the drug soon. Clowes learned in mid-October, upon analyzing a sample from an early lot produced by a scaled-up method, that the problem with diminishing strength of insulin was indeed due to the manufacturing process. The insulin deteriorated even before it left the plant. So, Lilly switched to a different large-scale method, which produced a stable product but had a small yield.[46]

That Lilly abandoned stability testing because physicians would use insulin soon was an unacceptable excuse. Clowes knew very well that stability considerations are an important part of quality control. But the question of demand for the drug was a more complex issue. The late Summer and early Fall was a chaotic time--to some extent a self-imposed chaos--for Toronto and Lilly. Both were overextending themselves, expanding the clinical program at a rate beyond their capacity to fulfill the demand for insulin. Toronto's production was struggling, and Lilly was hard pressed to pick up the University's slack. The company was trying to fill Banting's complement of the drug, and maintain the other clinicians' supplies too, while it was

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[46]G. H. A. Clowes to J. J. R. Macleod, 20 October 1922, "Insulin--Section 6," Lilly Archives.

strapped to either a small scale process or a poor industrial scale method of producing insulin. The ethical dilemma in this issue--whether or not the collaborators should distribute a product of undetermined stability--is too tangential to address here. But the point is that this was certainly a decision that Toronto and Lilly should have made together, in the spirit of a true collaboration. In any case, the issue soon became academic, because during the Fall of 1922 Lilly was working out a method that drastically improved insulin production.

The person most responsible for turning Lilly's production around, in the Fall of 1922, was George B. Walden. Walden joined the company in 1917, the same year that he received the Bachelor of Science degree from Franklin College in Indiana. At Woods Hole, Clowes introduced Walden to studies that the latter would use to refashion insulin manufacture.[47] The renowned physiologist Jacques Loeb recently had carried out important fundamental work at Woods Hole on the nature and importance of isoelectric points of proteins. Proteins and their constituent parts, amino acids, have the ability to behave as either acids or bases, depending on the circumstances. The isoelectric point of an amino acid or protein is that pH (a measure of hydrogen ion concentration) of the solvent at which the amino acid or protein has a balanced positive and negative charge. For example, the substance will not move to a positive or negative cathode in an electrical field. At the

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[47]Roscoe Collins Clark, Threescore Years and Ten: A Narrative of the First Seventy Years of Eli Lilly and Company, 1876-1946 ([Indianapolis: Eli Lilly], 1946), p. 59, and M. E. Krahl, "Obituary: George Henry Alexander Clowes, 1877-1958," Cancer Research 19 (1959):335.

isoelectric point, proteins are "less soluble [than at any other pH] and more readily coagulated and more readily salted out."[48]

Loeb showed that one could determine the isoelectric point of a protein in solution by plotting certain physicochemical properties of the protein, such as osmotic pressure, as a function of pH of the solvent. The isoelectric point occurred at the pH corresponding to the minimum values of any of these properties. For example, the osmotic pressure of a protein solution will decrease as the pH is increased, but beyond a particular pH, the osmotic pressure will increase; that particular pH is the isoelectric point of the protein. By examining several physicochemical properties, one can arrive at a fairly narrow range on the pH scale within which the isoelectric point lies.[49]

Walden applied the method of isoelectric precipitation to ipecac, squill, and some other medicinals at least a year before he began working on the isoelectric point of insulin. It took him a few months to perfect the process for insulin production, but by November Lilly was ready to apply isoelectric precipitation on a mass scale.[50] Walden discovered that the problems with deterioration of the insulin

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[48]Roger J. Williams, A Textbook of Biochemistry (New York: D. Van Nostrand, 1938), p. 101.

[49]Jacques Loeb, Proteins and the Theory of Colloid Behavior (New York: McGraw-Hill, 1922); see also W. J. V. Osterhout, "Jacques Loeb," Journal of General Physiology 8 (1928):xlv-l.

[50]G. H. A. Clowes, "Report of Scientific Research Work for Year Ending November 1st, 1921," 18-page typescript, "G. H. A. Clowes--Report of Scientific Research Work, Year Ending 1 Nov. 1921," XRDe, Lilly Archives, p. 14; Best, interview by McCormick, 24 September 1968, p. 15; and Eli Lilly and Company, General Letter No. 30, 6 April 1923, "General Letters to Salesmen Regarding Iletin, 1 Nov. 1922-9 Oct. 1923," Lilly Archives.

solutions and impurities had been due to the slow formation of an insulin-bearing precipitate from the solution, leaving some of the hormone and impurities in the latter. The aim of the Walden process was to stimulate as much precipitation as possible. He started with the old process. This essentially consisted of extracting insulin directly from the pancreas with some solvent, continuing the extraction with a more concentrated solvent, and evaporating the solvent so that insulin could be transferred to an aqueous solvent for delivery to the patient. Walden adjusted the pH of the insulin solution to what he determined to be the isoelectric point, between 4.5 and 5.3, and he let the solution stand for about a week. After collecting the precipitate, he readjusted the pH of the solution to the isoelectric point, obtaining as much additional precipitate as possible. He dissolved the precipitates in water, and adjusted the pH of the aqueous insulin solution so it fell outside of the isoelectric point.[51]

Walden's method markedly bettered the yield and purity of insulin, in addition to the stability. Theretofore, workers customarily discarded the insulin-containing precipitate during extraction. Isoelectric precipitation also solved the difficulties with manufacturing pure insulin: ". . . this purity is so great that out of several hundred patients to whom [insulin] has so far been administered, including some who exhibited sensitization effects with the best

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[51][George Walden], untitled report on the manufacture of insulin by isoelectric precipitation, n.d., nine-page typescript, attached to J. J. R. Macleod to H. H. Dale, 17 January 1923, 1092/23, Medical Research Council Records, National Institute for Medical Research, London.

product previously obtainable, not a single instance of sensitization or any other deleterious effect has been reported."[52]

Walden was not the only person in the early 1920s working on the isoelectric precipitation of insulin. Collip apparently investigated this subject for a time, but he had no success.[53] A biochemist at Washington University School of Medicine in St. Louis, Philip Shaffer, developed the isoelectric precipitation of insulin independently of Walden. Shaffer's interest in diabetes arose from his research, begun around 1910, on blood and urine analysis. When Banting and his associates announced their discovery, Shaffer tried unsuccessfully to obtain from Toronto some of the hormone for testing. Consequently, Shaffer's group started to produce insulin themselves, and in the course of their research discovered what Walden had found at about the same time. Shaffer and a colleague announced their discovery at the annual meeting of the American Society of Biological Chemists in Toronto, late in December of 1922. Shaffer's discovery was especially important to Toronto, as a means of blocking Lilly's attempt to monopolize the insulin market in the United States (see below).[54]

The improved process began to manifest a dramatic impact on insulin output late in the Fall of 1922. Also at this time, the University of Toronto Insulin Committee and the informal clinical advisory committee met in Toronto to work out a strategy for an efficient clinical

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[52]Ibid. (quotation on p. 6), and McCormick, "Insulin," 35.

[53]Bliss, Insulin, 274 n. 54.

[54]Edward A. Doisy, "Philip Anderson Shaffer," Biographical Memoirs of the National Academy of Sciences 40 (1969):321-336.

study of insulin in the least possible time. The participants charged certain clinics to examine particular problems associated with insulin therapy. They also decided to publish the first extensive clinical results with insulin together in a special issue of the Journal of Metabolic Research.[55]

Lilly was at the point where it could more than furnish insulin to the investigators in the clinical program. So, the Insulin Committee asked the company to increase the allotments to the cooperating clinics. For example, in December, 1922, Lilly was prepared to supply Toronto alone with 8,000-10,000 units weekly. By January the Connaught Laboratories were able to exploit Lilly's manufacturing advances, and the two were supplying insulin to about 250 physicians in 60 clinics. Two months later, Lilly alone supplied at least 100 clinics, producing nearly 300,000 units weekly for American and Canadian consumption. This was still at a time when the government did not control trials of experimental drugs. Clowes' declaration in March, 1923 spoke as much for his hard-sell approach for a Lilly insulin monopoly as it did for his company's technical accomplishments in the past few months:

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[55]McCormick, "Insulin," 34-35, and Banting, "History of Insulin," 10. The clinical reports, covering about 600 cases, appeared as the fifth and sixth numbers (November-December, 1922) in the Journal of Metabolic Research 2(1922):547-985; these issues were not actually published, however, until May of 1923, due to the clinicians' delays in getting data to the journal. Appearing in the issues were papers by Banting and his associates in Toronto, and other groups headed by Joslin, Wilder, Williams, Geyelin, Woodyatt, and Allen; a group from the Peter Bent Brigham Hospital in Boston--Reginald Fitz, William Murphy, and Samuel Grant--also contributed an article. Clowes had suggested collecting the early results in a special number of this journal a few months prior to the Toronto clinical conference (Clowes to Macleod, 12 August 1922).

". . . our over-production is now so tremendous that you can assure the Toronto Committee that there is not the remotest chance of our having any difficulty in supplying any amount that may be required, not only in the United States and Canada, but throughout the entire civilized world . . ."[56]

The number of clinical groups increased from the Fall of 1922 to the Spring of 1923, but the increase in distribution was not nearly as rapid as Lilly wanted. According to the contract of 30 May, Toronto and Lilly were supposed to collaborate on the selection of physicians for the clinical testing program. But the Insulin Committee continually rebuffed the pharmaceutical firm's requests for a much more extensive distribution of insulin during the experimental period. Toronto was waiting for the preliminary clinical reports to appear in print (see note 55), and for the establishment of a sufficient number of insulin instructional centers in major diabetes clinics, to educate the medical community about this new and potentially dangerous drug.[57] Lilly abided by Toronto's decision, holding its sales force at bay with circulars that cautioned against volunteering information on

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[56]Macleod to Clowes, 12 December 1922; G. H. A. Clowes to J. J. R. Macleod, 14 December 1922, "Insulin--Section 7," Lilly Archives; Eli Lilly and Company, General Letter No. 13, 20 February 1923, "General Letters to Salesmen Regarding Iletin, 1 Nov. 1922-9 Oct. 1923," Lilly Archives; McCormick, "Insulin," 35; Banting, "Story of Insulin," 19; G. H. A. Clowes to H. H. Dale, 16 March 1923, 1092/23, Medical Research Council Records, National Institute for Medical Research, London; and G. H. A. Clowes to J. J. R. Macleod, 2 March 1923, "Unitage and AMA on 'Iletin'," Lilly Archives (quotation).

[57]Minutes of the meeting of the Special Advisory Committee on Diabetes (hereafter Insulin Committee minutes), 14 February and 5 March 1923, Insulin Committee, Toronto Archives, and G. H. A. Clowes to J. J. R. Macleod, 23 February 1923, "Insulin--Section 8," Lilly Archives.

insulin to physicians.[58] The most important criterion employed for the expansion of the clinical program was the physician's access to adequate clinical and laboratory facilities for metabolic disorders. Hence, most of the cooperating physicians chosen early in the program were attached to university clinics or well established hospitals. The collaborators also had to supply the drug to the family physicians of patients discharged from distant diabetes clinics. Independent group clinics began to play an active part in the testing of insulin by the late Winter or early Spring of 1923. However, fearing that many of these clinics existed primarily for business reasons (as opposed to existing for the sake of efficiency), Macleod wanted to be absolutely sure that such clinics had proper facilities.[59]

The clinical results with insulin by the end of the experimental period mirrored Henry Dale and H. W. Dudley's assessment of the drug's therapeutic application seven months earlier: "These practical difficulties being clearly recognized as compromising the value of the treatment, we are left with the impression that the clinical application of insulin has, nevertheless, been brilliantly successful in its

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[58]See, e.g., Eli Lilly and Company, General Letters Nos. 141 (1 November 1922) and 24 (29 March 1923), "General Letters to Salesmen Regarding Iletin, 1 Nov. 1922-9 Oct. 1923," Lilly Archives.

[59]Macleod to Clowes, 12 December 1922; J. J. R. Macleod to G. H. A. Clowes, 10 January 1923, "Unitage and AMA on 'Iletin'," Lilly Archives; Insulin Committee minutes, 14 February and 5 March 1923; Lilly, General Letters Nos. 13 (20 February 1923) and 24 (29 March 1923); and J. J. R. Macleod to G. H. A. Clowes, 10 March 1923, "Lilly and Co.," Insulin Committee, Toronto Archives. On the formation of group clinics as a means of economizing in the early 20th century, see George Rosen, The Structure of American Medical Practice, 1875-1941, ed. Charles E. Rosenberg (Philadelphia, University of Pennsylvania Press, 1983), pp. 53-55.

general result."[60] Toronto maintained restrictions on the distribution of insulin through the Summer and early Fall of 1923. Finally, the Insulin Committee permitted Lilly to offer the drug through general distribution, beginning October 15th.[61]

Confrontations During the Experimental Period

Lilly, as mentioned above, desperately wanted to distribute insulin on a much wider scale than Toronto had planned. To some extent, Lilly's motivations had an altruistic component, to supply dying diabetics with this drug. President J. K. Lilly's proclamation at finding his company in the middle of this historic research illustrates this sense of humanitarianism: "I am almost overwhelmed with this tremendous situation, and experience some difficulty in keeping my feet on the ground and my brain in normal operation."[62] But profit clearly was the driving force for Lilly to spread insulin. Toronto guaranteed Lilly's exclusive license for only one year; having a short-term monopoly on a drug with a restricted distribution was hardly an ideal commercial situation, but Lilly made the best of it. The basic strategy,

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[60]H. H. Dale and H. W. Dudley, "Report to the Medical Research Council on Our Visit to Canada and the United States, Chiefly to Examine the 'Insulin' Treatment of Diabetes," 30 October 1922, 1092/23, Medical Research Council Records, National institute for Medical Research, London, p. 5. The "practical difficulties" were 1) insulin had to be administered indefinitely, 2) there was no other dosage form yet available besides the hypodermic injection, and 3) impurities in the extract were causing reactions in some patients.

[61]Eli Lilly and Company, General Letter No. 88, 9 October 1923, "General Letters to Salesmen Regarding Iletin, 1 Nov. 1922-9 Oct. 1923," Lilly Archives.

[62]Lilly to Clowes, 4 August 1922.

according to J. K. Lilly, was to "create [insulin] centers in every possible place, thus securing priority and cementing the doctors to us."[63]

Lilly cemented the doctors in two ways. The contract of 30 May 1922 left it entirely up to Lilly to offer insulin free to the participating clinics, or to charge cost for the drug. The company circulated insulin gratis from June through most of January, 1923. It considered switching to distribution at cost as early as September, 1922, but decided otherwise.[64] Of course, this approach put it deep into debt during the early months of the collaboration, but the company was planning for post-experimental period supremacy in the insulin market. If Joslin's experience was indicative, Lilly's decision paid off. Joslin affirmed his allegiance to Lilly insulin in an address at the company's dedication of its new research laboratories; he specifically mentioned that he routinely reminded salesmen of competing companies how his clinic received free insulin from Lilly for several months.[65]

The second way Lilly tried to assure itself of superiority in the future insulin market was by establishing a trade name for their product, "Iletin," early in the collaboration. The available evidence

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[63]J. K. Lilly to Eli Lilly, 23 January 1923, "Insulin--Section 8," Lilly Archives.

[64]G. H. A. Clowes to J. J. R. Macleod, 27 September 1922, "Insulin--Section 6," Lilly Archives, and Insulin Committee minutes, 30 September 1922, Insulin Committee, Toronto Archives.

