MERCK IN AMERICA: THE FIRST 70 YEARS FROM FINE CHEMICALS TO PHARMACEUTICAL GIANT*

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In 1668 Friedrich Merck purchased an apothecary, the Engel-Apotheke (the Angel Pharmacy) in Darmstadt, Germany. One hundred and fifty years later, Heinrich E. Merck, a friend and collaborator of Justus Liebig, took over the family business and began its conversion to a manufacturer of pharmaceuticals and fine chemicals. The company, E. Merck, became a major producer of alkaloids, including morphine, codeine, and cocaine (1).

Throughout the 19th century, E. Merck exported products to the US, but it did not have a sales or distribution office in this country. Late in the century, Lehn & Fink, E. Merck's US distributor, used E. Merck labels on inferior non-Merck products. In an effort to protect its American interests and its good name, E. Merck opened its own sales office in New York in 1887. Theodore Weicker, who had been with the firm in Darmstadt for 10 years, was placed in charge of the New York office.

Figure 1. George Merck holding his two-year-old son, George W. Merck in Darmstadt, Germany, 1896.

In 1891 the firm decided it was time for a member of the Merck family to begin tending the company's business in the US, and the company sent George Merck (Fig.1), Heinrich Merck's grandson, to New York. George, who was only 23 at the time, had already spent seven years being trained in the family business. When he arrived in the US, he founded Merck & Co. in partnership with Theodore Weicker. In the beginning the company concentrated on the importation of drugs and chemicals, primarily those of the parent company, E. Merck. The intent, however, must have been eventually to establish a manufacturing presence in the US. In 1903 Theodore Weicker sold his share of the business to George Merck and, with another partner, purchased E. R. Squibb & Sons (1, 2).

Merck & Co. had to endure a major US depression (1892-1895); but by 1896 the company occupied its own new building at University Place and 8th Street in New

York City, and in 1897 it opened a very stylish pharmacy on the north side of the new building (Fig. 2). Merck's best customers, the German druggists in New York and vicinity, were irate at this encroachment by their supplier. After two years, George Merck bowed to the demands of his customers and closed his elegant apothecary (3).

Figure 2. Merck & Co. pharmacy in New York city, 1897.

By 1897 Merck & Co. had annual sales of over $1 million. George Merck purchased 120 acres of wooded countryside near Rahway, NJ in February, 1900; in 1903, shortly after he became a US citizen in 1902, the company began manufacturing some of its own chemicals in a plant built on the Rahway property. Merck & Co. also began manufacturing in St. Louis in 1903, in a plant that was first leased and later (1905) purchased from Herf and Frerichs. This plant had already been producing iodides and other staples of the pharmaceutical industry. Manufacturing in St. Louis was abandoned in 1908, but the site continued to serve as the St. Louis branch of Merck & Co. and was used as a distribution center for the Midwest and western US.

Merck & Co. was no longer merely a branch of the German company. It incorporated in New York in 1908 and gradually expanded its product line of American-made narcotics — including morphine and cocaine. By 1910 sales had exceeded $3 million, and in 1911, Merck set up its own subsidiary in Canada; but there were still very strong ties to Germany. Most of the production was carried out according to German manufacturing processes; German immigrants were often used in the plants, and E. Merck was still the majority stockholder in the American company.

In 1917, when the US entered World War I, George Merck was forced to break formal ties with the German branch of the family and with E. Merck. He voluntarily turned over almost 80% of Merck stock, E. Merck's share of the company, to the Alien Property Custodian. In 1919, the Property Custodian decided to sell the Merck stock at public auction, much to the dismay of George Merck. Merck called upon and received the support of two investment banking companies, Goldman Sachs and Lehmann Brothers. There were five bidders at the auction. Monsanto started the bidding at 2.4 million dollars, but 25 minutes later George Merck once again had complete control of the company at a cost of 3.75 million dollars (4).

Merck continued to grow in the early 1920s and by 1925, when George Merck, warned of poor health, passed on the presidency to his 31-year-old son, George Wilhelm, Merck & Co., Inc. was one of the "Big Three" fine chemical producers in the US with sales of $6.1 million (5, 6). The senior Merck died a year later, on October 21, 1926 at the age of 59.

