



**Dr. Jokichi Takamine:
Japanese father of American Biotechnology**

Jokichi Takamine was born on November 3, 1854 in Takaoka City but spent most of his childhood in Kanazawa. His father, Seiichi, was a physician. His mother, Yukiko, came from a family that owned a sake brewery. From an early age, Jokichi showed an aptitude for languages and science and he was encouraged by his father to pursue western scientific interests. At the age of 12 he began the study of “foreign science” in Nagasaki; at 16 he was admitted to the medical school in Osaka; at 18 he transferred to a program in chemistry at the College of Science and Engineering in Tokyo; at 24 he was selected by the government to study technology at the University in Glasgow. While in Scotland he perfected his English, studied the industrial revolution and specialized in the practice of fertilizer manufacturing. Then he returned home to Japan and took a job with the newly established Japanese Department of Agriculture and Commerce. The goal was to apply western technology to Japanese products. However, his stay in Japan was short. In 1884, he was sent to the USA to be a co-commissioner of the Cotton Exposition held in New Orleans, Louisiana. While in New Orleans he rented a French Quarter apartment from a retired Union Officer, Colonel Ebenezer Hitch and befriended a young journalist named Lafcadio Hearn, who later emigrated to Japan and achieved fame as a writer. He also continued his research into fertilizer powders and more significantly, fell in love with his landlord’s daughter, Caroline Field Hitch. Before returning to Japan at the end of the Cotton Exposition, Takamine proposed marriage to Caroline, promising to return as soon as he had established himself financially. Good to his word, after having been appointed Acting Chief of the newly organized Japanese Bureau of Patents and Trade Marks, he was back to the USA within two years. The wedding took place in the heat of the New Orleans summer, on August 10, 1887. It was an unconventional match for the era and one which would eventually cement Takamine’s connection to the USA.

On their honeymoon, the young couple went to South Carolina where they visited fertilizer manufacturing plants and then to Washington D.C. where Takamine studied U.S. patent law. Finally they traveled west to California and then sailed to Japan. Once in his homeland, Takamine established the first Japanese super-phosphate plant to supply

fertilizer to the rice farmers, the Tokyo Artificial Fertilizer Company. The young couple lived near the fertilizer factory. Two sons, Jokichi Jr. and Eben were born in quick succession in 1888 and 1890. Although both children were healthy and the young couple was undoubtedly in love, the situation was difficult. The neighborhood around the fertilizer plant was “neither comfortable nor respectable” and it smelled bad. Caroline’s blond hair and blue eyes made her conspicuous. Jokichi’s mother made it clear that she did not like her foreign daughter in law. Because Caroline was unhappy living in Japan, Jokichi sought new business opportunities in the USA. He knew he could not compete in the well established American fertilizer industry. Therefore in a stroke of genius, Takamine decided to reverse what was then the usual cultural flow of technology. Rather than adopting a western technology to a Japanese enterprise, Takamine adapted a Japanese technology to a western industry.

*The diastatic enzyme from *Aspergillus oryzae**

Over the centuries, brewers in both eastern and western cultures learned by trial and error how to use yeast to make alcohol. Alcoholic fermentations start with sugar. Since yeast does not possess any starch degrading enzymes, starchy materials such as corn, rice and wheat must be saccharified before fermentation. Starch-degrading enzymes are variously called amylases or, in the older literature, diastases. In Western brewing, diastatic enzymes were traditionally derived from malt made from germinating barley. In Japan and some other Asian cultures, diastases were obtained from mold cultures grown on rice. These kojis are comparable to malt but more enzymatically active. Believing that a diastatic enzyme derived from *Aspergillus oryzae* could revolutionize the American distillery industry, Takamine and his young family returned to the USA in 1890. He worked first from Chicago and then from Peoria, Illinois, adapting the koji process for the beer and whiskey business. Sponsored by the Whiskey Trust, the Peoria distillery where he was employed was successful because the fungal diastase was faster to saccharify starch and cheaper to produce than the diastase from malt. Unfortunately but perhaps predictably, the local malt manufacturers did not welcome Takamine’s innovation. Historical records are unclear, but there is evidence of racist labor agitation and perhaps even arson. The distillery where Takamine worked was burned to the ground and he was financially ruined. To make matters worse, he was stricken with an acute liver disease and had to have emergency surgery in Chicago. It was the low point of his life and Caroline sold arts and crafts to support the family. Luckily, Takamine recovered his health and with good health he recovered his optimism. In 1894 Takamine applied for and was granted a patent entitled “Process of making diastatic enzyme” (U.S. Patent No. 525,823) on his method of growing mold on bran and using aqueous alcohol to extract amylase. It was the first patent on a microbial enzyme in the USA. Further Takamine recognized that the diastatic properties of the *Aspergillus* enzyme had potential medical applications and he licensed his enzyme preparation to Parke, Davis & Company of Detroit, Michigan, under the brand name “Taka-diastase.” Parke-Davis aggressively marketed it as a digestive aid for the treatment of dyspepsia said to be due to the incomplete digestion of starch. Takadiastase was enormously successful and Takamine became a consultant to the company. With Parke, Davis as his patron, he moved his family to New York and established an independent laboratory on East 103rd Street in Manhattan.