[65]J. K. Lilly to Eli Lilly, 23 January 1923; G. H. A. Clowes to J. J. R. Macleod, 20 December 1922, "Insulin--Section 8," Lilly Archives; McCormick, "Insulin," 35; and Elliott Joslin, "Address by Dr. Elliott P. Joslin," in Lilly Research Laboratories: Dedication (Indianapolis: [Lilly], 1934), p. 40.

suggests that Toronto not only consented to Lilly's use of a trade name, but recommended "Iletin", based on a term Banting and Best originally coined for insulin (isletin). The Toronto workers themselves used "Iletin" on occasion.[66] Lilly had been labelling their shipments to Toronto as Iletin for over three months when, in September of 1922, Henry Dale finally clued in the Insulin Committee on the real implications of the trade name:

> The Lilly game, which these people [i.e., the Insulin Committee] could not understand, seems to me now perfectly obvious. If they can make use of their start [i.e., the experimental period] to get the name "Iletin" used by all the clinicians as the name for the hormone they will easily upset the patent, get clear of control, and snap their fingers at competition.[67]

Dale, unlike the Toronto workers, was very familiar with the tactics of a pharmaceutical firm. Burroughs Wellcome and Company hired him in 1904, where he remained for a decade; he spent most of his time there as Director of the Wellcome Physiological Research Laboratories.[68]

In a meeting on 30 September 1922 between Banting, Best, Macleod, R. D. Defries (of the Connaught Laboratories), Dale, and Clowes, the

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[66]Dale and Dudley, "Report," p. 7; G. H. A. Clowes to J. J. R. Macleod, 14 March 1923, "Lilly and Co.," Insulin Committee, Toronto Archives; Bliss, Insulin, 71-72, 174; and Macleod to Clowes, 12 December 1922.

[67]H. H. Dale to Walter Fletcher, 26 September 1922, 1092/23, Medical Research Council Records, National Institute for Medical Research, London.

[68]Bliss, Insulin, 146; J. K. Lilly to Macleod, 22 July 1922; Dale to Fletcher, 26 September 1922; and Dale and Dudley, "Report," p. 7. On Dale see W. Feldberg, "Henry Hallett Dale, 1875-1968," Biographical Memoirs of the Fellows of the Royal Society 16 (1970):77-174 (pp. 92-102 cover his years at the Wellcome Physiological Research Laboratories).

participants agreed only as to how the name "Iletin" would be used in the upcoming clinical reports. The authors would use "Insulin" in the titles of their papers and in the text when referring to the hormone, "'Iletin' being used only when details of case histories was [sic] given."[69] The meeting closed with no decision on Lilly's use of the trade name as a means of curbing competition from other firms. The issue did not reappear until December 29th, when the Insulin Committee apparently had to remind Clowes of their earlier agreement. Presumably, clinicians had sent reports to Toronto using the word "Iletin" where they should have used "insulin." More important, on the following day the Insulin Committee and Clowes reached a wider understanding on Iletin. Clowes agreed that Lilly would stop using Iletin altogether. Within a week J. K. Lilly fired off a memorandum to Clowes, informing him of the fundamental necessity of a trade name wherever competition existed. Clowes passed on the memo to the Insulin Committee, saying that he had little influence on the issue since the trade name was a business matter. The company had no plans to relinquish its trademark. What Lilly would do, however, was label its product "Iletin (Insulin, Lilly)."[70]

Legally, Toronto was on shaky ground. Lilly could have pointed to the contract as its right to establish a trademark for insulin,

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[69]Insulin Committee minutes, 30 September 1922.

[70]J. K. Lilly to G. H. A. Clowes, 3 January 1923, "Unsorted," Insulin Committee, Toronto Archives; G. H. A. Clowes to J. J. R. Macleod, 8 January 1923, "Unitage and AMA on 'Iletin'," Lilly Archives; Macleod to Clowes, 10 January 1923; Lilly, General Letter No. 13, 20 February 1923; Clowes to Macleod, 14 March 1923; and Bliss, Insulin, 178-179.

although I have not seen any evidence suggesting that Lilly did this. The company did not take a more active stance on Iletin because 1) it was pushing hard for an extension of their exclusive license, and 2) Iletin could become an academic issue, since Lilly was in the process of filing a patent on its isoelectric precipitation method. If granted, it would essentially make the Toronto patent obsolete in the United States, giving Lilly a monopoly on American production.

Clowes petitioned Toronto to extend the experimental period as early as September. In the first place, he argued that Toronto should extend the exclusive license beyond 30 May 1923 so that Lilly could recoup its research and development expenses. That Lilly insisted on offering insulin free did not help Clowes' argument. Second, Clowes claimed the problems in production at Toronto forced Lilly to pick up the slack, which in turn delayed its experimental work by about two weeks. Clowes felt this put his company at a considerable disadvantage, because Lilly "knew that others were working on the problem [of insulin manufacture]," and because Macleod disclosed Toronto's method "to a few individuals with the result that the procedure was widely known" sooner than Lilly would have wanted.[71] As mentioned above, Toronto was not obligated under the contract to withhold information from others. But Macleod nonetheless cautioned those to whom he sent the process to keep the information away from other drug companies. Clowes may have had some reason to be concerned, but his concerns were exaggerated.

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[71]Clowes to Macleod, 5 September 1922.

Four months later J. K. Lilly made a bid, not just for an extension of the experimental period, but for a permanent exclusive license for his company. This, Lilly argued, would be in the best interest of Toronto and the diabetics, because without competition his company could ". . . produce at lowest cost, test at lowest cost, sell at lowest price, and be able to give, without charge, much larger quantities for indigent cases." With their strong stance against allowing their discovery to be monopolized, the University of Toronto was not about to entertain an offer of anything more than a temporary extension of the exclusive license. However, Lilly's argument that Toronto would only have to oversee one company in the case of a permanent exclusive license probably had some appeal to the Insulin Committee. We will see in the next chapter that Harvard refused to supervise any manufacturers of liver extracts other than Lilly for this very reason.[72]

As the end of the experimental period crept closer, Clowes' arguments for an extension grew increasingly frank and involved. First, he urged Toronto to continue the experimental period and not issue additional licenses, because Lilly could meet any demand for insulin. The University was not likely to pay much attention to this argument. Second, Clowes advocated restricting insulin distribution through the remainder of 1923, which "would mean that during the current year no additional licenses would be issued in the United States . . . ."[73] He believed such a restriction was necessary because of the possibility

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[72]J. K. Lilly to Clowes, 3 January 1923.

[73]G. H. A. Clowes to J. J. R. Macleod, 7 March 1923, "Lilly and Co.," Insulin Committee, Toronto Archives.

that the public might obtain insulin directly from the pharmacist without a doctor's prescription, and because the company was not yet certain of the stability of its product. Third, the company needed an extension to recover their expenditures on insulin research and development. It would not be possible to accomplish this goal by May 30, the last day of the experimental period. The collaborators had agreed earlier that general distribution could not begin until the clinical reports appeared in print, tentatively in November and December of 1922. But by March of the following year, the reports still had not appeared. This delay, according to Clowes, made it impossible for the company to "saturate" the United States with their product. So, Clowes argued that Lilly needed a six-month monopoly on insulin to recover their investment in insulin.[74]

Clowes also claimed that it would simply be unfair to Lilly if Toronto refused to extend the experimental period, and issued licenses to other firms. Those firms could take advantage of Lilly's improvements without having to make the same investments. Finally, Clowes reminded the Insulin Committee how much his company contributed to the project. He said Lilly was entitled to an advantage in the insulin market.[75]

Even though Clowes' arguments may have had some validity, they must have been confusing to the Insulin Committee because they

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[74]Ibid., G. H. A. Clowes to R. D. Defries, 13 March 1923, "Lilly and Co.," Insulin Committee, Toronto Archives; and Clowes to Macleod, 14 March 1923.

[75]Clowes to Macleod, 14 March 1923.

Figure 15. George Henry Alexander Clowes (1877-1958), Director of Research at Eli Lilly and Company from 1919 to 1946 (from Journal of Surgical Oncology 18 (1981):198; UW neg. no. 10270 C-3).



contained several inconsistencies. For example, the Lilly Research Director mentioned the need to continue restricting the distribution of insulin (at cost). Yet, he complained that the delay in publishing the reports (and in initiating a widespread distribution of insulin) prevented Lilly from recovering its expenditures. Also, Clowes cited the need for more data on the stability of the Lilly product as a reason for continuing the experimental period. But his letters earlier in the year claimed that the isoelectric precipitation process solved the stability problems.

But there was a deeper problem. Even if Clowes' arguments had been more lucid, it is doubtful he could have convinced the University to extend the exclusive license. Toronto and Lilly had inherently different conceptions of what the experimental period was and what it was supposed to accomplish. For Toronto, the experimental period primarily was a time to perfect the manufacture of insulin and to collect all the clinical data on the drug possible within about a year. The data collection obviously depended on the success of the manufacturing process. I have already mentioned Toronto's strong feelings against monopolies and against the commercialization of medical discoveries. These kinds of feelings were not at all unusual among academic biomedical researchers in North America at this time (see Chapter 3). Yet the Insulin Committee made a big mistake, because they naively assumed that Lilly, too, had the diabetic in mind above all else. With Lilly's long history as a respectable drug manufacturer, and with its recent hiring of a major scientist who was given at least some free time for fundamental research, one can perhaps appreciate how the academics

could have misconstrued Lilly's intentions. On the other hand, the University workers did not exercise much prudence in the matter of the trade name; Toronto not only affirmed Lilly's right to a trademark, they encouraged it. It was difficult, however, for Toronto to discern Lilly's long-term commercial goals when they signed the pact.

The pharmaceutical firm informed the University of Toronto very early in the collaboration that it wanted, and perhaps even expected, a head start (in the form of a trademark) on the competition in the insulin market. Eli Lilly and Clowes emphasized that Toronto was aware of this and even consented to it prior to concluding the contract.[76] The appearance of a clause in the contract specifically addressing the company's use of a trade name supports this contention. Moreover, Toronto should have realized that Eli Lilly and Company depended on the sale of pharmaceuticals for its livelihood. True, Lilly was one of the more scientifically oriented firms. But bottom-line reasoning rested in business interests, and the company expected a return on its investments. So the experimental period, from the standpoint of Lilly, was an opportunity to fulfill all possible demand with its brand of insulin, "cement" the doctors, and head off competition before the race even started. Unfortunately for the company, though, it was beginning to lose sight of the fact that the experimental period represented another opportunity: the chance to show that it could collaborate well with a university. If the insulin collaboration went smoothly and productively, it would establish a precedent for other

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[76]G. H. A. Clowes to J. J. R. Macleod, 14 April 1923, "Unitage and AMA on 'Iletin'," Lilly Archives.

academic workers to turn to Lilly for assistance in the development of new and profitable drugs. By March and April of 1923, neither Toronto nor Lilly was acting in a spirit conducive to the encouragement of future collaborations of this sort.

Macleod telegraphed Clowes on 16 March, informing him that the Insulin Committee rejected Clowes' petitions for an extension of the experimental period, for several reasons. The University of Toronto had already published statements that they would license additional firms once the manufacturing process was perfected,[77] and they felt the latter was finally effected. The Insulin Committee had received "insistent requests" from some pharmaceutical firms for licenses. Also, the Medical Research Council, whom the Toronto group had licensed to supervise insulin production in Britain, already granted licenses to several firms there. The belief that competition, rather than a monopoly, would see as much insulin as possible produced in the shortest time at the lowest possible price, entered into the group's decision, too. Finally, the Insulin Committee feared criticism from many sides, that they were favoring one company over others, if they extended the license.[78]

What ensued were several turbulent weeks of moves and countermoves involving the "collaborators," Shaffer of Washington University, and the Council on Pharmacy and Chemistry of the American Medical

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[77]See, e.g., Macleod, "Insulin preparation," 899-900.

[78]Insulin Committee minutes, 16 March 1923, Insulin Committee, Toronto Archives, and J. J. R. Macleod to G. H. A. Clowes, 16 March 1923, "Lilly and Co.," ibid.

Association. Walden filed a patent application in the United States on his isoelectric precipitation process two weeks prior to Macleod's telegram. Under the terms of the agreement of 30 May 1922, this was perfectly acceptable. The Insulin Committee requested several changes in the application, even though they had no contractual right to do this. They felt the application was so broad in its claims that, if granted, it would essentially defeat the Toronto patent application and give Lilly an American monopoly on insulin.[79] A comparison of the patent of Banting, Best, and Collip, and that of Walden, confirms the Insulin Committee's fears.[80] The Toronto patent, which runs two and one half pages, briefly describes the steps used to extract insulin from the pancreas. It makes eight claims for the pancreatic extract and the method used to collect it. Walden's patent, covering more than six pages, makes thirty product and process claims. He repeatedly mentions the superiority of his process, in terms of yielding a pure and stable pancreatic extract, over all previous methods.

The Lilly Company, despite Clowes' promise to the contrary, did

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[79]Insulin Committee minutes, 14 February 1923, and Clowes to Macleod, 7 March 1923.

[80]Frederick G. Banting, Charles Herbert Best, and James Bertram Collip, "Extract Obtainable from the Mammalian Pancreas or from the Related Glands in Fishes, Useful in the Treatment of Diabetes Mellitus, and a Method of Preparing It," United States Patent 1,469,994, patented 9 October 1923, and George B. Walden, "Purified Antidiabetic Product and Process of Making It," United States Patent 1,520,673, patented 23 December 1924. I am comparing here the patents themselves rather than the patent applications, which I have not seen. By March of 1923, the Toronto group already had filed a substitution (12 January 1923) for their original application of 22 May 1922. Walden, however, filed a substitution on 11 June 1924 for his original application of 2 March 1923.

not revise its patent application according to the wishes of the Insulin Committee.[81] The Toronto group then faced the problem of protecting themselves. This was not the first time Toronto felt threatened by a Lilly patent application. The company drew up an application, in late August or early September of 1922, to cover its developmental work in the three previous months and to protect itself against American competition. When some of the Toronto workers began to grumble, Clowes tried to explain away the patent application as nothing more than a formality, although he thought the Lilly counsel may have gone a bit too far: "It was drawn up by one of our patent attorneys who apparently was anxious to get everything possible into it and whose zeal was superior to his discretion. It is really a purely technical procedure and in my opinion has little or no value especially in the light of recent developments."[82] Not convinced that the application was next to worthless, the Insulin Committee asked Lilly to reword its patent application, so that it would not appear to threaten Toronto's application. The conflict subsided as Lilly's patent application fell into desuetude, probably because the "recent developments" Clowes referred to dealt with the isoelectric process.[83]

In April, Toronto launched an attack on both Iletin and the iso-

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[81]Insulin Committee minutes, 14 February and 2 April 1923, Insulin Committee, Toronto Archives.

[82]Clowes to Macleod, 23 September 1922.

[83]Clowes to Macleod, 5, 23, and 27 September 1922; G. H.A. Clowes to C. H. Best, 12 September 1922, "Lilly and Co.," Insulin Committee, Toronto Archives; Insulin Committee minutes, 30 September 1922; and Dale and Dudley, "Report," p. 7.

electric precipitation patent. Representatives of the Insulin Committee conferred with Philip Shaffer, the biochemist at Washington University in St. Louis who had independently discovered the isoelectric precipitation procedure. Shaffer agreed to file a patent on his discovery, which the Insulin Committee hoped would interfere with Lilly's patent application.[84] Meanwhile, the Committee informed the Council on Pharmacy and Chemistry of the American Medical Association that they did not approve of Lilly's use of "Iletin."[85] This step, like a patent interference from Shaffer, presented potentially damaging consequences to the pharmaceutical firm's anticipated marketing advantage.

The American Medical Association had established the Council on Pharmacy and Chemistry in 1905, as part of its war against the proliferation of questionable ethical and patent drugs. The function of the Council was to evaluate drugs on the basis of several rules dealing with composition, brand names, advertising, therapeutic claims, etc., for the benefit of physicians and the public. The Council compiled a list of drugs they accepted in New and Nonofficial Remedies, although it published information on unacceptable drugs, too. Many state and regional medical and pharmaceutical journals, and some popular lay journals as well, followed the example of the Journal of the American Medical Association by refusing to advertise drugs which the Council

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[84]Insulin Committee minutes, 2 April 1923, and Bliss, Insulin, 180.

