Prologue

I often remember the dread I felt as a child sitting in the dentist's chair; it was so different from the enjoyable sensation of sitting in the same type of chair at the barbershop, waiting for my turn while listening to the brisk snip-snip of scissors. Recently, I had to visit the dentist to have a wisdom tooth treated. This time, I felt the briefest flutter in my breathing and my heart when the dentist gave me a local anesthetic, but the procedure finished with no pain and no bleeding. The wonders of modern medicine made me realize how much science has advanced. I asked the dentist the name of the drug he had given me, and when I got home I looked up its active constituents. The drug contained the local anesthetic xylocaine, also known as lidocaine, and the vasoconstrictor epinephrine, otherwise known as adrenaline.

My first thought was that most people who have an injection when they undergo dental treatment probably do not realize that they are being given epinephrine (adrenaline). After further investigation, I was surprised to find that there is actually a huge number of drugs containing epinephrine on the market, so there must be a great many people who, just like me, have benefited from epinephrine without even being aware of it.

In the United States, the EpiPen® auto injector is used to deliver a minute dose of epinephrine to those going into anaphylactic shock due to peanut allergy or bee sting as an emergency procedure before the person is rushed to the hospital. Since 2012, schoolteachers in an increasing number of states are being advised to use the EpiPen in these situations.

Adrenaline was the first hormone to be isolated. Hormones are chemical substances produced within the bodies of animals that act in minute quantities on specific organs, enabling them to carry out functions necessary to maintain life. Adrenaline is secreted by the adrenal glands, which are tiny glands that sit one on each kidney. The adrenal glands have two layers of structures, and adrenaline is secreted by the inner layer, called the adrenal medulla. Once secreted, adrenaline is carried by the blood to the heart and other organs, where it exerts its physiological activity.

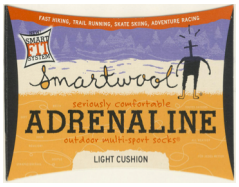
I imagine a golfer making his approach shot to the green for the last hole of the

championship. He is aware that victory hangs on this shot, but he sends it too far, overshooting the green. At an interview after the match, you might hear him say, “I guess I was pumping too much adrenaline out there.” This is the action of adrenaline.

The three figures below illustrate popular images of adrenaline. An old Japanese friend of mine found the canned soft drink on the left at a gas station while we were traveling in New Mexico in 2007 (of course, it contained no adrenaline). The others are advertisement and goods that he had collected for me by that time. In these examples, “adrenaline” refers to the energy and vitality associated with the hormone; these products do not actually claim to contain biologically active adrenaline.

Adrenaline, a drink to keep you awake. The main active ingredient is caffeine.

Fillup with adrenaline, and then just go!



Adrenaline socks that let you walk on and on.

It is by no means uncommon, at least in the U.S., to come across advertising or products like those shown in the above figures. Most people have an accurate understanding that adrenaline is a substance produced within the body that somehow works to make us more lively and energetic. However, there is no doubt that with the exception of professionals specializing in medicine and pharmaceuticals, few people realize that adrenaline is known as epinephrine when it is used in pharmaceutical drugs. Why does one substance have two different names, adrenaline and epinephrine? This is one of three things about adrenaline that has puzzled me for some time. Incidentally, I will use the name adrenaline throughout this book, except in special cases such as in the references or for trade names.

I worked for many years at Sankyo Co., Ltd., now Daiichi Sankyo Co., Ltd. This was Japan’s first pharmaceutical company, and the first company president was Dr. Jokichi Takamine (1854−1922).

Readers may have heard of Takamine, as even today he is greatly respected in the U.S. as the father of modern biotechnology (p-1). At an early age he set out for the new world of America to make a name for himself, and there he made two major discoveries.

His first success was the discovery of highly potent saccharifying enzyme isolated from culture of sake-brewing Kojikabi mold. This became the first enzyme to be extracted and purified on an industrial scale, and it first went on the market in 1895 as Taka-Diastase digestive medicine. This was produced in the U.S. by Parke-Davis and Company, now a subsidiary of Pfizer, Inc., and rapidly became a highly popular product. Not long after, Taka-Diastase appeared in the seminal novel *I Am a Cat* (pub. 1905−06) by the much-loved Japanese author Natsume Soseki. Soseki's alter ego in the book, Mr. Sneeze, was a keen user of Taka-Diastase.

Takamine's second remarkable achievement in the scientific field was the crystallization of adrenaline. Takamine achieved the feat at his laboratory in New York City in July 1900, five years before the word "hormone" was proposed. Crystallizing a physiologically active principle secreted within the body was a historic piece of scientific research, and a fitting prologue to the twentieth century.

Adrenaline was first discovered as a clump of innocuous-looking crystals at the bottom of a test tube. Chapter 1 tells of the excitement of the moment when the discovery was made, and how the substance was subsequently named and an application was filed for a patent on its manufacture. Chapter 2 takes a great leap back in time with a scientific history of how anatomists and physiologists from the time of Galen onward racked their brains to understand the adrenal glands, which were shrouded in mystery. The famous 18th-century French thinker and social commentator Montesquieu also makes an appearance in this tale.