Adrenalin

Once established in New York, Takamine turned his attentions to another biological product that is active in minute amounts, namely the “internal secretions” associated with glands, in particular a blood pressure raising principle from the adrenal glands. In 1897, Professor John Jacob Abel, working with Albert Crawford, had purified a crystalline blood pressure principle that they named epinephrine. It was later shown that they isolated a benzoyl derivative rather than the pure hormone (Davenport, 1982). Takamine studied Abel’s method, visited him at Johns Hopkins University, and hired a young chemist from Japan, Keizo Uenaka (sometimes transcribed as Keizo Wooyenaka) to assist him in his research.

It was Uenaka, working alone who first obtained a crystalline product, but it was Takamine who filed a patent application on November 5, 1900, entitled “Glandular extractive product” on a blood pressure raising principle. He named the crystalline substance “Adrenalin” and presented two papers, one before the Society of Chemical Industry and the other before the New York State Medical Society. In 1901, he published two single author papers in the scientific literature and applied for and was awarded the right to the word “Adrenalin” as a USA trademark. Almost immediately, Parke, Davis started manufacturing the product and selling it under the trade name of Adrenalin. Adrenalin was the first of many ‘blockbuster’ drugs introduced during the 20th century. It was effective in controlling hemorrhage in surgery and also found uses in cardiology, obstetrics and in the treatment of asthma and other allergies. It prolonged the action of certain anesthetics and it is still used today to relieve respiratory distress (Bennett, 2001). Takamine’s patent on the “Glandular extractive product” was originally filed on November 5, 1900, but subsequently the application was divided and resubmitted. Eventually, on June 2, 1903, five separate US Patents were granted to Takamine on adrenaline. He also obtained British and Japanese patent rights on the drug. Later, a rival company of Parke-Davis, H. K. Mulford, attacked the adrenaline patents with the argument that the hormone existed in nature, and that Takamine’s work had been anticipated by Abel and others. A famous American judge named Learned Hand listened to days of technical testimony and carefully studied the chemical arguments. His summation is a virtuoso piece of legal writing and it contains a sentence that has become famous in American biotechnology patent history: “I cannot stop without calling attention to the extraordinary condition of the law which makes it possible for a man without knowledge of even the rudiments of chemistry to pass upon such questions as these.” (Circuit Court, S.D. New York, April 28, 1911, Federal Reporter 189:115). Judge Hand ruled in favor of Parke, Davis; Mulford was ordered to cease infringing. It is important to note that because Takamine’s name was not mentioned in the title of the law suit (Parke, Davis & Co. v. H. K. Mulford Co.) most people who study patent history don’t realize that he was involved in this milestone legal precedent.

Takamine’s Golden Years

Takamine became increasingly famous and wealthy. The emperor of Japan acknowledged Takamine’s success by conferring the Order of the Rising Sun, Fourth

Class. The emperor also sent fifteen imperial cherry trees to Parke, Davis where they were planted in front of the administrative offices.