[85]Insulin Committee minutes, 2 April 1923.

did not approve.[86]

According to Rule 8 of the Official Rules of the Council on Pharmacy and Chemistry, the Toronto scientists, as discoverers of insulin, had the right to object to any name a firm used for the hormone.[87] Clowes' reaction to the whole affair, mixing lamentations with a sense of braggadocio, was typical of the Lilly scientist:

> If we are compelled to withdraw the product after having submitted it to the Council, it will be extremely detrimental to us and to everybody concerned. . . . we shall be prevented from advertising our preparation in the A.M.A. and the large majority of State Journals throughout the country. This would, of course, represent a great loss to us, but rather than expose ourselves and the public to the risk of confusion which is already arising over the name Insulin, our management is prepared to forego all commercial advantage that may accrue to them as a result of approval of the product by the Council.[88]

The company had already given in to Toronto, just a few days earlier, on the matter of the isoelectric precipitation patent.[89] So, the company's resolve to preserve its trademark was by no means surprising. Lilly was probably also aware that Toronto violated the contract by 1) working to overturn the company's United States patent application, and 2) refusing to approve Lilly's trade name for insulin. The Insulin

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[86]On the Council on Pharmacy and Chemistry, see, e.g., Morris Fishbein, A History of the American Medical Association, 1847 to 1947 (Philadelphia: W. B. Saunders, 1947), 865-886, and James G. Burrow, AMA: Voice of American Medicine (Baltimore: Johns Hopkins Press, 1963), 74-75, 109-114, 117-118, and 126-128.

[87]New and Nonofficial Remedies, 1924 (Chicago: American Medical Association, 1924), pp. 16-17.

[88]Clowes to Macleod, 14 April 1923.

[89]G. H. A. Clowes to J. J. R. Macleod, 8 April 1923, "Lilly and Co.," Insulin Committee, Toronto Archives.

Committee's primary objective was to persuade Lilly to assign them the isoelectric patent; the fight against Iletin was probably more for the sake of leverage. With the isoelectric patent in hand, the Committee allowed Lilly the use of a brand name: "Iletin (Insulin, Lilly)."[90] The Insulin Committee accomplished what they felt was necessary to prevent an outright American monopoly, and Lilly maintained what it regarded as a fundamental commercial necessity.

The events during the Spring of 1923 led to several safeguards in the new contract between Toronto and Lilly of 30 June 1923, wherein the former issued a non-exclusive license to the drug company. Toronto's contract with other firms bore almost the same provisions as the Toronto-Lilly pact.[91] The only major difference between the two agreements was Lilly's right to use a trade name; other licensees could use only the name "Insulin" on their products.[92] The licensing and cross-licensing stipulations were framed in such a way as to avoid the isoelectric patent fiasco. Lilly, and any other company Toronto licensed to produce and sell insulin, could retain any patents they

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[90]Bliss, Insulin, 276 n. 82. The AMA Council reported their approval of Lilly's brand name for insulin in June, 1923: Journal of the American Medical Association 80 (1923):1851. The Lilly Company officially assigned its isoelectric patent to the Insulin Committee a few days after the patent was granted; see J. K. Lilly to F. Lorne Hutchinson, 29 December 1924, "Insulin--Section 6," Lilly Archives.

[91]"[Contract between the Governors of the University of Toronto and Eli Lilly and Company on Insulin]," 30 June 1923, "Insulin Contracts and Patents, 1923-1945," XCA1, Lilly Archives, and "Contract December 1st, 1923," ibid. The latter is a summarized version of the contract form Toronto used for companies other than Lilly.

[92]"[Contract between Toronto and Lilly]," 30 June 1923, p. 10, and "Contract December 1st, 1923," p. 1.

received on insulin-related product or process discoveries, as long as these discoveries were "beyond the scope" of all present and future Toronto patents. Otherwise, if there were a potential conflict with the Toronto patents, the company had to assign its patent to the University. It was not clear who would decide if a patent were "beyond the scope" of the Canadians' patents, but the intentions of the Insulin Committee surely were to thwart any possible monopolies on the hormone. Once in their possession, the Insulin Committee licensed companies with the recently assigned patent as they did with any of their other patents.[93]

The new contracts allowed Lilly and other companies to reap some dividends from patents that fell outside the realm of Toronto's patents. A patented synthetic insulin substitute, for example, would meet this criterion. The company had to put its discovery into a patent pool by licensing Toronto (royalty free) and the firms operating on a license from the University. These firms paid the patentee a royalty not exceeding that which the patentee had been paying Toronto for the right to produce and sell insulin, i.e., 5 percent of the net sales from insulin.[94] Certain provisions from the 1922 agreement between Toronto and Lilly continued under these non-exclusive licensing pacts. For example, companies had to keep the University informed of

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[93]"[Contract between Toronto and Lilly]," 30 June 1923, pp. 7-8, and "Contract December 1st, 1923," p. 2.

[94]"[Contract between Toronto and Lilly]," 30 June 1923, pp. 6-9, and "Contract December 1st, 1923," p. 2. The Insulin Committee already had determined that they would charge their licensees a 5 percent royalty in the original contract with Lilly; see "[Contract between Toronto and Lilly]," 30 May 1923, p. 4.

their latest researches, patentable or not, and Toronto maintained control over companies' advertising. The cost of insulin treatment was an important consideration for the Insulin Committee, so this also received attention in the 1923 contracts. If the Committee and company could not agree on a fair price for insulin, a board of three arbitrators (two selected by the concerned parties, and a third chosen by the first two) decided the issue.[95]

Ironically, after all the controversy surrounding the extension of the experimental period and the efforts of Toronto to avert a monopoly on insulin, Lilly remained the only American producer for a year after the experimental period ended. Problems in standardizing insulin accounted for part of this delay, as did the time required for other firms to set up mass production facilities. Toronto and Lilly had difficulties agreeing on an insulin unit from the beginning of their collaboration, and the Insulin Committee wanted to resolve these differences before putting insulin on the market and issuing additional licenses. Two international conferences of the Health Organisation

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[95]"[Contract between Toronto and Lilly]," 30 June 1923, pp. 7, 14-15, and "Contract December 1st, 1923," pp. 2-3.

Lilly also concluded a contract with the University of Toronto late in 1923, which dealt specifically with foreign sale of insulin: "[Contract between the University of Toronto and Eli Lilly and Company for the Sale and Distribution of Insulin Outside of the United States]," 31 December 1923, "Insulin Contracts and Patents, 1923-1945," XCA1, Lilly Archives. Toronto probably used a contract of similar form for other countries interested in foreign distribution. Among the highlights of this contract were: 1) a list of 22 countries where Lilly could not distribute insulin (including the British Commonwealth), 2) Toronto's right to receive a 5 percent royalty on all sales, 3) Toronto's right to exclude additional countries from Lilly's license if the Toronto patents were threatened with invalidation there, and 4) the requirement that Lilly could not use a trade name for insulin.

Figure 16. Eli Lilly and Company employees testing the potency of insulin (from The Lilly Laboratories, 1930, C(38)a(I) "Lilly, Eli, and Co.," Kremers Reference Files, F. B. Power Pharmaceutical Library, University of Wisconsin, Madison, Wisconsin; UW neg. no. 10264 C-3).



of the League of Nations, which met in 1923 and 1925 under the direction of Henry Dale, addressed the unitage problems. The conference established an international standard of reference for the insulin unit.[96] In any case, Lilly had a considerable jump by the time their American competition began marketing insulin--Frederick Stearns and Company in June of 1924, E. R. Squibb and Sons in January, 1925, and Sharp and Dohme around April of 1925.[97] Lilly never relinquished the lead it established with its two-year head start.

Conclusion: Impact of the Collaboration on Toronto and Lilly

The collaborators reflected on their association with hearty thanks for the other's assistance. Banting lauded the "intimate reciprocation of all results" between the University and pharmaceutical firm, and the Insulin Committee measured their plaudits in terms of diabetics saved:

> The Insulin Committee desires to express its appreciation of the whole hearted manner in which the Lilly research laboratories have cooperated in working out the problems of large scale production of insulin. Without this collaboration it is unlikely that a non-irritating product of such satisfactory potency and durability could have been produced in adequate amounts to meet the demand of the medical

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[96]The problems of standardization between the collaborators is documented in the folder "Unitage and AMA on 'Iletin'," Lilly Archives; for example, see G. H. A. Clowes to F. Lorne Hutchinson, 22 September 1923, ibid. The reports from the international conferences are in League of Nations,Health Organisation, The Biological Standardisation of Insulin, Including Reports on the Preparation of the International Standard and Definition of the Unit, Publications of the League of Nations, No. 3, 1926.

[97]George B. Walden to G. H. A. Clowes, 26 April 1955, "G. H. A. Clowes, Correspondence to and from, 1940-1947 [sic]," XRDc, Lilly Archives.

profession, in this comparatively short time.[98]

Clowes not only referred to the "unselfish co-operation" and "best endeavors" of Toronto and Lilly, but also saluted the contributions of Philip Shaffer--a bit ironic, given the leverage that Shaffer's work had in April of 1923.[99] Notwithstanding the confrontations over the experimental period, the trade name, and the isoelectric precipitation patent, the insulin collaboration accomplished what it set out to do. Lilly and Toronto shared their research faithfully, and by the end of the experimental period diabetics had a mass produced, safe, effective, and fairly well standardized product. Insulin was expensive, even at cost,[100] but it was far preferable to alternative treatments.

Their insulin research and associated work benefited Toronto and Lilly in many different ways. The Toronto scientists were showered with numerous individual accolades. Most notably, Banting and Macleod received the 1923 Nobel Prize for Medicine or Physiology, the money from which they shared with Best and Collip, respectively. On the other side, the American Diabetes Association honored Clowes with the Banting Medal in 1947.[101] Insulin royalties, and the sale of the

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[98]Insulin Committee, "Insulin," 486, and Banting, "History of Insulin," 10.

[99]G. H. A. Clowes, "Address by George H. A. Clowes," in Lilly Research Laboratories: Dedication (Indianapolis: [Lilly,] 1934), pp. 52-3.

[100]Bliss, Insulin, 173.

[101]John R. Williams, one of the members of the informal clinical advisory committee, and Clowes attempted to secure the Banting Medal for Walden in the late 1950s, but they were unsuccessful; see John R. Williams to G. H. A. Clowes, 27 January 1958, "G. H. A. Clowes, Corre-

Connaught Laboratories, added considerably to the research funds of the University of Toronto. The University collected around $8 million in royalties from various patents, which expired in the late 1950s. A small proportion of the royalties covered the modest expenses of the Insulin Committee, which continued to test insulin samples from manufacturers. Half of the surplus royalties went towards research funds for Banting, Best, and Collip, while the general research funds of the University of Toronto received the other half. The University's Connaught Laboratories grew rapidly as the insulin supplier to Canada, so rapidly that the University's sale of the Connaught Laboratories in 1972 swelled their general research funds by $24 million.[102]

When the insulin royalties began tailing off, Best approached the Lilly Company for funds to support diabetes research at the University's Banting and Best Department of Medical Research. Lilly responded by initiating a number of grants and consultantships in 1957 that totalled $50,000 annually: $25,000 to the Insulin Committee for their work; $12,500 and $5,000 to the Banting and Best Department and the Collip Research Foundation Laboratory of the University of Western Ontario (where Collip was a long-time Faculty member), respectively; and consultantships for Best ($5,000) and Collip ($2,500).[103] The

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spondence to and from, 1940-1947 [sic]," XRDc, Lilly Archives, and G. H. A. Clowes to John R. Williams, 31 January 1958, ibid.

[102]Bliss, Insulin, 240-241.

[103]Charles H. Best to Eli Lilly, 4 June 1954, "Grants (Insulin): Best, Collip, Fisher," XRDng, Lilly Archives; E. N. Beesley to F. B. Peck and R. M. Rice, 15 November 1954," G. B. Walden--Insulin Corres., 1949-1960," XRDq, Lilly Archives; Franklin B. Peck to E. N. Beesley, 13 December 1954, ibid.; E. N. Beesley to Charles H. Best, 8 February

grants and consultantships, as the President of the Lilly Company explained, were a goodwill gesture; they were "not based upon any legal obligation but would be given merely as evidence of our high regard for the friendly relations which have existed for so many years with these individuals and groups."[104] The aid continued for many years. Collip's consultantship did not cease until the scientist died, in 1965; the grants to the Collip Research Foundation Laboratories ended three years later. Lilly terminated their support of the Insulin Committee in 1970, by mutual agreement. Best's consultantship, which had grown to $10,000 by the late 1960s, remained in effect at least until the mid-1970s, and probably lasted until Best's death in 1978. The grant to the Banting and Best Department continued at least until the mid-1970s as well.[105]

Insulin had an immediate impact on Lilly. Despite the fact that the Insulin Committee did not release the product for general distribution until mid-October, insulin was by far the highest selling specialty (in dollars) in the company's history. The restricted 1923 sales exceeded $1.1 million--over 14 percent of Lilly's total sales for that year. Insulin also accounted for half of the firm's profits of over $1.3 million for 1923. Iletin sales increased, even when the

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1955, ibid.; E. N. Beesley to J. B. Collip, ibid.; and E. N. Beesley to A. M. Fisher, ibid.

[104]Beesley to Peck and Rice, 15 November 1954.

[105]W. R. Kirtley to E. N. Beesley, 30 November 1966 and 28 November 1967, "Grants (Insulin): Best, Collip, Fisher," XRDng, Lilly Archives, and W. R. Kirtley to B E. Beck, 16 November 1971, ibid.

first three American competitors began marketing insulin.[106] From the standpoint of cooperative research, the successful collaboration on insulin helped put the company in touch with the research of groups from over a dozen different universities by 1925 (see Chapter 3). Five years after Lilly signed its first pact with Toronto, the company engaged in another major collaborative venture, with two university groups on the development of liver extracts for anemias. This will be the subject of the next chapter. J. K. Lilly, President of the firm during the early insulin years, reflected in 1941 on the importance of this drug to the company: "Insulin revolutionized our place in the industry and put us on the way to present and future greatness."[107]

The early university-industry collaboration on insulin obviously did not run smoothly. Two points must be realized, though. First, the problems did not prevent the overall success of the project. Second, the problems resulted more from a misunderstanding of the other's objectives than from a deliberate attempt to mislead the other collaborator. Collaboration between academe and industry on biomedical research was relatively new at this time in North America, and patterns and models needed to be worked out. The Toronto workers felt a monopoly would eventually impact deleteriously on the diabetic. Lilly could not understand Toronto's opposition to a monopoly, because the company believed its business could prosper under a monopoly without gouging the diabetic. Clowes, who was new to the pharmaceutical industry,

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[106]"Eli Lilly and Company: A History," unpublished typescript, n.d., Lilly Archives, pp. 69, 76, and Kahn, All in a Century, 100.

[107]Quoted in Kahn, All in a Century, 101.

could appreciate Toronto's position, but Lilly management had the final word. The University of Toronto could not fully understand the Lilly Company's wish for a commercial advantage on insulin, because the University of Toronto was not a business institution, where the bottom-line concern was revenue. Despite the misunderstandings and difficulties, the project came off well considering that it was the first long-term, large-scale case of biomedical collaborative research between a North American university and a pharmaceutical firm. In the next chapter I shall show how Harvard and Lilly, and Rochester and Lilly, were able to avoid many of the problems that confronted the insulin collaborators.

