working paper
department
of economics

# THE EVOLUTION OF THE MODERN PHARMACEUTICAL INDUSTRY

Peter Temin

Number 223 September 1978

massachusetts
institute of
technology

50 memorial drive
cambridge, mass. 02139

# THE EVOLUTION OF THE MODERN PHARMACEUTICAL INDUSTRY

Peter Temin

Number 223 September 1978

# THE EVOLUTION OF THE MODERN PHARMACEUTICAL INDUSTRY*

The discovery of sulfanilamide and penicillin between the two World Wars initiated a revolution in the production and distribution of drugs. Just as important, but less apparent, the increased government regulation of medicinal drugs at the close of the interwar period shaped the industry structure that this new technology gave rise to. Alfred Chandler has chronicled the industrial transformation that spread through the economy at the turn of the century, in response to both new production technologies and new marketing conditions.[1] The changes in drug technology and regulation correspond to the two changes noted by Chandler. Together they produced a revolution in the pharmaceutical industry comparable to the ones described by Chandler, but displaced in time by approximately half a century.

The story is interesting for several reasons. First, of course,the post-war pharmaceutical industry has been and still is a focus of recurrent Congressional concern. Second, it is interesting to see the interaction of new production technology and marketing conditions in the transformation of an industry. And third, the transformation in this industry differs in important ways from the archetypal pattern exposed by Chandler. Neither the degree of concentration nor the level of profits relative to all manufacturing rose in the course of this transformation. The nature of competition changed dramatically in the pharmaceutical industry, but not in the textbook fashion.

The four-firm concentration ratio stayed between 28 and 22 percent in the two decades following 1947, falling slightly within that range. The eight-firm concentration ratio fell from 44 percent in 1947 to 40 percent in 1968.[2] Stigler found in his study of manufacturing rates of return that the drug and toilet preparation industry's rate of return on corporate assets stayed over two standard deviations above the mean industry profit level, 1938-47, before the changes to be described. This discrepancy then fell, 1947-58, both absolutely and relative to the standard deviation of industry returns, while these changes were going on. Similarly, the high rates of return on equity in the drug industry found starting in the late 1950s were already present in the late 1940s.[3]

The story begins in the early 1930s. Drug companies in that decade were far different from the drug firms of today. They did not advertise to doctors because any non-narcotic drug could be purchased without a prescription before 1938. And they did not engage in large-scale research because drug technology was essentially fixed. The drug industry was another manufacturing industry in the 1930s. Drug manufacturers and distributors of the 1930s were working essentially within a known technology.

The range of products sold in the 1930s was described recently by the president of Merck, who joined one of the present firm's parent companies in 1937:

> You could count the basic medicines on the fingers of your two hands. Morphine, quinine,

> digitalis, insulin, codeine, aspirin, arsenicals, nitroglycerine, mercurials, and a few biologicals. Our own Sharp & Dohme catalog did not carry a single exclusive prescription medicine. We had a broad range of fluids, ointments, and extracts, as did other firms, but we placed heavy emphasis on biological medicines as well. Most of our products were sold without a prescription. And 43 percent of the prescription medicines were compounded by the pharmacist, as compared with 1.2 percent today.[4]

Digitalis and nitroglycerine were used for heart disease, the arsenicals and mercurials were primitive anti-infective agents, and the biologicals will be described shortly. "Exclusive prescription medicines" were non-existent before the post-war drug revolution; all ethical drugs were produced freely by more than one firm. Most ethical drugs, as the statement quoted asserts, were sold without prescription. And none of the drugs listed were the results of research done by the drug industry.

An exhaustive study of the cost of medicines in the early 1930s found an absence of controversy over the price of drugs. One explanation offered for the absence of conflict was that "medicines are relied upon by the public to cure or relieve conditions which do not interrupt the day's routine," and each patient "feels he can choose without disadvangage from among several brands of prepared medicines." The absence of serious illness in conditions involving drugs and the existence of choices apparently freed the sellers of drugs from the onus of charging too much. If a consumer did not like the price of any one medicine, he was free to buy another or do without. The price of drugs, the authors concluded, was no

different than the prices of automobiles, oranges, or theater tickets.[5]

Despite the absence of research, new products resulting from research, and controversy over the price of drugs, there was still a distinction between what we now call brand-name and generic products. The AMA exhibited a poster at its annual meetings during the 1920s showing that branded products cost approximately four times as much as the same products sold generically. The brand-name products were justified--then as now --on the basis of their convenience in prescribing and their excellent quality. The quality of branded products was proclaimed in the face of presumed universal compliance with USP and NF standards and without any arguments about bioavailability or comparable reasons to suspect them. The brand-name products were opposed on the grounds that their existence led to duplication of pharmacy stocks, raised prices, and encouraged self medication.[6] The context and the relative importance of brand-name or generic products were different, but the arguments and the profits from brand-name drugs are familiar.

Despite a large number of drugs existing in the early 1930s, there were still very few diseases that could be cured by drugs. Drugs could be used to reduce symptoms, to ease pain, or to induce sleep. But they could not in general be used to cure disease. A 1931 symposium on fighting diseases with drugs listed only seven diseases that could be controlled by the use of drugs. An additional seven were classified as partially controllable, while

others were stated to have as yet only inadequate preventives and cures.[7]

Of the seven diseases controllable with drugs, five of them (diptheria, smallpox, typhoid, rabies, and tetanus) were controlled by either vaccines or antitoxins. The two remaining diseases were controlled by man-made drugs: one (syphilis) by Paul Ehrlich's great discovery, Salversan, and the other (hookworm disease) by derivatives of carbon tetrachloride. The distinction between vaccines and anti-toxins on the one hand and synthetic drugs on the other corresponds to Ehrlich's distinction between passive and active therapy, which can be used to organize the description of drug research before the discovery of sulfanilamide.[8]

Some bacterial diseases are the result of toxins produced by the bacteria. The toxins can be isolated and separated from the organisms that make them, and they are opposed within the human body by antitoxins which the body makes in an attempt to ward off or recover from the disease. A vaccine is composed of a small amount of a toxin that allows the body to produce enough antitoxins to become immune to larger incursions of the toxins, should they occur. The vaccine itself does not fight the disease. An antitoxin serum adds to the body's supplies of antitoxin to facilitate the victory of antitoxin over toxin. It is obtained by injecting a toxin into animals--vaccinating them--and recovering and concentrating the antitoxin that the animals produce. With both the vaccine and with the antitoxin, the chemical manipulations undertaken to produce the vaccine

or antitoxin do not create a substance that fights disease. Instead, they allow either people or animals to produce or supplement the body's supplies of antitoxins which in turn fight the disease.

