Chapter 5
Good Fortune

Following the isolation of adrenaline, there was a wealth of fascinating research. This will be examined in Chapter 8, but for the moment we will go back in time again. As I noted at the beginning of this story, Jokichi Takamine was not an expert in the physiology or chemistry of physiologically active substances in the body. So what gave him the opportunity to start working on the extremely challenging research area of the "isolation of adrenaline," and why did he take this chance? To find out, we need to trace the difficult path he took and learn of the fateful encounters along the way.

1. Takamine's first turning point

Jokichi Takamine—hereafter referred to as Takamine—was born on November 3, 1854, in his mother's family home in present-day Takaoka, Toyama Prefecture. His father, Seiichi, and mother, Yukiko, had five sons and seven daughters, of which Jokichi was the eldest.

The year before Jokichi was born, Commodore Matthew C. Perry of the United States Navy led a fleet of ships, known in Japan as the "Black Ships," to Japan to try to force the country to open up to trade. Perry had a letter from US President Millard Fillmore, which was delivered to Shogun Tokugawa Ieyoshi.

Perry returned in 1854, the year Takamine was born, and after landing at Uraga Bay, signed the Convention of Kanagawa with the government of Japan at Yokohama Harbor, thus marking the start of substantial trade between Japan and the United States. It was indeed a historic year.

Takamine's father Seiichi had studied Dutch medicine, and was a doctor with a high social position as an employee of the lord of Kaga Domain. He lived near Kanazawa Castle, the home of the domain lord, and when Jokichi was one year old he went with his mother to live with his father.

The fourth feudal lord of Kaga Domain, Tsunanori Maeda (1643–1724) had been greatly interested in scholarship, and he had invited eminent scholars from all around the country to the domain, where he compiled an encyclopedia, introduced Noh drama, and was also committed to collecting, organizing and safeguarding ancient documents.

Since this period of benevolent rule, when it was said that "there were no beggars in Kaga," the domain had remained as one of Japan's leading cultural spheres, with an extremely high educational level. Jokichi grew up in this environment, and he was strictly disciplined in the academic atmosphere of a doctor's house.

In 1865, three years before the Meiji Restoration (when imperial rule was restored under Emperor Meiji), Jokichi left Kaga to study medicine in Nagasaki City at the age of 11. Once there, he realized that the times were changing—Dutch had previously been the main foreign language, but it was being replaced by English. Jokichi studied the basics of English at a private school under Reishi Ga (Noriyuki, 1840–1923), and subsequently studied English for about two years under Guido Verbeck (1830–1898) at a Saga domain school "*Chienkan*" in Nagasaki (5-1).

During this time, Japan underwent a period of great upheaval: the *Boshin* Civil War (1868–1869) broke out, leading to the demise of the *Shogunate*. Takamine bided his time reading Western books at a military school in Kyoto as he waited for the disturbances to die down. After the Tokugawa Shogunate was overthrown, which ushered in a new period in Japanese history, Takamine's ardent love of learning was to set him on a course that would determine the rest of his life.

In 1869, *Osaka Igakko* (Osaka Medical School, attached to Osaka Temporary Hospital) was established to the southeast of Osaka Castle by Koreyoshi Ogata (1843-1909) on the wishes of Emperor Meiji (5-2). The Dutch doctor Anthonius Franciscus Bauduin (1820-1885), a specialist in ophthalmology was put in charge of education at the school. In a precious photograph of the opening of *Osaka Igakko*; Takamine, who at the age of 15 had yet to lose his boyish looks, cuts a rather charming figure (5-3). Takamine had first started to study medicine with the aim of carrying on in his father's footsteps, and he had no hesitation in enrolling in the new medical school. Here, he was finally able to settle down and apply himself to scholarship.

The basic conception for education in chemistry in Japan was drawn up by Bauduin. He had traveled from the Netherlands to Nagasaki in 1862 to be the successor to the Dutch doctor Johannes Lijdius Catharinus Pompe van Meerdervoort (1829–1908), who had left behind a record of considerable achievement in Nagasaki City. Bauduin established chemistry and physics, which until then had been part of medical education, as a separate subject; and he sent for his pupil, Koenraad Wolter Gratama (1831–1888) from the

Netherlands, to take charge of the practical business of teaching this new field. The foundations for education in chemistry and physics in Japan during the turbulent period from the demise of the Shogunate through establishment of the new Meiji Government were built by the enthusiastic foreign teacher, Gratama.

Leaving out the subsequent rather complicated history that followed, let us just note that the college for chemistry and physics that was established was *Osaka Seimi-Kyoku*, which was built on the western side of Osaka Castle and opened its doors on May 1, 1869. The aforementioned *Osaka Igakko* was then opened to the southeast. *Osaka Seimi-Kyoku* was renamed *Rigakko* (Institute of Western Science) that year, and the number of students increased rapidly. In the year 1871–72, some 59 auditing students came to this college from the nearby *Osaka Igakko*. Bauduin's basic plan to establish chemistry and physics independently of medical education turned out to be remarkably successful due to the fact that the institute for chemistry and physics was established so close to the *Igakko* that students of the latter were able to walk there (5-4).

Rigakko was subsequently re-organized and became *Osaka-kaiseijo Rigakusho*, and Gratama, the first head of the institute, completed his term of office at the end of 1870. His position was taken over by Herman R. Ritter, a German chemist. Ritter had been invited to the forward-thinking Kaga Domain as a foreign teacher in 1869, but, like many other domains, Kaga Domain found itself in financial difficulty during the period of political turmoil, and was unable to employ Ritter. He had no choice but to seek employment with the new government. Ritter had gained considerable business experience since leaving his native Germany after completing his PhD at the University of Göttingen under Friedrich Wöhler, who in 1828 became the first person to synthesize an organic compound, urea, from inorganic compounds.

Seiichi Takamine, Jokichi's father, was a doctor, but he also had a vast knowledge of chemistry. He was responsible for extracting nitrogenous constituents from disused silkworm pupae, used to manufacture nitric acid salts in order to bolster Kaga Domain's store of gunpowder. Conjecturing from this, it is possible that inviting Ritter to Kaga may have originally been Seiichi's idea. And later, as his beloved son was studying in Osaka, Seiichi may well have let him know that a German chemist by the name of Ritter would soon be on his way to the same city.

When Ritter took up his new post at *Rigakusho*, he enthusiastically set about teaching German modern chemistry in English. In 1872, he performed three types of chemical experiment in front of Emperor Meiji, who was making an imperial visit to Osaka (5-4).

Jokichi Takamine had acquired a good level of English at Verbeck's school in Nagasaki City, so Ritter, coming to Japan from Germany, the world leader in chemistry, and lecturing in English, was better fortune than he could ever have wished for. As well as grounding in theoretical knowledge, Ritter also had experience in the chemical industry, and his lectures must have been fascinating for Takamine. This was to be the decisive turning point that changed Takamine's path away from medicine and toward chemistry instead.

Ten years after this, Nagayoshi Nagai, who was Takamine's senior by nine years, was studying in Germany as an assistant under the organic chemist A. W. Hofmann. He was so captivated by Hofmann's lectures that he changed from medicine to chemistry; interestingly, this is the same as the change that Takamine made during his time in Osaka, when he switched his goal from becoming a doctor to becoming a chemist. Moreover, when he returned to Japan, Nagai worked at the Tokyo Imperial University, where he taught Wooyenaka. It seems nothing short of destiny that Wooyenaka should then take his talents overseas to the United States, where he became Takamine's assistant and achieved the crystallization of adrenaline.

Ritter's lectures were published as an outstanding textbook of chemistry and physics, and this is still carefully preserved in libraries such as Waseda University. Ritter became a teacher of mining studies at *Tokyo Kaisei School* (now the University of Tokyo) in 1873, but he sadly later contracted smallpox, and despite the efforts of the German doctor Theodor Hoffmann (a German naval and army doctor and professor at the *Daigaku Tohkou [University Eastern Campus]*, the forerunner of the Faculty of Medicine of the University of Tokyo) to treat him, he passed away on December 25, 1874 at the age of 47. The Japanese government paid out condolence money with a value equivalent to 7 million yen today. His remains were interred at Yokohama Foreign General Cemetery, and his students had a splendid monument in his honor erected at Ueno-Yanaka Cemetery in Tokyo [Figure 5-1].

In the class registers of *Osaka-kaiseijo Rigakusho* (5-5), there is one name that cannot be overlooked. This is Mitsuzo Hida, who was in a lower grade than Takamine, but took the same classes in physics, chemistry, and mathematics. Hida remained on good terms with Takamine as Takamine's junior, and later, when he was working in the section for analyses of the Ministry of Agriculture and Commerce, he was to recommend an important character in this story to Takamine.

