

El Lilly: A Life. 1885-1977



James H. Madison

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For Jeanne

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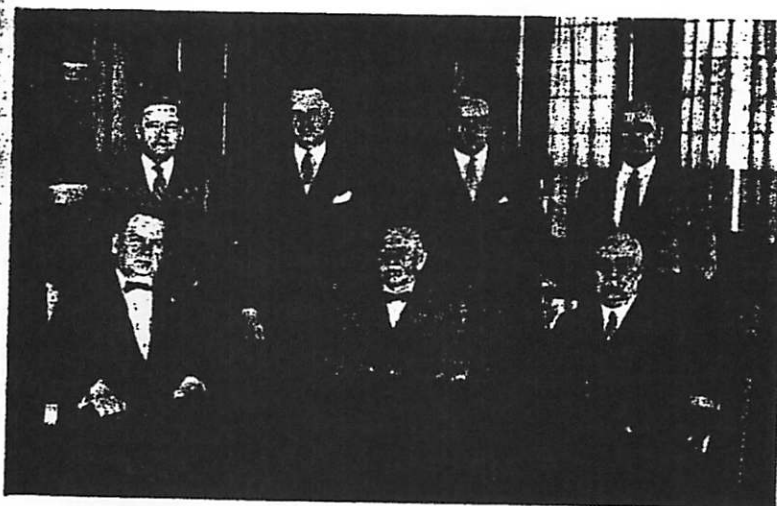
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Eli Lilly and Company Board of Directors, 1927. *Eli Lilly and Company Archives*
Left to right (seated): C. J. Lynn, James E. Lilly,
J. K. Lilly; left to right (standing): J. S. Wright,
N. H. Noyes, J. K. Lilly, Jr., Eli Lilly.

systematic management. Without these preparations the Indianapolis
company would not have been ready for the long trip to Toronto. "It was,"
Lilly later recalled, "as if we had rushed ourselves to a point of readiness
just to participate in this momentous event."⁵⁸

The success of insulin helped spark the rapid evolution of a more
sophisticated and systematic research effort at Eli Lilly and Company. Eli
and J. K. Lilly, Sr., were determined to develop new specialities. They hired
more scientists, who devoted more effort to research. And they paid more
attention to developing ties with university scientists. These trends toward
more emphasis on research were under way also at a few other American
pharmaceutical companies, but the Indianapolis firm was in the very front
rank of this shift.⁵⁹

Although not an active scientist himself, Eli Lilly became increasingly
involved in research administration during the 1920s, often building on

his experience with insulin and generally bringing to bear his enthusiasm for more systematic procedures. One of his major initiatives was establishing formal ties to university scientists. Building on the German model, several American research-oriented companies began closer cooperation with universities in the 1920s, and university scientists, in turn, became more receptive to industrial research, though there remained some academic reluctance and even stigma associated with commercially supported science.⁶⁰ Lilly's major reach into the ivory tower came with a program of research fellowships, which he began in 1928. Within a year he had set up fourteen fellowships, extending from Yale University to the University of California. By 1930 the number had expanded to eighteen, including a fellowship at the University of Munich, "to keep in touch with the important work going on in Europe."⁶¹

In planning the university fellowship program Lilly evidenced his customary attention to system. Rather than depend solely on Clowes' personal ties to the scientific community, as had been the case before insulin, Lilly developed a program that relied on other members of the research staff and depended on the growing prestige of the company rather than on one individual. These fellowships, Lilly wrote in 1929, "have increased the friendliness of the faculties of the various Universities for our house. Various members of our staff are now very welcome in most of the medical centers." As part of the fellowship program, Lilly established procedures to identify productive university laboratories and to prepare a "cream list" of "the men most important in research." He encouraged company researchers always to travel with this cream list, especially as they made their periodic visits to fellowship holders.⁶²

As the research program expanded in size and importance, there was the inevitable growth of confusion and uncertainty about objectives and responsibilities. As director of research, Clowes had the vision to see the need for generously supported fundamental research. Clowes worked hard and deluged Lilly with proposals and questions.⁶³ But Clowes had an impatience for detail and for the day-to-day administration of a growing research laboratory. He became, some thought, more stubborn and aloof, and there was often friction with other scientists. His long absences in the summers, when he worked in the company-financed laboratory at Woods Hole, Massachusetts, left the Indianapolis staff to their own devices, often happily so.⁶⁴ One particular conflict developed over a proposal to set up a company-sponsored research clinic at Indianapolis City Hospital. Clowes and Leon G. Zervas, the physician in charge of the clinic, had many quarrels over

details of the project. Even though on one occasion Woods Hole in September clinical effort will have a return. In the meantime have nothing to do with