Paul Ehrlich, regarded today as the father of modern chemotherapy, classified the use of vaccines and antitoxins as passive therapy, because the chemist was the body's second in the duel with disease, not a principal. The substances that fought the toxins were created by the patient or by a similarly infected organism, not by the chemist. In Ehrlich's immortal words: "The antibodies are magic bullets which find their targets by themselves."[9] The "magic bullets" of this sentence are the body's own products, although Ehrlich dedicated himself to the search for artificial "magic bullets" which would be similarly specific. His pursuit of active therapeutic agents was very important for the development of the theory of chemotherapy, but yielded only one new drug--Salversan.[10]

Instead, drug therapy made progress in other areas. Nutrition and the role of vitamins became better understood, although there was a persistent and understandable tendency to regard each new discovery as a panacea for all mankind's ills. Given the limits of known testing procedures and the optimism of the 1920s, it could hardly have been otherwise. And more and more biologicals, therapeutic products of man himself or of animals metabolically close to man, were found. The most dramatic of these was insulin, isolated in the early 1920s. Despite their importance in the treatment of syphilis

and diabetes, Salversan and insulin were dramatic, but isolated, steps in the development of medicinal drugs.

On the eve of what we now call the therapeutic revolution, then, progress appeared to be coming mostly from the realm of biological products. New man-made drugs derived from plants appeared from time to time, but systematic progress was being made only in isolating and producing toxins, antitoxins, and antibacterial serums. The future of drug research seemed to lie with Ehrlich's passive immunization. Thirty-two separate sera were developed for the thrity-two known strains of pneumonia, and the immunization idea was transfered to ailments that did not involve infectious diseases. The treatment for hay fever, consequently, was to inject the patient with an extract from the pollen of the offending plant. Sulfa drugs, antibiotics, and antihistamines were not just unknown; they were unanticipated.[11]

"The age of miracle drugs began with the announcement in 1935 that the first effective cure had been found for a number of bacterial diseases."[12] But the age of miracle drugs began slowly. As with any dramatic change, it took a while for observers and participants to realize the magnitude and extension of the revolution. The Federal Food, Drug, and Cosmetic Act was introduced into Congress in 1933, before the 1935 announcement. And the implications of that announcement were not appreciated until after 1938, when the Act passed.

There were in fact two announcements in 1935. In the first, Gerhard Domagk, a pharmacologist testing the antimicrobial properties of dyestuffs at I G. Farbenindustrie, announced the discovery of a new antiinfective called Prontosil. In the second, it was announced that Prontosil was decomposed by the body into two components and that one of them, sulfanilamide, was the active ingredient in Prontosil. The first announcement, therefore, reported a success in the tradition of Ehrlich. Extensive screening of chemical compounds had yielded another magic bullet that would destroy disease-causing micro-organisms without attacking the host. The second announcement rendered the patent on the new drug worthless by showing its active ingredient to be a substance that was first obtained in 1908 and allowed since then to go into the public domain. Anyone was free to manufacture the new drug.

There are several reasons why the discovery of sulfanilamide did not immediately revolutionize the drug industry. It took time to learn about the effects of this new drug and its newer derivatives and to discover which derivatives had what effects. Investigators in the 1930s had the example of Salversan and its tiny crop of derivative compounds before them; their expectations of further discoveries were not high. In addition, sulfanilamide was not produced under patent protection, and its production consequently did not generate enough profits either to finance or to stimulate a major program of chemical research. Even if it had, it is not clear that such a program would have been undertaken in such an apparently un-

promising direction in the midst of the Depression. And finally, when the Second World War brought prosperity to the drug industry, the sulfa drugs were partly superceded by penicillin and antibiotics in general as a focus for research. With the benefit of hindsight and with knowledge of the drugs developed from the sulfa drugs in the 1950s, we can see 1935 as the beginning of the age of miracle drugs. Only a seer could have seen the same in 1935.

To the extent that the Federal Food, Drug and Cosmetic Act was passed in reponse to the Elixir Sulfanilamide disaster, it appears as a legislative response to the new age. But this appearance is deceptive. The legislation was first introduced in 1933, well before the disaster. The section in the law dealing with new drugs was added in response to the Elixir Sulfanilamide disaster, but even this is not a response to the new age. The Elixir's problem was in the solvent, not in the sulfa drug. Diethylene glycol was not a new substance. The law consequently did not refer exclusively to newly produced chemical compounds; it referred to all substances newly introduced into use as drugs. The 1938 law was the product of regulatory experience under the old technology, not a response to the new.

An important section of the act provided for preregistration of new drugs with the FDA, giving the FDA the opportunity to prevent unsafe drugs from appearing on the market. Another part of the act increased the amount of information that a drug label was required to contain, subject to exceptions that

the FDA could specify. The regulations interpreting this provision created for the first time a distinction between over-the-counter drugs (which had detailed labels) and prescription drugs (which had limited labels and could not be sold except by a doctor's prescription). There previously had been prescription and over-the-couter sales, but any non-narcotic drugs could be bought either way.[13]

This regulation changed completely the way those drugs designated as prescription drugs were marketed. The customers were changed form individuals (patients) to doctors. While the advertising of "ethical" drugs had been directed at doctors before this time, most drug advertising still appeared in the popular press, not the technical medical literature.[14] As the number of prescription drugs increased--most new drugs were designated as such--the marketing of drugs was directed more and more at the medical profession. These new "customers" had a peculiar characteristic; they did not pay for the drugs they ordered. In fact, they often did not even know how much these drugs cost. As a result, the demand for prescription drugs was more inelastic than it would have been without the FDA's regulation on prescription sales. The demand for the post-war "wonder drugs" would have been quite inelastic in any case; the regulation decreased the elasticity of demand even further.[15]

Of all the new drugs, penicillin was the most important. Curing substantially the same infections that sulfa drugs did and then more in addition, penicillin captured the limelight from

its predecessor drug. Yet it is possible that penicillin might never have been developed if the sulfa drugs had not existed.