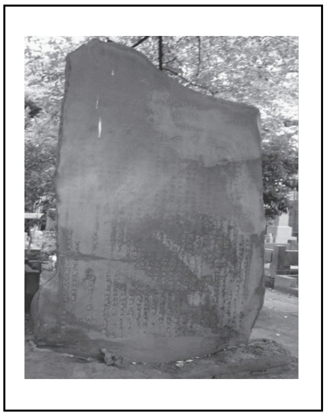

Figure 5-1. The monument to Herman Ritter at Ueno-Yanaka Cemetery in Tokyo. The monument was proposed by his students, and erected the year after his death. Even today, there are German visitors to the monument. (Photo taken by the author)

In 1872, Takamine left for Tokyo as a technical trainee sponsored by the newly established Ministry of Engineering. In 1879 he graduated at the top of the first graduating class of chemistry from the Imperial College of Engineering in Tokyo (the forerunner of Faculty of Engineering, the University of Tokyo), and was dispatched by the Japanese government to study for three years in the United Kingdom, at Anderson College in Glasgow, Scotland.

He studied chemical engineering across a wide range of fields. After returning to Japan, he started to aim at using scientific methods to turn around Japan's traditional industry as a senior member of the Ministry of Agriculture and Commerce (5-6).

2. Takamine's second turning point

In December 1884, the World Industrial and Cotton Centennial Exposition was held in New Orleans, in the southern United States. At this time, a century had passed since slaves had been brought from Africa and sold to work in the cotton fields. The government of Emperor Meiji in Japan decided to send the up-and-coming Jokichi Takamine, who had only returned from his three years in Scotland the previous year, to the exposition. Accompanied by Ichizo Hattori and Kizo Tamari (Agronomist), the 30-year-old Takamine, who was then working at the Ministry of Agriculture and Commerce, set sail from Yokohama in September, heading for New Orleans.

A detailed article praising the high quality of the Japanese display at the Industrial Exposition has been preserved. In particular, Takamine and Hattori, who were present at the display throughout the exposition and gave unfailingly courteous answers to even the most trivial of questions, gained a tremendous reputation for their manners (5-7).

The long overseas trip had a profound effect on the later course of Takamine's life, both professionally and personally [Figure 5-2] (5-8). During the time of the exposition he was invited to dinner by a local dignitary, and was immediately smitten by his daughter, whose name was Caroline Hitch [Figure 5-3] (5-9). They eventually became engaged and married three years later, when Takamine returned to the United States.


(Left) **Figure 5-2.** Jokichi Takamine at 30-year-old, when he returned to Japan after studying in Scotland and was working for the Ministry of Agriculture and Commerce.

(Right) **Figure 5-3.** Caroline Hitch (later Caroline Hitch Takamine), daughter of a noted local family.

At the exposition venue, Takamine noticed a display of phosphate rocks. After the exposition had finished, he visited Charleston, South Carolina, in order to get some of these phosphate rocks to take back to Japan with him. With these rocks, he founded a company called Tokyo Artificial Fertilizer Company, which is now Nissan Chemical Co. (5-10) (5-11). He probably gained the basic knowledge for manufacturing fertilizers when he visited a superphosphate factory in Newcastle, England, during his time studying in Scotland.

Among the people Takamine called on for investment in his new company were two leaders of the financial world during the Meiji Period: one was Eiichi Shibusawa, who founded Daiichi National Bank, and the other was Takashi Masuda, who was a head clerk in the Mitsui *zaibatsu* (family-owned business). Takamine remained friends with these two throughout his life. I will devote a little space here to what they had to say about Takamine.

Shibusawa: "Dr. Takamine is an extremely gentle person, and while originally a scholar, he is also a capable businessman. He is an elegant character, rather different from what is generally seen as the scholarly type, and he is a gentleman who would never go to extremes to compete with anyone else. However, no matter how capable he is of running a business, he is never so hurried that he tries to simply cut through difficult problems. This is because he is, after all, a scholar more than anything else." (5-12).

Masuda: "I first met Takamine in 1886, and I thought he was a splendid person. I felt like I had known him for 10 years, and we soon became such good friends it was almost as if we were related. I knew a little bit about chemistry, and the first time Takamine came and I heard him talk about various things, I thought that he was a credible scholar and I had to help him in a big way to realize his dream. That's why I agreed immediately to the artificial fertilizers. I dare say it was I, Masuda, who brought him out into the world." (5-13).

There were two more important encounters as a result of the exposition. One of these was the meeting between Patrick Lafcadio Hearn, a journalist covering the exposition, and Ichizo Hattori (5-11). The two became close friends. When Hearn later visited Japan, Hattori, then a bureaucrat at the Ministry of Education, intervened to help him find work as an English teacher at Matsue Middle School. Hearn married Setsu Koizumi while he was in Matsue, and became a naturalized Japanese. He adopted the name Yakumo Koizumi, and made a name for himself as a fiction writer. He was buried in Zoushigaya Cemetery in Tokyo, side-by-side with his wife Setsuko.

The other meeting was when Takamine provided the head of the display judging committee, Ferdinand Lascar, with a sample of diastase that he himself had prepared and brought with him. Lascar reported in an academic journal that he was surprised by the extraordinarily high activity of this substance (5-14, 5-15). This shows that at this time Takamine already had the idea of applying diastase to alcohol fermentation and digestive enzymes. Lascar wrote that the sample he received from Takamine was an “extract of malt,” but judging by the strength of its activity it was very likely to have been diastase prepared from *Nihon kojikabi*, a strain of fungus which will be discussed below.

After various twists and turns, Takamine was able to establish the technique for applying the microorganism used in brewing Japanese sake, *Nihon kojikabi* (*Aspergillus flavus* var. *oryzae*), to the manufacture of whiskey. This eventually developed into Takamine’s first discovery, TAKA=DIASTASE, which he was able to build into an international business with the business acumen he had inherited from his mother’s home. Takamine’s mother, Yukiko, was the daughter of the Tsuda family, who were sake brewers from Takaoka (present-day Toyama Prefecture along the Japan Sea coast).

The site where *Nihon kojikabi* was grown on the rice grains used to brew sake had been an excellent place for the young Jokichi to play [Figure 5-4]. From the close proximity of such activities, he was more than familiar with the color and flavor of the microbes, the aroma of sake during fermentation, and the complicated steps of the brewing process.

Takamine eventually devised a way to prepare a powder of dried spores of *Nihon kojikabi* microbes so that they could be stored. He packed this powder into a travelling bag along with the results of experiments in the whiskey manufacturing process, and, accompanied by Kosuke Fujiki, a specialist in brewing techniques, and his wife and two sons, left for the new land of the United States in November 1890.

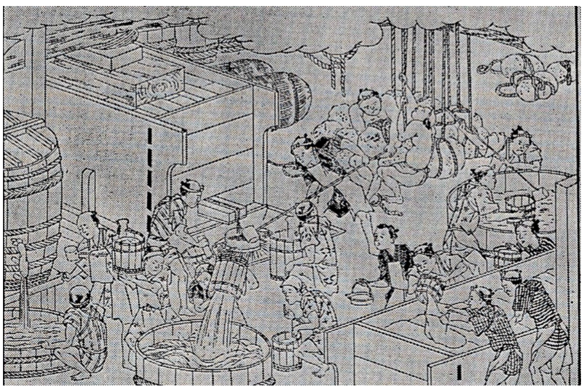

Figure 5-4. A late 18th century sake brewery in Japan. Robert William Atkinson: *The Chemistry of Saké-brewing*, 1881, Tôkiô: University of Tôkiô.

Fujiki was given the job of assistant to Takamine on the recommendation of Mitsuzo Hida, whom we met earlier as Takamine’s junior at *Osaka-kaiseijo Rigakusho* and at the government's Ministry of Agriculture and Commerce.

Simply explained, whiskey is made by using the power of enzymes to change starch into soluble sugars inside a tank, and these saccharides are then converted to ethanol by the action of yeast. In the traditional method, the enzyme used for saccharification is a diastase extracted from malt; the preparation of malt required considerable time and effort and yet the diastase thus prepared was not very powerful, so this method was inefficient. Takamine developed a groundbreaking new brewing method using a diastase that contained amylase [Note 5-1], an extremely potent enzyme that could be collected from *Nihon kojikabi* in a very short time (5-16).