The combination of interests doubtless prompted in 1926, giving more Rhodochel, who served important, in the late 19 regular research committee. Eclectic methods, Lilly encouraged those attending the result, Zervas later resigned on some subject. President Lilly, who often traveling, one scientist regular research meetings of conversations with Clowes and decision making to

The stepped-up attention. The most important problems, were Amytal, Meperidine, a barbituric acid derivative, and an indicator of the growth of work in organic chemistry introduced in 1930 after Clowes had with support of a company. It derived from the fact that he was educated at the University. He had visited Eli Lilly and had obtained ephedrine from the Massachusetts. Following his return to Indianapolis and convinced him of the need for receiving more orders for the product. Later Chen joined the company in the position he held until

details of the project. In such instances Lilly often became the arbiter, though on one occasion, at least, he, too, lost patience. Writing Clowes at Woods Hole in September 1924, Lilly exploded: "I suppose our whole clinical effort will have to wallow along like a dismasted frigate until you return. In the meantime I wash my hands of all responsibility, and will have nothing to do with it."⁶⁵

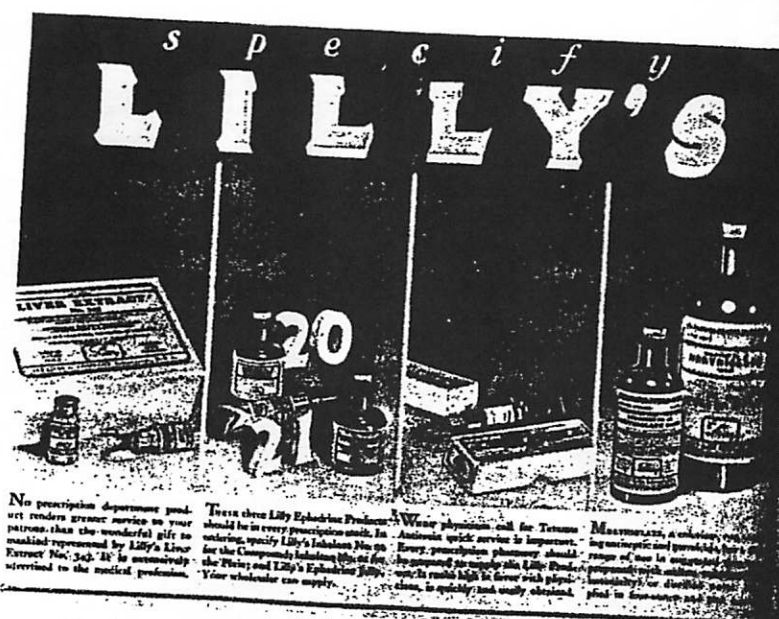
The combination of company expansion and Clowes's particular interests doubtless prompted Lilly's reorganization of the Scientific Division in 1926, giving more responsibility to others, particularly Harley W. Rhodemann, who served as director of research development. Even more important, in the late 1920s Lilly took the responsibility to call and chair regular research committee meetings. In contrast to Clowes's informal and eclectic methods, Lilly sent a formal agenda in advance of the meeting and encouraged those attending to discuss issues and proposals openly, with the result, Zervas later remembered, of "an oftentimes verbal knock-down, shake-out on some subjects."⁶⁶ Each scientist had his say directly to Vice-President Lilly, who often made the necessary decision. "It was a marvelous feeling," one scientist recalled, to have Lilly chair these sessions.⁶⁷ These regular research meetings replaced the "time-consuming, irregular jumble" of conversations with Clowes and brought more systematic communication and decision making to the growing Scientific Division.⁶⁸

The stepped-up attention to research in the 1920s produced results. The most important products introduced by the company, in addition to Iletin, were Amytal, Merthiolate, ephedrine, and liver extract.⁶⁹ Amytal was a barbituric acid derivative, the first American sedative of this kind and an indicator of the growing sophistication of the Indianapolis company's work in organic chemistry. Merthiolate was the antiseptic and germicide introduced in 1930 after it had been formulated at the University of Maryland with support of a company research fellowship. Ephedrine was more exotic. It derived from the work of Ko Kuei Chen. Born in China, Chen was educated at the University of Wisconsin, where as a pharmacy student he had visited Eli Lilly and Company. On his return to China, Chen isolated ephedrine from the Ma Huang plant and demonstrated its effectiveness as a vasoconstrictor, useful in treatment of asthma, hay fever, and allergies. Following his return to the United States in 1925, he met with Eli Lilly and convinced him of the value of ephedrine. By 1926 the company was receiving more orders for the versatile drug than it could fill. Three years later Chen joined the company as director of pharmacological research, the position he held until his retirement in 1963. Highly impressed earlier

to bear his enthusiasm for his establishment of the German model, in closer cooperation with, in turn, became a supported science.⁶⁰ program of research had set up fourteen university of California. including a fellowship at important work going