Takamine used the new royalties from Adrenalin, and the continuing royalties from Taka-Diastase, to expand his business operations in both enzyme and pharmaceuticals. He invested in Japanese industries in aluminum, asbestos, bakelite and caustic soda. He founded three major companies; Sankyo Pharmaceutical Company of Tokyo, the International Takamine Ferment Company of New York, and the Takamine Laboratory of Clifton, New Jersey. Among the products manufactured at the Clifton laboratory was Salvarsan, the first true chemotherapeutic agent, where he hired a young scientist named Selam Waksman to oversee toxicity testing. In addition to managing his own companies and his investments, he turned his energies towards improving the position of the Japanese in the USA. It was an era when many Asian immigrants were denied basic civil rights and there was widespread discrimination against Japanese. For example, even though Takamine had an American wife, the laws of the time prevented him from becoming a US citizen. Nevertheless, his wealth allowed him to move in high society where he made a point of dressing in Japanese clothes and talking about Japanese culture. His homes were built in the Japanese style, and furnished with traditional Japanese furniture so that Americans could be exposed to the refined aesthetic of his native country. His summer home, Sho Fu Den in Merriewood, New York is still in existence containing much of the original furniture, and is maintained by the Japanese Heritage Foundation. He helped found both the Nippon Club and the Japanese Society to foster better relations between Americans and the Japanese. When he learned that the US President's wife, Mrs. William Howard Taft, was working to beautify the Tidal Basin Area around the Potomac River in Washington, D.C, Takamine funded the gift of cherry trees from the Mayor of Tokyo to the City of Washington. The Japanese cherry trees have become a major tourist attraction.

Epilogue

Jokichi Takamine died of the liver ailment that had plagued him most of his life on July 22, 1922. His funeral was held at St. Patrick's Cathedral in New York and he was interred at Woodlawn Cemetery in an elaborate crypt with a stained glass window that depicts Mr. Fuji. In his will, he left most of his estate to Caroline, who commissioned a vanity biography for her late husband, sold off the Japanese style homes, and then married a much younger American man who eventually dissipated much of her fortune. Jokichi Jr. died under mysterious circumstances well before World War II and with his death the International Ferment Company of New York was dissolved. Eben continued running the Clifton company. After his death in 1953, Eben's widow sold it to Miles Laboratories of Elkhart, Indiana. In 1978, Miles was acquired by Bayer Corporation and several years later the antiquated facilities in Clifton were leveled and the land sold off for a suburban housing development. In 1989, Bayer sold the Miles enzyme business to Solvay, a Belgian company, which in turn sold the business to Genencor International in 1996. The old Miles facility in Elkhart, Indiana, which had housed some archival Takamine materials was closed. Mr. Jay Shetty of Genencor International, working with Yutaka Yamamoto, arranged to have Takamine's papers and other artifacts from the Miles Archives moved to "The Great People of Kanazawa Memorial Museum" in

Kanazawa, Japan. In addition, Arthur Sears of Valley Research, Inc. South Bend, Indiana, established a Takamine Memorial Room at his company headquarters.

In “The Great People of Kanazawa Memorial Museum,” Dr. Takamine is one of five people with a special exhibit devoted to him. One display gives a detailed description of the process for extracting the diastatic enzyme from *Aspergillus oryzae*. Also featured are evening clothes worn by Jokichi and Caroline, family photographs and information on Adrenalin. Takamine’s death mask is kept in storage along with original correspondence, diary and other materials from the Miles Archives.

Sankyo Company is the only part of Takamine’s business empire that survives. It has grown into one of the largest pharmaceutical companies in Japan. At their research and development center in Shinagawa, Tokyo, a special room is maintained containing Takamine’s desk and some other personal effects, as well as a handsome portrait in oils.

Takamine was a great man who built a great fortune yet his road to success began with a humble koji mold. Some of Takamine’s methods for culturing filamentous fungi are still used in modern solid state fermentation for the commercial enzyme industry, where there is increasing demand for fungal amylases in baking and for starch conversion processes. Remarkably one hundred and ten years after its introduction, Taka-diastase continues to be available as a popular digestive aid.

Takamine’s work on the extraction and commercialization of the diastatic enzymes of *Aspergillus oryzae* led, through his ties to Parke, Davis to even more ground breaking work on mammalian hormones. Adrenalin (now sold under the generic name epinephrine) remains an important drug. Thus, in addition to being a pioneer of enzymology Takamine was a major figure in endocrinology, isolating epinephrine, and patenting and copy righting it under the name Adrenalin. Unlike many scientists, he was brilliantly entrepreneurial: he knew how to turn his biochemical extracts into profitable products. Quite remarkably, he held two of the earliest patents in biotechnology: the first patent on a microbial enzyme and the first patent on a purified hormone.

Jokichi Takamine understood the power of philanthropy. During his lifetime, he did much to improve cultural and political relationships between Japan and the USA. The cherry trees in Washington D.C are a lasting legacy of his foresight. 150 years after his birth, it is important to remember his contributions not only to biotechnology but also to cultural understanding.

Written by Joan Bennett & Yutaka Yamamoto
Reprinted with permission from Joan Bennett.