Note 5-1.
A diastase is a group of enzymes which catalyses the breakdown of starch into soluble sugars. Amylase is a group of enzymes that catalyze the hydrolysis of **α**-1→4 glucosidic linkages of polysaccharides such as glycogen, starch, or their degradation products.

Takamine first took up residence in Chicago, and the following year, 1891, he moved to Peoria, halfway between Chicago and St. Louis. There he established the Takamine Ferment Co., with the aim of perfecting his brewing technique with diastase. In 1892, his business was progressing well enough for him to build a pilot plant.

However, Takamine's good fortune was not to last. Faced with the impending huge success of his plan, the local malt manufacturers saw their jobs threatened and they mounted a furious opposition that was little short of intimidation. In the spring of 1893, Takamine's pilot plant was destroyed by a suspicious fire. Seeing the wreckage of the burned-out factory before his eyes, Takamine stood rooted to the spot, unable to hold back his tears. To make matters worse, he was visited by further ill fortune when he was hospitalized for a chronic liver ailment. His life plan had hit a major setback.

3. Fighting back with a new idea

However, Takamine was not one to give up easily. During the period when his prospects in the whiskey industry were bleak, the way forward seemed to have been blocked off, yet he still devoted himself to research. Even on his sickbed, he thrashed out a new idea: the powerful enzymes of *Nihon kojikabi* were highly effective in the saccharification tank, so they should also work in the stomach, the body's internal tank. He reasoned that the enzymes would surely digest the starch in barley, wheat, or corn that had been eaten.

Having polished his idea, he made a fresh start by perfecting a method for the industrial production of the digestive medicine TAKA=DIASTASE (5-16, 5-17). In all likelihood, he recalled how he had given Ferdinand Lascar a sample of powdered diastase at the exposition in New Orleans nine years earlier, and how Lascar had been enthusiastic in his praise for the extraordinary activity of the powder (5-7).

Takamine later recalled that the concept for industrial production of the digestive medicine first came about in early 1892, and we can assume that it took shape around the time that he called Tetsukichi Shimizu [Figure 5-5], his junior from the Imperial College of Engineering, to come to Peoria from Tokyo. Shimizu was working in the Japanese government's Ministry of Agriculture and Commerce when he received the invitation from Takamine in 1892. Aged 28, he resigned from his job and traveled to the United States, where he joined the research at the laboratory in Peoria that was aiming to develop an industrial process for making whiskey. However, it was shortly after this that the project was thrown into disarray by the fire that destroyed the pilot plant. For a short while, Shimizu found himself deprived of his goal.

Figure 5-5. Tetsukichi Shimizu, Takamine's junior at the Imperial College of Engineering, who traveled to the United States to act as his assistant (5-18).

In the project to develop the technique for producing whiskey with *Nihon kojikabi*, Takamine had been entirely reliant on the professional sake brewer Kosuke Fujiki. They had resolved to develop the technique and had traveled to the United States together. However, after that dream was shattered and Takamine abruptly changed course and set his sights on the development of the digestive medicine TAKA=DIASTASE, the most important person was his trusted friend Shimizu, who had studied the same applied chemistry at the same university.

In 1902, after Takamine had achieved success in the United States and returned in triumph to his home country, he was invited to give a lecture to the Japan Federation of Engineering Societies, of which Shimizu had also been a member. In his lecture, he courteously and publicly expressed his gratitude to Shimizu, saying that much of the credit for the success of TAKA=DIASTASE went to Shimizu's hard work (5-17).

Sadly, however, Shimizu never returned to his home country. He contracted tuberculosis—whether this was because he was so engrossed in his work he was unable to relax, or because he took on too much work when Takamine was hospitalized, we will never know—and he died in Chicago in 1896 at the age of only 34. His remains were buried there.

Not far from where Takamine was working, there was a man taking a particular interest in the TAKA=DIASTASE digestive medicine. This was George Davis, one of the proprietors of Parke, Davis & Co., a pharmaceutical company. In the letter shown below [Figure 5-6], which was sent to Takamine just before Christmas of 1893 by J. B. Russel, a department manager at Parke, Davis & Co., we can see that the company had confirmed the uncommonly high enzymatic activity of the powder and was very keen to take charge of its commercialization.

Parke, Davis & Co.

Detroit, Mich., December 22'1893
Jokichi Takamine, Esq. 2111 N. Jefferson Ave. Peoria, Ill.

Dear Sir;

We have been delayed in conveying our final report with regard to the Takamine Diastase, owing to the writer's absence from his desk.

Tests made subsequent to these already reported fully convince us that the product is possessed of unusual strength, and if it can be produced in the dry form at a reasonable cost, it is our impression that we could create for it a large scale. Certain it is that our reputation and facilities for reaching the medical profession are such that we could introduce it more quickly and perhaps more successfully, than any other house in this country, and we therefore hope that you will decide to make us terms which will warrant our accepting them.

We shall be very glad to have you call upon us here in Detroit, or if necessary, the writer will meet you in Chicago.

Very truly yours.

(signed) Parke, Davis & Co.
J. B. Russel

Fig. 5-6. A letter from Parke, Davis & Co. (Courtesy of Yutaka Yamamoto)

Takamine had most likely sent samples to a number of possible companies and was considering the results of their evaluations. Receiving a reply like this from a trustworthy company such as Parke, Davis & Co. must have given Takamine confidence in his product. On February 23 of the following year (1894) he applied for a US patent for TAKA=DIASTASE and obtained the patent rights on September 11 (5-19).

In Brief 5-1. Parke, Davis & Co., the leader of the pharmaceutical industry (5-20).

1874: Catalog listed 254 types of fluid extracts, 300 types of sugar coated pills, 74 solid extracts, 53 concentrations, 46 medicinal elixirs, 23 medicinal syrups, 15 medicinal wines, 8 alkaloids, and chloroform.
1879: A process for standardization by chemical assay was developed.
1886: Initiation of the practice of using lot numbers on the labels of all products. This was made obligatory by the United States government 76 years later, in 1962.
1890: Branch was established in London (extending sales into Europe).
1893: Introduction of desiccated thyroid gland as a treatment for glandular disorder.
1895: TAKA=DIASTASE goes on sale. On March 19, the first injections in the United States of diphtheria therapeutic serum made by Parke, Davis & Co. are given. Two years later, Parke, Davis & Co. market a therapeutic serum for streptococcus and tetanus.
1897: Product quality control through bioassays begins (20 years later, 1,100th product tested).
(**1899:** Sankyo Shouten established in Yokohama, Japan.)
1913: Daughter company Sankyo Co., Ltd., Japan's first pharmaceutical manufacturing company founded in Tokyo. Jokichi Takamine appointed as the first company president.

The Detroit, MI research institute of Parke, Davis & Co. (1900). Inside are laboratories for performing bioassays and elementary analyses, and Takamine and Wooyenaka were probably frequent visitors for their collaborative research.

Davis was a very shrewd businessman, and he was in charge of all areas of the company except for the finances, which were the responsibility of the joint proprietor, Hervey Parke. Various letters sent to Takamine around 1894 have been preserved, and they show that Takamine sent out samples of TAKA=DIASTASE to different companies and also engaged a technical lawyer when he was looking for a company to buy the product. There are letters showing that the lawyer repeatedly urged Takamine to meet with Davis as soon as possible (5-21, 5-22).

Davis was a highly original individual, and he had been at the forefront of the American pharmaceutical industry since the early 1870s by building and developing novel system models in areas such as quality assurance and stock management (see In Brief 5-1, above).

Davis and Takamine met during a period of tremendous growth in the pharmaceutical industry, and Davis was greatly impressed. He saw Takamine's talent, and immediately signed a contract with him. The following year (1895) a digestive medicine in fine powder form went on sale under the trademark "TAKA=DIASTASE" [Figure 5-7]. This new product quickly gained popularity, and sales increased rapidly (5-20, 5-23).

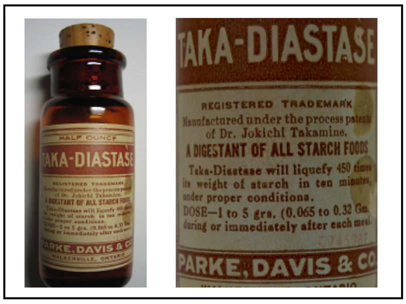

Figure 5-7. A half-ounce bottle of TAKA=DIASTASE, which went on sale in 1895. The label states, "Manufactured under the process patents of Dr. Jokichi Takamine," and the lot number, "C745087" is written to the upper right of the company name (Photo by Kouichi Inoguchi)

The digestive medicine TAKA=DIASTASE was indeed fortuitous for Takamine, but why did it sell so well? The answer can be seen in an advertisement. Figure 5-8 shows an advertisement for TAKA=DIASTASE that Parke, Davis & Co. posted in the *American Journal of Pharmacy*, an academic journal, in 1895 (5-23).