The antibacterial action of penicillium mold--as the precursers of penicillin were known--were observed several times in the late nineteenth century. The research extended up to animal trials that demonstrated the therapeutic usefulness of the primitive penicillin, but the implications of these trials were not realized until after the usefulness of penicillin had been demonstrated independently of them. The development of penicillin dates instead from Alexander Fleming's 1929 paper on the use of penicillium in laboratory investigations. And while Fleming appreciated the germicidal properties of his mold, even he was not sanguine about the possibility of developing it for therapeutic use. In 1929, Domagk had not yet broken the ice and made the realization of Ehrlich's dream seem possible.[16]

The medical history of penicillin began during the Second World War when British scientists at Oxford undertook the study and development of penicillin as a germ killer. The combination of the Second World War, increasing the demand for anti-infective agents, and the discovery of sulfa drugs, increasing the perceived possibility of finding such agents, had changed the context in which research on penicillin took place. The Oxford team announced its first results in 1940 and detailed them the following year. Having demonstrated the therapeutic properties of penicillin, they then joined in a cooperative venture with the American military establishment

to discover production techniques for the new drug. New methods of culturing penicillin molds, new strains of penicillium, and selective breeding all contributed to enlarging the output of penicillin. The first successful human use of penicillin was in 1941. Only about 100 cases could be treated in 1942. But enough penicillin was being produced by the end of 1943 to satisfy the military demand. Prior to that time, as all viewers of old World-War-Two movies know, sulfa drugs were the standard wartime therapy.[17]

As the war wore on, the factors that had minimized the impact of the sulfanilamide discovery on people's expectations were systematically altered. Investigators began to accumulate knowledge about the therapeutic properties, the modes of activity, and the ease of manipulation of both sulfa drugs and penicillin. The discouraging specter of Ehrlich's long and largely fruitless investigations was replaced by the more promising experiences of Domagk, Fleming, and the Oxford team. Penicillin was no more patentable than sulfanilamide, since it was a known substance before its therapeutic properties were appreciated, but we may presume that the manufacture of scarce anti-infectives was nevertheless a profitable activity in wartime. The government spent almost three million dollars subsidizing penicillin research, sold the penicillin plants it built to private manufacturers at half their cost after the war, and allowed accelerated amortization on private construction.[18] The profitability of sulfa drug and penicillin production was further reinforced by the change in business climate around 1940; any investment with government blessing

looked better during the war than before. And, even though the discovery of penicillin distracted attention from the sulfa drugs, it showed that there was more than one route to the discovery of new and important drugs.

The result was a great mushrooming of drug research. The faint tentative stirrings of the late 1930s were encouraged and enlarged. The drug industry began to transform itself from a fairly typical manufacturing industry to one based on the continual progress of technical knowledge. This tranformation involved the development of a new technology, the growth of a new industry structure, and the marked intensification of certain older marketing practices. The new technology grew from the exploration of the research opportunities opened up by the possibility of finding new sulfa drugs and new antibiotics. It would be hard to say which line has been more productive, but the latter is more amply documented. Our story therefore will trace the development of the "wonder drugs" of the post-war years, the antibiotics, and the changes in the industry that accompanied their introduction. After telling the story of antibiotics in some detail, the development of sulfa and other drugs will be filled in more simply. While the antibiotics are completely typical of the drug industry as a whole, the wealth of published material about them allows us to see the changes taking place within the drug industry more clearly than through any alternative source.[19]

Penicillin was produced by 19 different American companies in 1944, but the largest five accounted for 88 percent of the total. Only one firm, Squibb, was vertically integrated;

that is, Squibb was the only firm that manufactured the drug, packaged it, and sold it directly to pharmacies and hospitals. Squibb was not the largest firm; Pfizer, which was not integrated forward, made almost twice as much penicillin as Squibb. Although integrated drug companies existed in the mid-1940s, the industry was not dominated by them.

The share of penicillin produced by the top five penicillin producers in 1944 fell to 43 percent in 1950, and the price of penicillin dropped from $3,955 a pound in 1945 to $282 in 1950. Entry into the manufacture and packaging of penicillin was sufficiently easy to make its production highly competitive.[20]

Three developments of the immediate post-war years combined to change the context within which new antibiotic drugs were introduced. First, Selman Waksman at Rutgers University discovered a technique of screening soil samples to find new antibiotics. Since harmful micro-organisms do not survive in the ground, it was reasonable to assume that the soil contained a variety of substances which killed them. And if these substances were in the ground,careful search of soil samples should expose them. Waksman used his technique to discover the first new antibiotic since penicillin, streptomycin, vividly demonstrating his method's effectiveness. Unlike Salversan, penicillin was not to be an isolated phenomenon.[21]

Second, the Patent Office reversed its previous stand and decided that antibiotics could be patented, even though the drugs themselves were no newer than penicillin. The molds by themselves were not patentable, but the Patent Office

decided that the use of the molds as drugs was. More precisely, the therapeutic uses of the drugs were not considered to be patentable ideas by themselves; instead, the Patent Office said that a compound and all its properties are inseparable. Discovering new properties is like discovering new compounds. The new policy was established when the Patent Office accepted Merck's claim of patentability for streptomycin, which Merck had introduced commercially in 1946.[22]

While Merck's patent was important for the development of the industry, it did not change the way drugs were marketed. Worried about possible criticism for using public facilities at the university and a valuable public-health discovery for private gain, Waksman convinced Merck to license streptomycin production on an unrestricted basis. Merck consequently assigned its patents to the Rutgers Research Foundation. Merck was not an integrated firm, and it used its patent, made streptomycin and sold it to packagers and distributors in competition with other firms. Streptomycin consequently appeared on the market in the same way as penicillin, produced by many firms and sold under its generic name. The price of streptomycin followed the price of penicillin as competition amoung its producers forced it down during the 1950s.[23]

The third development was operational. Instead of licensing other firms to use their patents, innovating firms began to utilize their patent rights to retain a monopoly over the production of their new drugs. In doing so, they acquired control over the quantity produced, enabling them to restrict output to obtain monopoly profits. Output was

restricted by announcing a high price for the new drugs and then only producing the amount that could be sold at that price. Despite the large quantities of the new drugs that were sold, their high prices still need to be seen as a way of reducing the quantity sold.

