

Moving to Medicines

The pharmaceutical industry arose from public and private investment.

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Bridging the gap between chemistry and health care, the pharmaceutical industry provides the drugs and biologicals—the therapeutics and the diagnostic kits—required to analyze and treat human pain and disease. In 2002, sales in the prescription drug sector alone topped \$400 billion, with the top 10 pharmaceutical companies taking a proud place among the world's major multinational corporations.

But it was not always so. Throughout human history, medicines have been the stuff of craft, not industry; created and marketed by individuals, not corporations; and compiled of natural substances, not synthetics.

How did the transformation from community healer to drug company technician come to be? In the main, it was the result of the union of biology and chemistry—the discovery that all bodily processes were chemical ones and that body chemistry could be triggered to promote or hinder the process of disease. From the ad hoc chemistry of the coal tar industry of the 19th century to the target-specific drugs born of biotechnology companies today, the biochemistry of health provides the foundation for the pharmaceutical industry.

And it all started with coal tar dye and aspirin.

The Chemistry of Drugs

Modern medicinal chemistry was born of the coal tar industry when, in 1856, William Henry Perkin, in his efforts to synthesize quinine, stumbled on the first synthetic coal tar dye, mauve. Synthetic dyes, and their associated “medicinal side effects,” helped launch both the German and Swiss organic chemistry and pharmaceutical industries. The anti-fever drug Antifebrin, which was the dye intermediate acetanilide, was trademarked by the dye works Kalle and Co. in 1886. Further developments in organic synthesis dedicated to drug discovery led researchers at Bayer in Germany to develop the pain reliever phenacetin (1887) and then the much less toxic acetylsalicylic acid (aspirin), first marketed in 1899.

Parallel developments in microbiology created the germ theory of disease and led to the rise of the

vaccine industry based on Pasteur's first demonstration in 1885 of an effective rabies prophylactic for humans. The immunologicals industry followed closely—these drugs were the classic antitoxins, in reality, antibodies, purified from animal blood. By 1892, Hoechst (now Aventis) was marketing a tuberculin antitoxin. Difficulties in production of these animal-based materials helped lead to early efforts at good manufacturing practices and government inspections. In the United States, one example of this trend was the passage of the 1902 Biologics Control Act. Ultimately, most developed nations would create special authorities for the monitoring of pharmaceuticals, similar to the U.S. Food and Drug Administration, established in 1906.

Through the early part of the 20th century, purified plant alkaloids such as digitalis, codeine, and morphine formed the major product lines for companies like Boehringer Ingelheim.

A half-century after Perkin, Paul Ehrlich, convinced that drug design could take a rational, chemical approach, investigated the arsenical compound atoxyl, first used by British researchers to treat trypanosomes. He modified its chemistry to reduce its toxicity and developed the drug Salvarsan. The new drug was marketed by Hoechst in 1910 as the first effective treatment for syphilis. It was the birth of the “magic bullet” concept and the dawn of effective chemotherapy.

By the 1920s and 1930s, the isolation of vitamins and hormones had become routine. Canadian researchers Frederick Banting and Charles Best and colleagues isolated the first hormone, insulin, from the pancreas of animals and demonstrated its effectiveness in humans. Connaught Laboratories in Canada and Eli Lilly Co. in the United States purified and distributed the new drug, and within a few years, diabetes went from being a rapidly lethal to a long-term manageable disease. In the field of



Top: Merck Manual and drugs, Merck & Co.



Center: Frederick Banting, National Library of Medicine



vitamins, Tadeus Reichstein at the University of Basel synthesized ascorbic acid (vitamin C) in 1933, and in 1948, the Merck Co. produced vitamin B₁₂ in its efforts to develop a pernicious anemia therapeutic. Companies such as Glaxo and Takeda made their early mark distributing vitamins and vitamin-enhanced products.

The first of the classic anti-infectives, the sulfa drugs, was an orange-red azo dye, Prontosil, first used medicinally by Gerhard Domagk of the German company I. G. Farben in 1935. The active, noncolored part of the compound was found to be sulfanilamide by researchers at the Pasteur Institute; the stripped-down drug was later marketed by Rhône-Poulenc

CORPORATE EVOLUTION

A good example of what can happen in the realm of business history is found in the evolution of GlaxoSmithKline (GSK), whose corporate threads weave in and out of pharmaceutical history, which ultimately produced one of the world's largest pharmaceutical companies.