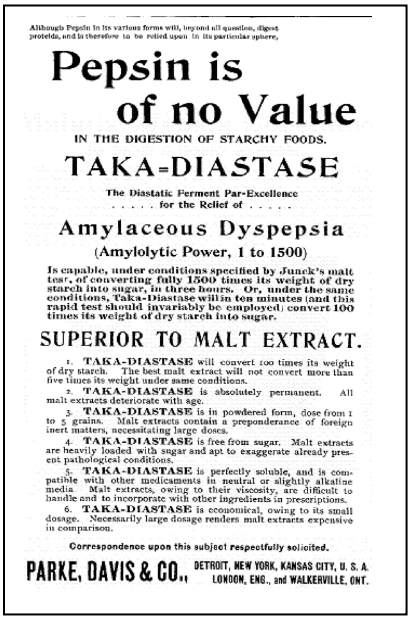

Figure 5-8. An advertisement for TAKA=DIATASE that appeared in the advertisement supplement of the *American Journal of Pharmacy* (1895). (5-23)

Reading the benefits and merits of this medicine, we can imagine that doctors confidently prescribed it for patients with stomach problems. The "starch-digesting diastase" that had been marketed up until then was manufactured through extraction from malt with water and concentrating it. However, the constituents extracted from malt with water are overwhelmingly sugars and other carbohydrates, which form a starch syrup when concentrated. Even if this product is separated into smaller quantities at the factory, measuring it out and packaging it is difficult and time-consuming for doctors when they prescribe it to patients. Also, as it cannot readily be mixed with other medicines, administration of this product is very inconvenient for doctors.

Compared to this, the powder medicine TAKA=DIASTASE was not only stable, but it was ground-breaking in the way it could be separated into smaller quantities and mixed with other medicines. It is easy to see why not only manufacturing plants but also doctors and patients welcomed this new product, and TAKA=DIASTASE was even more successful than expected.

Back in Japan, Jokichi Takamine's homeland, this medicine caught the eye of a young businessman. He was Matasaku Shiobara (1877-1955), who ran a silk trading company. Shiobara had heard about the good reputation TAKA=DIASTASE enjoyed in the United States from a friend, Shotaro Nishimura (1864–1945), and after gaining the trust of Takamine through the intermediation of the Japanese consul in Chicago, Tatsugoro Nose (1857–1911), Shiobara successfully acquired a license to import and sell TAKA=DIASTASE in Japan.

As a result of meeting Takamine, Shiobara was able to expand his business by establishing Sankyo Co., Ltd. in 1913; he asked Takamine to take the post of president and carry out research and development of new medicines while still in the United States, and he himself concentrated on running the business in Japan. This was Japan's first pharmaceutical manufacturing company.

For a long time, the catalogue of Parke, Davis & Co. had eighteen different TAKA=DIASTASE compound drugs in a wide variety of formulations, which included combinations of TAKA=DIASTASE with pepsin and strychnine (5-24). Without the benefit of a stable, fine powder that could be mixed with other medications, this would have been unimaginable.

Takamine subsequently worked to improve the fungus strains and the culture conditions in order to obtain even greater activity. Wooyenaka, who was employed by Takamine in 1900, started work straight away with research into TAKA=DIASTASE. He later recalled that although he interrupted this research to work on the crystallization of adrenaline, once that was finished he once again devoted himself to screening for higher TAKA=DIASTASE production strains over a long period, and in 1907 he established an excellent patent.

The key that led to the technical success of TAKA= DIASTASE was the use of the branny parts of grain for the cultivation of *Nihon kojikabi*—this was the same as when Takamine was producing whisky.

In the patent description, he explains the advantage of using these parts (5-19) as follows: "They not only are materials practically and economically suited for the purpose of my invention, but also they have the following merits, viz: First. Being of a loose and coarse nature, they afford a large surface for the growth of the fungus, and a ready access of air, one of the necessary conditions to its growth. Second. Being rich in albuminoids and phosphates, they supply the most necessary ingredients for the production of the enzyme. Third. They contain a large percentage of woody fiber, which renders their use of special advantage in the process of extraction as described below. Fourth. They are cheap and abundant, and in constant supply at all seasons of the year."

This shows Takamine's superb powers of observation, which bordered on divine revelation.

After cultivation, the grains were air-dried and the diastase was then extracted with water or water containing alcohol. The diastase was concentrated and settled with alcohol, and after drying was made into a powder. This principle of the extraction is the same method that was used by the French scientist Anselme Payen (1795–1878) and his coworkers when they discovered diastase in 1833 (5-25).

The idea of producing TAKA=DIASTASE in this way represents the beginning of biotechnology, in which microbes are used industrially to produce useful chemicals. This concept subsequently developed through its application to various different fields. In recent years especially, it has been used in genetic engineering, and has shown rapid growth as an indispensable technique in a wide range of fields, such as the economical production of insulin and other medicines, and amino acids such as *l*-glutamic acid. For this reason, Jokichi Takamine is now seen as "the Father of Modern Biotechnology" in the United States.

4. The meeting with Davis

As Takamine approached the milestone of his fortieth birthday, fortune seemed to be on his side. He was lucky to be given the chance to work on the challenging problem of the "isolation of adrenaline," which had continued for more than 40 years, and we can guess that this chance came from the corporate culture of Parke, Davis & Co., which had been built up by Davis, a man brimming with curiosity. Takamine's meeting with Davis was a fateful encounter, and is worth looking at in a little detail.

On October 26, 1866, Dr. Samuel Duffield, a pharmacy manager, jointly established a pharmaceutical company on the northeast shore (*le Côté du Nord-Est*) of Detroit with Hervey Parke, the 38-year-old manager of a mining and steel company.

The following year, 1867, an ambitious young salesman, George Davis, joined the company at the age of only 22, and business started to take off. Duffield later retired due to poor health, and Parke took charge of the company's finances while Davis was responsible for all the other areas, which included research, development, manufacturing, and sales.

This marked the start of Parke, Davis & Co, which linked the two men's names. In both his business and his private life, Davis was somewhat unconventional. He was born into a noted Detroit family, and after graduating from high school he elected to go into business rather than continuing his education to university. By the time he joined Parke, Davis & Co., he had already established himself as an outstanding salesman. In their dispositions, Parke and Davis were completely different— Parke was taciturn and had an air of authority behind his luxuriant white beard, while the young Davis was more showy and overflowing with ideas for expanding the business.

The company showed unprecedented growth under the leadership of these two men, but they always stuck to the motto that Duffield had originally adopted: *Medicamenta vera* (Pure medicine) [Note 5-2]. The first project Davis worked on was the collection and commercialization of *Cephaelis ipecacuanha*, a plant native to South America that is effective as a therapeutic remedy for amoebic dysentery, for preventing vomiting, and as an expectorant. He had to overcome a great many problems, but he was successful and he boosted the company's reputation through the development of a new product.

Note 5-2.
Albert B. Lyons (1841–1926) was a technician who put in place a system for Parke, Davis & Co. to conduct quality control through chemical analysis. He subsequently established the Scientific Division of the United States Pharmaceutical Manufacturers Association (5-26). Parke, Davis & Co. started to market the world's first standard solutions that were guaranteed by chemical analysis in 1883.

His subsequent business development was extremely creative, and it is no exaggeration to say that he largely put in place the structure of the modern pharmaceutical industry. For example, he published a bidirectional research journal as a means of ensuring collaboration with doctors and pharmacists and dissemination of accurate information on drug efficacy and side effects. The company's policy of putting a lot number on all its products to ensure quality even after sales was ground-breaking at that time (5-20). I own an old 1/2-ounce brown TAKA= DIASTASE bottle, on the label of which is printed the lot number "C745087" [Figure

5-7].

At the time when the company was steadily developing under Davis' outstanding leadership, he had an interview with Takamine. Davis was greatly impressed and he could see Takamine's abilities, so he immediately signed a contract with Takamine as a consultant. Judging by a letter that has been preserved from the contract agent George Whitney to Takamine dated November 5, 1894, this must have been around late fall of 1894. About the same time, the United States became caught up in the panic of 1893, an economic depression that had its epicenter in the United Kingdom. The collapse of an American railroad company was the trigger for the panic in the United States, and by the following year the unemployment rate had surged to between 12.3% and 18.4% and society was in turmoil. It was a similar situation to the panic brought on by the Lehman shock due to subprime loans at the start of the 21st century, which is still a recent memory.

