Chapter 7

Confusion over the Name

At one time or another, adrenaline has had four different names. Even until very recently there was a great deal of confusion, caused around the world because the substance that the American John J. Abel extracted from the suprarenal glands and named "epinephrin," believing it to be the active principle, turned out to be inactive.

The authorities wanted to use "adrenaline" as the official name in the *United States Pharmacopeia*, and a request was made to Parke, Davis & Co., which until then had dominated the market for the drug with this name. However, this came at a time when the company was desperately defending its trademark, "ADRENALIN," because the manufacturing patent had expired. The company was unable to accept the request, which further added to the confusion over the name.

1. Four people, four names

The adrenal medulla hormone was the first hormone to be isolated. Because this was in an age when separation and analysis technology had yet to be developed, the road to extracting the hormone in pure form and verifying it as a separate chemical substance was long and tortuous.

This in turn meant that the process of naming the hormone had various twists and turns, and it was given a different name by each of the four researchers that extracted it. In chronological order, it was variously named sphygmogenin, epinephrin, suprarenin, and adrenalin.

In 1894 to 95, Oliver and Schäfer verified that there were blood pressure-raising principles in the adrenal gland. Their student and a member of physiology research group at University College London, Benjamin Moore, attempted to isolate the specific compounds, but he did not give a name to the principles.

Neither did William H. Bates, who discovered the clear hemostatic effect. There was little point in naming the principles when no one knew for sure if there were one, two, or even

more components.

The first name, Sphygmogenin, was given by Sigmund Fränkel of the University-Institute for Medical Chemistry in Vienna to the syrupy constituent he extracted from the adrenal glands. He was convinced the constituent was pure, but the purity was inconsistent and he was unable to clarify the chemical formula, and there the matter rested (7-1).

Chronologically, the next name was epinephrin, which was given by John J. Abel of Johns Hopkins University. The most important part of the text of his research report, from the point of view of the present story, is the part in which he explains how he named the active component, so I will include the essential parts of the text in their original form. In his most important paper (7-2), he gives the name in two places. The first section of the main body of the paper is titled Epinephrin, and he writes, "*Ich nenne daher die blutdruck-steigerunde Substanz in Uebereinstimmung mit Hyrtl's Nomenclatur Epinephrin* (Therefore, I call this vasopressor substance "epinephrin" according to Hyrtl's nomenclature)". This means that he named the active component by defining it as the blood pressure-raising principle. Abel followed the nomenclature of Hyrtl, an Austrian anatomist. Hyrtl was keen on Greek, so for "kidney" in the stem of the word he used the Greek *nephr-* rather than the Latin *ren.* Incidentally, Hyrtl and the German anatomist Henle, whose research into the tissue of the adrenal glands using the chromaffin reaction we saw in Chapter 3, both published well-known books on dissection that have become textbooks used globally.

Now, however, we come to a dead end. In the final summary (*Zusammenfassung*) of the same paper, Abel writes, "*die Formel* $C_{17}H_{15}NO_4$ *ausgedrückt wird und welche ich Epinephrin nenne* (The formula of the substance which I call epinephrin is $C_{17}H_{15}NO_4$)". He named the active principle in the body of the paper, so after defining the chemical structure there would seem to be no problem with using the name for this as well. Thus in the final summary he writes the molecular formula $C_{17}H_{15}NO_4$ and specifically gives the name "epinephrin" to this compound. This means that he applied the name to this molecule rather than to the active principle, which is an abstract concept.

Unfortunately, the molecule in question has absolutely no activity at all. Abel was convinced that this molecule was the active principle, so he cannot really be blamed, but the dual nature of this name subsequently caused a degree of confusion that he would never have been able to imagine.