The companies that have been a part of the formation of GSK are an impressive litany of the history of drug discovery and development. They include John K. Smith & Co. (founded in 1841), Beecham's Pills (1842), Burroughs Wellcome and Co. (1880), and Mcleans Ltd. (1919). The G in Glaxo in the current name traces its history to Wellington, New Zealand, where Joseph Nathan established a trading company in 1873 that was a forerunner of Glaxo's milk-powder drying operation.

In 1842, Englishman Thomas Beecham founded the Beecham's Pills laxative business, and in 1859, he opened the first factory built solely to manufacture drugs. By the late 1920s, it was a major diversified pharmaceutical manufacturer, and by the 1940s, a major hub of pharmaceutical research. As the Beecham Group, the company would be a major international producer of antibiotics and other pharmaceuticals, merging with SmithKline Beckman in 1989.

In 2000, the umbrella SmithKline Beecham dropped the name, becoming only the SK of GlaxoSmithKline, creating one of the largest pharmaceutical companies in the world. Similarly, the Wellcome name might have once seemed sacrosanct in the history of pharmacy. Burroughs Wellcome and Co. was founded in London by two American pharmacists, Henry Wellcome and Silas Burroughs, in 1880, independent until its merger with Glaxo in 1995. Then, in 2000, GlaxoWellcome became simply the G in the GlaxoSmithKline moniker.



(now Aventis). Other important drugs in this early heyday of synthetic chemistry included anesthetic agents such as Pentothal, developed by Abbott Laboratories in 1936.

One company generally absent in references to GSK corporate history (see sidebar) is the S. E. Massengill Co. And yet, in its day, Massengill held both fame and infamy in a history spanning from 1897 to 1971—a past now represented more clearly in the history of the U.S. Food and Drug Administration. For the S. E. Massengill Company is remembered not for its commercial successes but for its tragic role in helping to ensure the passage of the 1938 Federal Food, Drug, and Cosmetic Act. The company marketed the toxic Elixir of Sulfanilamide in 1937, killing more than 100 people in 15 states, many of

them children.

A major triumph of the pharmaceutical industry was the rapid production of the antibiotic penicillin during World War II by industrial

fermentation through a collaboration between Merck, Pfizer, and Squibb. The Wyeth Co. (a subsidiary of American Home Products) was also instrumental in providing sulfonamides, penicillin, and quinine to the Allied war effort. The tremendous impact of penicillin and the monies poured into its development by government agencies led to a postwar boom in pharmaceutical manufacturing capability and promoted the search for new and better wonder drugs. The antibiotic streptomycin, for example, was developed by Selman A. Waksman, a Merck consultant, and was shown to be effective against tuberculosis in 1944. In 1950, Eli Lilly introduced vancomycin, one of the most important antibiotics even today for treating drug-resistant bacterial infections. And by 1962, Pfizer produced tetracycline, the first fully synthetic broad-spectrum antibiotic.

With improvements in instrumentation such as chromatography and mass spectrometry (see Part II), as well as the development of new synthetic chemistries throughout the postwar era, the drug industry was able to enter the world of rational analysis, if not quite always rational design.

The burgeoning development of pain relievers and anti-infectives was by no means the only focus of the pharmaceutical industry as its confidence in the biochemical basis of human health increased with a wealth of physiological research. Soon the development of drugs that directly affected mood and behavior formed a controversial, though intensely popular, core of the drug market, from the antipsychotic Thorazine (Smith Kline, 1952) to the tranquilizers Miltown (Wallace Laboratories, 1954) and Valium (Roche Pharmaceuticals, 1963), and the stimulant Ritalin (Ciba, now Novartis, 1950), which is currently, and controversially, prescribed for attention deficit disorder.

One of the earliest anticancer agents, methotrexate, used initially for leukemia, was developed by Lederle Laboratories in 1948. A concerted attempt to develop DNA-based antimetabolites for cancer therapeutics formed the basis of the work of George Hitchings and Gertrude Elion at the Burroughs Wellcome Co. Beginning work in 1942, the researchers by 1948 had synthesized and demonstrated the anticancer activity of 2,6-diaminopurine, which was fine-tuned by Elion to the less toxic 6-mercaptopurine, also used for leukemia.

In the 1970s, when President Nixon declared war on cancer in the United States, more monies became available for research. In 1976, combination therapy CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) was developed to treat breast cancer at the Istituto Nazionale Tumori in Milan, Italy. It proved a radical improvement over surgery alone.

Another major evolutionary trend in drug development in the postwar period was the development of drugs for so-called lifestyle issues. These ranged from the development of birth control pills in the 1960s to compounds such as Rogaine (Phar-

macia) for hair loss and Viagra (Pfizer) for male impotence in the 1990s.