CHAPTER 7

HARVARD UNIVERSITY, THE UNIVERSITY OF ROCHESTER, ELI LILLY AND COMPANY, AND LIVER EXTRACTS

Like the insulin project, the liver extract collaborations focused on the development of an organ extract useful against a deadly disease. However, these two projects differed in many ways. The most obvious difference was that Lilly worked with two university medical schools, one collaboration following the other on different extracts from the same organ, for two related illnesses. Lilly worked with Harvard University scientists to produce an extract from mammalian livers useful against pernicious anemia. This agreement lasted from about the Spring of 1927 to the Autumn of 1928. The pharmaceutical company engaged researchers at the University of Rochester in 1929 to test various liver fractions for the firm for activity against secondary, or chronic, anemia. Unlike the Harvard collaboration, this agreement remained in effect for a quarter of a century. Before characterizing and comparing these cooperative endeavors, some background is necessary to explain how liver emerged as an antianemic agent, and how Rochester, Harvard, and Lilly became involved in liver research.

Thomas Addison presented the first clinical picture of pernicious anemia. In the preface to On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules (1855), the same work that marked the birth of modern endocrinology, Addison described this disease in detail, from its "slow and insidious" onset to its relatively painless,

fatal termination.[1] Pernicious anemia, like other anemias, is not a disease itself, but a symptom complex. The blood is actually destroyed in pernicious anemia, and the body's blood-producing ability is diminished. This is the type of anemia that the Harvard workers investigated, an anemia resulting from an abnormality in blood production. The other collaborators of Lilly, the Rochester group, instead were interested in simple post-hemorrhagic anemia; as the name indicates, this results from a loss of blood. General recognition of pernicious anemia as a deficiency illness lagged until well into the 20th century, primarily because of the unitary nature of the germ theory of disease. However, once scientists--particularly F. G. Hopkins at Cambridge, the Polish biochemist Casimir Funk, and a group of agricultural chemists at the University of Wisconsin--established the importance of trace nutrients in certain diseases during the early 20th century, the medical community began to take a more open view of dietary treatment of pernicious anemia.[2] The results of extensive studies at the University

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[1]William D. Castle, "The Conquest of Pernicious Anemia," in Blood, Pure and Eloquent: A Story of Discovery, of People, and of Ideas, ed. Maxwell W. Wintrobe (New York: McGraw-Hill, 1980), p. 284, and idem, "George Richards Minot," Biographical Memoirs of the National Academy of Sciences 45 (1974):347. The preface to Addison's 1855 monograph is reproduced in Logan Clendening, Source Book of Medical History (1942; reprint, New York: Dover Publications, 1960), pp. 502-506.

[2]On the development and significance of early vitamin research, see Aaron J. Ihde and Stanley L. Becker, "Conflict of Concepts in Early Vitamin Studies," Journal of the History of Biology 4 (1971):1-33; Aaron J. Ihde, The Development of Modern Chemistry (New York: Harper and Row, 1964), pp. 644-656; and Stanley L. Becker,"The Emergence of a Trace Nutrient Concept through Animal Feeding Experiments" (Ph.D. diss., University of Wisconsin, 1968). Dietary therapy for anemias was by no means new in the early 20th century, but it did not attain wide appeal until after the results from Rochester and Harvard appeared; see Castle, "Pernicious Anemia," 291-293.

of California and the University of Rochester provided an even more compelling reason to investigate dietary therapy in pernicious and chronic anemia.

George H. Whipple (1878-1976) was an associate professor in pathology at the Johns Hopkins Medical School when he accepted an invitation in 1914 to head the new George Williams Hooper Foundation for Medical Research of the University of California Medical School in San Francisco. Whipple continued his research on the function of the liver in the conversion of hemoglobin to bile pigments when he arrived at the Hooper Foundation. Whipple and his assistant, medical student Charles W. Hooper, reported in 1916 that the production of bile pigments (and thus the production of hemoglobin, which contributes most of these pigments) varied according to the diet. Fresh pig or sheep's liver was much more productive than any other foodstuff, including blood and bile itself. Whipple and his group followed up this result by testing different diets on artificially-induced anemia in dogs. After removing half of the animal's total blood, they compared the time required for different diets to correct the post-hemorrhagic anemia. Whipple's results, published as a series in 1920, were far from conclusive, but he indicated that liver was particularly promising at returning the anemic dogs to their normal states.[3]

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[3]George W. Corner, George Hoyt Whipple and His Friends: The Life-Story of a Nobel Prize Pathologist (Philadelphia: J. B. Lippincott, 1963), pp. 62-64, 98-102; idem, "George Hoyt Whipple," American Philosophical Society Year Book, 1976:135-140; and G. H. Whipple, F. S. Robscheit, and C. W. Hooper, "Blood Regeneration Following Simple Anemia. IV. Influence of Meat, Liver and Various Extractives, Alone or Combined with Standard Diets," American Journal of Physiology 53 (1920):236-262.

Whipple left California in 1921 to become Professor of Pathology and Dean of the new (and yet-to-be-erected) University of Rochester Medical School. The Whipple group resumed their experiments a year later, this time correcting their investigations for the possibility of spontaneous recovery from anemia. First, they devised a special basal diet that kept the dogs (otherwise healthy) in their severe anemic condition. In addition, the diet did not contribute to the production of hemoglobin and red blood cells. Second, in the Rochester investigations, they bled the animals continuously during the feeding experiments, to maintain a constant low hemoglobin level. In contrast, at the Hooper Foundation Whipple and his assistants had bled the dogs only at the beginning of the experiment. Through this changed procedure they could measure the blood regenerating capacity of the test foodstuff by the volume of blood they had to remove to preserve the original hemoglobin level. Whipple and his colleagues reported in 1925 that liver was by far the most potent producer of hemoglobin and red blood cells in sustained severe anemia. Even inorganic iron, which was a fairly standard remedy for this type of anemia, fell significantly below the results achieved with liver. These results, according to the Rochester group, suggested that physicians should give more consideration to dietary treatment in the management of anemia.[4]

Charles Hooper was the first to apply his colleague's ideas in the

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[4]Corner, Whipple, 179-182; idem, "George Hoyt Whipple," 137-138; Castle, "Pernicious Anemia," 292; and F. S. Robscheit-Robbins and G. H. Whipple, "Blood Regeneration in Severe Anemia. II. Favorable Influence of Liver, Heart and Skeletal Muscle in Diet," American Journal of Physiology 72 (1925):408-418.

clinic--actually before the original feeding experiments began. Based on his bile pigment work with Whipple, Hooper and an instructor at the California Medical School treated eight pernicious anemia patients with subcutaneous injections of liver tinctures, during the Summer of 1916 at the university hospital. Even though at least some of the patients began to recover, Hooper abandoned the clinical work. Apparently, the clinicians drove the young and timid laboratory scientist away, believing that the hopeful results were merely spontaneous remissions.[5] Shortly after Whipple published a summary of his California work in 1922,[6] a biochemist and physician at the University of Iowa found beneficial results with a liver and meat diet for a few of their pernicious anemia patients. However, the Iowa work had little impact, probably because most specialists attributed the improvements to spontaneous remission.[7]

George R. Minot (1885-1950) and William P. Murphy (1892-), who spent most of their careers at the Harvard Medical School, applied Whipple's laboratory results in the clinic and compiled unequivocal evidence that liver feeding indefinitely remitted pernicious anemia. Minot had begun to manifest his acumen in hematology as early as his medical student days at Harvard. He spent most of 1914 working with

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[5]Corner, Whipple, 100; George Hoyt Whipple, "Autobiographical Sketch," Perspectives in Biology and Medicine 2 (1959):266; and idem, interview by Gene E. McCormick, University of Rochester, 8 October 1970, transcript, Eli Lilly and Company Archives, Indianapolis, Indiana (hereafter Lilly Archives), p. 4.

[6]G. H. Whipple, "Pigment Metabolism and Regeneration of Hemoglobin in the Body," Archives of Internal Medicine 29 (1922):711-731.

[7]Castle, "Pernicious Anemia," 293, and Corner, Whipple, 185.

physiologist William Henry Howell at Johns Hopkins, where he honed his skills in hematology. Minot returned to Massachusetts General Hospital the next year, about the time when Whipple was starting his anemia work at California. When he returned to Boston, Minot resumed recording copious dietary histories of his patients, including his pernicious anemia patients, as he had as an intern at Massachusetts General. It is not clear why Minot originally took such an interest in diet, but the point is that, when Whipple published his experimental results on the effect of liver on blood regeneration, Minot was more than prepared to apply these findings to his patients.[8]

In 1922, following the reports of Whipple's research at the Hooper Foundation, Minot and Murphy began treating their private patients (they shared a practice in Boston, with a few other physicians) with a diet that included liver. Several of their patients, treated on an outpatient basis, responded well on diets that featured liver. This, coupled with the recent appearance of the Whipple group's first substantial report of their research at Rochester, led Minot and Murphy to initiate a controlled study of the effect of liver feeding on hospitalized pernicious anemia victims, beginning in 1925.[9] Minot and

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[8]Castle, "Minot," 338-339, 349; idem, "Pernicious Anemia," 294; and Maurice B. Strauss, "Of Medicine, Men and Molecules: Wedlock or Divorce," Medicine 43 (1964):619.

[9]Castle, "Pernicious Anemia," 294; idem and Richard P. Stetson, interview by Gene E. McCormick, Veterans Administration Hospital, West Roxbury, Massachusetts, 3 December 1968, transcript, Lilly Archives, p. 7; Lawrence Kass, Pernicious anemia, Major Problems in Internal Medicine, ed. Lloyd H. Smith, vol. 7 (Philadelphia: W. B. Saunders, 1976), p. 24; and "Medicine's Living History: Recollections of Liver Therapy," Medical World News 13, no. 33 (1972):40.

Murphy made a quick and accurate determination of the efficacy of liver by measuring the increase of reticulocytes, which are nascent red blood cells.[10] Convincing their patients to ingest one quarter to one half pound of lightly cooked or even raw liver daily was not easy. One of their patients actually died because he could not tolerate the nauseating diet. Apparently, the physicians did not realize they could have used a stomach tube to feed this patient. The patients had to take raw liver cocktails, raw liver soup, or very lightly cooked liver steak, without onions or any other dressings; pâté, Braunschweiger, or liver tartare were out of the question. It was difficult, but on the whole the patients cooperated.[11]

The treatment was enormously successful. The patient's reticulocyte count usually returned to normal within two weeks, and the diet sustained this level. Minot first reported his results at a local medical society meeting in late April, 1926; his results did not generate excitement. But a week later he and Murphy addressed the meeting of the prestigious Association of American Physicians. The two physicians made the rather conservative announcement that, based on a study of 45 patients who had taken the liver and high protein diet for six weeks to two years, ". . . the dietetic treatment of pernicious

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[10]On the emerging recognition of the role of reticulocytes in blood regeneration, beginning with Paul Ehrlich in the 1880s, see Kass, Pernicious Anemia, 22-24, and Castle, "Pernicious Anemia," 287.

[11]"Medicine's Living History," 40-41, and Castle and Stetson, interview by McCormick, 3 December 1968.

anemia may be of more importance than hitherto generally recognized."[12] The Association received their paper well, although Frederick Allen (of insulin fame) expressed some doubts about the value of liver. Actually, Minot and Murphy did not explicitly state that liver was the key to remission of the disease until the following year.[13]

They must have had liver in mind, though, because in 1926 Minot's group began a cooperative research project with Edwin J. Cohn (1892-1953), Professor of Physical Chemistry at the Harvard Medical School, to test different fractions of liver in pernicious anemia. It is not surprising that the Harvard team started a search for the active fraction of liver. In the first place, whole liver was an unsatisfactory regimen from the patient's standpoint. Second, the liver work came in the wake of discoveries by others of trace nutrients in different foods, such as milk, used to treat disease or promote health maintenance.[14] Cohn, a protein chemist, isolated different extracts of liver through an array of physicochemical manipulations. Minot, Murphy, and their associates tested these extracts in theretofore untreated

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[12]George R. Minot et al., "Observations on Patients with Pernicious Anemia Partaking of a Special Diet," Transactions of the Association of American Physicians 41 (1926):72.

[13]Ibid., 74; Pernicious Anemia, 39-40; Castle, "Pernicious Anemia," 294; and idem, "Minot," 350-351. Minot and Murphy first published their results in August, 1926, in "Treatment of Pernicious Anemia by a Special Diet," Journal of the American Medical Association 87 (1926): 470-476.

[14]See, e.g., n. 2, and Stanley L. Becker, "Will Milk Make Them Grow? An Episode in the Discovery of the Vitamins," in Chemistry and Modern Society: Historical Essays in Honor of Aaron Ihde, ed. John Parascandola and James C. Whorton, ACS Symposium Series 228 (Washington, D.C.: American Chemical Society, 1983), pp. 61-83.

pernicious anemia patients. An appropriate bioassay was not yet devised, but the method of measuring reticulocyte increase furnished results in less than two weeks. Whipple's group, too, was searching for the active ingredient of liver at this time. The Rochester scientists, however, tested fractions in their chronically anemic dogs.[15] This was the situation when Lilly launched their joint investigations with Harvard and with Rochester.

Birth of the Harvard-Lilly Collaboration

The Lilly Company was collecting different liver fractions for some time prior to Minot and Murphy's announcement of their liver feeding success. However, the pharmaceutical firm was investigating liver fractions of an entirely different pharmacological nature. Sometime between 1923 and 1925, Lilly began extracting portions of liver effective against high blood pressure, based on the results of a few American and Canadian workers. The available evidence suggests the the research of biochemists A. A. James and W. J. MacDonald and physiologist N. B. Laughton, all of the University of Western Ontario, and the work of Ralph Major of the University of Kansas, attracted Lilly

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[15]Castle, "Minot," 351-352; John T. Edsall, "Edwin Joseph Cohn," Biographical Memoirs of the National Academy of Sciences 35 (1961):56; and Corner, Whipple, 183. The first publication on liver fractionation by the Harvard group appeared in 1927: Edwin J. Cohn et al., "The Nature of the Material in Liver Effective in Pernicious Anemia, I," Journal of Biological Chemistry 74 (1927):lxix-lxxii. The Rochester group's first report on their study of liver fractions appeared in the same year: G. H. Whipple and F. S. Robscheit-Robbins, "Simple Experimental Anemia and Liver Extracts," Proceedings of the Society for Experimental Biology and Medicine 24 (1926-1927):860-864.

to antihypertensive liver fractions.[16] The company may have formed their Canadian connections through its old insulin ally, J. B. Collip, who was a biochemist at Western. By the Spring of 1925, Lilly was supplying Major with fractions for laboratory testing, and the company was negotiating with MacDonald to test its extracts in the clinic.[17] But Lilly's interests in antihypertensive fractions changed sharply over the following year.

Leon Zerfas, the person most responsible for the establishment of the Lilly Clinical Research Laboratories at the Indianapolis City Hospital (see Chapter 3), arrived at the company in 1925. Zerfas had acquired a strong interest in pernicious anemia during his tenure as chief resident physician at the Thorndike Memorial Laboratory of Boston City Hospital, which was affiliated with Harvard. He was working on antihypertensive liver fractions with Edward Campbell, a company biochemist, when the wife of the company president, Lilly Lilly, came down with pernicious anemia in 1926. Zerfas, who was probably more familiar with pernicious anemia than any other physician in the Indianapolis area, diagnosed the disease. He contacted his former chief at the Thorndike Laboratory, Francis Peabody, to see if he would

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[16]For example, see A. A. James and N. B. Laughton, "The Control of Blood Pressure with Liver Extracts," Canadian Medical Association Journal 15 (1925):701-702; W. J. MacDonald, "Extractives of Liver Possessing Blood Pressure Reducing Properties: Report of Clinical Tests," Proceedings of the Society for Experimental Biology and Medicine 22 (1924-1925):483-485; and Ralph H. Major, "The Effects of Hepatic Extract on High Blood Pressure," Journal of the American Medical Association 85 (1925):251-253.