The firms could have accomplished the same end by licensing other producers. Royalty payments are a cost to the licensee; they raise the price at which a competitive producer can sell above the competitive price without the license. High enough royalty payments can duplicate the monopoly price and therefore output. The problem is that the required royalty is very high indeed when demand is inelastic at the competitive price. If the elasticity of demand is one and a quarter at the monopoly price, then this price is five times the competitive price (for constant costs) and the required royalty is 80 percent of sales. The FDA regulation introducing a class of prescription drugs allowed the manufacturer to classify his new drugs, and most of the drugs discovered after the Second World War were classified as prescription drugs. As noted above, they consequently were ordered (prescribed) by doctors who did not pay for them and often did not know their price. In light of this fact and of the newness and effectiveness of the "wonder drugs," the elasticity of demand might well have been less than one and one fourth. The profit-maximizing royalty was too high.

It is highly unlikely that any drug firm conceptualized the issue in this way. In their view, retaining a monopoly over production offered the promise of greater profits than

licensing others to use their patents. It is only an academic exercise that reveals the firm's ability to realize its goals--maximize its returns--by either path. And as with many academic exercises, this one has interesting implications. It shows that the choice between licensing and producing was not determined by the technology; it was determined by the firm's inability to charge the appropriate price under the licensing system. And the height of the profit-maximizing price was partly the result of the FDA's regulation partitioning the drug market into two segments. Most new drugs were in the prescription category where demand was very inelastic, and the resulting monopoly price was very high. Royalty rates in the neighborhood of 80 percent of sales may well be impossible to collect. They certainly would have been politically untenable.

This change in industry practice can be seen most clearly in what came to be called broad-spectrum antibiotics. Lederle introduced Aureomycin (chlortetracycline) in 1948, Parke Davis introduced Chloromycetin (chloramphenocol) in 1949, and Pfizer introduced Terramycin (oxytetracycline) in 1950. All of these drugs were presented as superior to penicillin and more or less the same. The chemical structures were unknown; their generic names (given in parentheses) were not introduced until later. The chemical similarity of Aureomycin and Terramycin was only worked out in 1952, when their generic names were coined. And the harmful side effects of Chloromycetin only became apparent in the same year.[24] Up to then, the drugs were for all practical purposes identical.

Each drug was produced only by the firm that held the patent. In addition, Lederle and Parke Davis were already integrated firms, that is, they packaged and marketed their products, but Pfizer was not. It had been the largest producer of penicillin in 1944 and seen its position eroded by Squibb. Then the introduction of new drugs had reduced the position of penicillin in the antibiotic market, diminishing Pfizer's share of the market for antibiotics even further. Pfizer consequently decided to integrate forward to exploit its own drugs and regain its competitive position.

By not licensing their patents, these firms were able to restrict production of their own drugs. But the simultaneous discovery of three similar drugs limited each producer's market power. The producers attempted to regain this market power by differentiating their products along the lines that any other consumer good is differentiated. Since the therapeutic effects of the drugs appeared to be identical, other--more familiar--quality dimensions had to be employed. So the firms intensified their advertising, their detailing, and their reliance on company identities. The post-war pattern of integrated drug companies competing by introducing and marketing new drugs was beginning to take shape.[25]

The pattern was not yet stabilized by the beginning of the 1950s, however. Despite the presence of patented monopoly positions and integrated marketing organizations, the price of Aureomycin fell by two-thirds in its first few years on the market. The prices of the different new drugs stayed close together, and other drugs experienced smaller price declines

as they joined the price slide along the way. Clearly, competition between similar drugs was a good substitute for competition among the suppliers of a single drug. The Waksman technique apparently made introduction of a competing drug almost as easy for an integrated firm as initiating production of an existing one. A patent monopoly and a marketing organization may have been necessary for the creation of market power; they were not sufficient.

Pfizer, the newcomer to integrated production and marketing and the low man on the antibiotic totem pole, employed Robert Woodward of Harvard University to elucidate the chemical structure of Terramycin. Woodward did so, exposing its chemical affinity to Aureomycin and leading a Pfizer scientist to find a new, related drugs by removing the chlorine atom from Lederle's Aureomycin. Reflecting this chemical manipulation, Aureomycin acquired the generic name of chlortetracycline, and the new drug was named tetracycline.

Lederle heard about Pfizer's investigations and reactivated its discontinued antibiotic research program. Lederle produced tetracycline by the same method as Pfizer and filed patent applications in competition with Pfizer. Publication of Pfizer's and Lederle's discoveries led other firms to search their files for evidence that they had previously isolated tetracycline without recognizing its therapeutic properties. Birstol and Heyden Chemical Corporation, both primarily non-integrated penicillin manufacturers, found that they had made tetracycline by a different method--one that did not start

from chlortetracycline--and filed patent applications also.[26]

All this made for a very intricate position. Each firm filed both product and process patent applications. That is, they each wanted exclusive use of a new product, tetracycline, and of a new production process, whether the original process starting from chlortetracycline or the alternative one. If--as might easily have been predicted--Pfizer had obtained both product and process patents, and Hayden or Bristol had obtained a patent on its alternative process, then the following condition would have emerged. Pfizer could only have produced tetracycline by getting a license from Lederle to produce chlortetracyline or by getting a license from the patent holder on the alternative process to use it. Lederle could only have produced tetracycline by getting both product and process patents from Pfizer, and Bristol or Hayden would have needed the use of Pfizer's product patent to exploit its process patent. In any case, cooperation among at least some to these firms was necessary for production.

Cooperation there was, but not in this form. Lederle purchased Hayden and its patent application. If Hayden's application for a process patent was successful, then Pfizer would be compelled to reach agreement with Lederle to use its product patent, either to get the raw material for its own process patent or to acquire use of the alternative process patent. Similarly, of Pfizer got the product patent, then Lederle would need Pfizer's cooperation to exploit its new process patent. Foreseeing this symbiotic relationship Pfizer and Lederle reached an agreement before the Patent Office ruled

on the many patent applications. The agreement eliminated the risk attendant on going through the Patent Office by providing for all the contingencies and by removing some of the disputes the Patent Office was supposed to resolve.

The agreement stipulated that Pfizer and Lederle would determine between themselves who had priority. They resolved on Pfizer, and Lederle withdrew its application for a product patent. However the decision was made, it had the force of logic, for if Lederle had the product patent, it had no need for Pfizer and its process patent. Pfizer had no incentive to reach an agreement that froze it out of the market.

