

► Memories of Mannheim

Roche took the lead role in diagnostics by absorbing an historic innovator.

BY RICHARD A. PIZZI

In 1998, the Swiss medical technology firm Roche acquired the Corange Group, which consisted of the diagnostics company Boehringer Mannheim and the orthopedics manufacturer DePuy. With the acquisition of Boehringer Mannheim, Roche became the global leader in diagnostic technology.

The origins of Boehringer Mannheim can be traced to Kircheim, Germany, where Christian Friedrich Boehringer was born in 1791. At age 19, Boehringer moved to Stuttgart to work as an assistant to the court apothecary, Christian Gotthold Engelmann. The two men became close friends, and in 1817, they opened a Goods and Paint Shop, which was the 19th-century equivalent of a modern drugstore. The store was prosperous and, in the early 1830s, the partners built a laboratory and began to manufacture some of their own products.

Apothecary beginnings

Among the first chemicals that Engelmann and Boehringer produced were ether, chloroform, and santonin, a bitter substance drawn from wormseed blossoms and still used today to treat roundworm. Early successes led them to expand production, making sulfur, saltpeter, ethyl acetate, potassium iodide, and silver nitrate. These first products found a ready local market in Stuttgart but also sold well in the rest of Germany and abroad in Switzerland.

In the late 1840s, manufacturing became a major priority, as the partners and their sons built a new laboratory and a tar and wood vinegar factory in 1849. But it was not until the 1850s that the future of the company was determined, when Engelmann and Boehringer became interested in the

production of quinine.

Boehringer thought that quinine offered great prospects for the future of drug production and grew increasingly interested in its purification. In 1859, the company purchased a quinine factory and renamed itself C. F. Boehringer and Sons, as Engelmann had died years before and his children chose not to remain in the business.



Roche researcher loads a Cobas TaqMan unit for analysis.

C. F. Boehringer died in 1867. Five years later, his sons moved the company to Mannheim, where entrepreneur Friedrich Engelhorn joined the firm in 1883. Engelhorn's leadership would turn the company into a world-famous research-based enterprise. Engelhorn took over sole control of the company in 1892. The direct role of the Boehringer family ended here, as the founder's grandson Albert gave complete attention to his own tartaric acid factory in Ingelheim. Albert placed his father's initials, C. H., in the name of his business to distinguish it from C. F. Boehringer in

Mannheim. Albert's separate firm later became Boehringer Ingelheim.

Therapeutics

Engelhorn's leadership expanded the company's research plan significantly. He emphasized research into alkaloids as their curative power became ever more evident, and soon Boehringer Mannheim was producing a broad variety of alkaloid products. The company was also a leader in the manufacture of aromatic substances and flavorings, such as coumarin. In the 27 years during which Engelhorn directed the company, more than 700 patents were awarded,

highlighting the aggressive and original research the company undertook when led by him.

Engelhorn understood that synthetic chemistry would provide vast new opportunities for the pharmaceutical industry, and he wanted to make certain that Boehringer Mannheim was prepared for the new era. In 1889, he established a Central Scientific Laboratory to synthesize therapeutically effective substances. Prior to this, products had been produced primarily from natural plant derivatives. Some major successes in the early years were the first production of synthetic caffeine, acridine dyes, and theophylline.

Boehringer Mannheim enjoyed early-20th century triumphs in medical research. It initially focused on the glycosides, following the work of Oswald Schmiedeberg, who had obtained a pure glycoside from the foxglove plant, the source of digitalis. The Mannheim chemists were particularly interested in the glycoside strophanthin, a water-soluble substance derived from the seeds of an African plant. Working with the physician Albert Fraenkel, the company standardized in 1906 a form of the medication that could be injected intravenously and used to treat cardiac failure.

The field of biochemistry did not really exist in the 19th century, so when Boehringer

Mannheim made the decision to open a special laboratory for pharmacological and toxicological experiments it was a move toward the future. The work on strophanth was a precursor to the broader work in biochemistry that the company would undertake throughout the 20th century.

One of the most important events in the development of biochemical research at Boehringer Mannheim was the establishment of research facilities at Tutzing in Upper Bavaria. The Tutzing project began during World War II, when large parts of the pharmaceutical production facilities were moved out of Mannheim to avoid Allied air raids of the city. Fritz Engelhorn, Friedrich's son and now head of the company, kept a research branch in Tutzing after the war, designated to advance the new science of biochemistry.