[17]Leon G. Zerfas, interview by Gene E. McCormick, Camby, Indiana, 22 and 25 October 1968, transcript, Lilly Archives, p. 13, and G. H. A. Clowes to J. H. Mullin, 25 May 1925, Lilly Archives.

come to Indianapolis to confirm Zerfas' diagnosis. Peabody, by this time in the throes of stomach cancer, had to decline, but he suggested that Zerfas contact Minot instead. Zerfas wrote to Minot in late October of 1926, but other engagements forced the Boston physician to decline. Minot eventually came to Indianapolis, sometime between January and April, 1927, but by that time Mrs. Lilly was already beginning to recover.[18]

After Minot and Murphy's first publication on the liver treatment of pernicious anemia appeared in August, 1926, Mrs. Lilly tried raw liver soup. However, she could not keep this down. J. K. Lilly then approached Campbell and Zerfas, to see if they could extract the component from liver that was active against pernicious anemia. Zerfas directed Campbell to save some of the alcoholic extracts that the latter had been discarding in his antihypertensive extract work. Mrs. Lilly responded well to these fractions, and Zerfas also treated at least two other pernicious anemia patients at Indianapolis City Hospital with these liver extracts. Lilly carried out all of this experimental and clinical work, not knowing that Harvard was working on the same problem. The two groups were not aware of their similar interest in liver fractions effective against pernicious anemia until early

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[18]Zerfas, interview by McCormick, 22 and 25 October 1968, pp. 4-6, 8, 13, 15; E. J. Kahn, All in a Century: The First 100 Years of Eli Lilly and Company ([Indianapolis: Lilly, c. 1976]), pp. 60-61; L. G. Zerfas to George Minot, 28 October 1926, "Liver Extract No. 343: Pre-Product Introduction, 1925-1927," Lilly Archives; George Minot to L. G. Zerfas, 2 November 1926, ibid.; and L. G. Zerfas to Henry Jackson, 21 April 1927, ibid.

November, 1926.[19] Lilly and Harvard most likely were not aware that each had isolated and clinically tested liver fractions until Minot visited Indianapolis, early in 1927, to visit Mrs. Lilly and address the Academy of Medicine of Indianapolis.[20]

Although there is some difference of opinion about who approached whom, most of the evidence suggests Lilly approached Harvard about a possible cooperative project.[21] Harvard chose to work with Lilly, even though several reputable firms with research staffs, such as Squibb, Stearns, Parke-Davis, Abbott, and Mulford, offered to collaborate with the university.[22] The Lilly company was an attractive potential col-

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[19]Zerfas to Minot, 28 October 1926, and Minot to Zerfas, 2 November 1926.

[20]Kahn, All in a Century, 61; Zerfas, interview by McCormick, 22 and 25 October 1968, pp. 13, 15-16; George B. Walden, interview by Gene E. McCormick, Eli Lilly and Company, Indianapolis, Indiana, 5 November 1968, transcript, Lilly Archives, pp. 15-16; and G. H. A. Clowes to J. K. Lilly, 11 July 1927, "Liver Extract No. 343: Pre-Product Introduction, 1925-1927," Lilly Archives. Zerfas, late in 1926, was testing dessicated whole liver as well in pernicious anemia patients. He sent some dessicated liver capsules (containing one gram of powder, representing five grams of whole liver) to Minot and to a friend at the University of Michigan Medical School for their evaluations. See L. G. Zerfas to George R. Minot, 24 November 1926, ibid.; George R. Minot to L. G. Zerfas, 26 November 1926, ibid.; L. G. Zerfas to John Huston, 16 November 1926, ibid.; and John Huston to L. G. Zerfas, 24 February 1927, ibid.

[21]Castle, "Minot," 353; Edwin J. Cohn to Dr. Hörlein, 25 January 1928, "H-I-J," box 2, Pernicious Anemia Committee Papers, Francis A. Countway Library, Harvard University Medical School, Boston, Massachusetts (hereafter P. A. Committee, Harvard); and Committee on Pernicious Anemia, "Report of the Committee on Pernicious Anemia of the Harvard Medical School," Journal of the American Medical Association 93 (1929): 1144.

[22]For example, see George R. Minot to Edwin Cohn, 22 April 1927, "Correspondence, George R. Minot et al. regarding anemia, 1927," Edwin Cohn Papers, Francis A. Countway Library, Harvard University Medical School, Boston, Massachusetts (hereafter Cohn Papers); W. H. Blome to George R.

laborator, in the first place because it was already working on liver extracts, but more importantly, because Lilly could point to its overall successful experience with the University of Toronto on insulin. Like the Canadians, Harvard chose to work with only one firm, for the sake of efficiency. It is difficult to pin down the starting date of the collaboration, and the stated responsibilities of each party, since I have not found a contract (if one was ever drawn up) between Harvard and Lilly. The two parties probably began exchanging information on their liver extract research in April, 1927. The initial negotiations more than likely transpired during Minot's visit to Indianapolis (date unknown). The basic strategy was that Lilly could "manufacture under the direction of the [Committee on Pernicious Anemia] one of the extracts developed in the laboratory of physical chemistry" at Harvard Medical School.[23] While this may appear to indicate that Lilly would not be much more than a mass producing servant of the university, with Harvard assuming all laboratory scale investigations, we shall see that this was certainly not the case.

Harvard, upon the recommendation of A. Lawrence Lowell, President of the University, and David Linn Edsall, Dean of the Medical School, formed a committee to organize and direct the development of liver

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Minot, 25 June 1927, box 1, P. A. Committee, Harvard; W. B. Castle to W. H. Blome, 30 June 1927, ibid.; O. W. Smith to Pernicious Anemia Committee, 1 July 1927, ibid.; E. H. Volwiler to George R. Minot, 29 July 1927, ibid.; W. B. Castle to E. H. Volwiler, 11 August 1927, ibid.; R. H. Hutchinson to W. B. Castle, 11 February 1928; "H-I-J," box 2, P. A. Committee, Harvard; and W. B. Castle to R. H. Hutchinson, 23 February 1928, ibid.

[23]Committee on Pernicious Anemia, "Report," 1144.

extract research. This was much like the University of Toronto's Insulin Committee--not surprising, given Harvard's stated wish to follow the example of Toronto's experience in the development of insulin as a therapeutic agent.[24] In addition to Minot and Cohn, the Committee on Pernicious Anemia included Walter Bradford Cannon (Chairman), William B. Castle (Secretary), Elliott Joslin, and Edwin A. Locke. From its inception in May, 1927, the Committee exercised several functions: 1) securing and supervising a manufacturer to produce a liver extract according to Cohn's laboratory directions, 2) arranging for clinical evaluations (an especially important function, since clinical tests were the only available means of estimating the value of liver extracts), and 3) collecting and analyzing the clinical data.[25]

By the time the collaboration began, Harvard had already isolated and clinically tested the fraction of liver containing the active ingredient against pernicious anemia, just as Toronto had isolated and tested their pancreatic extract prior to their original agreement with Lilly. But in the case of the liver extract program, Lilly, too, had a tested liver fraction in hand when the company began working with Harvard. Lilly's extract represented the company's understanding of the physicochemical problems involved in research on the pernicious

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[24]William B. Castle to O. H. Robertson, 20 September 1927, "R," box 3, P. A. Committee, Harvard.

[25]Francis Minot Rackemann, The Inquisitive Physician: The Life and Times of George Richards Minot (Cambridge, Mass.: Harvard University Press, 1956), p. 150; Castle and Stetson, interview by McCormick, 3 December 1968, p. 9; W. B. Castle to John Reichel, 2 February 1928, "R,", box 2, P. A. Committee, Harvard; and Committee on Pernicious Anemia, "Report," 1144.

anemia principle from liver--an understanding that Harvard did not fully appreciate at first.

Progress on Extracts and Clinical Evaluation

Cohn's laboratory prepared an extract effective against pernicious anemia, the so-called G fraction, within two months of starting their search for a useful extract. He undertook a "chemical dissection" of the liver, that is, a procedure "to divide the liver into the smallest possible number of fractions, to discover which one of these fractions was most active, and to continue by subdividing the active fraction."[26] Cohn's group employed five steps to collect fraction G: 1) extracting raw minced beef liver in an alkaline aqueous solution, producing a residue (fraction A); 2) adjusting the pH of the solution to acid, yielding a precipitate (fraction B); 3) heating the solution to 70°C, giving the heat-coagulable fraction C, and then concentrating the solution to produce fraction D; 4) extracting with ether, removing only a small part of D and producing fraction E; and 5) extracting with strong alcohol, which yielded the alcohol soluble fraction F and the insoluble fraction G. The Boston clinicians tested all but the C fraction in patients; they did not test C because they believed it was derived from blood in the liver, not liver tissue itself. Fractions D and E caused a regeneration of reticulocytes in the anemia patients. The alcohol-soluble F fraction contained the antihypertensive principle

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[26]Edwin J. Cohn et al., "The Nature of the Material in Liver Effective in Pernicious Anemia. II," Journal of Biological Chemistry 77 (1928): 325-326.

that Lilly had been interested in. The remaining fraction, G, promoted rapid recovery from pernicious anemia.[27] The Harvard group continued to work on additional fractions,[28] but the workers focused on fraction G during the collaboration.

The process Lilly used to produce its so-called L fraction, which the company championed during the early months of the collaboration, is unknown. However, it was probably not too different from Harvard's G fraction. Lilly was working for some time with the blood pressure-lowering extract of liver (similar to Harvard's F fraction), and their L fraction was an alcoholic extract of the antihypertensive fraction. Also, Minot counseled Lilly on their pernicious anemia extractives when he was in Indianapolis. The company had good results with the L extract, based on its effect on Mrs. Lilly and a few other patients.[29]

The immediate plans of the Committee on Pernicious Anemia were to 1) have Lilly manufacture as much of the G fraction in the least possible time, and 2) organize a small clinical trial of the liver fraction among a few scattered medical centers, similar to the early setup during the insulin project. I will discuss Lilly's task and the resulting

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[27]Cohn et al., "Material Effective in Pernicious Anemia, I," lxx-lxxii, and Cohn et al., "Material Effective in Pernicious Anemia, II," 329-345.

[28]For example, see Edwin J. Cohn, Thomas L. McMeekin, and George R. Minot, "The Nature of the Material Effective in Pernicious Anemia. III," American Journal of Physiology 90 (1929):316-317, and idem, "The Nature of the Material Effective in Pernicious Anemia. IV," Journal of Biological Chemistry 87 (1930):xlix-lii.

[29]Walden, interview by McCormick, 5 November 1968, pp. 15-16; Zerfas, interview by McCormick, 22 and 25 October 1968, pp. 15-16; and Clowes to J. K. Lilly, 11 July 1927.

problems below. Although several area hospitals cooperated with the Committee (Boston City, Huntington, Peter Bent Brigham, etc.), Boston alone possessed an insufficient number of cases for an adequate assessment of the liver extract. So the Committee engaged physicians familiar with the treatment of pernicious anemia at several medical centers to assist them in evaluating the liver extract: Johns Hopkins, Stanford, Bellevue Hospital (New York), Albany (New York) Hospital, University of Michigan, University of Wisconsin, University of Chicago, Presbyterian Hospital (New York), Indianapolis City Hospital, and an Atlanta private practice. In addition, St. Bartholomew's Hospital in London and the University of Toronto tested the liver extract for the Committee.[30]

Harvard had considerable difficulty during the Summer of 1927 convincing Lilly to manufacture their liver fraction G. The Pernicious Anemia Committee wanted fraction G, as crude as it was, made available to the cooperating medical centers as soon as possible. The collaborators could refine this preparation later, according to the Committee, when the patients would already have a tested extract (G) if needed. Thus, Minot firmly stated this view to Clowes early in the collaboration:

> Of course it would be nice to give [a liver extract] in very concentrated form. Undoubtedly the time will come when that can be done, but I frankly believe we are wasting time both of your company and of patients suffering from the disease by trying now to obtain a fraction that is efficient in but

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[30]W. B. Castle to Arthur Bloomfield, 30 June 1927, "B," box 3, P. A. Committee, Harvard, and W. B. Castle, form letter, 21 September 1927, "Liver Extract No. 343: Pre-Product Introduction, 1925-1927," Lilly Archives.

> a few grams a day. I feel convinced we should not send material to other clinics until we have a preparation known to be effective that you have prepared. I likewise feel that it will be a great mistake to send to other clinics at this time material that only may be [Minot's emphasis] effective.[31]

Minot was really taking issue with some of Lilly's recent practices: trying to create an elegant extract, favoring its own L fraction, and pursuing research in its own laboratory--when Lilly's prime task supposedly was to scale up Cohn's findings. Lilly was trying to refine both the L and the G fractions. Harvard knew the G fraction worked, but Lilly's L fraction was comparatively untested; only a handful of cases in Indianapolis received this extract, including Mrs. Lilly. So, the Committee must have wondered why Lilly was emphasizing L rather than G. Lilly certainly was more familiar with the L fraction, but more importantly, the company could file a patent application on L. If Lilly could circulate its extract among the cooperating clinicians and get good results, this would solidify its patent claim.

The mere fact that Lilly was devoting time to the study of extracts, unrelated to mass producing these, seems to have annoyed some members of the Committee, as witnessed by Minot's letter to Clowes above. It was not as if Cohn's laboratory was struggling in trying to produce the anti-anemic fraction; it was a very different situation than what Macleod's laboratory faced at the time they started working with Lilly. Harvard, I believe, underestimated the research

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[31]George R. Minot to [G. H. A.] Clowes, 30 April 1927, "Correspondence, George R. Minot et al. regarding anemia, 1927," Cohn Papers. Fortunately, for the sake of the pernicious anemia patient (as opposed to the diabetic), if an organ extract were not yet available, liver feeding could save the patient; cf. the concluding section of this chapter.

Figure 17. George Richards Minot (1885-1950), Professor of Medicine at Harvard Medical School from 1918 to 1950 (from John Francis Marion, The Fine Old House, p. 123; UW neg. no. 10275 C-3).



capabilities, and the ambitions, of Lilly. It is worth mentioning that George Walden, who had so much success in isolating the pancreatic extract, joined Campbell and Zerfas in their liver extract research by the start of the collaboration.

The Pernicious Anemia Committee, after waiting weeks for Lilly to send them enough G extract to initiate the clinical program, received a rather ironic letter from President J. K. Lilly (through Clowes). This time it was Mr. Lilly who charged that the collaborators were stalling, because the company had extensive evidence that their extract--the L fraction--produced "uniform improvement" in pernicious anemia cases. As we saw in the case of President Lilly's effort to increase distribution of insulin, he had both humanitarian and business motivations here. On the one hand, he emphasized that "My principal concern, however, is to save a lot of lives." Yet, he also called attention to the fact that the Armour Company and possibly another firm already were distributing liver extracts for pernicious anemia, which could be a threat to his firm's position in the market.[32] That other companies could be producing extracts was a surprise to the Pernicious Anemia Committee, so Castle asked a disinterested faculty member of the Harvard Medical School to look into the situation. Armour and the Wilson Company, meat packers with pharmaceutical divisions, were indeed marketing liver preparations. Armour's product, which the company claimed they did not bill as a pernicious anemia treatment per se, was a concentrate of whole liver. Wilson's preparation was an encapsulated

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[32]J. K. Lilly to G. H. A. Clowes, 11 July 1927, "Liver Extract No. 343: Pre-Product Introduction, 1925-1927," Lilly Archives.

extract, of unknown manufacturing method, marketed as a treatment for pernicious anemia. It is not clear if the Committee attempted to take any action against these companies.[33] At this time, the Committee had little if any legal recourse, since there were still no federal laws dictating that a remedy be either tested or effective.