In 1903, Abel's assistant Samuel Amberg published a short report titled "The Toxicity of Epinephrin (Adrenalin)" (7-3). It is interesting to note that he used the name "epinephrin" given by his teacher, Abel, together with the name "adrenalin." However, von Fürth read this

article and haughtily declared that as epinephrin was not the true active principle, he would not use this term (7-4). The German von Fürth subsequently put forward the third name, suprarenin. From 1897 onward he published a series of reports of his quest to find the physiologically active adrenal principles in a German physiological chemistry journal (*Hoppe-Seyler's Zeitschrift für Physiologische Chemie*). In the third of these, published in 1900, he wrote "*Der Kürze wegen will ich für die von mir als wirksam angesprochene Substanz die Bezeichnung Suprarenin benutzen* (To put it simply, I would prefer to call the substance that I regard active "suprarenin")" (7-5).

The fourth name is adrenalin(e), which was announced by Takamine five years after the first name, sphygmogenin. In a paper published in an academic journal in 1901, he wrote, "I have therefore, termed my substance, as I isolated, 'Adrenalin.'" Takamine had isolated the substance himself and verified its activity, and he gave it this name regardless of its molecular formula—strictly speaking, this was therefore not a compound identified by its chemical formula (7-6).

As we saw earlier, the molecular formula Takamine put forward was soon found to be mistaken. However, as he had not applied the name adrenalin to a specific molecular formula, this did not present a problem.

2. Trademark rights

We saw in Chapter 1 how Takamine decided the name "adrenalin" on the advice of Norton Wilson, a friend of his. Takamine applied to register the trademark ADRENALIN in the US, and it was registered on April 16, 1901. The rights to the trademark were transferred to Parke, Davis & Co. five years later, on May 14, 1906 (7-7). Twenty years later, when adrenal medulla hormone was listed in the *US Pharmacopeia* for the first time, these trademark rights were to become the reason for a very important decision, as we will see. Takamine also applied to register the trademark in Japan on March 28, 1902, and it was registered on May 3 of the same year. The name "epinephrin" was coined by Abel, the university professor—unlike Takamine with "adrenalin," he had no intention to acquire trademark rights.

3. The War of Words

The first person to find a problem with "epinephrin," the name given by Abel, was von Fürth from Germany. In one of the footnotes to his own scientific report (1903) (7-4), he

stated that the term epinephrin was not appropriate, and that he would therefore avoid using it. The reason for this, he declared, was that the substance isolated by Abel was not a natural active substance.

In 1904, the year after von Fürth's initial objection, another German, Pauly, argued strongly against the name epinephrin in an academic paper titled "Zur Kenntnis des Adrenalins." (7-8) In a long footnote (26 lines), he put forward his view that Abel's names epinephrin and epinephrin hydrate were not appropriate terms because the concept of the words was vague, they did not include the active principle, and there were cases of researchers who had been under the misunderstanding that Abel was the first person to collect the adrenal active principle.

In the war of words over adrenaline and epinephrine, the argument that took place in London in 1906 seems to overwhelm the others in its ferocity and intensity. I will give some of the details here. It was an extremely interesting incident, and it occurred during the transitionary period in medical history from an age of trickery, fraud, and chicanery by many peddlers of patent medicines and quack cures to ethical drug manufacture and sales. The dispute was sparked off by a physiological and pharmacological research report by Henry H. Dale of the Physiological Research Laboratories of the pharmaceutical company Burroughs, Wellcome & Co. The laboratories were established in 1894 for research into biological medicines and therapeutic serums. Dale was conducting research into ergot, a group of alkaloid-producing *fungi* that grow on *rye* and related plants, and his report included the results of an experiment using adrenaline.

In the six weeks following publication, a fierce dispute broke out, with over 40 letters on the topic exchanged. E.M. Tansey of the Wellcome Institute for the History of Medicine gives an account of the affair in a paper titled, "What's in a Name? Henry Dale and Adrenaline, 1906." This paper is 18 pages long and is an extremely detailed report, but it reads like a short novel, unexpectedly drawing the reader in (7-9).

When Dale wanted to publish his research report, he first submitted it to the Research Director, Walter Dowson, in order to get approval for publication. The proposed publication came to the attention of Henry Wellcome, the owner of the company, who said that use of the word adrenaline was to be avoided because this was a registered trade name of Parke, Davis & Co., and "epinephrine" should be used in its place. Dale, however, refused. The Wellcome laboratories were managed independently of the everyday commercial activities of the company, and he believed that the researchers should be able to carry out their activities freely. Dale may have been an employee of the company, but he was also a

world-class scientist; he made no attempt to follow the orders of the owner of the company.