Despite the profitability, George Merck had heavily mortgaged the company when he purchased the shares from the Alien Property Custodian. He had financed the purchase with the sale of preferred stock (7); and, according to Adolph Rosengarten, Jr., a former director (1932-1942, 1946-1974) and the largest Merck stockholder, by 1925 or 1926, Merck was in arrears on the preferred stock (8). As luck would have it, the four Rosengarten brothers, Adolph, Frederick, George, and Joseph, the owners of Powers-Weightman-Rosengarten (PWR), a large fine chemical company based in Philadelphia, "…wanted to retire and enjoy life." In the words of Adolph Rosengarten, Jr., (8):

> Father (Adolph senior) liked to shoot grouse in Scotland in the summer, Uncle Fritz liked to fish anywhere he could, Uncle George liked to fish for tarpon off the Florida Keys, and Uncle Joe was satisfied to stay home and play golf because he was stone deaf.

PWR wanted to merge with another chemical company and leave the day-to-day operations to the new partner.

They wanted to merge with Pfizer, but the Attorney General determined this merger would violate anti-trust laws. Merck was an ideal candidate because, as Adolph, Jr. put it, "We were solvent and they weren't." With the merger in 1927, a new company, Merck and Co., Inc., was formed. The Merck Corporation, the new name adopted by the original firm, and PWR transferred all property to the new company, which now had combined assets of about $9 million, and PWR lent $5 to 6 million to the new company. As part of the merger, Frederick Rosengarten became chairman of the board, and Adolph and George became members of the board. George W. Merck became president of the new company (9). This was the first of two major mergers that determined the future of Merck. In each instance the merger significantly influenced the continued growth and development of the company.

PWR was, like Merck, a long-line chemical firm, selling over a thousand products. The offerings of the two companies were sufficiently different that they complemented one another. As a result of the merger the combined company had a "large enough inventory to carry it through three years of the Depression without having to make anything (10)."

Figure 3. Randolph T. Major (*left*) Director of Research and Development, William H. Engles (*second from left*), Associate Director, examining an intermediate in the synthesis of pantothenic acid with team of chemists who synthesized it in 1940: (*left to right*) Karl Folkers, Assistant Director of Research, J. Finkelstein, J. C. Keresztesy, and E. T. Stiller.

The new company, with sales in 1928 of over $13 million, could afford to make a heavy investment in research and development. After the merger George Merck brought in his brother-in-law, George W. Perkins, the son of a famous banker, as chief operating officer. Perkins was influential in establishing the new research unit. Merck and Perkins, with the advice and guidance of Alfred Newton Richards, a noted clinical pharmacologist at the University of Pennsylvania, went searching for someone to run the new research operation (11). They first went to Princeton—Perkins' alma mater—where they found a young organic chemist, Randolph Major, who was to lead Merck research for the next 26 years.

A research unit had actually begun in 1916, probably an acknowledgment that chemicals would no longer be available from Germany. William Engels had become director of the research laboratories in 1918. Until 1930 the "research labs" were spread throughout the manufacturing facility in Rahway, probably because the primary function of "research" was to service the manufacturing end of the company. In a 1932 memo, Major listed four main functions of "research" prior to 1930 (12):

- Transformation of laboratory processes into processes suitable for the factory.
- General improvement of processes.
- Study of methods for keeping and preserving materials after they are made.
- Investigation of complaints by customers which could not be handled by others.

In 1930 Major set up the Laboratory for Pure or Fundamental Research with six chemists and made plans for a new research laboratory to house this unit. Engels headed up the Laboratory for Applied Research with an additional ten chemists. At the end of his 1932 memo, Major made a point of mentioning papers that had been published in the previous two years and his intention of publishing most of the "results of scientific value" from the "laboratory of pure research." This set the tone for Merck research. George W. Merck had a vision of a research laboratory the equal of any academic department, and publications from the new research unit were a step in that direction.

Major had a knack for choosing productive programs and productive people.

His most successful early program was to isolate, determine the structures of, and synthesize as many vitamins as possible. The origin of this program is not clear. He may have observed considerable activity in vitamin research in Europe and little in the US, and/or he may have foreseen the possibility of enriching foods with vitamins or using pills to treat people with vitamin deficiencies. It is difficult to believe that he had any idea of just how profitable this program would become.