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Advertisement, early 1930s.

Eli Lilly and Company Archives

by the company's role in insulin, Chen soon became a great admirer of the Lillys and the independence they permitted researchers. His highly productive research career later won him the Remington Medal of the American Pharmaceutical Association. Chen was a man of broad tastes. He had an interest in Chinese art and later advised Eli Lilly on collecting it. Chen also loved playing the tuba and watching the spectacle of college football marching bands.⁷⁰

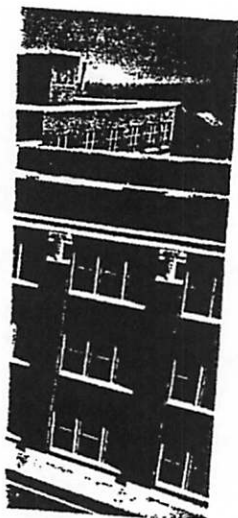
The development of liver extract came close to home for the pharmaceutical family. Eli's mother, Lilly Ridgely Lilly, began to suffer from pernicious anemia, an abnormality in blood production that was once nearly as deadly as diabetes had been. By early 1927 she had reached the stage where she could not tolerate the blandest foods. Through Zervas, who had been studying the condition before Mrs. Lilly developed it, the family was able to bring to Indianapolis George R. Minot, a Harvard physician who was then making important breakthroughs on pernicious anemia. Minot prescribed a treatment for Mrs. Lilly of a calf's liver extract that had

in the short term, near company's earlier interest in collaboration with Minot. The Harvard scientists agreed with the Indianapolis firm. Their earlier success in this together they developed a uniform liver extract (Lilly No. 55). This project won George Whipple of the treatment for second-degree liver extract No. 55.⁷¹

All parties to the treatment, Minot, Murphy, and Whipple, the Indianapolis company, and the collaboration in the Progress Through Research.

The work on anemia built on the model lessons learned from the collaboration contributed to scientists and businessmen and such matters as drug values, which Lilly overcame in 1922-23. By then, which contained which he would share with outside researchers, subjected to Lilly's drive.

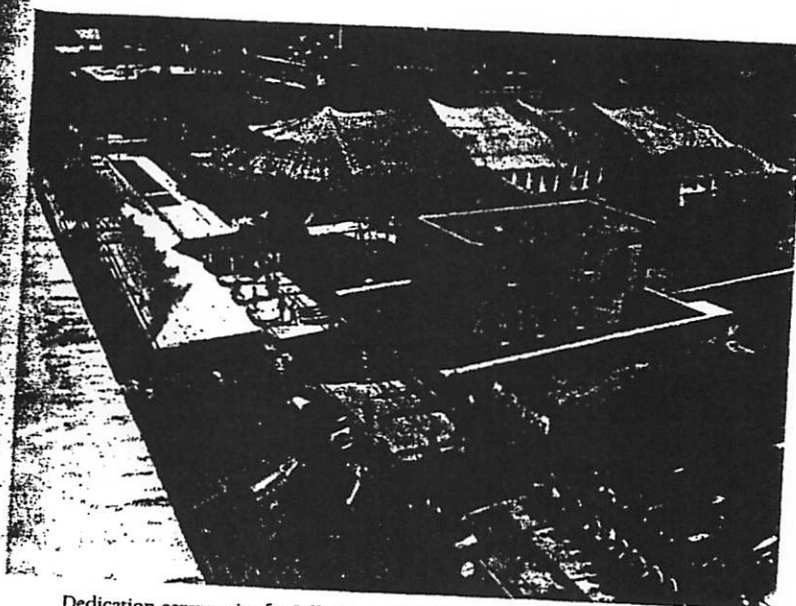
That drive was unbroken success. By the start of the decade, Eli Lilly, nurtured by his father, the values of modern business in America. He was not,