Davis had invested heavily in land in California, and the losses were so huge that his income of Parke, Davis & Co. was insufficient to cover them. He became bankrupt in November 1896, and was forced to resign from the company [Note 5-3].

Unfortunately, because of Davis' unexpected resignation as a result of his bankruptcy, Takamine and Davis only had close dealings for about three years or so.

Note 5-3.
Davis was a lifelong bachelor, but there were incessant rumors linking him to glamorous women. At the height of his success, he lived in a fabulous mansion and owned 500 acres of farmland, where he kept racehorses. He had a magnificent yacht on Lake Saint Clair and lived an extravagant lifestyle, and there was no one in Detroit who did not know his name.

He was a great admirer of Napoleon, and had an extensive collection of items that had belonged to him. He also collected first editions of books, and by 1886 he had a library of over 5,000 volumes. So great was his fall that when he died in 1930 at the age of 85, it is said that only a handful of people attended his funeral. It was indeed a life of extremes (5-20).

However, before Takamine's assistant Tetsukichi Shimizu died in Chicago at an early age, he was able to savor the excitement surrounding the launch of TAKA=DIASTASE in 1895 thanks to Davis' decisive action. This must have been a great comfort for Shimizu, who had put his heart and soul into the development of a technique for industrial production of the digestive medicine TAKA=DIASTASE. For Takamine as well, the commercialization of the product within just one year of the patent application was enormously good fortune that gave him sufficient time and income from royalties to set up his base in New York.

5. The participation of Keizo Wooyenaka

Takamine would never have been able to achieve his success in the United States without the collaboration of Parke, Davis & Co. I have devoted considerable space to TAKA= DIASTASE, which was the world's first biotechnology product, because although it was a digestive enzyme with no direct relation to hormones, it was the first strong link between Takamine and the company. Another key to Takamine's success was the participation of Wooyenaka. This could be seen as a predestined encounter between two people brought together by history, but a closer look reveals that it was a link between scientists that you might call the destiny of wisdom.

Table 5-1. Board members of the Tokyo Chemical Society

Year	Chairman	Permanent board members	Secretary, clerk	Notes
1887	Nagai	—	Shimizu and nine others	—
1888	Nagai	Takamine and four others	Shimizu and three others	Society constitution decided
1889	Nagai	Takamine and four others	Shimizu and three others	—
1890	Nagai	Takamine and four others	Shimizu and three others	Takamine leaves for the United States
1891	Nagai	Five people	Shimizu and three others	—
1892	Matsui	Tamemasa Haga and four others	Four people	Shimizu leaves for the United States
1893	Takamatsu	Tamemasa Haga and four others	Four people	—

[This table is prepared from Kozo Hirota, *Meiji no Kagakusha* (in Japanese), Tokyo Kagaku Dojin, Tokyo (1988)].

Please look at Table 5-1, showing the Board members of the Tokyo Chemical Society during the early days of its establishment. This shows the relationship between Nagayoshi Nagai, Jokichi Takamine, Tamemasa Haga, and Tetsukichi Shimizu. First, let us start by looking at Wooyenaka's teachers, Nagayoshi Nagai and Jokichi Takamine. Table 5-1 shows that these two scientists were companions that helped develop the Tokyo Chemical Society, Japan's first academic society in the field of chemistry, which came into being in 1878. Takamine was a permanent member of the board of the society until he left for the United States.

We have already looked at Tetsukichi Shimizu during the period of development of the TAKA=DIASTASE digestive medicine, and this table shows that as secretary of the society he would have been in contact with Nagai, who was chairman of the society, for five consecutive years.

Shimizu undertook the important task of drawing up the Tokyo Chemical Society constitution in 1888 in collaboration with Jintaro Takayama and Iwata Nakazawa, which tells us that he was an indispensable figure for the society.

Wooyenaka and Shimizu did not cross paths, as Wooyenaka joined a non-regular course at the Pharmaceutical Department of Tokyo Imperial University in 1893, the year after Shimizu went to the United States. However, Wooyenaka had a big problem in that had he been a student on a regular course, he would have had free access to all the documents in the library, but the discriminatory treatment of non-regular course students meant that they were not allowed to take books from the bookshelves at will.

After graduating from the non-regular course, Wooyenaka worked on the isolation of natural active substances as an assistant to Professor Dr. Nagai, and during that period he would undoubtedly have heard about Shimizu from his mentor.

It was probably also a good opportunity for Wooyenaka to become familiar with Takamine's outstanding activities in the United States. Wooyenaka would have heard from Nagai about Takamine's success in launching "TAKA=DIASTASE" in 1895, shortly before Shimizu fell ill. He must have been excited to learn that Shimizu's work had been instrumental in this success.

The third person to appear in the table above is Professor Tamemasa Haga of the Faculty of Science of the Tokyo Imperial University. Haga was Takamine's junior by two years at the Department of Chemistry of Imperial College of Engineering, and thus two years senior to Shimizu.

Both Takamine and Haga were students of Edward Divers, a foreign chemistry teacher at the Imperial College of Engineering (later incorporated into the Tokyo Imperial University) brought in to assist Japan on its path to modernization at that time. Haga later had studied at the University of Kiel in Germany and returned to Japan in 1898, and he took over the inorganic chemistry course taught by Professor Divers. Haga's lectures were somewhat difficult to understand, but he took great care of his students (5-27). He would most likely have been close to Nagai through the Tokyo Chemical Society, and he wrote a letter to introduce Wooyenaka to Takamine.

In the spring of 1899, at the age of 23, Wooyenaka left his job as an assistant at Prof. Nagai's laboratory. After studying English he left for the United States at the end of 1899, carrying the letter of introduction from Haga. He arrived at Takamine's laboratory in New

York in the beginning of February 1900 [Figure 5-9].

Figure 5-9. The site of the Takamine Laboratory in a basement in New York. The windows near street level were probably the windows of the laboratory (5-28).

Wooyenaka was taken on by Takamine in February, and the first job he was given was to cultivate *Nihon kojikabi*. This had been the job of the previous assistant, a student of Columbia University called Yoneda who had helped with the research into diastase before leaving for France. Wooyenaka next helped with the job of a researcher called Matsuo, who was in charge of developing a fire retardant using ammonium phosphate. For his third job, he was directed toward research into the active principle of the suprarenal glands. Wooyenaka did not complain about being given jobs that were not his area of specialty as it was an age in which you did whatever was needed in order to earn a living (5-29).

6. The diligent preparations of Parke, Davis & Co.

Takamine and Wooyenaka would probably never have achieved their success were it not for the scrupulous research system that Parke, Davis & Co. had built. For 44 years, researchers at numerous institutions and laboratories in Europe and the United States had failed in their attempts to isolate the active principles of the adrenal glands; the one thing they all lacked was a systematic approach.

One thing about the successful team that is worth noting is that in 1894, Davis, one of the proprietors of Parke, Davis & Co., scouted two medical scientists from the University of Michigan, Elijah M. Houghton (See page 78) and Charles McClintock, to establish the first biological laboratory in the United States for the company's launch of a diphtheria therapeutic serum. It is likely that without this, the success of adrenaline isolation would never have come about. In an age without chromatography or spectroscopic analysis, research into endocrine substances required highly accurate, rapid activity tests to be carried out in large numbers. We have already seen the importance of this in Chapter 4, and the rivals in the race to isolate the adrenal principle did not have this capability. The isolation of natural active substances was a task that was beyond chemists working on their own.

The two medical scientists from Michigan were able to finish the job of developing the diphtheria therapeutic serum within just a few months. After this, only Houghton remained with the company, and he became head of the research department while at the same time taking teaching jobs at Detroit Medical College and the University of Michigan.

Parke, Davis & Co. turned its attention to putting together an adrenaline project team. The team was headed by Houghton, and Thomas B. Aldrich, the assistant to Prof. Abel, who was the researcher at the forefront of the world of chemical research into the active principle of the adrenal gland, was scouted to be an advisor. Two laboratories, one for activity tests and one for elemental analysis, were set up, and the company signed an agreement with Takamine.

Aldrich had completed his doctor's degree in Germany and then returned straight away to the United States, and the following year (1893), as soon as Abel had been welcomed by the newly established Johns Hopkins University Pharmaceutical Department as a professor, Aldrich became Abel's assistant. He was a solid organic chemist, working diligently on research for five years. Consequently, when Wooyenaka arrived from Japan, he was able to commence research with everything more or less in place. As we saw in Chapter 1, as Wooyenaka carried out his experiments, he sent the crystals that he obtained to Parke, Davis & Co. and he received the results of the activity tests without delay so that he could use them for planning the next experiments.