Because of the increase in coronary artery disease, especially in developed nations, some of the most effective lifestyle drugs have been created to deal with this illness. These include drugs for hypertension and high cholesterol. The first ganglionic blocker used to treat high blood pressure was hexamethonium, developed in 1948. Beta-androgenic receptor blockers such as propranolol (synthesized by Sir James Black) followed in the 1960s, with ACE (angiotensin-converting enzyme) inhibitors such as Capoten (Bristol-Myers Squibb) developed in the 1970s. Also developed in the 1970s by major players Sankyo Co. and Merck, the statins countered hypercholesterolemia by inhibiting the effects of HMG-CoA reductase.

Over-the-counter remedies have been a major market for the pharmaceutical industry for everything from acid indigestion to vertigo. Pain relievers other than aspirin have formed a major part of this drug market. Ibuprofen, a nonsteroidal anti-inflammatory drug, or NSAID, discovered by British researchers and introduced in 1969, and acetaminophen (first discovered in 1893) have rapidly taken a large share of the pain-relief market. In 1982, in Chicago, several people died after ingesting Tylenol (acetaminophen) capsules, produced by Johnson & Johnson, that had been laced with cyanide. Although the murderer was never found, the tragedy led to an industry-wide transformation of safety protocols in food and drugs. Part of the response led to the elimination of fillable capsules in over-the-counter drugs and to the creation of tamper-indicating safety seals.

As with the war on cancer in the 1970s, the AIDS crisis of the 1980s led to a dramatic increase in both public and private biomedical research funding. Coupled to the explosion of genetic engineering and molecular biology techniques, such social demand led to the development of major new medicine categories in the 1990s, such as the antiviral reverse-transcriptase inhibitors, typified by AZT, first marketed by Burroughs Wellcome, and the various proteinase inhibitors such as Invi-rase, Crixivan, and Norvir, produced in the 1990s by Roche, Merck, and Abbott Laboratories, respectively.

CombiChem and Computing

By the dawn of the 21st century, the drug discovery paradigm was transforming. There was a new world of combinatorial chemistry, high-throughput screening, target molecules identified through genomics, and even virtual reality in which both compounds and targets could be accurately modeled, allowing vast libraries of “virtual” candidates to be screened without the need for prior wet chemistry synthesis. The new foundation of modern drug research became predicated on automated instrumentation, experimentation, and analysis. Such approaches required the convergence of

bioinformatics and traditional research in biology and chemistry. It was a new kind of medicinal chemistry, requiring a new and different industrial commitment.

By the 1990s, companies such as Accelrys and Tripos were creating virtual combinatorial libraries for drug development, and companies such as Chemical Diversity and Maybridge were providing real-world small-molecule libraries for drug discovery to order.

Driven by the demand for information management, companies such as Applied Biosystems, Beckman Coulter, Discovery Partners International, Genomic Solutions, Gilson, IBM, and SRI International have all moved to develop the software and hardware needed to validate and analyze real and virtual targets. For example, Advanced Chemistry Development (founded in 1993) provides software packages enabling pharmaceutical researchers to organize and analyze the wealth of data generated on drug candidates and targets by techniques such as NMR, IR, MS, UV, LC, and GC. And companies such as Caliper Life Sciences (formerly Zymark) and Caliper Technologies) have developed robotic systems for real-world assays and handling the information generated by such studies.

All the while, in university, industry, and government labs, research has been done for the analysis of human and animal physiology and genetics so that real and virtual model systems might be developed for drug screening.

Similar studies are being performed on all other aspects of the ADMET (absorption, distribution, metabolism, excretion, and toxicology) equation, creating a new model for drug discovery—a systems biology approach to diseases and drugs spearheaded by companies such as Entelos, which are pioneering the construction and use of “virtual patients”—that the pharmaceutical industry and its collaborators hope will improve on the all-too-random process of finding and screening new drugs.

With such developments, it is likely that drug discovery in the future will be radically different than in the past, that is, it will be knowledge-based rather than hit-or-miss, target-driven rather than compound-driven, and above all, a more complete blending of chemistry, instrumentation, and biology. It will encompass a systems approach capable of designing the small molecules needed to impact the complexity of the human body to maximal effect. Yet, no matter how virtual the drug, the reality of pain, disease, and death will remain to spur the pharmaceutical industry to greater efforts, not to mention greater profits. ♦

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Above: Carl Djerassi, *Chemical & Engineering News*