The agreement therefore reduced both firms' risks and guaranteed them both a share of the tetracycline market. The agreement further stipulated that Lederle would provide Pfizer with bulk tetracycline until its own manufacturing facilities were ready. This would enable Pfizer, which had only recently stopped selling solely in bulk, to employ its nascent marketing organization and develop its ability to compete with other integrated firms. Pfizer's sales force had contained only 10 men in early 1950. It rose to over 300 by late 1951 as Pfizer promoted Terramycin.[27]

The only remaining competitor was Bristol, which was almost entirely a bulk supplier of penicillin, like Hayden. While Bristol had a sales force, it was still small, containing no more than 40 detail men.[28] Bristol asked Lederle and Pfizer for licenses, but was told it could have them only under the condition that it renouced bulk sales. Bristol refused, since its sales force was too rudimentary to give it the

opportunity to generate large sales without using other packagers and marketers. It was already apparent to Bristol that the size of a marketing staff mattered and that it was not possible to compete with firms who had large marketing organizations without having one of your own. It was not yet apparent that the manufacture of drugs in bulk did not generate the magnitude of profits that integrated production and sale did.

Having failed to get licenses on terms it liked, Bristol decided to produce tetracycline anyway. In addition, it agreed to supply Squibb and Upjohn with bulk tetracycline. Squibb and Upjohn in return agreed to bear the cost of any litigation arising from patent conflicts with Pfizer. Bristol was a marginally profitable maker of penicillin; by itself it did not have the resources to fight with Pfizer over patents. Squibb and Upjohn had the resources, but no means of entry against Pfizer's will. The arrangement gave Bristol the financial strength and the other two firms the legal position to enter the tetracycline market.

Tetracycline had been discovered in 1952. Bristol began production in mid-1954. The Patent Office had not yet decided if tetracycline was patentable. The issue was whether tetracycline was new, or whether it had been obtained previously in the course of producing chlortetracycline. The issue resolved into the question of whether tetracycline could be recovered from the intermediate fermentation products used to produce chlortetracycline under Lederle's patent. The answer to this technical question is unclear, but it does seem clear that Pfizer withheld information damaging to it and structured the experiments carried

out during the Patent Office's investigations in ways favorable to it. Pfizer received the product patent in early 1955, but the evidence for it did not appear strong enough to withstand a court challenge by Bristol and its backers. Pfizer reached an agreement with Bristol under which Bristol would accept no more bulk purchasers and with Squibb and Upjohn--even though neither produced bulk tetracycline and neither therefore needed a license to operate--specifying that they too would not sell tetracycline in bulk. With Bristol eliminated as a potential challenger, Pfizer's patent was now secure.

The stakes in this game were high. The price of broad-spectrum antibiotics--the tetracyclines and chloramphenicol--had fallen by two-thirds between the end of 1948 and the end of 1951. They then remained unchanged until the fall of 1961. Even the entry of Bristol and its backers in 1954 did not disturb the market price.[29] The cooperative agreements and licensing arrangements of the early 1950s were able to arrest the price decline.

Now prices cannot fall forever; the question is when they stop. If prices had fallen to the level of long-range costs by the end of 1951, then there would be no reason to think that the legal shenanigans just chronicled had any effect. But if costs were far below the price and profits were high, then we could conclude that the legal actions were indeed potent. Manufacturing costs for tetracycline were below ten percent of the wholesale price throughout the 1950s. Did other costs--marketing, advertising, overhead--bring the

figure for total costs enough to approach the price, or was there a considerable profit? Table I gives the answer.

These data were compiled in the course of court action questioning the propriety and legality of the events just chronicled. As such, they are as reliable as any such aggregate profit figures, but subject to all the usual caveats about arbitrary classifications and allocations. Given the magnitudes involved in this discussion, these caveats fortunately are of relatively little import. The first column shows Lederle's sales, costs and profits on all drugs combined. The second column shows the same data for Lederle's antibiotic production of that year, including penicillin, sulfonamides, chlortetracycline and tetracycline. The final column, obtained by subtracting the second column from the first, shows these data for Lederle's non-antibiotic drug products. As the bottom row shows, Lederle obtained a comfortable 20 percent rate of profit on its entire drug business. This is a high rate, but not out of line with manufacturing profit rates in other rapidly growing industries.[30]

Lederle's total drug profit rate was the weighted average of the profit rate on antibiotics and other drugs, as shown in the last two columns of Table I. There it can be seen that Lederle's activities fell into two distinct groups. The firm earned a 35 percent profit rate on antibiotics, and almost nothing--three percent--on all other drugs. The contrast is even sharper than that. Lederle lost money on its sales of penicillin and sulfonamides, so the profits shown in the second

TABLE I

Costs and Profits for Lederle Laboratories, 1955
(millions of dollars)

| | All Drugs | Antibiotics | All Other Drugs |
|---|---|---|---|
| Net Sales | 123.2 | 81.0 | 42.2 |
| Costs | 104.5 | 63.7 | 40.8 |
| Income after Taxes | 18.7 | 17.4 | 1.3 |
| Capital Employed | 93.5 | 50.0 | 43.5 |
| Return on Capital | 20% | 35% | 3% |

Source: Costello (1968), p. 40.

column came exclusively from the manufacture and sale of chlortetracycline and tetracycline.[31] Lederle's 20 percent profit rate on drugs, therefore consisted entirely of profits on its patented tetracyclines; the production and sale of other drugs barely broke even.[32]

Lederle's tetracycline sales did not come as a great surprise to the firm. Lederle spent $2.5 million advertising Achromycin in 1955, of which over a million dollars was spent for detailing. A market-research study in Wisconsin reported that 47 out of the 55 doctors studied had been detailed on Achromycin in 1955. It was prescribed by almost all the doctors studied who prescribed any drugs at all.[33] Because the prescription-only restriction delineated the market so precisely, Lederle was able to send a representative to visit personally almost every potential customer, that is, prescriber.

Data for the other four firms selling tetracycline in the 1950s are not available in this detail, but we may presume that they would show a roughly similar picture. The production of traditional drugs and of unpatented newer drugs like penicillin and the sulfonamides did not generate large profits. The profitability of these firms derived directly from their membership in the privileged few enjoying the fruits of the patent monopoly on tetracycline.

More generally, they and the other producers of broad-spectrum antibiotics belonged to what we may call the broad-spectrum antibiotic cartel.[34] The cartel--by explicit or implicit means--determined the market price for these drugs,

holding it constant for a decade. But it did not specify market shares for each producer of tetracycline or for tetracycline as opposed to the other drugs. Sales went to whichever company attracted them, and the companies increased their marketing efforts to maintain or increase their market shares. The companies did their own advertising because their interest in advertising and marketing exceeded the interest of a packaging firm. The drug producers gained from the ability to sell their increased production at a price above its cost, and they consequently wanted more advertising than independent packagers would have supplied. In addition, they wanted to advertise their own brands to enhance their market shares.