In 1934, Merck hired Karl Folkers who had earned a Ph.D. with Homer Adkins at Wisconsin and then served as a postdoctoral fellow with Treat B. Johnson at Yale. Johnson instilled in Folkers an interest in compounds with biological activity. Folkers made a life's work—some say an obsession—of isolating and synthesizing biologically active molecules. He was the perfect fit for Merck's vitamin program. Folkers' description of Major's approach to directing his researchers is revealing (13):

> He was not a man who directed you. He said, "Here's a problem. Good luck." Then he left you on your own.

After a few years of Majors' leadership, Merck, collaborating with R.R. Williams at Bell Labs, had done significant work on thiamine, vitamin B_1 (14). Synthesized in 1936, it soon accounted for over10% of Merck's sales. In 1938-39 Folkers and his group isolated and synthesized vitamin B_6, and in 1940 they reported the synthesis of pantothenic acid, another of the B vitamins (Fig. 3).

It was one thing to search for biologically active molecules, determine their structures and synthesize them. This was the work of organic chemists. It was quite another matter to determine whether molecules were, in fact, biologically active, and once isolated, whether they would prove useful and safe for the prevention or healing of disease. For this there was a need for pharmacologists and biologists. It was difficult to hire first rate pharmacologists in this country because of the stigma attached to working in industry. Pharmacologists working in industry were not permitted membership in the American Society of Pharmacology and Experimental Therapeutics; and a member who went to work in industry was forced to resign from the Society. Alfred Newton Richards, one of the founders of the Society, had to resign his membership when he began consulting for Merck. The restriction was eventually withdrawn and Richards' membership in the Society was reinstated.

With the help of Richards, Merck hired Dr. Hans Molitor of Austria in 1932 to head the new Merck Institute of Therapeutic Research. Molitor expected to return to Vienna within a few years but, in the end, remained as head of the Institute until 1956. The Institute, housed in Rahway and funded by Merck, was an independent facility because a New Jersey law prevented industrial companies from conducting animal research. Cooperation between the Institute and the Laboratory for Pure and Fundamental Research was essential for isolating and developing new pharmaceutical products. In 1933 the three research arms of Merck, the Laboratory for Pure and Fundamental Research, the Laboratory for Applied Research, and the Merck Institute of Therapeutic Research, moved into a new building at the Rahway facility.

In 1937, Major hired Max Tishler, another eventual key participant, for his research team. Tishler (Fig. 4) had graduated from Tufts and had taken his Ph.D. under Elmer Kohler at Harvard (15). After obtaining his doctorate, he stayed on at Harvard for another three years, teaching, doing research, and revising James Conant's textbook (16) (Conant was, by then, president of Harvard). Tishler, because he was Jewish, had difficulty finding an academic or industrial position. Kohler recommended Tishler to Major; Conant recommended him to George Merck, and Max was hired. Carl Addinall, a Merck employee and a former Harvard graduate student who had been Max' instructor in Chem 5, also rec-

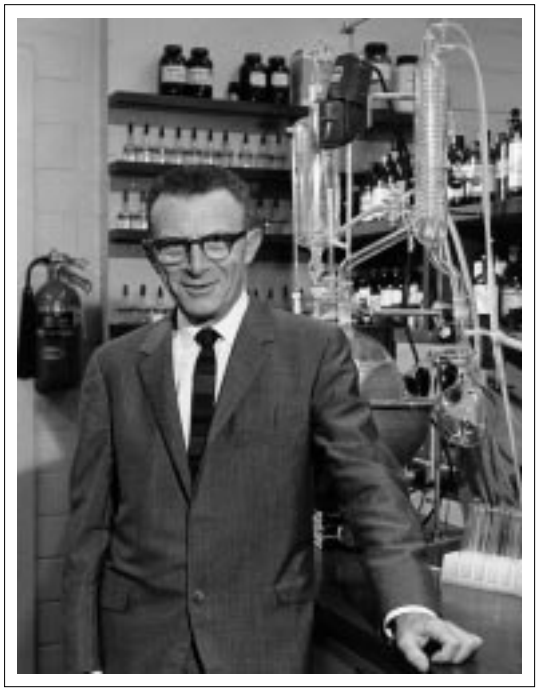

Figure 4. Max Tishler, circa 1963

ommended Max to his supervisor at Merck (17). Randolph Major, Karl Folkers, and Max Tishler, were to lead Merck's research and development programs for almost 40 years.