President Lilly's claims about the value of the L fraction had some serious problems. In the first place, they were based largely on the evaluations of Zerfas, who was a Lilly employee.[34] There was no reason for the Committee to question Zerfas' integrity, but this was simply not in the realm of proper protocol, at least as far as the Harvard Pernicious Anemia Committee was concerned. The Committee also had doubts about the L extract on the basis of their own experiences with the preparation. In fact, the Committee had poor results with both of the Lilly-produced G and L fractions, perhaps because the products deteriorated, or perhaps because Lilly's alcoholic extractions did not adequately remove the proteolytic enzymes in liver tissue. Lilly apparently did not heat its extracts the way Cohn had, which could explain why Cohn's extracts were more successful than the company's.[35] Lilly's former associate on the insulin project and a member of the Pernicious Anemia Committee, Elliott Joslin, tried to explain to

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[33]W. B. Castle to E. D. Churchill, 30 September 1927, box 1, P. A. Committee, Harvard; A. C. H[enderson] [of Armour] to Edward D. Churchill, 6 October 1927, ibid.; and David Klein [of Wilson] to Edward D. Churchill, 7 October 1927, ibid.

[34]For example, see L. G. Zerfas to John Huston, 20 June 1927, "Liver Extract No. 343: Pre-Product Introduction, 1925-1927," Lilly Archives.

[35]C. H. A. Clowes to J. K. Lilly, 14 July 1927, ibid.

the company why a restricted distribution of extracts was still necessary: ". . . if a product were widely distributed with the name of the P. A. Committee and the Lilly Company attached to it, and if such a product should deteriorate or prove in any way unsatisfactory, it would be very unfortunate for both the P. A. Committee and Company."[36]

The rest of the Committee thought it would be unfortunate, too, such that in early August they contacted President Lilly to inform him that they could no longer consider the L fraction a feasible liver extract for widespread distribution; that it would require some time for the cooperating clinical group to assess the value of an extract prior to general distribution; that the collaboration could be dissolved if Mr. Lilly were not satisfied with these arrangements.[37] Lilly was beginning to push itself out of a collaboration again. While the company had not gone as far to threaten its good relations with Harvard as it earlier had with the University of Toronto and the insulin collaboration, it was approaching a point at which termination of the agreement was possible. The Pernicious Anemia Committee seemed to be on their guard, from the start of the collaboration, for any attempt by Lilly to turn the collaboration in their favor. In April of 1927, upon receiving an attractive offer for cooperative work from John Anderson of Squibb (see Chapter 3), Minot wrote Cohn that, "Should it come to pass that the Eli Lilly Co. played some game we do not expect

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[36]Joslin, quoted in ibid.

[37]W. B. Castle to David L. Edsall, 4 August 1927, box 1, P. A. Committee, Harvard.

I should think Anderson might be a very good man to deal with."[38] Charles Best's revelation to the Committee, in August, of Toronto's difficulties with Lilly, could only have made Harvard more dubious about their connections with the Indianapolis company.[39]

Lilly, I think, genuinely felt it had a solid product in fraction L. The company had too much at stake to market a questionable product and thereby possibly damage its good reputation among the medical community. But Harvard believed, quite reasonably, that Lilly came to this conclusion about fraction L on the basis of inadequate testing. Fraction G, unlike fraction L, was "tried and true." Thus, "by bringing steady pressure to bear" on the pharmaceutical firm, the Committee finally convinced Lilly to manufacture a "reliable" extract, which the company produced through a slight modification of Cohn's fraction G process. Following successful preliminary tests of this preparation in Indianapolis and Boston, the Committee distributed the extract to the clinical group, beginning in September, 1927.[40] Two months earlier, Clowes told J. K. Lilly that the Committee most likely would permit the company to submit other fractions for testing, as long as a fully potent extract based on the G fraction was available to the clinical group. The Committee did agree to have additional fractions tested, although they cautioned at least one member of the group to

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[38]Minot to Cohn, 22 April 1927.

[39]George R. Minot to Edwin Cohn, 24 August 1927, "Corres., George R. Minot et al. regarding anemia, 1927," Cohn Papers.

[40]William B. Castle to C. C. Sturgis, 24 September 1927, "S," box 3, P. A. Committee, Harvard, and Castle, form letter, 21 September 1927.

test only material that he and the Committee deemed worthy of evaluation.[41] The company's search for a reliable testing center for its anti-anemic liver extracts eventually led Lilly to George Whipple (see below).

Since the results with the G-modified fraction were "invariably good," the Pernicious Anemia Committee significantly widened the distribution of the fraction, beginning in December. In the same month, they introduced the fraction to the Council on Pharmacy and Chemistry of the American Medical Association, as Liver Extract No. 343.[42] The Council promptly reported their approval of the extract in February, 1928.[43] Many of the problems over patenting, trade names, AMA Council

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[41]Clowes to J. K. Lilly, 14 July 1927, and Castle to Sturgis, 24 September 1927. I have not seen a reply from Sturgis, although Castle's caveat certainly was not encouraging:

> I am writing to ask you whether you would be willing to undertake the work of testing special fractions for the Lilly Company. We have not been impressed with the quality of thought behind many of the suggestions made by the Lilly laboratories in the past. It seems only fair to say that you would in this endeavor have to deal with Dr. Clowes who is a somewhat difficult person. I think therefore that you should have it clearly understood with him that you were only willing to test material that you and we thought was worthy, and, furthermore, [material] that was made in quantity sufficient so that two or three cases could be given identical material. In other words, it would certainly be advisable for you to have all the information possible about any fraction before you undertook to study it, and a guarantee of its possible utility. (Ibid.)

[42]The designation of the extract came from the number that Walden arbitrarily assigned to the experiment which led to the successful modification of Cohn's G fraction. The extract was not the 343d that Walden tested. See Walden, interview by McCormick, 5 November 1968, pp. 16-17.

[43]Edwin J. Cohn to Odin Roberts, 5 November 1927, "Odin Roberts regarding anemia, 1927," Cohn Papers; W. B. Castle to L. G. Zerfas, 5 December 1927, "Liver Extract No. 343: Pre-Product Introduction,

approval, and so on that emerged between Lilly and the University of Toronto simply did not exist in the collaboration with Harvard, for reasons I will mention below.

Monopoly on Liver Extract 343

According to personnel who were involved on both sides of the liver extract collaboration, Lilly patented Liver Extract 343 and proceeded to give the patent to Harvard. Not having seen the original agreement between Harvard and Lilly (if one even existed), it is unknown if this were part of their agreement. The university then dedicated the patent to the public, so that anyone having the inclination could manufacture the product.[44] Harvard considered applying for a patent on Cohn's extract by early 1927, but the university temporarily waived that idea. The university believed such a patent would conflict with a patent application on the antihypertensive liver extract. As mentioned above, the methods for extracting the liver principles that were active against high blood pressure and pernicious anemia were similar. Lilly already had applied for a patent on the blood pressure principle and the process to prepare it by the Spring of 1927. The university wanted to see if Cohn could resolve the pernicious anemia principle sufficiently to justify a patent applica-

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1925-1927," Lilly Archives; Committee on Pernicious Anemia, "Report," 1144; and Council on Pharmacy and Chemistry, "New and Nonofficial Remedies," Journal of the American Medical Association 90 (1928):385.

[44]Castle, "Pernicious Anemia," 297; idem, "Minot," 353; G. H. A. Clowes to Francis M. Rackemann, 31 March 1954, "Liver Extract No. 343: Pre-Product Introduction, 1925-1927," Lilly Archives; and Walden, interview by McCormick, 5 November 1968, pp. 21-22.

tion.[45] Actually, scientists did not reduce this principle to its essence until 1948, when a group at the Merck Company under Karl Folkers isolated vitamin B_{12} in crystalline form.[46]

Recall that Lilly battled Toronto over the Walden patent and the trade name, Iletin. In the case of the liver extract collaboration, the company voiced no objections (as far as I have seen) to handing over its patent, and the firm did not push a trade name. The differences here rest in the very different ways that the Insulin Committee and the Pernicious Anemia Committee handled the issue of the monopolization of their discoveries. The Insulin Committee, as we saw in Chapter 6, took many steps to ensure that no company could control insulin. The Pernicious Anemia Committee, on the other hand, was satisfied ". . . to provide a supply of potent liver extract adequate to the needs of those suffering from conditions which could justifiably demand treatment with this specific principle of liver," and leave their responsibility at that.[47] In other words, the Committee tested the fraction that Lilly manufactured--and only Lilly's product--to a point where they were confident of its strength, purity, and longevity, and then they terminated the collaboration and the Committee itself. It

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[45]Cohn to Roberts, 5 November 1927; Henry Jackson to L. G. Zerfas, 1 April 1927, "Liver Extract No. 343: Pre-Product Introduction, 1925-1927," Lilly Archives; and Zerfas to Jackson, 21 April 1927.

[46]Edward L. Rickes et al., "Crystalline Vitamin B_{12}," Science 107 (1948):396-397. Ever since their liver research began in 1942, the Merck group had collaborated with Randolph West of the College of Physicians and Surgeons of Columbia University, who evaluated the Merck concentrates clinically; see Randolph West, "Activity of Vitamin B_{12} in Addisonian Pernicious Anemia," ibid., 398.

[47]Committee on Pernicious Anemia, "Report," 1145.

is no surprise, then, that the liver extract collaboration did not have the same kind of confrontations that the insulin collaboration did. Other companies could (and did) manufacture liver extracts, but only Lilly's preparation had the blessing of the Pernicious Anemia Committee. The pharmaceutical firm took advantage of this de facto monopoly. For example, Lilly instructed its "detailers": ". . . you should convey to the medical profession at large the fact that Lilly Extract No. 343 is the only product that has the unqualified approval of the Harvard Pernicious Anemia Committee." The company included this "unqualified approval" in its medical journal advertisements as well.[48]

Other companies knew very well how this exclusive arrangement between Harvard and Lilly would affect their positions in the liver extract market. For example, a representative from the H. K. Mulford Company complained to William Castle, ". . . for the Committee to test the product of one commercial laboratory and permit it to market the same with their approval, places other firms at a decided disadvantage, even though no patent, trade-mark or other restrictions enter into the question at all."[49] The Committee felt that any kind of mass testing was simply beyond their capacity. True, the Insulin Committee managed

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[48]Eli Lilly and Company, General Letter No. 35, 19 October 1928, "Liver Extract No. 343: 1928 ff.," Lilly Archives. One advertisement that the company ran in the AMA Journal (a copy is attached to the General Letter above) reproduced a brief report that the Committee published in the Journal, summarizing their experimental and clinical experiences with No. 343 and citing their approval of the Lilly product. See Council on Pharmacy and Chemistry, "New and Nonofficial Remedies," Journal of the American Medical Association 90 (1928):2102-2103.

[49]Hutchinson to Castle, 11 February 1928.

to supervise several companies, but the Harvard Committee believed that this was an unfair comparison:

> The Committee on Pernicious Anemia has decided not to collaborate directly with any other manufacturing firm for the present than the Eli Lilly Company because of the impossibility of really supervising and therefore guaranteeing the product. The difference from insulin which has involved this decision has been the impossibility of testing the potency of material except by feeding it to patients with pernicious anemia.[50]

Whereas the Insulin Committee easily checked on the products of various insulin manufacturers by bioassay tests on rabbits at Toronto, the Pernicious Anemia Committee did not enjoy the advantage of a bioassay. Physicians had to evaluate liver extracts by administering the test extract to a patient for ten days. If the extract failed to produce any results, the patient had to try an extract of proven benefit for another ten days, to make sure he could respond to therapy. Transfusions were resorted to if the patient's blood readings approached a dangerous level. Physicians determined the strength of the test extract on the basis of the patient's (measured) reticulocyte response to the treatment, in relation to standard values for this response. The laborious process of standardization, combined with the scarcity of clinical material (i.e., compared to the prevalence of diabetes), accounted for the fact that the dozen or so clinics in the testing program only reported on about 80 cases up to May, 1928. This method of standardization remained in effect until the late 1940s, when a scientist at the University of Maryland found that concentrates of

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[50] William B. Castle to Carl J. Herzog, 8 March 1928, "H-I-J," box 2, P. A. Committee, Harvard.

the pernicious anemia principle could be assayed in certain Lactobacillus cultures.[51]

Harvard's reluctance to enter into a supervisory role in the liver extract industry thus is understandable. The type of organization needed for standardizing several different brands of pernicious anemia liver extracts finally emerged in the late 1930s, under the auspices of the United States Pharmacopoeial Convention through its Anti-Anemia Preparations Advisory Board.[52] So, Lilly launched Liver Extract No. 343 into the market with a decided advantage. The company, with considerable experience in pernicious anemia therapy behind it, logically branched out into the field of secondary anemia. Soon after Harvard ceased testing Lilly's liver extract (in the Fall of 1928), the company approached another leader in the field, George Whipple, with an offer of collaboration.

The Agreement between Rochester and Lilly

George Whipple's Department of Pathology at the University of Rochester was one of two "Special Laboratories" that Harvard's Pernicious Anemia Committee included in their early group of testing centers.[53] Whipple reported in a September, 1928 publication that

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[51]Castle and Stetson, interview by McCormick, 3 December 1968, pp. 13-17; Castle, "Pernicious Anemia," 297; and "Medicine's Living History," 40.

[52]The collected papers of this Board, covering the years 1937 to 1960, are in boxes 80-82 of the United States Pharmacopoeial Convention Records, American Institute of the History of Pharmacy Collection, State Historical Society of Wisconsin, Madison, Wisconsin.

[53]Castle, form letter, 21 September 1927.

Liver Extract 343 had very little effect on his dogs suffering from severe secondary anemia.[54] (Today we know that No. 343 had an insignificant benefit in Whipple's experiments because pernicious anemia and secondary anemia--in this case, post-hemorrhagic anemia--react to different components in the liver.) According to Clowes, he and Whipple were acquaintances for many years, and he occasionally supplied Whipple materials when the latter was building up his anemia investigations. Whipple's recent publication gave Clowes an opportunity to remind Whipple that, ". . . the facilities and resources of our laboratories are always at your disposal and that should you so desire we shall be glad to prepare any fractional products for you on a larger scale than would be possible in a purely research laboratory." Whipple promptly replied that he would be happy to cooperate with Lilly.[55]

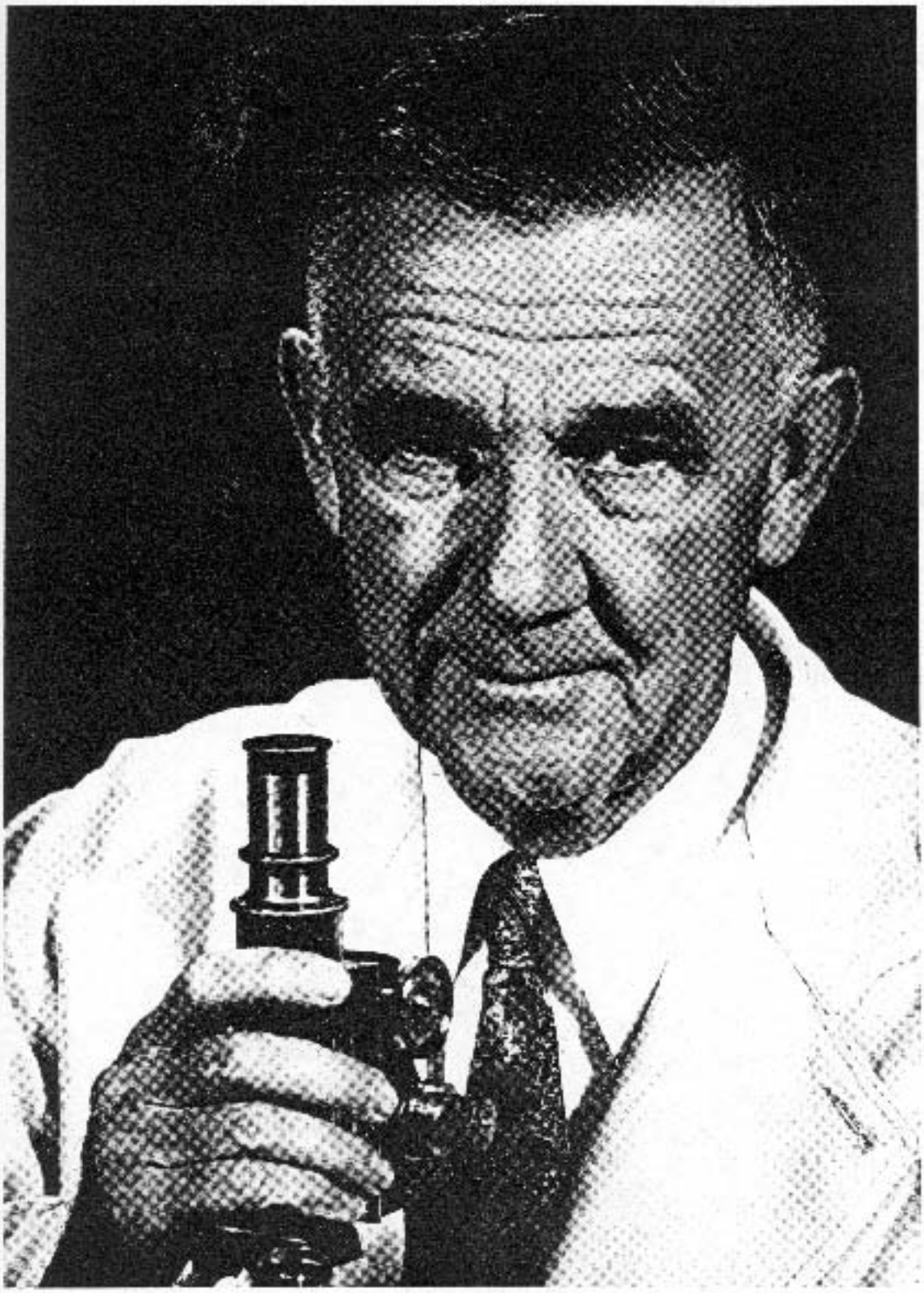
That Whipple unhesitatingly agreed to work with Lilly can be attributed to several circumstances. Clowes' steady contact over the years certainly was important, as was Lilly's experience with the Insulin Committee and especially with the Pernicious Anemia Committee. Whipple's own experience played no small part, too. A botulism

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[54]G. H. Whipple, "Experimental Anemias, Diet Factors and Related Pathologic Changes of Human Anemias," Journal of the American Medical Association 91 (1928):864, 866.

