The ALLERGY ARCHIVES

Pioneers and Milestones

Abel, Takamine, and the isolation of epinephrine

In the second half of the 19th century, medical researchers paid increasing attention to the so-called ductless (endocrine) glands. In 1848, German physiologist Arnold Berthold provided the first evidence that one of these glands could secrete a physiologically active substance directly into the bloodstream. A castrated rooster normally exhibited a shrinking of its comb, but Berthold showed that this shrinking did not occur if the excised testes were transplanted into the abdominal cavity. He suggested that the testes must be secreting some substance into the blood that affected the comb.

Shortly thereafter, the research of other investigators, such as Charles-Edouard Brown Sequard in France, suggested that other ductless glands, such as the adrenal glands, might also secrete physiologically active substances into the bloodstream. Toward the end of the century, a number of glandular secretions were introduced into medicine as a form of "organotherapy." Brown-Sequard believed that he had developed a testicular extract from animals that was capable of rejuvenating elderly men, although it was soon shown that his conclusions were erroneous. In the 1890s, Eugen Baumann in Germany had some success in the treatment of goiter with thyroid extract.[1]

In 1894, George Oliver and Edward Schäfer of the University of London reported that they had produced an extract of the adrenal gland that had a strong action on the blood vessels, the heart, and the skeletal muscles. Several investigators set out to try to isolate the active principle of the adrenal extract in a pure form. The successful isolation of this substance, epinephrine (or adrenaline), the first hormone to be isolated in a pure state, involved a certain amount of controversy over priority. Before discussing this complex history, however, it will be useful to provide some biographic background on the 2 main protagonists, John J. Abel and Jokichi Takamine.

JOHN J. ABEL

John Jacob Abel was born in Cleveland, Ohio, on May 19, 1857. After graduating as the top student in the Cleveland high school system, Abel enrolled at the University of Michigan in 1876. His education was interrupted at the end of his third year for financial reasons, and he spent the next 3 years as a teacher, principal, and then superintendent of schools in La Porte, Indiana, where he met his future wife, fellow teacher Mary Hinman. During his stay in La Porte, Abel made the decision to study medicine. He returned to the University of Michigan in 1882 to complete his undergraduate education, spending much of his last year studying under Victor Vaughan and Henry Sewall in the medical school.

On graduation, Abel married Mary Hinman, and they moved to Baltimore, where Abel spent a year working in the laboratory of physiologist Henry Newall Martin at Johns Hopkins University. In 1884, lured to Germany by its growing reputation as the world center of medical research, Abel obtained a place in the laboratory of noted physiologist Carl Ludwig in Leipzig. He soon decided, however, that he lacked the necessary background to undertake sophisticated medical research, and therefore he enrolled at the medical school at Leipzig to enhance his knowledge of basic biomedical science. Abel spent a total of $6\frac{1}{2}$ years of study in universities in Germany, Austria, and Switzerland, obtaining his MD degree from the University of Strassburg in 1888.

In Strassburg Abel came under the influence of Oswald Schmiedeberg, one of the key figures in the emergence of experimental pharmacology as an independent discipline. Schmiedeberg also encouraged Abel's interest in the application of chemistry to medicine. In 1891, Abel assumed the chair of *materia medica* and therapeutics at the University of Michigan. Although the traditional title was retained for the chair, Abel's appointment at Michigan must be considered the first professorship of experimental pharmacology in the United States. In 1893, as plans were being made for the opening of the new medical school at the Johns Hopkins University, Abel was offered and accepted the chair of pharmacology there. Abel's laboratory became the most important training ground for American pharmacologists for the next 4 decades. Abel was also the key figure in the establishment of a national society and a journal for the discipline. In 1908, the American Society for Pharmacology and Experimental Therapeutics was established in Baltimore, with Abel as its first president. The following year, Abel founded the *Journal of Pharmacology and Experimental Therapeutics*, which he edited until 1932. He was also a founder of the American Society for Biological Chemists and the *Journal of Biological Chemistry*.

Abel's most important research centered around the isolation and characterization of hormones. We shall shortly discuss his work on epinephrine. In 1926, Abel reported that he had obtained the hormone insulin in crystalline form. His results suggested that insulin was a protein, a conclusion that was challenged because there was considerable skepticism at the time