In his later years, Wooyenaka remembered the elementary analysis device in the chemical laboratory of Parke, Davis & Co. that he used: "The laboratory combustion furnace that I was using on loan for elementary analysis was faulty, and the amount of hydrogen after combustion was too high. I got the result $C_{10}H_{15}NO_3$, whereas the sample analyzed in the same laboratory by the German chemist Aldrich gave the correct result of $C_9H_{13}NO_3$" (5-30) [Note 5-4].

Note 5-4.
According to the *American Webster's Biographical Dictionary* (5-31), Aldrich was American, born in Port Jefferson, NY. Apparently, Wooyenaka mistakenly thought he was German because he had obtained his PhD at Jena University, Germany, in 1892.

At the time, the only available method for analyzing the constituent elements of a molecule was a destructive analytical method, and this method required large quantities of samples. At the end of one paper, Aldrich wrote, "Samples of sufficient quantity have already been obtained." This was because at that time, this analytical method was the only way to determine the composition of a substance (5-32).

7. Takamine's continuous advertising

In Chapter 4, we saw in detail how Takamine embarked on a vigorous program of publicity at academic conferences from the year following the successful crystallization of adrenaline, but following this his publicity activities were more attuned to the business side of science. That was an age without the abundant means of rapid information dissemination we enjoy today, and the most effective way for researchers to communicate the results of their research was for them to go out into the world personally and move from place to place, announcing the results. As this research was carried out under a contract with Parke, Davis & Co., Takamine put Wooyenaka in charge of developing a manufacturing method for pure adrenaline that would not run counter to the company policy of "*Medicamenta vera*," while he was in charge of communicating their achievements to the world.

During these publicity activities, Takamine must certainly have felt very happy to give an invited lecture at the Meeting of Medical Men, which was held at the School of Medicine in Edinburgh, Scotland, on December 3, 1901 (5-33).

Twenty-one years earlier, he started his three-year period as a student abroad in Glasgow, one of the centers of the Industrial Revolution, which was not far from Edinburgh. Having achieved research results that excited the scientific world, he was now making a triumphant return to his adopted home.

On March 20, earlier that same year, Thomas Maben had given a lecture at a pharmaceutical society meeting in Edinburgh (5-34) with a very suitable explanation and presentation of Takamine's announcement from New York the previous year (5-35), so we can imagine that there was an enthusiastic reception when Takamine appeared on the stage.

The following year, Takamine returned in glory to Japan, his native country, where he gave lectures in different parts of the country. The first was a public lecture at the Mitsui Assembly Hall in Hibiya, Tokyo, on February 27, 1902. This was very likely at the request of Takashi Masuda of Mitsui. In his lecture, Takamine looked back over the many hardships along the way to his success with TAKA=DIASTASE and adrenaline, recounting his memories with passion. He ended by expressing his thanks to his assistants, Tetsukichi Shimizu and Keizo Wooyenaka, for their achievements (5-36).

Takamine next spoke at the annual meeting of the Osaka Medical Society in April (5-37), and the annual meeting of the Engineering Society in Tokyo in September (5-17). At these lectures as well, he announced in detail the research processes of TAKA=DIASTASE and adrenaline. That same year, he published a report with more or less the same content in the journal of the Tokyo Chemical Society, which he himself had nurtured (5-38).

In his lecture in Osaka, Takamine presented the mistaken formula for the adrenaline molecule. Later, in his doctoral thesis for his Dr. of Pharmacy, in September 1906, seven years after he was awarded his Doctorate of Engineering, he presented his mistaken C_{10} molecular formula along with Aldrich's correct formula (C_9) and the formulae put forward by von Fürth and Abel. He stated that in the future, it would be shown which of these four formulae was correct. As far as he was concerned, as long as the molecule showed high activity, the exact molecular formula was secondary and was not a particularly big problem. This seems typical of Takamine, the "practical scientist."

While on the topic of practical science, the following passage from the end of Takamine's paper in the *American Journal of Pharmacy* of November 1901 mentioned earlier (5-39) clearly shows that "chemical industry" always occupied his mind: "There are several useful applications of adrenalin in arts and industry; for instance, a developer of photographic plates, as a reducing agent in chemical analysis, art of dyeing, etc."

Medical scientists and physiologists were probably dumfounded at the thinking of this Japanese scientist that an endocrine substance secreted in minute quantities from a small internal organ could be provided to the chemical industry. However, Takamine was not one to be constrained by the narrow preconceptions to which specialists are prone, and the following research, which emerged a short while later, is evidence that this was his way of thinking.

In 1907, five years after his lectures in Japan, two British scientists published a report in the *Pharmaceutical Journal* of joint research into a method to detect the iron content of commercial products containing oleic acid, an unsaturated fatty acid. Oleic acid was produced in huge quantities at that time, usually as an ingredient of soap, but it was also listed in the Pharmacopoeia as a solvent for use in medicines. An analysis method was needed because of the restrictions on adulteration with iron, which mainly came from the iron vessels used in production.

Readers will remember Vulpian's color reaction, introduced in Chapter 3, in which adrenaline reacted with ferric chloride presents a characteristic sea-green color. At that time there were no satisfactory analysis methods, so it hardly needs saying how useful a reaction giving a specific color with just a small quantity was. These scientists were proposing a method that could be carried out straight away, anywhere and by anyone, using only the naked eye as the analyzer—they had come up with the idea to use adrenaline to control the product quality of medicinal oleic acid to meet the specifications of the Pharmacopoeia (5-40).

Perhaps Vulpian would have smiled at Takamine's abundant creativity and the unexpected use of his own discovery.

8. Ensuring stable product quality

There is one important thing that is not mentioned in detail in the many papers and essays about Jokichi Takamine and adrenaline. This is the history relating to making adrenaline commercially available as a medicinal product that could be used with confidence by doctors after it had been extracted from animal organs and purified, which was extremely important from the point of view of society in general.

As we saw earlier, before Takamine and Wooyenaka succeeded in crystallizing adrenaline, the American doctor Solis-Cohen used himself as an experimental animal to examine the effects on hay fever of the tablet "Supra-renal Tabloid," which was manufactured by the London company Burroughs, Wellcome & Co. and sold worldwide. However, he recorded that one lot of the tabloids had deteriorated in quality (5-41). There were also probably times when this passed unnoticed, and we can assume that cases like this may have been common.

Apparently, a problem with liquid medicines containing adrenaline that were available on the general market was that discoloration became visible over time. In 1908, the detailed results of a study of discoloration of liquid medicines were published in the United Kingdom. This study used the term "makers" in the plural, so it is likely that products from more than one company were investigated [Note 5-5].

In his later life, Wooyenaka said that for four or five years after the success of crystallization, he was busy with the task of completing the product. He was in charge of the field of technical development for mass production, and he seems to have devoted himself wholeheartedly to this job. TAKA=DIASTASE has a very wide range of permissible doses, and even today it is available over the counter. Adrenaline, on the other hand, is a very active substance that requires extremely strict control, and only doctors are allowed to prescribe it.

Note 5-5.
If we look at just the section headings of the 1908 report, we can see that the study covered considerable ground: "Action of Alkali," "Atmospheric Oxidation," "Influence of Light," "Influence of Iron," "Possible Cause of the Colouration," and "Physiological Activity of Coloured Solution." The study concluded that discolored products showed marked reduction in their effectiveness (5-42).

The authors of this study, Alex Gunn and E.F. Harrison, reported the development of simple qualitative confirmation tests for adrenaline the previous year, in which they state that they used a product manufactured by Hoechst A. G. as well as a number of other products, with names such as Suprarenaline and Solutio Haemostasin Hydrochlor (5-43).

There were two extremely difficult problems that needed to be resolved in order to perfect an adrenaline product that doctors could use with confidence. The first of these was that the results of the activity tests of adrenaline were not always constant, but depended on the type and age of the animal from which the suprarenal glands had been taken, so that the adrenaline preparation needed to be adjusted accordingly. Wooyenaka must have eagerly continued to make great efforts to manufacture a formulation that would be reliable enough for use in medical settings even after the launch of the product.

The other problem was preventing decomposition of the formulation and breakdown of the active ingredient. The adrenaline solution that went on sale in 1901 was mixed with chloretone (chlorobutanol) as a preservative (5-44).

A stable product was achieved, and Parke, Davis & Co., which always aimed to live up to its motto "*Medicamenta vera*," did not change the compositional formulation of its extracted adrenaline even after the advent of synthetic adrenaline until 1975; this is testament to the confidence the company had in the techniques developed at the start by Wooyenaka and Aldrich (5-24).