[55]G. H. A. Clowes to J. K. Lilly, 28 July 1930, "Liver Extract No. 55, 1930-," Lilly Archives; G. H. A. Clowes to George Whipple, 9 November 1928, ibid. (quotation); George H. Whipple to G. H. A. Clowes, 13 November 1928, ibid.; George H.Whipple to G. H. A. Clowes, 28 January 1929, ibid.; and G. H. A. Clowes to George H. Whipple, 30 January 1929, ibid.

Figure 18. George Hoyt Whipple (1878-1976), Professor of Pathology and first Dean of the University of Rochester School of Medicine and Dentistry from 1921 to 1955 (from George W. Corner, George Hoyt Whipple and His Friends, frontispiece; UW neg. no. 10268 C-3).



outbreak occurred when he was at the University of California. The problem was traced to the ripe olive industry in California, among other states. Eventually Karl Meyer, a bacteriologist at California, designed a canning method to safeguard olives against this poisoning. Whipple was very impressed by the conduct of the industry during this crisis. The industrial representatives that Whipple had personal contact with were not interested in stopgap measures alone; they wanted to know everything they could about botulism, to prevent such an incident from reoccurring. Whipple said this was an "enlightening experience," and that he henceforth looked forward to contacts with industry.[56]

Rochester and Lilly began exchanging research data around February of 1929. Although their early negotiations suggested that the company would provide Whipple with different liver fractions according to Whipple's specifications, the Rochester scientist did not object when Lilly began requesting him to test the firm's own extracts.[57] Among the liver fractions which the Rochester group tested in 1929 and early 1930, one was particularly beneficial in the anemic dogs. It was 3 percent of the weight of whole liver, yet it possessed up to 75 percent of the latter's activity in secondary anemia. Its rather simple preparation consisted of heating a preparation of ground liver in dilute sulfuric acid to about 80°C, evaporating the filtrate to a syrup, and

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[56]Whipple, "Autobiographical Sketch," 268, and idem, "Address by Dr. George H. Whipple," in Lilly Research Laboratories: Dedication (Indianapolis: [Eli Lilly,] 1934), pp. 48-49.

[57]G. H. A. Clowes to George H. Whipple, 7 March 1929, "Liver Extract No. 55, 1930-," Lilly Archives, and George H. Whipple to G. H. A. Clowes, 12 March 1929, ibid.; cf. Clowes to J. K. Lilly, 28 July 1930,

collecting the precipitate that formed when 50-75 percent alcohol was added to the syrup.[58] Despite the fact that the patent on this extract bears only the name of George Walden, much evidence suggests that Whipple clearly contributed significantly to this discovery. First, Whipple simply would not allow his name to appear on any patent (see below). Second, the contract between Rochester and Lilly (discussed below) referred to the University of Rochester as the discoverer of this extract. Finally, several of the fractions that Whipple and his associates mentioned in a publication of research performed prior to the Lilly-Rochester collaboration closely resemble the patented extract.[59]

Lilly put this so-called Liver Extract No. 55 on the market as a treatment for secondary anemia in September, 1930. In the following month, after finding that Whipple and the University of Rochester had no objections, the company filed a patent application on Extract No. 55.[60] Whipple had strong feelings about the commercialization of

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[58]G. H. Whipple, F. S. Robscheit-Robbins, and G. B. Walden, "Blood Regeneration in Severe Anemia. XXI. A Liver Fraction Potent in Anemia Due to Hemorrhage," American Journal of the Medical Sciences 179 (1930):628-643, and George B. Walden, "Liver Extract for Secondary Anemia and Process of Making It," United States Patent 1,813,788, patented 7 July 1931.

[59]Warren M. Sperry et al., "Blood Regeneration in Severe Anemia. XV. Liver Fractions and Potent Factors," Journal of Biological Chemistry 81 (1929):251-265 (see especially the sulfuric acid fractions, pp. 255-258); cf. Clowes to Whipple, 7 March 1929.

[60]Eli Lilly and Company, General Letter No. 25, 30 September 1930, Lilly Archives; "[Contract between the University of Rochester and Eli Lilly and Company for Liver Extracts]," 1 January 1931, p. 1, "Liver Extract No. 55, 1930-," ibid.; and Walden, "Liver Extract for Secondary Anemia." According to Corner, Whipple, 188, "No. 55" came from the fact that this extract precipitated out in 55 percent alcohol, which

medical discoveries, feelings which his mentors at Johns Hopkins, such as William Henry Howell and William Henry Welch, inculcated in their students. Whipple refused to patent Liver Extract 55; in fact, he had never even considered a patent. He maintained an aloofness from the commercial aspects of the development of this extract. For example, Lilly marketed No. 55 largely on the basis of Whipple's excellent experimental results with his dogs, even though clinical evaluations were sparse. This generated some controversy, from which Whipple kept his distance:

> Some people used to say that the reaction of anemic dogs to liver extract was all right, but it didn't necessarily prove that it would be the same with humans. We hadn't anything to do with that argument because we were not concerned with the marketing of the substance. [Lilly] used whatever they thought would be fair to the situation, always sending it to us for review. We were glad to know that sick people thought they were benefiting.[61]

We shall see in the conclusion of this chapter that, although Whipple may not have been concerned with the marketing of No. 55, his research program and the University of Rochester Medical School profited enormously from the marketing of the extract.

Three weeks before Liver Extract 55 went on the market, Lilly offered a formal agreement to Whipple. Theretofore the collaboration operated on a handshake rather than a contract, just the way Whipple preferred. Though the two groups had not yet signed an agreement, Lilly reimbursed Rochester $4,000 for their expenses incurred in the

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distinguished it from Liver Extract No. 343.

[61]Whipple, interview by McCormick, 8 October 1970, pp. 2-3 (quotation), 6-8, and Clowes to J. K. Lilly, 28 July 1930.

liver extract project.[62] The contract which the university and pharmaceutical firm concluded on 1 January 1931 underwent some changes over the years, but it remained in force for 25 years. According to the contract, Rochester would continue testing extracts, Lilly would produce and sell these, and both parties were expected to recommend extracts for consideration. The agreement by no means emphasized patent matters as, for example, the Toronto-Lilly agreement of 30 June 1923 had. Rather, Rochester allowed Lilly to patent any product or process it wished, whenever the company wanted to file a patent. Rochester would receive a 5 percent royalty on No. 55 and any other patentable discovery emanating from this agreement. As in the case of the Toronto-Lilly agreements, Rochester had the right to inspect any of Lilly's relevant records, to demand that the Lilly products met the university's standards of quality, to approve Lilly's advertising related to any products covered by the agreement, and to call for arbitration if the company and university could not agree on a fair price for a product. Given Whipple's predilection for an informal collaboration, the contract (at least from the academics' side) was probably more for the benefit of President Rush Rhees and other members of the university's governing board.[63]

The only significant changes in the agreement during the following

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[62]Eli Lilly to George H. Whipple, 8 September 1930, "Liver Extract No. 55, 1930-," Lilly Archives; G. H. Whipple to Eli Lilly, 12 September 1930, ibid.; J. K. Lilly to G. H. Whipple, 15 September 1930, ibid.; George B. Walden to George Whipple, 6 August 1930, ibid.; and George H. Whipple to George B. Walden, 8 August 1930, ibid.

[63]"[Contract between Rochester and Lilly]," 1 January 1931.

years concerned the method of reimbursing Rochester. Presumably, the collaborators made these changes by mutual agreement when extract sales (and thus royalties) exceeded by far what both parties had anticipated in 1931. The royalty was reduced to 2½ percent in 1933, and ten years later Lilly began paying Rochester a flat fee of $10,000 per year for the testing work. The fee rose to $18,000 in 1946.[64] The collaboration between Lilly and Rochester on liver extracts active against secondary anemia ended when Whipple retired, in 1955.

Conclusion

The cooperative research projects on liver extracts between Harvard and Lilly and between Rochester and Lilly differed, in many ways, from the insulin project. First, Harvard apparently carried out their work with Lilly without a formal agreement.[65] Liver Extract 55 was on the market before Rochester signed an agreement with Lilly. In this case, the delay was almost certainly due to Whipple's preference for informal arrangements, and to his desire to remain apart from the commercial affairs of the collaboration. In contrast to Harvard and Rochester, Toronto concluded three detailed contracts with Lilly from May, 1922 to December, 1923. Toronto probably wanted to spell out the

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[64]Information on changes in the reimbursement policy comes from unsorted matter in the Lilly Archives: G. H. Whipple to George B. Walden, 21 October 1946, "Liver Extract No. 55, 1930-," Lilly Archives; and W. M. Wheeler, Jr. to George H. Whipple, 12 November 1946, ibid. See also Whipple, interview by McCormick, 8 October 1970, pp. 15-16.

[65]I cannot state that this is definitely the case. However, I could not find a contract, nor any references to one, in the Pernicious Anemia Committee Papers, the Cohn Papers, or the relevant records in the Lilly Archives.

responsibilities of each party because they did not know the company they were dealing with too well. This was not as much of a problem after the insulin project for the Pernicious Anemia Committee and for Whipple's group. However, a contract that explicitly stated the responsibilities of both parties might have saved the Harvard Committee (and Lilly) some frustrations over the matter of Lilly's L extract.

The liver extract and insulin projects also differed with respect to the company's experience with the research problem before contacting the university. Lilly had some background in extracting substances from glands, and testing these through biological assay, prior to the insulin collaboration. But the company was not familiar with pancreatic extracts. On the other hand, Lilly had prepared and clinically tested liver extracts for pernicious and secondary anemia before negotiating agreements with Harvard and Rochester. This definitely enhanced Lilly's image as a desirable potential collaborator when those two universities decided to link up with a firm. Of course, Lilly's rapid success with insulin demonstrated that prior experience with the focus of the collaboration was not crucial, as long as the company was willing to invest the necessary time, funds, and personnel to make up for the lack of experience.

Third, from the standpoint of therapeutics, one of the collaborations was more important than the other. Minot and Murphy, based on Whipple's research, discovered that feeding whole liver to victims of pernicious anemia could put the disease into indefinite remission. The use of the liver extract, indisputably, had many advantages over liver feeding, but when it came to healing the patient, as Murphy explained,

"The use of liver, itself, is just as satisfactory except that it is sometimes a little more difficult to take the required amount than it is to take the extract."[66] If the liver extract work was a complete failure, there is no reason why victims of pernicious anemia should have continued to die from this disease. Even among the few patients who preferred the consequences of the disease to the treatment, the feeding of raw liver through a stomach tube was available. If scientists failed to isolate a pancreatic extract useful in diabetes, victims of that disease would not have been as fortunate.

Finally, the academics involved in the collaborations on insulin and anti-anemic liver extracts had radically different opinions about permitting monopolies on their discoveries. The Insulin Committee's position was explicitly anti-monopolistic. Following the temporary exclusive arrangements with Lilly, the Committee issued licenses on their patent to several manufacturers, whose insulin they periodically tested. The Harvard Pernicious Anemia Committee, by contrast, dedicated the patent on Liver Extract 343 to the public and tested only Lilly's preparation. The University of Rochester divorced itself from the marketing of Liver Extract 55, although it accepted royalties and other fees from Lilly far above testing expenses. Rochester basically allowed Lilly to patent and market any extract it wished to develop cooperatively. The Insulin Committee pursued their course, they said, to protect the diabetic. This by no means indicates that the Pernicious Anemia Committee or Whipple cared less about the anemic patient. The

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[66]William P. Murphy to Henry Berlin, 17 August 1927, box 1, P. A. Committee, Harvard.

Harvard Committee claimed that the pharmacological circumstances of their liver extract prevented them from pursuing a course similar to Toronto's. Whipple's personal opinion of medical patents taken out by academics motivated his decision to avoid having the University of Rochester exercise any kind of Torontonian controls over the liver extract market. All three universities had very different reasons for dealing with the commercial applications of their discoveries the way they did. Harvard and Rochester also may have had in mind the inconvenience and expense of supervising liver extracts of several firms, particularly Rochester, a medical school barely on its feet in the early 1930s.

As in the Toronto-Lilly cooperative project, the liver extract collaborators derived benefits from their association. Harvard did not receive any compensation from the sale of Liver Extract 343 per se, but Lilly supported the later research of a few members of the Pernicious Anemia Committee, Minot most notably. Minot received grants from the company of $5,000 per year from 1928 through 1936. Lilly continued the support from 1937 until Minot's death in 1950, at $6,500 yearly, for a total in excess of $100,000 of support during the post-collaboration period.[67] For Minot, this money was support for research on pernicious anemia and other blood disorders. For Lilly, it was

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[67]George R. Minot to [G. H. A.] Clowes, 10 April 1928, "Lilly Laboratories, Liver Extract," box 3, P. A. Committee, Harvard; Minutes, Research Committee, Eli Lilly and Company, Committee Report no. 10, 1 July 1942, "Research Committee, 1942," +XRDj, Lilly Archives; J. K. Lilly, Jr. to James B. Conant, 31 May 1950, "Grants, Fellowships and Awards to Harvard University, 31 May-5 June 1950," XCAc, ibid.; and J. K. Lilly, Jr. to [E. C.] Kleiderer, ibid.