We then witness a ground-breaking discovery in 1856 that instigated the race among scientists to extract pure adrenaline. This was the discovery by the French scientist Alfred Vulpian (1826−1887) that adrenaline has a particular color reaction; if a minute quantity of a chemical substance is added to adrenaline, a reaction takes place that produces a characteristic color. I wondered what had led Vulpian to be interested in a substance originating from the adrenal glands in the first place, and why he was searching for it. This was the second thing about adrenaline that had puzzled me for so long. To get my answer, I carried out a detailed study of research papers primarily from France, Germany, and the UK, which were the most advanced countries in the natural sciences at the time. I discuss the results in Chapter 3, and in Chapter 4, I turn once again to the race to isolate adrenaline.

In Chapter 5, I try to get to the bottom of the third question that was puzzling me. Curiously, it turns out that Takamine carried out no other research into hormones either before or after his isolation of adrenaline. He does not seem to have shown any interest in these active substances produced and secreted in minute quantities within our bodies. In the

44 years from the discovery of the characteristic color reactions of adrenaline until Takamine's success, over 20 researchers took part in the race to extract pure adrenaline, including some of the greatest scientists of that time. So why was it that for 44 years not one of them was able to make it to the finish line, while Takamine, who entered the race all of a sudden, far behind anyone else, succeeded in almost no time at all? This was the third big question puzzling me. The background that helps unravel this mystery is given in detail, and it is here that Parke-Davis and Company had a major role to play.

Chapter 6 examines the clear ruling passed by Judge Learned Hand in a dispute over infringement of the patent on the manufacture of adrenaline. Judge Hand dared to challenge the idea that natural products should not be subject to patents, which was the accepted wisdom among lawyers up until the end of the 19th century. The controversy surrounding this decision continues to this day, and in 2013 the U.S. Supreme Court ruled that a patent could not be granted on naturally occurring DNA.

In Chapter 7, a valuable historical document—a letter to Takamine from one O.W. Smith, president of Parke-Davis and Company—helps unravel the mystery of how the name epinephrine came to be used in the *US Pharmacopeia*. I will also look at the confusion that has been caused by the double naming. This chapter gives a glimpse of Takamine at the end of the nineteenth century, already focused on his mission as he carried out contract research for companies.

With the crystallization of adrenaline in 1900, there was no longer any need for the laborious and time-consuming task of extracting the hormone from the adrenal glands of domestic animals. Scientists were now able to obtain commercially available adrenaline crystals for use in experiments with just a single telephone call. Their subsequent research is described in detail in Chapter 8, and the rapid succession of new advances represented a paradigm shift. While these three chapters may appear to be a lecture transcript on the history of modern biochemistry, they have a great many implications with respect to the integrity that is expected of scientists of the future.

Although the subject matter is inevitably somewhat technical, I have tried to present it in a way that will be readable even for those with no background in chemistry. Where I have used slightly technical terms, I have included simple explanations in separate columns.

Finally, I would like to touch on the reasons why I chose to publish this book. I have spent many years carefully reviewing the literature relating to adrenaline, and other than a brief but meticulous review in Japanese by Dr. Yutaka Sano (p-2), there does not appear to be anything in the vein of a science history book that tells the story of adrenaline from recognition of the

adrenal glands to isolation of the hormone. There are numerous books and articles, particularly in Japanese, relating to Takamine's achievements, but most of these were written to honor Takamine and his collaborator, Keizo Wooyenaka (also spelled Uenaka). While these publications give detailed accounts of the characters of Takamine and Wooyenaka, many are essentially the biographies of important figures; there is almost no treatment of the scientific articles and materials on their historical achievements in the fields of physiology, medicine, and chemistry.

Adrenaline was the first substance to be established as a hormone, and is therefore of monumental importance to human scientific endeavor. Nonetheless, although people from the country where adrenaline was crystallized have made fragmentary records of the history of this research, I have not found any books in English, German, or French that cover all aspects of the story. It therefore became my mission to bring out an English version of this book after it was published by the Kyoto University Press in 2012 in Japanese.

I found out recently that in June 2013, six months after this book was published in Japanese, the science history book *Adrenaline* by Dr. Brian B. Hoffman was published. Dr. Hoffman is a researcher who has studied the cellular action of adrenaline for many years, and is a professor of medicine at Harvard Medical School. Dr. Hoffman's book naturally gives a very full account of adrenaline from the perspectives of physiology and medicine, and he also devotes many pages to the glorious history of advances after adrenaline was first crystallized. I am delighted that Dr. Hoffman's book and mine complement each other perfectly, and his book in no way lessens the significance of making an English version of my own book.

History of the quest for the role the adrenal glands play is of course, linked to the history of scientific development in the particular country where research took place. At the same time, it is an enormously interesting scientific drama that played out across a wide area in an age of rudimentary information technology. It is a drama of courageous challenges and human conflict, as well as the woes of a small country with a minor language.

I hope this book will tell that story, and at the same time illustrate the struggle of scientists working in an age in which technology for separation and analysis of organic compounds was unbelievably primitive by today's standards.

Literature Cited

(p-1) Map of the Woodlawn Cemetery (1990).

(p-2) Sano, Y., "Adrenaline Hakken eno Michi (Road to the discovery of adrenalin)." *Microscopia,* **6**: 194–200 (1989).