Tishler's first job at Merck was to find ways to synthesize riboflavin, vitamin B_2, to bypass the German process patents. Within two years Merck was manufacturing and marketing riboflavin. Folkers was driven to find new vitamins and exploit their use. Tishler was motivated not only to find new products, but also to follow them all the way to the customer. In a 1983 interview, he said (18):

> One of the greatest thrills I had in riboflavin was when the plant was producing the first kilogram of stuff. I was there! It was a great thrill.

He had followed riboflavin from the bench through the pilot plant and the factory, getting involved in every step of the process.

Figure 5. Lewis Sarett (*left*) with Edward C. Kendall and George W. Merck (*seated*) in 1950 in Sarett's Rahway laboratory.

Tishler was the ultimate process chemist. He loved to take new compounds from the research bench and develop efficient processes for producing the compounds on a large scale and interacting with the chemical engineers in building a production plant. He was also endowed with enormous energy. Lew Sarett, in a 1990 interview, said (19):

> Max was born with an energy level that was like an avalanche and a brain that was incandescent. It was scintillating— the combination of energy and ability was extraordinary. I've never known a guy like that.

Next came World War II and Merck became involved in two projects that had an enormous impact on the future development of the company. The first project was one involving the adrenal corticosteroids. The isolation and synthesis of these steroids were a major government priority, and the project was organized as an international consortium. At the time Merck signed up to participate in the program, there was no steroid chemist on the staff. However, Professor Everett Wallis of Princeton, a Merck consultant, recommended that Merck hire one of his graduate students, Lewis Sarett (Fig. 5). Sarett had only been attending graduate school for 2 1/2 years, but under the circumstances Princeton approved his leaving with a doctorate. In January of 1942 Sarett was sent to the Mayo Clinic in Rochester, Minnesota to work with E. C. Kendall, one of the world's experts on these hormones (20). His mission was to find out how Merck could be of help. By 1944, Sarett had prepared 18 mg of the first synthetic cortisone (21, 22). Sarett would go on to lead Merck's fundamental research efforts and eventually succeed Tishler as president of Merck Sharp & Dohme Research Laboratories (MSDRL).

The development group, under Tishler's direction, supplied Sarett with large batches of intermediates as he worked toward the final synthesis. They were gearing up to produce large amounts of cortisone in case it proved to be useful. It turned out not to have any war time use, but Merck process chemists eventually produced about a kilo of cortisone for testing. This was fortunate for Merck, the medical community, and the public, because, in 1948, Philip Hench at the Mayo Clinic, using Merck produced material, discovered that cortisone was an effective anti-inflammatory agent that could be used to alleviate the severe symptoms of rheumatoid arthritis. Tishler reported that Hench did not discover the value of cortisone until he had used about 100 g of Merck product (23). If Merck had made only 25 g of material, the Golden Age of Steroid Chemistry, the late 1940s and the 1950s, might have been set back several years. Hench and Kendall, along with Tadeus Reichstein, shared the 1950 Nobel Prize in Physiology or Medicine for their work on cortisone. One of the many beneficiaries of cortisone was the painter Raoul Dufy whose arthritic condition had essentially ended his

career. Cortisone restored his ability to paint, and as a gesture of gratitude he gave Merck the reproduction rights to five of his paintings. Merck was then in a position to begin manufacturing cortisone. Under Tishler's leadership the development group, starting from desoxycholic acid, reduced the number of synthetic steps from over 40 down to 26; and they improved the yields sufficiently to make synthetic cortisone economically viable (24). The Merck process was so efficient that it continued to be economically competitive even after Upjohn discovered the biological oxidation of C-11 that significantly reduced the complexity of the cortisone synthesis (25).