Only Dale, who exactly 30 years later would go on to win a Nobel Prize, could have shown such conviction and fighting spirit. The reason was perfectly clear: the Physiological Society (UK) had decided that the term "adrenaline" should be used in writing to refer to the physiologically active principles of the adrenal medulla, and it was common knowledge that this did not refer to any specific commercial product. Dale considered the term "epinephrine" to be inappropriate and inaccurate. Dale's immediate boss, Dowson, gave him all the support he could, but Wellcome would not change his instructions to use "epinephrine."

The deputy director of the Chemical Research Laboratories (established a year after the Physiological Research Laboratories), Hooper A. D. Jowett, joined the dispute—he had already used the term "epinephrine" in his own research reports, and he urged the director Dowson to abide by the wishes of the company owner. Dale, however, was totally unprepared to accept the order. He stood firm in his view, supported by a paper by Dr. Thomas R. Elliott of the University of Cambridge that used the term "adrenalin" and an official statement by Prof. John N. Langley in support of this as the scientific name. Dale's view was still not accepted, so in the end he declared that if the paper was not published he would be unable to remain in the laboratory and would thus be forced to tender his resignation. The result for this was a complete about-face, and Wellcome approved Dale's manuscript.

It looked as though the matter had been settled, but less than 24 hours later the research director, Dowson, was surprised to receive a telegram from Wellcome saying that approval for publication had been withdrawn. Jowett had suggested the company could face litigation over the use of a trademark. A protracted dispute ensued, into which a number of prominent intellectuals were dragged. There is insufficient space here to go into the details, but eventually Wellcome agreed to approve Dale's manuscript on the condition that it included a cautious footnote explicitly stating that the research was unrelated to any trademark.

For several months after this, Jowett continued his campaign from the Chemical Research Laboratories to use the name epinephrine, but the Physiological Research Laboratories paid him no attention whatsoever (7-9). At the top of a paper published in 1904 titled "The Constitution of Epinephrine," Jowett noted that various names had been given to the active component, but he maintained that even with an impure extract the name first given by Abel—epinephrin— should be used. Interestingly, at the end of this paper Jowett added a section, in which he noted that Abel still insisted on the existence of a "hydrate" that included $1/2 \cdot H_2O$, but that he and his colleagues had shown experimentally that there was no

water formed with the crystallization.

Even though Jowett did not consider Abel's chemistry to be correct, he still maintained that epinephrine was the legitimate term—he appeared to be indifferent to the question of the physiological activity of the substance. Jowett was a chemist who simply could not engage with Dale, who emphasized physiological activity (7-10). Strangely enough, however, at around the same time Jowett co-authored a paper with G. Barger of the Physiological Research Laboratories, titled "The Synthesis of Substances Allied to Epinephrine," at the end of which the following note was added: "The necessary physiological experiments in connection with this inquiry were performed by Dr. H. H. Dale, to whom we wish to tender our best thanks." (7-11).

In 1907, Thomas Maben (his position was given only as "F.C.S.," which appears to mean that he was a fellow of the Chemical Society) published a concise and accurate history of the active principle of the adrenal glands in the *Pharmaceutical Journal*, a British publication. He noted that the name "adrenalin" was not accorded the same status as "epinephrin," but he put forward his explanation that adrenalin was the only name for the substance in question and said that Jowett's argument for the legitimacy of "epinephrin" could not be justified (7-12). At the end of his paper arguing for the appropriateness of "adrenalin," Maben expressed his hope that this could be used as a generic name without trademark rights being asserted. However, this could not be accepted by the business world, for which trademark rights are assets. We will examine the reasons in detail later on in this chapter.

Maben prided himself on his speed. Six years earlier, Takamine gave an oral presentation in New York in January 1901—by March of that year, Maben had given his own concise lecture on adrenalin at a Pharmaeutical Society meeting in Edinburgh, and just three days later a summary of his lecture was published in the society's journal. He probably felt a certain responsibility as well (7-13).