The end of patent licensing (other than the restricted licensing within the cartel) therefore increased advertising for two reasons. First, since the returns to advertising were composed of both manufacturing and selling profits and because they were not shared with other producers, the firms realized higher returns from each dollar of advertising expense than independent packagers of generic drugs. Second, since the patent monopolies were in fact only memberships in an oligopoly or price-fixing cartel, advertising was an important determinant of market shares within the cartel. The first reason emphasizes the role of advertising in increasing the demand for the new antibiotics at a given price. The second reason emphasizes its role in allocating a given demand among competing suppliers. There is no way of telling which effect--demand "creating" or demand "diverting"--was more important.

High profits lead to rapid growth, and access to the tetracycline patents promoted the growth of these firms. Lederle was the largest seller of antibiotics in the mid-1950s, while Bristol was one of the smallest, but the effects of tetracycline profits on growth can be seen in one as well as in the other. Bristol had a detail force of only 40 men when it began to sell tetracycline under its own name in 1954. It had increased this force to 130 men by the end of 1956. By this time too, Bristol had introduced seven new product forms of tetracycline in an effort to differentiate its product from its competitors. In the words of its president:

> None of these [product variations] would qualify as a major scientific advance, but they were practical and useful improvements. They lay in such areas as making liquid suspensions more stable, making liquid forms simpler and more pleasant for the patient to take, combining injectible forms with a superior local anesthetic, and the like.[35]

The importance of tetracycline for Bristol was that it enabled Bristol to transform itself from a bulk supplier of drugs to an integrated producer that combined the discovery and development of new drugs with the sales of these drugs to doctors and pharmacies. Pfizer, which only began to package its own drugs in 1950, must have also expanded its sales force primarily to market the profitable tetracycline. Not only did this wonder drug earn large profits for its producers in the 1950s, it encouraged their growth and their reorientation from manufacturing firms to the integrated innovating, producing and marketing firms that we know today.

The story of tetracycline is dramatic and well documented. And while the legal aspects of the case are the exception in

the drug industry, the economics of this story extend to the industry as a whole. The new technology extended beyond antibiotics. Patent protection was available for many new drugs. And the combination of a patent monopoly and an integrated company--that is, a firm that combined discovery to obtain the patent and packaging and selling to create a market--meant high profits and rapid growth. While the connection between a single product and profits or growth cannot be documented in general as it can with Lederle and Bristol, three kinds of information confirm indirectly the generality of the story.

First, the five firms involved with tetracycline were among the largest dozen or so drug producers at the end of the Second World War, and they occupied roughly the same place in the industry a quarter of a century later.[36] While high profits encouraged the growth of these firms, high profits from the production and sale of other drugs fueled the growth of other firms at more or less the same rate. Second, other firms who had previously manufactured and sold drugs only in bulk followed the example of Pfizer and Bristol and began to package and sell their own drugs directly to doctors and pharmacies. For example, Merck, which had not been integrated when it introduced streptomycin in the 1940s, merged with Sharp and Dohme in 1953 and began to market its own packaged products.[37] Third, almost all the major drug firms got much of their revenues from a very few drugs.

The new drugs were of many types. Erythromycin, introduced in slightly different forms by Lilly and Abbott, was another broad-spectrum antibiotic. Chlorothiazide, marketed first by Merck, Sharp and Dohme as Diuril, was the first and most

important thiazide diuretic derived from the sulfa drugs. Tolbutamide, introduced by Upjohn as Orinase, and chloropropamide, introduced by Pfizer as Diabinese, were oral anti-diabetic drugs also derived from the sulfonimides. Cortisone and its variants, marketed most successfully by Upjohn, were potent anti-inflammatory drugs produced first from animal and then from plant sources. Reserpine, a sedative and diuretic isolated from snake root, was introduced by Ciba as Serpasil. And chlorpromazine, marketed in the United States by Smith Kline and French as Thorazine, was a potent psychoactive drug derived from a dye first noticed for its (rather different) therapeutic properties in the early twentieth century.

These new drugs were critical to the growth and profitability of the firms marketing them, as the early broad-spectrum antibiotics were for their producers. Each of them remained a major source of revenue for the producing firms at the end of the 1950s, and their share of profits undoubtedly was far higher than their share of sales.

The broad-spectrum antibiotics were very important to their suppliers in 1960. Lederle still received 38 percent of its drug sales in 1960 from its brands of tetracycline, Achromycin and variants. Pfizer made 33 percent of its 1960 sales from Terramycin (oxytetracycline) and Tetracyn (tetracycline) Parke Davis was even more dependent on its patented antibiotic in 1960; 45 percent of its sales came from chloramphenicol. Lilly, by contrast, was somewhat more diversified, receiving a more modest, but still important, 16 percent of its 1960 sales from erythromycin.

The derivatives of the sulfa drugs were equally important for their discoverers and producers. Merck Sharp and Dohme had 39 percent of its 1960 sales in Diuril (chlorthiazide) and its variant, Hydrodiuril, while Upjohn had 20 percent of its 1960 sales in Orinase. And the pattern extended even further than this: Smith Kline and French had 18 percent in Thorazine, with and additional 15 percent in the related Compazine (prochlorperazine). Each of these drugs was a critical factor in the profitability and growth of these firms.[38]

This brief account of other firms brings us back to the industry as a whole. These companies competed with each other in research and in advertising more than in price. The rate of introduction of new drugs rose from an annual average of around 20 in the 1940s to almost 50 in the 1950s, showing the results of and providing the incentive for increased research expenditures.[39] And the rise of medical journal advertising and physician detailing was also a result of the increased pace of drug discovery. The added marketing expense was needed to obtain the maintain markets for each new drug in competition with other new drugs. Only part of the increased marketing effort went to increase the total demand for the new drugs; much of it went to reallocate market shares between drug firms.

Vertical integration was a part of this process. As the drug firms began to produce their new drugs rather than licensing their production, they discovered they needed to package and sell their products as well. It did not make sense to retain a monopoly over production but not over marketing.

The increase in firm size was a direct result of the vertical integration. The size of producing establishments did not rise over this time, suggesting an absence of economies of scale in production.[40] But the size of drug firms did rise, presumably as a result of economies of scale in marketing.