". . . part compensation for favors in [the] early days of liver extracts."[68]

Rochester's compensation was no less impressive. The required testing of the liver extracts did not burden Whipple's research. Rather, Lilly's royalties and fees paid to Rochester supported a broad research program in Whipple's laboratory. Whipple reflected near the end of the collaboration:

> Much of the money coming to this department as a result of these contracts has been used to further our research program, dealing not only with experimental anemia, but with general body pigment metabolism and the complex reactions of various proteins in the body, within the blood plasma, within the tissue fluid and within organ parenchymal cells; the whole complex problem designated as "a dynamic equilibrium of body proteins."[69]

The funds also supported the University of Rochester Medical School overall. Over the years, Whipple had set aside Lilly funds, above those required to support both the testing expenses and his own research program, into a Lilly Research Fund. Two years before his retirement, Whipple proposed a few ways to disburse the Fund, which by this time (1953) had grown to about $700,000. First, $250,000 would go towards the establishment of a chair in the Department of Pathology. Second, $300,000 would be spent on a scholarship program for premedical and medical students at Rochester, and for fourth-year medical students. Finally, Whipple suggested that $75,000 be used to endow visiting lectureships in physiology, biochemistry, and pediatrics. The

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[68]Minot to Clowes, 10 April 1928, and Minutes, Lilly Research Committee, 1 July 1942.

[69]G. H. Whipple to Eli Lilly, 4 January 1955, "Liver Extract No. 55, 1930-," Lilly Archives.

University Trustees would use the remainder at their discretion. As he requested, the Trustees effected Whipple's proposals upon his retirement.[70]

Lilly derived direct and indirect benefits from the liver extract collaborations, too. For example, while Harvard no longer guaranteed Lilly's liver extract, they were willing to serve as one of the clinics to test Liver Extract 343 after the collaboration. In addition, Minot assured the company that Harvard would keep Lilly abreast of the latest developments at the Medical School. Thus he suggested that Lilly approach Cohn about mass producing an extract which he was on the verge of obtaining, a liver extract pure enough for intravenous injection. Five years later Harvard was still keeping Lilly up-to-date on their progress with injectable liver extract.[71] Both of Lilly's extracts for pernicious and secondary anemia sold well. In 1933, Lilly introduced Lextron, a shotgun approach to anemia therapy. This preparation included Liver Extract 55, the pernicious anemia principle,[72] iron, and

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[70]G. H. Whipple to Raymond L. Thompson, 21 April 1953, "Liver Extract No. 55, 1930-," Lilly Archives, and Corner, Whipple, 287-288.

[71]George R. Minot to [J. K.?] Lilly, 25 June 1929, "Liver Extract No. 343: 1928 ff.," Lilly Archives, and L. G. Zerfas to Eli Lilly and G. H. A. Clowes, 8 November 1934, "Post-Clinical, Liver Extract 343 and 55; Nobel Prize," ibid. On the work at Harvard in the early 1930s dealing with injectable liver extracts for pernicious anemia, see Maxwell Finland and William Castle, The Harvard Medical Unit at Boston City Hospital, 2 vols. in 3 (Boston: Harvard Medical School, 1982), vol. 1, pp. 22, 250.

[72]This principle was not Liver Extract 343, but dessicated hog stomach lining, an innovation stemming from William Castle's research on the connection between pernicious anemia and defective gastric digestion, beginning in 1927. Castle had found that the partially digested stomach contents of a normal person following a meal of meat could elicit a positive response when fed to the pernicious anemia patient. Castle

to stimulate the appetite, vitamins B_1 and B_2. Despite receiving some criticism from the medical community for marketing such a multipurpose remedy,[73] Lextron was an especially popular anemia remedy.

The prestige afforded by collaborating with another pair of Nobel laureates enhanced Lilly's established image as a progressive, research-oriented company. It is no coincidence that Lilly's contacts with academic workers grew to 18 by 1930 (see Chapter 3). The reputation of Lilly's Clinical Research Laboratories, under Zerfas, grew as well. This was one of only a handful of medical centers that took part in the early testing of pernicious anemia liver extracts under the supervision of Harvard's Pernicious Anemia Committee.[74] In summary, the liver extract projects produced solid rewards for the collaborators. For Minot (indirectly, through goodwill grants) and Whipple (directly, through royalties and fees for assay work), the collaborations were the source of considerable research support for the rest of their careers. For Lilly, the collaborations satisfied both the business and scientific interests of the company. The projects yielded drugs that fared very well in the market, and they reinforced Lilly's image among the academic community as an enlightened pharmaceutical

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explained his results by assuming the existence of a factor in gastric secretions that helped to assimilate the component in certain foods that were beneficial in pernicious anemia. This gastric factor was *faulty or lacking in pernicious anemia patients*. By 1929, two University of Michigan workers applied Castle's results to discover the value of dried hog stomachs in pernicious anemia. See Kass, Pernicious Anemia, 43-44; Strauss, "Medicine, Men and Molecules," 620-621; and Castle, "Pernicious Anemia," 303-304.

[73]Walden, interview by McCormick, 5 November 1968, p. 21.

[74]Zerfas, interview by McCormick, 22 and 25 October 1968, pp. 35-36.

firm. For the public health, the collaborations on liver extracts may not have been as crucial as the joint work on insulin, but the liver extracts nonetheless were an important addition to the therapeutic armamentarium.

CHAPTER 8

EPILOGUE: COLLABORATIVE RESEARCH TODAY

Research interactions between academe and industry grew rapidly during the 1920s and 1930s. In the decades following World War Two, however, such contacts slowly weakened, and reached their depth by the early 1970s. Some experts on science and technology policy have partially blamed this decreasing level of collaborative research for the decline of American industrial innovation.[1] Several reasons account for this change. First, the post-World War Two era witnessed the rise of mega-support for academic research by the federal government. Consequently, university researchers had less incentive to engage in work for industry. In particular, the support that federal defense and aerospace agencies offered to academic scientists led more and more of the latter to focus on the "performance improvements" of high technology rather than the "cost improvements" of other industrial research. Second, graduate students increasingly lost interest in industrial research careers, as more federal funds filled university research coffers, and as higher education in general expanded in the post-war years. Faculty appointments seemed more promising than in the past, and professors began training their students primarily for positions in academe. Finally, industry's involvement in basic research declined; firms supported less basic research in universities after the mid-1950s. This eroded an important point of contact for academic and

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[1]See, e.g., Denis J. Prager and Gilbert S. Omenn, "Research Innovation and University-Industry Linkages," Science 207 (1980):379-384.

industrial scientists.[2]

In the late 1970s and early 1980s, however, research links between academe and industry were on the rise again. The purchasing power of the research dollar plummeted in the inflated economy, and competition for federal research support intensified within academe. At the same time, growing federal regulations over experimentation challenged the flexibility and independence of the academic investigator. From the standpoint of American industry, stiffening competition from abroad and the need to meet environmental, health, and safety regulations called for a reinvigorated, science-based technology.[3] Both sides had strong incentives to step up research connections. Representatives from universities and firms advocated more links between the two estates of science, urged educators to facilitate interactions through industry-oriented coursework, and even issued extensive guidelines for effective research agreements between academe and industry. Today the more common issue is not whether to collaborate, but how to collaborate.[4]

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[2]Bruce L. R. Smith and Joseph J. Karlesky, eds., The State of Academic Science, 2 vols., The Universities in the Nation's Research Effort (vol. 1), Background Papers (vol. 2), (New York: Change Magazine Press, 1977-1978), 1:62-64.

[3]Prager and Omenn, "University-Industry Linkages," 380.

[4]See, e.g., "ACS Ninth Biennial Education Conference," Journal of Chemical Education 53 (1976):672-674; Robert D. Varrin and Diane S. Kukich, "Guidelines for Industry-Sponsored Research at Universities," Science 227 (1985):385-388; Lois S. Peters and Herbert I. Fusfeld, "Current U.S. University/Industry Research Connections," in University-Industry Research Relationships: Selected Studies, Report of the National Science Board of the National Science Foundation, [Washington, D.C.: Government Printing Office, c. 1982,] 1-161; and Prager and Omenn, "University-Industry Linkages," 379-384.

Academe and industry have developed a wide variety of research contacts in recent years. Industrial research parks near universities, for example, are becoming a popular way to establish links between industry and academe. Nearly four dozen universities are actively engaged in or seriously considering establishing such research parks, including major research institutions like Wisconsin and Yale.[5] A few universities have had successful research parks for over twenty years, most notably the Stanford Research Park and a joint venture of North Carolina, North Carolina State, and Duke, the Research Triangle Park.

Typically, a number of firms representing chemical, electronics, pharmaceutical, communications, and other industries rent space in these parks for multidisciplinary research and development facilities. Research parks can contribute significantly to a university's funds. The Princeton Forrestal Center, for example, concludes 50-year prepaid leases with its industrial tenants, for an average of $250,000 per acre.[6] Since these parks can create thousands of new jobs (the Princeton Forrestal Center and the Stanford Research Park employ about 5000 and 26,000 people, respectively), it is not unusual for local and state governments to provide investigative funding for these projects, as in the case of New Haven and North Carolina. Ideally, from the standpoint of industry, research parks facilitate the integration of university research into commercial products, particularly through consultantships. However, a recent survey of research parks suggests

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[5]"Attracting the Research Dollar," New York Times, 9 March 1985.

[6]Ibid.

that few so far have stimulated a transfer of technology from universities to industry.[7]

Research consortia are another popular way by which academe and industry have developed links. In this case, a group of firms pay a fee to support research at a single university in area in which the university excels. The participating firms receive special reports, briefings, and access to university facilities. Cornell, Michigan, Wisconsin, Minnesota, and the University of Washington, among others, engage in consortial interactions with industry. The MIT Polymer Processing Program involves a dozen companies, including Xerox, ITT, and General Motors, which pay up to $100,000 annually to support about 25 projects connected with polymer research.[8] Compared to research consortia, industrial associates programs are much broader in nature. In these programs, several companies pay a fee to have access to research in many areas at a single university. Industrial associates programs are especially useful to firms interested in getting an overview of a new field. The university in turn arranges faculty contacts with companies, provides directories of current research, and makes courses and symposia available to participating firms. The number of member companies and the fees involved vary from program to program. MIT has the most extensive industrial associates program, which began

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[7]Ibid.; Peters and Fusfeld, "Current University/Industry Research Connections," 107; and Smith and Karlesky, State of Academic Science, 1:73-74.

[8]Peters and Fusfeld, "Current University/Industry Research Connections," 81-82, 139; Smith and Karlesky, State of Academic Science, 1:68-70; and Prager and Omenn, "University-Industry Linkages," 381-382.

in the late 1940s; 265 companies take part, and pay a total of $4 million annually in fees.[9]

These and many other examples of general links between universities and industry suggest that collaboration is stronger than ever today.[10] Cooperative research in the biomedical sciences is very much a part of this trend. The pharmaceutical industry continues to be one of the most research-conscious industries in the United States. Drug companies spent $2.8 billion on research and development in 1982 (13.8 percent of total sales), and an estimated $3.3 billion in 1983 (14.4 percent of sales).[11] Also, the pharmaceutical industry is still one of the most research intensive industries, as witnessed by the number of research and development scientists and engineers per 1000 total employees in the drug industry (62), compared to the proportion of research personnel in the chemical industry (41 per 1000) and the average for all industries (27).[12]

The drug industry clearly has the resources to support work in academe, and the manpower to carry out joint projects with university workers. Although the industry devotes only about two percent of its

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[9]Peters and Fusfeld, "Current University/Industry Research Connections," 92-93, 139, and Prager and Omenn, "University-Industry Linkages," 381.

[10]See the extensive study by Peters and Fusfeld, "Current University/Industry Research Connections."

[11]The Pharmaceutical Manufacturers Association compiled these data; see "Pharmaceutical R and D Expenditures Estimated at $3.3 Billion for 1983," American Pharmacy, n.s. 25 (1985):266.

[12]Lois S. Peters, "Pharmaceuticals," Technology in Society," 5 (1983): 191.

research budget to the support of fundamental research in universities (which is one-tenth of what firms spend for clinical testing of drugs), this amounts to over $50 million annually.[13] In pharmacy schools alone, an announcement of the latest awards and grants to pharmacy faculty indicated that firms funded nearly three dozen grants, worth over one million dollars.[14] Long-term agreements for research in the biomedical sciences have surfaced in recent years. Harvard Medical School, for example, entered into extended research partnerships with Du Pont, Hoechst, and Monsanto, separately, for work in molecular genetics, medicine, and biology; the firms provide both financial and scientific support. In the Harvard-Monsanto agreement, which lasts from 1975 to 1987, the company is providing up to $23 million in funds, as well as supplying starting materials, analytical services, and developmental expertise. In return, Monsanto will receive limited-term exclusive licenses on all patents that Harvard receives based on Monsanto-supported research.[15] The pharmaceutical industry still relies heavily on consultants, as it did in the 1920s and 1930s. Many firms have 100 or more consultants on retainer.[16]

Academic scientists, too, are taking the initiative to stimulate contacts with industry scientists. In 1979, the University of

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[13]Ibid., 192.

[14]"Grants and Awards," American Journal of Pharmaceutical Education 49 (1985):224-227.

[15]Smith and Karlesky, State of Academic Science, 1:66; Prager and Omenn, "University-Industry Linkages," 382; and Peters and Fusfeld, "Current University/Industry Research Connections," 20, 137-138.

[16]Peters, "Pharmaceuticals," 192.

Wisconsin School of Pharmacy established the Louis W. Busse Lectures as a tribute to a retiring faculty member who had close contact with industrial pharmaceutical research throughout his career at Wisconsin. The School invites a distinguished scientist from the drug industry to spend one week every year giving lectures and interacting with graduate students at the School of Pharmacy. According to the Dean of the School who organized the program, the Busse Lectures provide an opportunity for "valuable contact between industrial scientists and our students and faculty."[17]

The Academy of Pharmaceutical Sciences of the American Pharmaceutical Association, in conjunction with the American Association of Colleges of Pharmacy and the Pharmaceutical Manufacturers Association, will launch a broader program late in 1985 to put industrial scientists in contact with pharmacy schools. This so-called "Pharmaceutical Industry Visiting Scientist Program for Colleges of Pharmacy" will consist of one- or two-day lecture programs by industrial workers in pharmacy schools. According to the sponsors, the Visiting Scientist Program will stimulate interest in graduate work among pharmacy students, give pharmacy schools access to the expertise of industry scientists, encourage communication between the pharmaceutical industry and

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[17]George Zografi, circular letter of 5 April 1978, A(2) "Busse, Louis W.," Kremers Reference Files, F. B. Power Pharmaceutical Library, University of Wisconsin, Madison, Wisconsin (quotation); idem to Pharmaceutics Group, 11 January 1979, "Busse Lectures, 1980," Files, Dean's Office, University of Wisconsin School of Pharmacy, Madison, Wisconsin; and "First Annual Busse Lecture to Be Presented at U.W.," press release, 18 July 1979, Center for Health Sciences of the University of Wisconsin, ibid. The first Busse Lecturer, Everett N. Hiestand, was a senior scientist at Upjohn and an adjunct professor at the University of Michigan.

pharmacy schools, and serve as a public relations vehicle for industry's concerns such as costs associated with drug discovery.[18]

We cannot necessarily assume that the future of collaborative research is secure simply because it has experienced a renaissance in the past decade. Many social, economic, and scientific factors conducive to joint research between academe and industry must remain in effect for collaborative research to be a reality. University scientists, for example, must foster attitudes favorable to, or at least tolerant of, industry. Visions of academic research like that which G. Stanley Hall promoted in the late 19th century are inimical to cooperative research with industry. On the other hand, industry must have a favorable or tolerant perception of academic work. Industry, as J. K. Lilly argued, serves as its own endowment, and certainly has the right to expect a return on its investments in academic research. But companies must understand that the long-term investments in fundamental research are just as important as the short-term investments in applied work. Essentially, collaboration, by definition, is not a one-sided enterprise. As long as academe and industry appreciate the symbiotic nature of collaborative research, and as long as both sides appreciate the potential benefit of collaborative research to public health in terms of progress in therapeutics, the pooling of academic and industrial resources will be a mainstay of American biomedical research.

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[18]"Visiting Scientist Program Launched as Tripartite Project," Academy Reporter (of the Academy of Pharmaceutical Sciences, American Pharmaceutical Association) 21, no. 2 (1985):1, 10.

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