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Dedication ceremonies for Lilly Research Labora-
tories, with the 1876 replica in center. Eli Lilly and Company Archives

H Noyes, argued against such a lavish building project in the depths of the Great Depression. Lilly stood his ground, responding that research was more important than large dividends to stockholders. Excavation began in the summer of 1933.⁵

Dedication of the new Lilly Research Laboratories occurred on a bright autumn day in 1934. Four hundred scientists came from major universities in America and Europe. More than a thousand visitors gathered for lunch under a huge tent set up outside the new building. President Lilly presided over the ceremonies. He introduced each of the four main speakers: his father; Irving Langmuir, associate director of the Research Laboratories of General Electric Company and recipient of the Nobel Prize in chemistry in 1932; Sir Frederick Banting, the University of Toronto scientist who had received the Nobel Prize in 1923 for his insulin work; and Sir Henry Dale, director of the National Institute for Medical Research, London, and one of the most distinguished scientists in Britain. A dinner in the evening provided the occasion for remarks from seven eminent scientists. The next day included research seminars and tours of the new

laboratories. Visitors saw a most impressive three-story building, with an entrance hall of Italian marble and with laboratories fitted out with the latest scientific equipment.⁶

The dedication ceremony was a bright showcase for the Indianapolis company's achievements in research. Nearly all the distinguished speakers commented on the company's successes, particularly the work on insulin. They could not but be impressed by the new laboratories and by the research staff, which was one of the largest in the industry. No one proposed, however, that the enterprise could rest on the laurels of insulin, liver extract, or Merthiolate. The competitive environment of the pharmaceutical industry made that clear, for at least three other companies, Merck, Squibb, and Abbott, were also building special research laboratories in the 1930s.⁷

Although the building dedicated in 1934 enabled an expansion of research activity on McCarty Street, the firm continued to rely also on cooperation with university scientists. Most important, Eli Lilly expanded the fellowship program he had begun in 1928. Through the 1930s he oversaw an increasingly elaborate system of contacts with university scientists in which company fellowships were the key ingredient. He urged careful screening of university scientists to be sure that the company was "dealing with a man or men of exceptional ability and trustworthiness." By 1942 forty-five scientists in twenty-seven universities and medical schools received fellowship support from the company. In negotiating with university researchers, Lilly pointed to the company's production and sales expertise and to its record of respect for serious research, suggesting that cooperation with Indianapolis had led to successes as grand as the Nobel Prize.⁸

Lilly continued also to chair meetings of the research committee, held in the library of the new laboratory building. Part of his challenge in these meetings was to ease the tension between those workers devoted primarily to fundamental research and those more interested in products with immediate and practical medical applications. The general problem was omnipresent in most sophisticated American companies engaged in research. One position at McCarty Street was represented most vigorously by George Henry Alexander Clowes. In a thirty-two-page confidential memorandum to Lilly, a "sort of Last Will and Testament," written in late 1944, Clowes summarized the case he had long argued. He expressed his disdain for practical-minded medical doctors and profit-oriented business executives who failed to appreciate the importance of fundamental research: "the more we build up desk executives who are not greatly interested in the fine

points of research but are to the company and part of ultimate deterioration." to separate research into group, headed by a Ph.D. sphere (but with higher development group, with their energies on finding

Clowes's antagonism headed the Lilly Clinic a drugs through systematic and doubtless the man oriented executives, was increasing responsibility. Lilly tried to please both irrepressible Clowes, even a bull-in-the-china shop. Clowes hastily assigned it underway and then rushed to Massachusetts, leaving a state of Clowes because, he wrote, have developed virtually our catalogue."¹⁰ It was emerged in the 1930s. research development, by the company, he listed Merthiolate, all products

Eli Lilly allowed Clowes in cancer, but he did not be separated from applied hand in hand. Moreover attention to medical research. Clowes's nemesis, Adair research, a move doubtless the laboratories.¹²

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points of research but are tremendously interested in the financial returns to the company and particularly to themselves the greater is the danger of ultimate deterioration." It was necessary, therefore, Clowes advised Lilly, to separate research into two functional divisions: a fundamental research group, headed by a Ph.D. scientist and working in a university-like atmosphere (but with higher pay than professors); and a separate industrial development group, with a staff composed largely of M.D.s who focused their energies on finding immediate medical applications for new drugs.⁹