The other major wartime project was penicillin. Merck again volunteered to become involved in the government program even though the company had little experience in fermentation. Merck scientists initially thought they could synthesize penicillin, as opposed to isolating it from a fermentation broth, but as one Merck chemist put it, "this was not the right horse to bet on." When early attempts at the preparation of penicillin by fermentation went badly, Merck again turned to an outside consultant, Selman Waksman from Rutgers (Fig. 6). Waksman sent one of his graduate students, Boyd Woodruff, to Merck to observe and help solve the fermentation problems. The difficulties were eventually solved and Merck became a contributor of penicillin during the war. Compared to Pfizer and Squibb, Merck was not a big producer of penicillin immediately after the war, but eventually the company became one of the largest manufacturers of penicillin. Fermentation became very important for Merck and has been used for the production of a number of major Merck products, among them streptomycin, cefoxitin, ivermectin, and lovastatin.

Figure 6. Selman W. Waksman (*left*), Randolph T. Major, and Alexander Fleming, the discoverer of penicillin, circa 1948. Fleming shared the 1945 Nobel Prize in Medicine with Chain and Florey for their work on penicillin. Waksman won the 1952 Nobel Prize for his work on antibiotics.

After World War II Merck planned to build a plant at its Stonewall facility in Elkton, Virginia for the production of streptothricin, an antibiotic discovered by Waksman and Woodruff, which was effective against bacteria where penicillin failed. However, before construction began, they found that streptothricin was highly toxic. Fortunately, within a few months Waksman and his students discovered streptomycin, which exhibited the same antibacterial spectrum as streptothricin but was not toxic. Streptomycin turned out to be effective against tuberculosis; and Merck, at the request of Waksman, turned its exclusive patent rights to streptomycin over to a Rutgers foundation for licensing to all the pharmaceutical houses. This magnanimous act was partly in the interests of public health and partly in the long-term interests of Merck in maintaining productive relationships with foundation and academic research (26, 27).

In the early 1940s Karl Folkers and his group began searching for the anti-pernicious anemia factor present in liver extracts (28). The Merck group was not alone; Glaxo and Lederle were also working on the problem. The relatively small number of patients suffering from this debilitating disease could only survive by consuming large amounts of liver on a daily basis. Obviously there was something in the liver that was important, but isolating the factor seemed nearly impossible. Although one could obtain liver extracts and divide them into fractions, the only assay available required a patient who was suffering from the disease. To find a patient and follow the effect of feeding a specific liver fraction was a slow, frustrating process. With luck and a prepared mind, Folkers located a researcher at the University of Maryland, Mary Shorb, who had discovered a simple biological

assay that responded to liver extracts. Merck microbiologists soon found Shorb's assay was specific for the anti-pernicious anemia factor, vitamin B_{12}. At about the same time Merck researchers discovered that the streptomycin broth, the waste from the production of streptomycin, contained vitamin B_{12}. Using this new source of B_{12} and the new assay, B_{12} was isolated in a short period of time, just ahead of the isolation by Glaxo and Lederle. Vitamin B_{12} turned out to be a red compound, but the color is only discernible at high concentration. Once it is sufficiently concentrated, the color can be used as a guide in its isolation. Just months before B_{12} was isolated, the company had decided to drop the project because too much time and too many resources had been expended in this search for the cure for a relatively minor disease. But Major and Folkers, realizing how close they were to success, quietly carried on the quest (29).

After all this effort Merck had isolated the anti-pernicious anemia factor: a scientific achievement, but hardly one to provide much income for the company. Then they discovered that B_{12} was, in the words of Karl Folkers (30):

> **the** growth factor for animals, and that meant that Merck would have a profit deluxe in contrast to a vitamin for a rare disease.

After World War II Merck rapidly expanded into a number of foreign markets, taking up some of the void left by the decimation of the European chemical and pharmaceutical houses. By the early 1950s exports constituted about 20% of Merck's sales, which had soared from $24 million in 1940 to $171 million in 1951 (5); but Merck was still selling chemicals in traditional industry style. It produced chemicals and pharmaceuticals and sold them in bulk to others for packaging, distribution,and sales to the consumer. Some of Merck's biggest customers, the pharmaceutical houses, were now producing their own products. If Merck were to retain a significant market share, its newest products, penicillin, streptomycin, and cortisone seemed to call for a different approach, one where a sales force would contact physicians directly (31).