The first big breakthrough for Boehringer Mannheim after the war was the development of a new process for synthesizing the broad-spectrum antibiotic chloramphenicol. Chemists at Parke-Davis were the first to discover the bacteriostatic effect of chloramphenicol, but Boehringer Mannheim found a way to produce the antibiotic in half as many steps and used a much less expensive raw material. Chloramphenicol was marketed in 1953 as Paraxin.

Diagnosics

Another major triumph for the company, and specifically its Tutzing research division, was the development in 1953–1954 of the first enzymatic laboratory test for measuring blood alcohol levels. The new test spurred Boehringer Mannheim to form its first diagnostics department.

Diagnosics proved to be an area in which the company would, in time, be considered among the world leaders. One of Boehringer Mannheim's young chemists, Hans Ulrich Bergmeyer, would ultimately be considered a pioneer of modern diagnostics because of his research in enzymatic analysis. Bergmeyer translated his findings on enzymatic extracts into useful products, and his writings on the subject became standard reference material for researchers in the field. He and his colleagues demonstrated that the enzymes that accompany chemical reactions in the human body provide pointers to specific illnesses. The term

“enzymatic diagnosis” was used to underline the value of enzyme analysis for clinical chemistry.

The midcentury golden age of the biochemical industry extended to Boehringer Mannheim. For instance, scientists at the company in the 1950s and 1960s were responsible for a series of products that transformed the way diabetes was treated. In 1956, the company introduced the medication Nadisan, which was a carbutamide tablet used to treat Type II diabetes. The research into an effective oral medication also helped to clarify the medical distinction between the two forms of diabetes, the insulin-dependent Type I and the adult-onset Type II.

On the diagnostic side, Boehringer Mannheim researchers developed a test

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stick for measuring glucose in urine, which was termed Glukotest. This achievement signaled the rise of “dry chemistry”, in which reagents were applied to papers. Doctors no longer had to manipulate sometimes toxic liquid reagents for testing purposes. At the same time, however, Boehringer Mannheim also developed a “test combination” kit in which all the substances necessary for diagnostic testing were included in a single pack. This was the first example of standardization in the “wet department” of diagnostic chemistry.

Boehringer Mannheim excelled in other diagnostic areas as well. The company produced a pioneering transaminase test, which would allow transaminase levels to be measured in the blood and provide doctors with information about cell damage in the body. And in 1961, scientists at Tutzing developed a creatine phosphokinase (or CPK) test for diagnosing myocardial infarction.

But it was in diabetes-related diagnostics that Boehringer Mannheim maintained its reputation in the latter half of the 20th century. In 1963, the development team pro-

duced the first combined urine test stick, the Combur test. This stick allowed for the simultaneous testing of three parameters: glucose, protein, and pH. Five years later, the company produced the Haemo-Glukotest, a test for blood glucose that revolutionized diagnostics by eventually allowing diabetics to monitor their own blood sugar levels without the need for outside assistance.

Movements and mergers

In the 1970s, Boehringer Mannheim expanded its reach and became involved in the production of laboratory equipment. To that end, the company formed Labora AG in Germany and in 1974 purchased BioDynamics (including DePuy Orthopaedics, Inc.) in the United States. The company also collaborated with Hitachi to launch several automated diagnostic analyzers, including the Hitachi 706 for serum testing. Throughout the 1970s and into the 1980s and 1990s, Boehringer Mannheim continued to make substantive contributions to diagnostic technology, particularly in regard to the needs of diabetics.

In 1981, Boehringer developed the Autoclix injector, a device for obtaining blood samples that could be pre-set to multiple skin penetration depths. A second-generation sampler, Softclix, was released in 1993. These devices helped reduce the pain of blood sampling for people with diabetes. A major step forward in the self-monitoring of diabetes was the production of Reflolux, later called Accu-Chek, in 1983.

In 1997, Roche purchased Corange for an estimated \$11 billion. DePuy was sold off in 1998 to Johnson & Johnson.

By acquiring Boehringer Mannheim, Roche not only inherited a long history of innovation in biomedicine, it also became an instant leader in a new market, for the company that evolved from a small drugstore in Stuttgart had become a major international force in diagnostic and therapeutic technology.

Further reading

Fischer, E. P. *Selling Science: The History of Boehringer Mannheim*; Boehringer Mannheim GmbH: Mannheim, Germany, 1992.

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