Clowes's antagonists included Leon Zerfas, a medical doctor who headed the Lilly Clinic and urged more attention to medical application of drugs through systematic clinical studies. Also disagreeing with Clowes, and doubtless the man Clowes most had in mind in criticizing profit-oriented executives, was Adam H. Fiske, a hard-driving administrator whose increasing responsibilities in research annoyed some company scientists. Lilly tried to please both factions. He remained loyal to the egotistical and irrepressible Clowes, even when J. K. Lilly, Jr., strongly condemned "the bull-in-the-china shop tactics of our friend Clowes." Joe was furious that Clowes hastily assigned theoretical work without regard for projects already underway and then rushed off to his laboratory in Woods Hole, Massachusetts, leaving a state of "virtual chaos" in Indianapolis. Joe also condemned Clowes because, he wrote in 1940, "for five years . . . our research men have developed virtually nothing in the way of an important addition to our catalogue."¹⁰ It was indeed the case that relatively few new products emerged in the 1930s. When in 1938 J. P. Scott, the assistant director of research development, identified the five most important drugs introduced by the company, he listed Iletin, Amytal, ephedrine, liver extract, and Merthiolate, all products of the 1920s.¹¹

Eli Lilly allowed Clowes his freedom to pursue his own basic research in cancer, but he did not agree to Clowes's request that fundamental research be separated from applied research, arguing instead that the two must go hand in hand. Moreover, to Clowes's dismay, Lilly supported increased attention to medical research along practical lines. And in 1945 he appointed Clowes's nemesis, Adam Fiske, to the new position of vice-president for research, a move doubtless designed to bring more administrative order to the laboratories.¹²



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smaller and smaller pieces of paper for his letters and memoranda, causing comment and emulation in offices throughout the company. At home on Sunset Lane he closed off part of the house and turned back the thermostat to reduce heating oil consumption by 40 percent.⁴⁵

In a talk to employees at the end of the war Lilly summarized the difficulties the company had endured. "We have not had the proper space. . . . We have been short in trained personnel. . . . We have had inadequate equipment and our material shortages have dogged us at every turn. The result has been exasperation and a nerve wracking strain. . . ." ⁴⁶ Under these conditions output per worker declined sharply, causing special anguish for a company president who had always taken great pride in production efficiency. Profits also suffered. Although sales more than doubled in the war years, the large increase in taxes contributed to a balance sheet in which after-tax income as a percentage of sales dropped from 23.0 percent in 1940 to 10.5 percent in 1945. In addition to higher taxes there were more directives and controls from the federal government and its growing wartime agencies, particularly the Office of Price Administration, which closely watched drug prices. Research plans suffered, too, as scientists abandoned prewar programs in order to produce antimalarials, blood plasma, and penicillin.⁴⁷

Blood plasma was one of the first major production challenges and provided evidence of Lilly's cultivation of a wartime patriotic spirit. A year after Pearl Harbor Lilly wrote a friend that he was struggling under "an enormous avalanche of business at the pill foundry," but that the important work included producing ten thousand packages of blood plasma a week. Lilly took great pride in this work, which was done in cooperation with the American Red Cross. He refused to allow any company profit because he "didn't think it was the right thing for anybody to make any profit on blood which had been donated." By the war's end the firm had dried over two million pints of blood, about 20 percent of the United States' total.⁴⁸

War patriotism was evident also in the production of encephalitis vaccine. Not only did it require fifteen thousand white mice a week, but the vaccine was difficult and dangerous to produce. The risks were carefully explained to "our most careful girl operators in the Biological Department," Lilly wrote his father, and, with "real patriotism and bravery," all volunteered to do the job.⁴⁹ Lilly and the employees were particularly proud also of the Army-Navy "E" award granted for exceptional work.

The Indianapolis company made all manner of other drugs for special wartime demand. There was typhus and influenza vaccine, gas gangrene

antitoxin, and Merthiolate. Merthiolate was an army standard issue, and twenty-two tank cars of this popular antiseptic departed from McCarty Street during the war.⁵⁰ Among the most important drugs and also among those causing the largest challenges were the old company standby of insulin (Insulin, Lilly) and the very new antibiotic, penicillin.