Once these problems were overcome, the "Solution Adrenalin® Chloride" [Figure 5-10] with its stabilized product quality was launched, and soon every doctor always had a bottle in his bag. It was also an extremely attractive medicine for athletes; boxer James Joseph "Gene" Tunney, "the Fighting Marine" who defeated the great Jack Dempsey to become heavyweight champion in a legendary bout in 1926, apparently always had adrenaline in his hand when he stepped into the ring (5-45).

Figure 5-10. An advertisement for new products from Parke, Davis & Co. with a photo of "Solution Adrenalin® Chloride" (appeared at the end of *Therapeutic Notes*, **9**(4), 1902). Hay fever is shown as the complaint for which adrenaline may be used.

The wide use of adrenaline can be seen from the 1907 *Journal of the American Medical Association*, which gave a thorough explanation of the appropriate methods of use of adrenaline against a wide range of diseases, and the side effects that might occur (5-46).

We have already seen how being able to perform activity tests using experimental animals gave Takamine and Wooyenaka, and consequently Parke, Davis & Co., a huge advantage in research into the isolation of adrenal active principles.

At least according to the literature and data available from that time, none of the research institutions in Europe or the United States that were involved in the quest for the adrenal active principles appear to have been equipped with laboratories that could quantitatively check the activity of a large number of extracts.

It has already been pointed out that there was no spectroscopic analysis or chromatography at this time, and the techniques for isolating organic compounds were largely undeveloped—it is easy to see how effective activity tests would have been a powerful weapon in the hunt for physiologically active substances.

However, investigating whether there was physiological activity was not especially difficult; the problem was that demonstrating this with statistically significant numerical values was a very high-level technique for that time. It called for workers with high technical capability and a great many homogenous test animals, such that the costs were very high. Parke, Davis & Co. stated this publicly.

This valuable research system was managed and directed by Dr. Houghton, with the understanding of the owner of the company, Davis. Houghton's reports in academic journals were written in great detail, even including the methods used for dealing with—in other words, the welfare of—dogs used in adrenaline activity tests after the tests were finished. As he reported the methods for preparing the standards for activity tests up until adrenaline was crystallized, it seems likely that he started the preparations for a special laboratory straight after Oliver and Schäfer's blood pressure-raising effect and Bates' hemostatic effect were announced, probably in 1897 (5-47).

In Japan, Sankyo Shouten (the forerunner of Sankyo Co., Ltd.) signed an exclusive distribution agreement with Takamine. The company imported "Solution Adrenalin® Chloride," "Adrenalin Ointment," and "Adrenalin Inhalant," and these first went on sale on May 10, 1902 (5-48) [Note 5-6].

Note 5-6.
Adrenalin Ointment was a preparation of 0.1% adrenaline chloride packaged in a container that allowed easy application to the nose, the urethra, and the external ear. Adrenalin Inhalant was a preparation of 0.1% adrenaline chloride dissolved in perfumed natural oil with 3% chloretone added, which was administered using a nebulizer inhaler (5-49).

9. An English translation of Vulpian's paper

Judging by their past histories, Takamine and Wooyenaka were both undoubtedly proficient in English and German, but I imagine they might have struggled with French. When Parke, Davis & Co. signed the adrenaline research contract with Takamine, it is not unreasonable to suppose that the company would have delivered all the relevant scientific literature to him.

This is purely my own conjecture, but if that were the case, I would assume that the documents would have included an English translation of Vulpian's report, which was originally in French. Consequently, Takamine and Wooyenaka may perhaps have been fully aware not only of the experimental methods used by the previous researchers who had wrestled with adrenaline, but also of Vulpian's elaborate techniques.

Parke, Davis & Co. was established in Detroit, MI which was originally a town opened up by the Frenchman Antoine de la Mothe Cadillac for French people doing business with the indigenous Chippewa people. Detroit became well known as the center of the automotive industry, and the name Cadillac became synonymous around the world with luxury cars. The name Detroit is from the French le détroit, meaning "strait," and the reason for this is apparent if you look at a map.

Because of the history of the city, there must have been many employees at the research center who spoke French at home, so it would undoubtedly have been easy to find a technician to translate Vulpian's papers.

In an interview later in his life, Wooyenaka recounted, "Fifty years earlier, which would now be about 100 years ago [1856], Vulpian showed that there was something in the adrenal medulla that gave a green color with ferric chloride (5-30)." "As I said before, Vulpian had written everything down properly, so it was already clear. So really, if someone had followed Vulpian's experimental method, they would have been able to isolate adrenaline before me" (5-50).

Even if Wooyenaka was unable to read French, it is surely reasonable to suppose that he would have read an English translation, and would therefore have started his work fully aware that Vulpian's report was pivotal. If he had heard that Vulpian was seen in France as the "discoverer of adrenaline," he would have probably nodded in agreement.

10. Wooyenaka stays faithful to Nagai's teaching

Wooyenaka reflected on that time on July 21, 1900, when he observed crude crystals of adrenaline at the bottom of the test tube. "The very first thing I found was at the bottom of the test tube," he said. "Even so, I remembered what Prof. Nagai taught. Whatever he was working with—alkaloids or anything else—instead of test tubes, he always used watch glasses for observing reactions. For example, he would line up watch glasses of about 10 cm in diameter on a piece of white paper, put a sample in each one, and then add the test reagent made up to different concentrations with his own self-made narrow tipped pipette, first one drop and then a tiny drop at a time. He could then judge by the color as the reagent sank into the sample what the most suitable amount of reagent to use was. This was an extremely effective method." (5-30).

I remember that when I first read this, I could not help feeling the difference between the young Japanese today and that of in Meiji era. Compared to today's youth, the young people in Meiji era were very patient. Wooyenaka, like his teacher Nagayoshi Nagai, was a typical example of that kind.

Reading Nagai's paper on ephedrine (5-51, 5-52, 5-53), it is clear that the task of purification requires a degree of repetition and perseverance that would be intolerable for most people. Wooyenaka saw this dedicated figure while studying the non-regular course at the Pharmaceutical Department of the Tokyo Imperial University, and was doubtlessly reminded of Nagai when he worked in the semi-basement laboratory in New York.

Figure 5-11. Former teacher of Wooyenaka: Nagayoshi Nagai, Head of Pharmaceutical Department, Tokyo Imperial University and his wife Therese（Courtesy of The Pharmaceutical Society of Japan）

However, Wooyenaka did not simply do everything just as Nagai [Figure 5-11] had taught him. In the interview in his later life, he said, "Unfortunately I don't have it now as I lent it to someone, but I bought a book in the United States around that time that shows an experimental method where you select crystals that have formed in the precipitate you get as I explained, and from the state of the crystals you can distinguish different types of alkaloid. Not many people used this method, but it seemed to work very well."

11. Should Wooyenaka be a co-author?

Many Japanese people have been unhappy that in all the academic papers on the crystallization of adrenaline, including the historic first report (5-35), the author is given only as Jokichi Takamine, with Keizo Wooyenaka [Figure 5-12] not credited as a co-author. This is felt to be rather unfair.

Figure 5-12. Keizo Wooyenaka and his wife Yaeno, in 1905, shortly after they were married (5-54).

However, the people making this argument do not appear to have made any attempt to verify the accepted practice of scientific circles at that time. Let us look at how researchers in leading positions at that time decided whether to make coworkers or assistants co-authors.

Wooyenaka was perhaps closest to his former teacher, Dr. Nagayoshi Nagai, a professor of the Tokyo Imperial University. What did Nagai do with respect to co-authorship? Let us look at his research paper on the alkaloid “ephedrine,” from the plant mahuang (*Ephedra sinica*), which brought him sudden, worldwide fame. His paper on ephedrine is a masterly work on the organic chemistry of natural products, comprising five reports totaling a considerable number of pages, but the authorship is credited to Nagai alone. In the introduction to the first report, Nagai writes, “Mototada Yamashina worked on the analysis of *mahuang* at Osaka Inspection Station and collected a type of alkaloid, but he died suddenly, leaving the extracted liquid with a minute quantity of needle crystals. I carried on the research with Yuzo Hori as assistant (5-51).”

Not even Yamashina, who had extracted the alkaloid as far as the crystallization stage, was credited as an author. Dr. Kinnosuke Miura of the Medical Department of Tokyo Imperial University received a sample of ephedrine from Dr. Nagai, and he used this to carry out pharmacological research. Miura reported the mydriasis effect in the German journal *Berliner Klinische Wochenschrift* (5-55), and he is credited as the sole author.