The process, therefore, went like this. New technological opportunities led to patent monopolies. Maximization of monopoly profits with very inelastic demand required monopoly production rather than licensing. The presence of shared patents and competing patents on similar drugs led to vertical integration and increased advertising in the pursuit of larger market shares in the market for the similar drugs. And economies of scale in advertising and marketing generally led drug firms to increase their size.

The impact of the new technology on the industry was determined by two changes in the government's role. First, the patent office allowed drugs made from natural substances to be patented after 1947, creating the opportunities for patent monopolies. And second, the FDA restricted the sale of some drugs (including almost all of the new drugs) to prescription sales, reducing sharply the elasticity of demand and creating incentive for monopoly production rather than patent licensing.

Historically, the advent of a new technology and a new marketing stragegy has led to the emergence of a small number of dominant firms. The introduction of machine-made cigarettes in the 1880s changed American smoking habits and led to the dominance of the American Tobacco Company in the tobacco industry. The introduction of roll photographic film at about

the same time changed that product from a producer good used by professioanl photographers into a consumer good used by amateurs and led to the market dominance of Eastman Kodak.[41] And the emergence of general purpose digital computers contemporaneously with the drug revolution chronicled here led to the present contrast between IBM and its competitors. Yet the large drug firms today are the successors to the large firms before the Second World War, and the concentration ratio in the drug industry remained virtually unchanged after the war.

Concentration did not rise in the drug industry because the nature of the technical change in drugs was not the same as in the other industries named. There was no single drug that constituted the "center" of the drug industry. The revolution in drug research allowed many different drugs to be discovered and promoted, so that even though patents conferred market power on the discoveries of new drugs, the existence of patent monopolies did not lead to the emergence of a dominant firm as Eastman's patent monopoly did in photography. The new technology was a method of research rather than a method of production, and that method could not be patented.

Profits were high in the resulting drug industry, but no higher (relative to total manufacturing profits) than they had been before the introduction of the new technology. The older industry, with few new and potent products, had differentiated its products in much the same way as the new industry did with its wonder drugs. This was a profitable undertaking

as the selling of cosmetics is today. And any added profits available from the introduction of the new drugs apparently were eaten up by the advertising expenses needed by each firm to preserve its market share. Competition among drug firms--albeit non-price competition--acted to reduce the profits of the patent monopolies.

Footnotes

* This research was supported by a grant from the Sloan Foundation to MIT on the Public Control of Economic Activity. It has benefited from comments by Alfred Chandler, Peter Diamond, Paul Joskow, and Michael Piore. All remaining errors, however, remain mine.

[1]Alfred Chandler, The Visible Hand: The Managerial Revolution in American Business (Cambridge, Mass.: Harvard University Press, 1977).

[2]U.S. Bureau of the Census, Census of Manufactures (Washington D.C.: Government Printing Office, 1947-1967); Walter Adams, (ed.), The Structure of American Industry (4th ed. New York: Macmillan, 1971), p. 166.

[3]George J. Stigler, Capital and Rates of Return in Manufacturing Industries (Princeton: Princeton University Press for the National Bureau of Economics Research, 1963), pp. 58-62, 152-226. The new SIC classification in 1947 separated drugs from toilet preparations. Profits for these two activities were almost identical in 1947, but the change in industrial classification may have affected the comparison of the two subperiods reported by Stigler. The FTC only began publishing rates of return on equity in the drug industry in 1956, but IRS data from the Sourcebook show the same picture of drug profits in the late 1940s. These two data sets diverge during the 1960s due to different treatments of depreciation and earnings from foreign subsidiaries, but the differences are not great in the years just after the Second World War; U.S. Federal Trade

Commission-Securities and Exchange Commission, Rates of Return for Identical Companies in Selected Manufacturing Industries, (Washington, D.C.: Government Printing Office, 1947- ); U.S. Internal Revenue Service, Sourcebook of Statistics of Income, (Washington, D.C.: Government Printing Office, 1948-1970).

[4]U.S. Congress, Senate, Examination of the Pharmaceutical Industry, 1973-74, Committee on Labor and Public Welfare, Hearings before the Subcommittee on Health, 93rd Congress, 1st and 2nd sess. (1973-74), Part 3, p. 867.

[5]C. Rufus Rorem and Robert P. Fischelis, The Costs of Medicines, Publication No. 14 of the Committee on the Cost of Medical Care. (Chicago: University of Chicago Press, 1932), pp. 5-6, 120, 127. Another explanation offered was that drug expenditures were spread evenly across the population, so that no small group bore the burden of their expense.

[6]Rorem and Fischelis, pp. 83, 149, 208. JAMA, Vol. 97, p. 1226 (October 24, 1931), contains a reproduction of the poster exhibited at the annual meeting showing that an ounce of each of 12 common drugs cost four times as much when bought by brand name than when bought generically.

[7]John D. Krantz Jr. (ed.), Fighting Disease with Drugs, (Baltimore: National Council of Pharmaceutical Research, 1931), pp. 7-9.

[8]Krantz, pp. 7, 99-141; Martha Marquardt, Paul Ehrlich (New York: Henry Schuman, 1951), pp. 119-20. The seven diseases which were only partially controlled were treatable by more

antitoxins, by a synthetic arsenical drug chemically related to Salversan, and by drugs derived from plants. Drugs obtained from plants will reappear in the story. Curiously, diabetes is not listed.

[9]Marquardt, p. 91.

[10]Marquardt; M.P. Earles, "Salversan and the Concept of Chemotherapy", Pharmacy Journal, Vol. 204 (April 18, 1970),PP. 400-02. Ehrlich received the Nobel prize in 1908 for his ideas, not for the discovery of Salversan.

[11]Krantz, pp. 116-17; Joseph D. Cooper (ed.), The Economics of Drug Innovation (Washington: American University Center for the Study of Private Enterprise, 1970),p. 44; Paul Talalay (ed.), Drugs in Our Society (Baltimore: Johns Hopkins, 1964),p. 30.

[12]Cooper, p. 42. The account that follows draws heavily on Cooper's clear exposition of this story, pp. 41-54 of the cited volume. For references to and excerpts from the classic papers, see B. Holmstedt and G. Liljestrand (eds.), Readings in Pharmacology (New York: Macmillan, 1963),pp. 296-304.

[13]Temin, "The Origin of Compulsory Drug Prescription" Journal of Law and Economics (forthcoming).

[14]Rorem and Fischelis, p. 153.