The major difficulty in producing insulin was caused by the wartime shortage of pancreas glands from which the hormone was manufactured. In addition to difficulties in obtaining pancreas glands from meat-packers there was the tendency of some Americans to hoard goods they thought might become scarce. Doubtless swayed by shortages of all manner of goods, from tires to toilet paper, diabetics panicked and began to purchase insulin far in advance of their needs. By the spring of 1943 Lilly and Clowes were deeply worried that the company was reaching a point where it could no longer supply the amount of insulin diabetics needed. The two men struggled fiercely with the problem. Lilly was convinced that the most fruitful mode of attack was to encourage "some of the best men in the country to work on the synthesis of a substance having action the same as or similar to Insulin." Synthesis of insulin was one of the most important problems facing the research division, Lilly told Clowes, and "we must do something about it in short order."⁵¹ Both men were convinced that development of a synthetic insulin would require interdisciplinary cooperation. "The problem," Clowes urged, "will never be solved by protein or biological chemists on the one hand or synthetic organic chemists on the other, working individually." Joint, interdisciplinary research, particularly by young scientists, they agreed, was required.⁵²

The obstacles to producing a synthetic insulin were twofold. First, the scientific problem was exceedingly complex, requiring not only the best talent, but also large quantities of labor and luck. Second, as Clowes several times reminded Lilly when he pushed for research on the problem, the company's and the nation's university scientists were strained to their limits by war work already underway. Clowes and Lilly continued to fret over the problem but failed to find an answer. Like many other Americans in wartime they crossed their fingers and muddled through. Insulin hoarding and shortages continued after the war, and not until mid-1947 did Clowes report that the company had begun to build up its reserve stock.⁵³

Many of the scientists most capable of working on insulin synthesis were fully engaged in twelve-hour days and seven-day weeks on a drug of major significance. Penicillin bore some resemblance to insulin in that it was soon proclaimed as a miracle drug, with powers beyond any imagined

and with demand far outstripping its scientific and hospital laboratory and hospital laboratory pharmaceutical company production involved the pharmaceutical company of the United States government, and the rest.

British scientist Alexander Fleming discovered penicillin in 1929. The antibiotic began, however, in 1941, with strains of the bacterium that traveled from a Nazi-occupied pharmaceutical company to persuade the Americans. Florey visited Eli Lilly and his researchers had already had no real success, partly with the fermentation process they converted to penicillin at the company's Greenfield Works. They were obtained a few days later.

Large-scale production of the new drug and the frantic search for the eventual cooperation of the United States on Medical Research of the War Relocation Authority, headed by Alfred N. Richards. In the wartime development of the Regional Research Laboratories, which gave much larger contributions than the Lilly and Company's. In October 1941, and in 1942, Lilly had close written communication with the Committee on Medical Research.

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and with demand far outstripping the capacity to produce.⁵⁴ Like insulin, penicillin had its scientific origins outside the United States and in university and hospital laboratories, followed by development in the modern pharmaceutical company. Unlike the case of insulin, large-scale penicillin production involved the efforts and sometimes the collaboration of many pharmaceutical companies rather than one and the close involvement also of the United States government. Penicillin came to symbolize one of World War II's most important consequences—the close interaction of business, government, and the research university.⁵⁵

British scientist Alexander Fleming published the pathbreaking article on penicillin in 1929. Not until 1940 did serious work to produce the antibiotic begin, however, led by Oxford University scientist Howard Florey. In 1941, with strains of Fleming's penicillin mold in his baggage, Florey traveled from a Nazi-besieged Britain to the United States. There he visited pharmaceutical companies and universities in an energetic campaign to persuade the Americans to attempt large-scale penicillin production. When Florey visited Eli Lilly and Company that summer before Pearl Harbor, researchers had already begun experiments with the antibiotic but had met no real success, partly because company scientists had little experience with the fermentation processes by which it was produced. Late in 1941 they converted to penicillin production a building that once housed rabbits at the company's Greenfield laboratories. The first yields in Indianapolis were obtained a few days after Pearl Harbor.⁵⁶

Large-scale production of penicillin proved an immense challenge. The technical difficulties combined with the unparalleled potential of the new drug and the frantic wartime demand to bring about the involvement and the eventual cooperation of many pharmaceutical companies, universities, and the United States government. In Washington the Committee on Medical Research of the Office of Scientific Research and Development, headed by Alfred N. Richards, provided coordination and strong direction in the wartime development of the new antibiotic. The government's Northern Regional Research Laboratory in Peoria, Illinois, made major technical contributions that it shared with pharmaceutical companies, most notably in the development of the submerged or deep fermentation procedure, which gave much larger yields than the surface culture method first used. Eli Lilly and Company sent scientists to visit the Peoria laboratory as early as October 1941, and its scientists and executives, particularly Clowes and Lilly, had close written and telephone contacts with Richards and the Committee on Medical Research.⁵⁷