Next, let us look A.W. von Hofmann, Nagai’s mentor at Berlin University. Hofmann had been enchanted by Italy, where his father took him on a trip at a young age, and he aspired to literature. However, he ended up becoming captivated by the lectures and experiments of Justus Freiherr von Liebig, the father of German organic chemistry, who was teaching the latest advances in chemistry at Hofmann’s hometown of Gießen, and he went on to make a name for himself in organic chemistry. Over the course of 25 years, Hofmann published some 150 papers, of which only nine were credited with a co-author, while all the rest were credited to Hofmann alone. In Germany at that time, students would sometimes be credited as co-authors, but they could not be authors once they had graduated and become salaried assistants, even if they played a substantial role in the research of a professor. So if someone was receiving a salary for carrying out your research, the common practice at that time was to regard that person simply as a worker (5-56). Looking next at Abel, his first paper on epinephrine credited Crawford as a co-author, but while some of his other papers give names of people who collaborated, none of these people are made co-authors.

My understanding is as follows. The extraction and purification of adrenaline was research carried out under a contract between Takamine and Parke, Davis & Co., and Takamine appointed Wooyenaka to the research after making arrangements for all the reference documents, the materials for the experiments, and the expenses. This was accepted academic practice for the time, and Keizo Wooyenaka, who had not published an academic report in this field, was an assistant.

At least Takamine gave Wooyenaka the title of "associate" in the first academic report (5-39), and this can be interpreted as Takamine showing his appreciation for Wooyenaka's exceptional achievements. Given the normal thinking of the time, it is not reasonable to criticize Takamine. It might perhaps have been extremely forward-thinking to make Wooyenaka a co-author, but from the point of view of the general etiquette among scientists of the time, it would probably have seemed inappropriate. In an interview when he had reached an advanced age, Wooyenaka himself looked back over the research: "This adrenal medulla hormone, adrenaline, was just a question of running into it by chance," he said. "I just happened to be the one that did the experiment at that time, and adrenaline was easy to obtain. Parke, Davis & Co. wanted to use the story for their publicity, so they exaggerated it a bit. It was rather as though we simply collected them!" he laughed (5-30). "I was very disappointed that my husband didn't receive a PhD in Japan," recalled Wooyenaka's wife, Yaeno, at the same interview. It was only natural she should feel that way after the merit of crystallizing adrenaline became ever more highly commended.

Wooyenaka himself would have probably felt the same way if he had finally found success after struggling with research into adrenaline extraction as an assistant for many years. But he had been a young man of 24 who had only arrived in the United States six months earlier, and to come across the crystals like that was actually something of an anticlimax. It was as though in a high hurdle race he had skipped over the hurdles with no run-up at all—only when looking back from the finishing line did he appreciate how high he had soared. In the same way, perhaps he only gained a true understanding of his achievement as he grew older.

Takamine later shared with Wooyenaka the benefits he obtained from adrenaline and TAKA=DIASTASE. He arranged work at Sankyo Co., Ltd., the company to which he had granted exclusive sales rights in Japan for the ground-breaking new medicines, and gave these jobs to Wooyenaka, ensuring that the latter was well looked after until late in his life [Note 5-7].

Note 5-7.
An example of the jobs that Takamine arranged for Wooyenaka is "Bakelite." This was the discovery of Leo Henricus Arthur Baekeland, a close friend of Takamine's from the Chemical Society of New York. Baekeland was born in Gent, Belgium, and went to the United States where he successfully developed "Velox," the first photographic printing paper. He then created the world's first plastic by combining formalin and phenol, aptly named "Bakelite." Takamine was enormously interested in this, and Baekeland provided his friend with the technology, free of royalties, and authorized production in Japan by Sankyo Co., Ltd in 1911. Baekeland and Takamine had both worked to the utmost to realize their dreams in the unforgiving society of a new continent, a long way from their home countries, and thus must have felt a strong desire to support each other.

Wooyenaka returned to Japan in 1916, and devoted himself to the pharmaceuticals business at Sankyo Co., Ltd., respecting the wishes of Takamine, even after he had passed away, by continuing to play an active role there, which included a long spell in the United States in 1926 to work on problems with the technology for manufacturing Bakelite. Japan's first domestic plastic industry was taken over by Sumitomo Bakelite Co., Ltd., and has developed into a worldwide business.

With respect to the consideration that Takamine showed him, Wooyenaka felt throughout his life that he was fully rewarded for the contributions he had made [Figure 5-13].

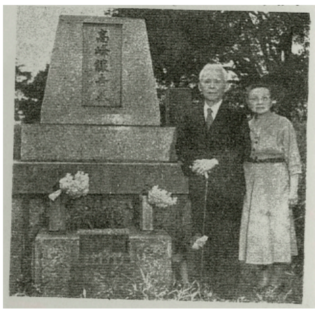

Figure 5-13. Mr. and Mrs. Wooyenaka at the tomb of Jokichi Takamine in Aoyama Cemetery, Tokyo (5-57).

12. Applied and pure science

Science is like a two-wheeled cart, needing both logic and practical application to advance. The success of Takamine and Wooyenaka is clearly the latter.

Their main interest, and also that of Parke, Davis & Co., the company to which they were contracted, was purely in marketing the active principle they extracted as a therapeutic medicine. Their interest in the scientific principles of hormones was secondary—it was for this reason that they were so careless with the molecular formula of adrenaline.

Logic and practical application go hand-in-hand to make science evolve, but the people that aim for this all have different characters and different circumstances. This is shown by the example of the crystallization of adrenaline [Note 5-8].

Takamine took classes in pure scholarship at the Imperial College of Engineering, but for the rest of his life following his period of study in the United Kingdom, his work was based on practical applications. In an interview, Wooyenaka had this to say about Takamine: "Dr. Takamine had no contact at all with universities in the United States. When he was studying in the UK, he studied at the University of Glasgow, but then after that as a scientist he was involved in big business, pioneering a very wide range of work, such as the exposition and the chemical fertilizer company (5-30)."

Note 5-8.
There is a very interesting history in the relationship between applied science and pure science. The Japanese scientist Katsusaburo Yamagiwa (1863–1930) was interested in the irritation theory of Rudolf Virchow (1821–1902), whom Yamagiwa had studied under as a student at Humboldt University in Berlin. Yamagiwa successfully created the world's first induced cell carcinomas by continuous application of coal tar, and should have been awarded the Nobel Prize. After this historic discovery, Yamagiwa chose to work on treatments for cancer rather than clarifying the substances that caused it. The cancer specific substances in coal tar were found by the Briton E. L. Kennaway (1881–1959) and his co-workers. Kennaway's interest was practical: he wanted to control the onset of skin cancer in chimney sweeps, which was seen as an occupational disease. He first determined that the strength of the carcinogenicity of the substances stuck to the inside of the chimney depended upon the site in the chimney, and from samples with high concentrations of the carcinogen he determined that the causative compound was 3, 4-benzpyrene. He then tried to reduce skin cancer in chimney sweeps by guiding them to work in such a way that they would not absorb this substance (5-58).

Anderson College in Glasgow, at the time when Takamine, then a young man with a promising future, mainly studied chemical engineering. Takamine's family on his mother's side, the Tsuda family, ran a sake brewing business in Takaoka City, and from an early age he had grown up watching sake brewing. At Anderson College, he had lectures in basic chemistry from Dr. E. J. Mills, and he also studied the latest fermentation science (5-6). It was this combination that would lead to the success of TAKA=DIASTASE.

In those days, it was not uncommon for Japanese students who studied in a developed country to act arrogantly based on their adherence to the teachings of their former teachers or the country of study on their return to Japan. Takamine shows no traces at all of having been influenced in that way; he was a self-reliant scientist who stressed knowledge and experience, and fully applied these to his chosen subjects.

The adrenaline crystals were born of practical science, and they subsequently led to the magnificent and dramatic flowering of the logic of hormones, nurturing the development of many researchers in both theoretical and applied science, and even yielding a number of Nobel Prize winners.

◇ ◇ ◇

These are two of the many quotes that the great French scientist and patriot Louis Pasteur left behind, expressing his convictions (5-59).

"In the field of observation, chance favours only the prepared mind."

"If science has no country, the scientist should have one, and ascribe to it the influence which his works may have in this world."

Parke, Davis & Co. established a research organization, and the company was motivated to call on Takamine to collaborate in the planning by his record of achievements as a pioneer of biotechnology. He was joined by Wooyenaka, who had shown perseverance in refining his methods for handling natural products as an assistant to Nagayoshi Nagai. Chance undoubtedly favored these two minds, and the two men both took a great many benefits from their work back to their home country.

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