[15]In Kefauver's words, "He who orders does not buy; he who buys does not order." U.S. Congress, Senate, Administered Prices: Drugs, Senate Report 448, 87th Congress, 1st Sess. (1961), p. 3. See D.C. King, Marketing Prescription Drugs, Michigan Business Reports No. 56 (Ann Arbor, MI.: Bureau of Business Administration, University of Michigan, 1968), p. 11, for a congruent opinion by a marketing source.

[16]Cooper, pp. 45-48; Holmstedt and Liljestrand, pp. 305-09.

[17]Cooper, pp. 48-50; Holmstedt and Liljestrand, pp. 309-15.

[18]See U.S. Federal Trade Commission, Economic Report on Antibiotics Manufacture (Washington, D.C.: Government Printing Office, 1958),pp. 47-49, 235-57, for a full account of wartime penicillin production.

[19]The account here draws extensively on the excellent treatment by Peter Costello, "The Tetracycline Conspiracy: Structure, Conduct and Performance in the Drug Industry," Antitrust Law and Economic Review, Vol. 1 (Summer, 1968), pp. 13-44.

[20]U.S. FTC, pp. 95-95. These are shares of penicillin production, not total antibiotics. Costello's data occasionally confuse the two. They also show the relative decline of unintegrated producers. The top four integrated firms produced 82 percent of the penicillin made in 1956. U.S. FTC, p.9?

[21]Holmstedt and Liljestrand, pp. 315-320. For a concise description of the technique, see U.S. Congress, Senate, Administered Prices in the Drug Industry, Committee on the Judiciary, Hearing before the Subcommittee on Antitrust and Monopoly, 86th Congress, 1st and 2nd Sess. (1960-1961), Part 25, pp. 15304-05.

[22]For a critical view of the evolution of patent doctrines for drugs, see R.L. Landau, Regulating New Drugs (Chicago: Center for Policy Study, University of Chicago, 1973),pp. 81-107.

[23]Selman A. Waksman, My life with the microbes (New York: Simon & Schuster, 1954),p. 204; U.S. FTC, pp. 24, 162-189. U.S. Congress, Senate (1960-1961), Part 24, pp. 13658, 13664.

[24]H.F. Dowling, Tetracycline (New York: Medical Encyclopedia, 1955),C.N. Lewis et al. "Chloramphenicol (Chloromycetin) in Relation to Blood Dyscrasias with Observations on other Drugs." Antibiotics and Chemotherapy, Vol.2 (December 1952), pp. 601-609. Chloromycetin causes fatal aplastic anemia in a small proportion of cases.

[25]William S. Comanor, in "Research and Competitive Product Differentiation in the Pharmeceutical Industry in the U.S." Economica N.S. Vol, 31 (November 1964), pp. 373-84, discusses the role or research in this process, but ignores the quantitatively more important advertising.

[26]U.S. FTC, pp. 245-57, contains a detailed history of the patent litigation. See also U.S. v. Chas. Pfizer and Co., Inc, et al., 426 F. 2d 32 (1970).

[27]U.S. FTC, pp. 140-42.

[28]U.S. Congress, Senate (1960-61), Part 24, p. 13849.

[29]U.S. Congress, Senate (1960-61), Part 24, pp. 13663-64; Costello, p. 39.

[30]U.S. FTC, pp. 203, 216-17, gives profit data for all antibiotic manufacturers, showing them to be in this range. The FTC's decomposition of profits by source, however, is unilluminating because of the need to protect the confidentiality of company data. See U.S. FTC-SEC for manufacturing profit rates in general.

[31]Costello, p. 40.

[32]This conclusion obviously depends on the allocation of costs shown in Table 1. While the allocation method used by Lederle is not known, it is probable that costs of joint activities, like research and marketing, were allocated in proportion to sales. Reallocation of these expenses to the most profitable lines (in terms of easily allocated costs) is possible, but problematical. It assumes that Lederle engaged in research and marketing solely to enhance its tetracycline sales and that the effects of these expenditures on the sales of other products was pure serendipity. Since Lederle presented its data in the firm shown in Table 1, this does not appear to have been Lederle's view.

[33]Ben Gaffin & Associates, The Fond du Lac Study: An Intensive Study of the Marketing of Five New Ethical Pharmaceutical Products in a Single Market, Resulting in Some Theory of Scientific Marketing and Service Programs for Action (Chicago: American Medical Association, 1956).

[34]It is worth noting that the drug firms were not found to have violated the antitrust laws. Their initial conviction was reversed on appeal, and the reversal was sustained by the Supreme Courts. See U.S. v. Chas. Pfizer and Co., Inc., et al., 426 F. 2d 32 (1970), 404 U.S. 548 (1972). Nevertheless, the drug companies paid out almost $200 million dollars in settlements of private damage suits brought while the criminal suit was in progress. See Charles W. Wolfram, "The Antibiotics Class Actions," American Bar Foundation Research Journal, Vol. 1976, pp. 253-363 (1976).

[35]U.S. Congress, Senate (1960-61), Part 24, p. 13849, reproduced in King (1968), p. 63. The data are from that quote and Costello, p. 23.

[36]The ranking of firms in the drug industry in hard for several reason. There has been an extraordinary amount of merger activity in this industry, and the units of observation keep changing. This creates problems in itself, but it also means that the data for different firms are not comparable. Integrated firms seldom report drug sales in their annual reports or other generally available publications, and their size has to be estimated from more aggregated behavior. The statement in the text is based primarily on the firms' annual reports, on Moody's, and on scattered information about firms like Roche, Ciba-Guigy and Lilly that are not subject to SEC rules on disclosure of financial information.

[37]Tom Mahoney, The Merchants of Life (New York: Harper and Bros., 1950), p. 201.

[38]Sales data from David Schwartzman, Innovation in the Pharmaceutical Industry (Baltimore: Johns Hopkins Press, 1976), pp. 124-25. These firms were seven out of the top ten drug firms by sales in 1960, according to Schwartzman (p. 125). Of the other three firms, American Home Products had 28 percent of its sales in its brands of meprobamate, while Squibb and Abbott were more diversified. Roche and Ciba were not listed.

[39]This is the rate of introduction of new chemical entities (NCEs), Paul de Haen, Nonproprietary Name Index (New York: Paul de Haen Inc., 1974).

[40]U.S. Bureau of the Census. Data for SIC 2834.

[41]Chandler, pp. 290-92; Reese V. Jenkins, Images and Enterprise: Technology and the American Photographic Industry, 1839-1925 (Baltimore: Johns Hopkins Press, 1975).

[redacted]