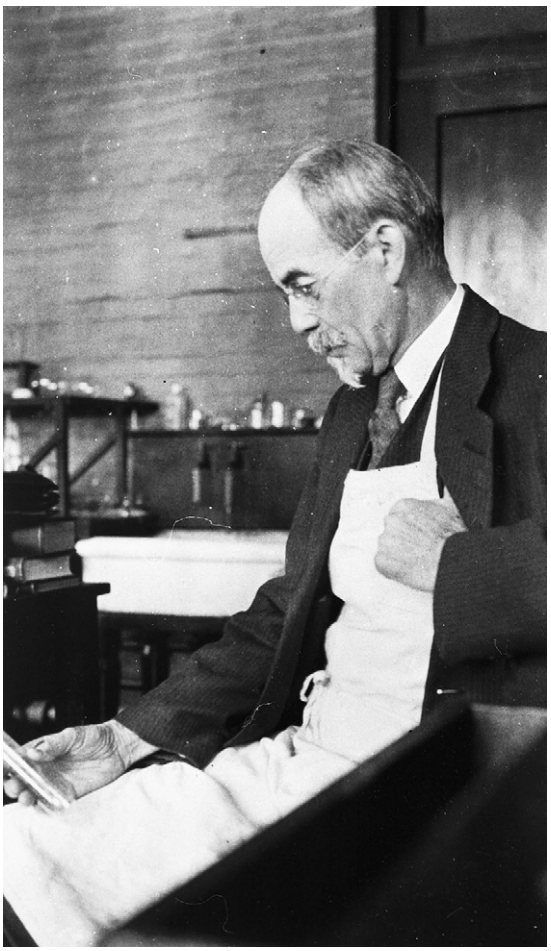

FIG 1. John Jacob Abel.

about the ability of proteins to have the high degree of specific biological activity characteristic of hormones. Subsequent research proved Abel to be correct. Abel retired from the chair of pharmacology in 1932, but he continued his research as professor emeritus, focusing on the study of tetanus toxin. He died in Baltimore in 1938, hailed by his contemporaries and still recognized by pharmacologists today as the ''father'' of American pharmacology.[2]

JOKICHI TAKAMINE

Jokichi Takamine was born on November 3, 1854, in Takaoka City, Japan. He was admitted to the medical school in Osaka at the age of 16, and 2 years later, he transferred to a program in chemistry at the College of Science and Engineering in Tokyo. At the age of 24, he was selected by the government to study technology at the University of Glasgow, Scotland, where he perfected his English, a language that he had first learned from a Dutch family in Japan. Takamine then returned home to Japan and took a position with the Japanese Department of Agriculture and Commerce. In 1884, he was sent to the United States to serve as a cocommissioner of the Cotton Exposition in New Orleans.

FIG 2. Jokichi Takamine.

Although he returned to Japan at the end of the Exposition, Takamine returned to New Orleans in 1887 to marry Caroline Filed Hitch, whom he had met on his earlier visit.

The Takamines soon left for Japan, where Jokichi established a superphosphate plant to supply fertilizer to rice farmers. However, Caroline was unhappy living in Japan, and therefore Jokichi took a position with a distillery in Peoria, Illinois. In 1894, he patented a process for growing mold on bran and using aqueous alcohol to extract the enzyme amylase. He licensed his enzyme preparation to Parke, Davis & Company, and they marketed it under the name of ''Taka-diastase'' as a digestive aid for the treatment of dyspepsia. The product was very successful, and Takamine became a consultant to the company. He established an independent laboratory in New York City, where he carried out his work on epinephrine. Takamine became wealthy based on the royalties on his patents and greatly expanded his business operations, founding 3 major companies. He funded the gift of the cherry trees from the Mayor of Tokyo to Washington, DC, where they still adorn the Tidal Basin. Takamine died on July 22, 1922.[3,4]

THE ISOLATION OF EPINEPHRINE

Soon after his arrival at Johns Hopkins, Abel became interested in the newly emerging field of research on the secretions of ductless or endocrine glands, substances that English physiologist Ernest Starling would call ''hormones'' in 1905. His first venture into the field involved an effort to isolate the active principle of the thyroid gland. However, he abandoned this work in 1895 on learning of Eugen Baumann's isolation of an organic compound of iodine from the gland.[5]

Abel next turned to an attempt to isolate the active principle of the adrenal glands. Using sheep adrenal glands provided by Armour and Company, Abel (working with Albert Crawford) obtained a crystalline product that appeared to be the blood pressure–increasing substance of Oliver and Schäfer's extract. He called it ''epinephrin'' and described it in a paper read before the Association of American Physicians on May 6, 1897, and published in the *Bulletin of the Johns Hopkins Hospital* later that same year.[6] It was later shown that Abel had actually obtained the active principle in the form of a crystalline benzoyl derivative, which he had then subjected to hydrolysis to remove the benzoyl groups. The residue that he obtained was physiologically very active, and Abel believed it to be the blood pressure–increasing constituent of the adrenal gland, although in a state that was not quite pure. In 2 further papers over the next 2 years, he expanded on this work and published a chemical formula for the compound.[7,8]

Early in 1901, Jokichi Takamine published the results of his own research on the adrenal substance, claiming that he had obtained the active principle in a pure crystalline form. It is not clear when Takamine began this research, but he certainly had isolated this compound by sometime in 1900 at the latest. Takamine argued that Abel's compound was either a modified substance or the benzoyl derivative that had withstood his hydrolysis treatment. Takamine gave a different chemical formula for his active principle, which he called ''adrenalin.'' The compound was patented by Takamine and marketed under the trade name ''Adrenalin'' by Parke, Davis & Company, with whom Takamine had a working relationship. In his initial paper on adrenalin in the *Therapeutic Gazette*, Takamine already claimed that the drug had given satisfactory results in the treatment of ''acute conjunctivitis, some cases of deafness, bloodless operations on the nose and throat; laryngeal phthisis; hay-fever; nasal hemorrhage; diseases of the heart; diseases of the nose and throat; asthma; laryngitis; diseases of the urethra; Addison's disease; exophthalmic goiter, etc., etc.'' No clinical evidence was presented, however, to support these extravagant claims, which make epinephrine sound almost like a panacea.[9,10]