Merck could not effect this change easily on its own, but a merger with Sharp and Dohme seemed to be an ideal solution for both companies. Sharp and Dohme was a Philadelphia firm with research, pharmaceutical manufacturing, packaging, and marketing skills. With no chemical manufacturing facilities of its own, however, it had, in fact, been a major Merck customer. Merck brought a world class research unit and an extensive chemical and pharmaceutical manufacturing organization to the merger. Combining the two companies—particularly the research units—caused some pain, but resulted in a far stronger company. The merger was eased somewhat by the fact that the president of Sharp & Dohme, William Dempsey, and the chairman of its board, John Zinnser, had previously worked for Merck.

Two scientists helped enormously in the success of the merger, as far as Merck Sharp & Dohme Research Laboratories (MSDRL) was concerned. One was Max Tishler, who was appointed president of MSDRL in 1956, a post he was to hold until 1969. The other was Karl Beyer, who was employed at Sharp & Dohme in the West Point laboratories outside Philadelphia. An MD whose specialty was medical physiology and pharmacology, Beyer felt his major goal in life was to find and produce therapeutic substances. As a "biological Max Tishler" he fit beautifully into the new system. Had it not been for the merger, Beyer would have resigned from Sharp and Dohme because it had no development chemistry or chemical manufacturing facilities (32).

Within a few years of the merger, Beyer and James Sprague, a former Wisconsin student of Homer Adkins who had followed Karl Folkers to Yale and Treat Johnson's Laboratory and who was the head of Medicinal Chemistry at West Point, produced chlorothiazide (Diuril). As the first major diuretic, its sales exceeded all expectations. This was Merck's entry into the area of hypertension, and it was done with enormous success (33, 34).

In 1950, a few years before the 1953 merger, George W. Merck, who had been president of Merck from 1925, gave over the presidency to James Kerrigan. George W. Merck remained as Chairman of the Board until his death in November 1957. Kerrigan, who had worked for the senior George Merck as a teenager, eventually served George W. Merck as vice president for sales and later commercial vice president before he was appointed president. His tenure as president, from 1950 to 1955, included the merger with Sharp & Dohme and the expansion of global operations; but Kerrigan was not the person to guide Merck through all the problems of the merger. So, in 1955, John (Jack) Connor, who had been general counsel and secretary of Merck, was appointed President and CEO, positions he held until 1965 when he became Secretary of Commerce under Lyndon Johnson. Connor led Merck through the consolidation with Sharp & Dohme, the enormous expansion of international operations (MSDI) and through some serious attacks by the Federal Trade Commission and Senator Kefauver (35).

These are some of the highlights of the first 70 years of Merck in America. This was a period in which Merck & Co., enhanced by major mergers in 1927 and 1953, grew from a distributor of German chemicals, to a manufacturer of fine chemicals, to a manufacturer of pharmaceuticals with an outstanding research organization, and, finally, to a full fledged pharmaceutical company with worldwide manufacturing, research, and distribution.

ACKNOWLEDGMENT

I wish to thank Merck & Co. for permission to use written and photographic material from the Merck Archives and material from interviews with former Merck scientists, executives, and directors. My thanks, too, to Dr. Jeffrey Sturchio for providing guidance and information when needed, and to Tracy DelDuca and Joseph Ciccone for invaluable assistance in the Merck Archives.

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*Presented at a symposium on the History of US Pharmaceutical Companies, 216th ACS National Meeting, Boston, MA, August, 1998, HIST 010.

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17. Ref. 15 (a), pp 8-10.
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20. B, E, and F. Compound E turned out to be cortisone.
21. Ralph Hirschmann in his article, "The cortisone era: aspects of its impact. Some contributions of the Merck Laboratories," *Steroids*, **1992**, *57*, 579-592, says the first partial synthesis was completed in 1944. This is also the date cited by Sarett and Roche in Ref. 15 (c), p 6. In the 1990 interview, Ref. 19, pp 6-8, Sarett said the date was December, 1942. Only a closer examination of Merck records and Sarett's notebooks can resolve this discrepancy.

22. The wartime work was not published until 1946. Sarett's first paper on cortisone was: L. H. Sarett, "Partial Syntheses of Pregnene-4-triol-17(b), 20(b), 21-dione-3,11 and Pregnene-4-diol-17(b), 21-trione-3, 11, 20 Monoacetate," *J. Biol. Chem.*, **1946**, *162*, 601-632.
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