In August of 1901, Parke, Davis & Company chemist Thomas Aldrich, who had worked in Abel's laboratory from 1893 to 1898, used a method differing slightly from that of Takamine to also isolate a crystalline substance from the suprarenal glands. Aldrich compared his compound with that of Takamine, which was made available to Aldrich through Takamine's relationship with Parke, Davis & Company, and found the 2 substances to be identical. Aldrich then conducted an elementary analysis of adrenalin. His formula for the compound was somewhat different from Takamine's and was later shown to be the correct one.[11]

Because Takamine visited Abel's laboratory in 1899 or 1900, there were suggestions in some quarters that he may have ''borrowed'' some of Abel's ideas. Horace Davenport, however, has reviewed the evidence and concluded that Takamine would not have learned anything in this way that he could not have obtained from Abel's published work, and depending on the time of his visit, he might have been well on his way to his own success before meeting with Abel. Davenport commented, ''A clever chemist, Takamine or Aldrich, could see that somehow Abel had blundered into a morass and that his method did, in fact, need simplification.''[12]

Parke, Davis & Company was very sensitive to any statements that appeared in the literature identifying Abel as the person who had first isolated epinephrine and undertook efforts to correct this view. The company consistently pointed out in advertisements and informational brochures that it was Takamine who had first obtained adrenalin in pure form. When the firm received a copy of the galley proofs of an article that was scheduled to appear in the *Journal of the American Medical Association* in 1911, its general manager wrote to the editor of the journal objecting to certain statements in the article. Among the complaints registered was that the article was unjust to Parke, Davis & Company and its employees because of ''language that implies that Professor Abel was mainly responsible for the discovery and preparation of the pure, active principle of the suprarenal gland.'' Abel, although declining to get involved publically in priority disputes, was still privately expressing the view many years later that he had essentially isolated the hormone in its active form, even though his epinephrine turned out to be a derivative of the native substance present in the gland and still retained a chemical radical that he was unable to remove.[13-16]

CONCLUSION

In conclusion, it can be stated that Abel had isolated the monobenzoyl derivative of the hormone rather than the active principle itself. Takamine had actually isolated the hormone, although it was later shown that the natural product is itself a mixture of 2 substances, epinephrine and norepinephrine. Finally, Aldrich deserves the credit for determining the correct chemical formula of epinephrine.[6]

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REFERENCES

1. Sneader W. Drug discovery: a history. Chichester: Wiley; 2005. p. 151-4.
2. Parascandola J. The development of American pharmacology: John J. Abel and the shaping of a discipline. Baltimore: Johns Hopkins University Press; 1992.
3. Kline R. The legacies of Dr. Jokichi Takamine. MD Adv 2008;1: 36-43.

4. Bennet J, Yamamote Y. Dr. Jokichi Takamine: Japanese father of biotechnology. Available at: www.deerland-enzymes.com/files/Dr_Jokichi%20Takamine_Bio.pdf. Accessed December 26, 2009.
5. Voegtlin C. John Jacob Abel, 1857-1938. J Pharmacol Exp Ther 1939;67:373-406.
6. Abel J, Crawford A. On the blood-pressure-raising constituent of the suprarenal capsule. Bull Johns Hopkins Hosp 1897;8:151-7.
7. Abel J. Further observations on the chemical nature of the active principle of the suprarenal capsule. Bull Johns Hopkins Hosp 1898;9:215-8.
8. Abel J. Ueber den blutdruckerregenden Bestandtheil des Nebenniere, das Epinephrin. Z Physiol Chem 1899;28:318-62.
9. Takamine J. The blood-pressure-raising principle of the suprarenal glands—a preliminary report. Therapeutic Gazette 1901;7:221-4.
10. Takamine J. Adrenalin the active principle of the suprarenal glands and its mode of preparation. Am J Pharm 1901;73:523-31.
11. Aldrich T. A preliminary report on the active principle of the suprarenal gland. Am J Physiol 1901;5:457-61.
12. Davenport H. Epinephrin(e). Physiol 1982;25:76-82.
13. Swift E. To Simmons G, letter of February 23, 1911. In: John J. Abel Papers. Located at: Alan Mason Chesney Archives, Johns Hopkins University, Baltimore, Md.
14. Abel J. To Johnson S, letter of September 21, 1935. In: John J. Abel Papers. Located at: Alan Mason Chesney Archives, Johns Hopkins University, Baltimore, Md.
15. Advertisement for Adrenalin. British Col Drugg, Vol. 58. October 7, 1910.
16. Takamine J, et al. Adrenalin. Detroit: Parke, Davis & Company; 1901.