To add a brief word about the owner of Burroughs, Wellcome & Co., Henry Wellcome was invited by his friend, Silas Burroughs, to establish a company together, and the two men established Burroughs, Wellcome & Co. in London in 1880. After Burroughs died, the company became the Wellcome Foundation Ltd., which grew to become one of the world's leading pharmaceutical companies; both men were American. Wellcome's life is an incredible story of success: he came from a poor farming community in northern Wisconsin, and his parents, who traveled around the area as Adventist preachers, brought him up strictly. He broke free by studying at the Philadelphia College of Pharmacy, where he was able to demonstrate his innate talent. He eventually took British nationality and became a member of

the British aristocracy.

Before Wellcome went to London, he worked as a traveling salesman for two of America's top pharmaceutical companies, and he later had to labor hard to retain the rights to the "Tabloid" trade name of the "Tabloid products" that brought rapid success to Burroughs, Wellcome & Co. This, together with the fact that he was extremely well attuned to industrial property rights and was an enormously careful manager with respect to American products, may perhaps explain why he wavered over the decision concerning Dale's paper. We have already seen in Chapter 4 that Burroughs, Wellcome & Co. was marketing tablets of adrenal glands under the name "Supra-renal Tabloids" (see page 84).

In the conclusion of his paper on the war of words that took place within Burroughs, Wellcome & Co., Tansey notes that there were legal, scientific, and human lessons to be learned from the dispute at various different levels. However, I have been unable to find any documents that shed light on whether the circumstances of this altercation ever reached the ears of J. J. Abel in the US, who first named the substance "epinephrin."

4. The struggles of a researcher: the fifth name

Correctly using the various different names that appeared throughout this history was a major headache for academics and researchers. A fifth generic name, "adrenine," appeared in the United Kingdom. An article was published in the *Pharmaceutical Journal* of August 3, 1907 that would probably have been of great interest to Takamine. This was a report of research into a method for detecting the iron content of oleic acid, a type of unsaturated fatty acid, in medicinal products. With this method, adrenaline was added to the product and the Vulpian color reaction indicated the presence of iron. This has already been briefly mentioned in Chapter 5. The footnote on the first page of the report reads as follows: "The substances used in the experiment and included under the name "adrenine" were adrenalin, suprarenin, suprarenalin and various commercial solutions of the blood-pressure-raising principle of suprarenal gland". Even before this, the term "adrenine" is used in the title of the paper (7-14). From this time onward, "adrenine" came to be widely used in papers published in the United Kingdom (7-15), and even Prof. Schäfer, one of the researchers who discovered the blood pressure-raising effect, stated that the name was appropriate during an invited lecture he was giving (7-16).

Another example is a brief paper dated May 23, 1908, which was written by A. R. Cushny of the Pharmacological Laboratory of University College, London, who demonstrated that the synthetic product "suprarenin" produced by the German company Höchst A.G. had only

half the activity of adrenaline extracted from adrenal glands; the title was "Synthetic Suprarenin or Adrenine" (7-17). In another full paper he uses the term "adrenalin" in the title, and in a footnote he states, "The bodies used were really "suprarenin," but as natural suprarenin is identical with adrenalin and the latter is the more familiar term I have adopted it throughout" (7-18). It was three years after this (1911) that the historic ruling was passed in the US patent lawsuit recognizing the inventiveness of the method of producing adrenaline, a natural product, as we saw in Chapter 6.

Moving forward to 1913, the American physiologist Walter B. Cannon, who was well known for proposing the concept of homeostasis (the steady state of the organism), attempted to verify in his final work that adrenaline was the chemical transmitter in adrenergic nerve impulses. He was unsuccessful, but in a paper titled "The Depressor Effect of Adrenalin on Arterial Pressure," he used the term "adrenalin" (small "a," no final "e"), and he specified that he used the fresh product of Parke, Davis & Co. in the experiments (7-19).

However, in his celebrated work on physiology published about 20 years after this, *The Wisdom of the Body*, the explanation of adrenalin (small "a," no final "e") that starts on page 44 has the following brief definition in the margin [Figure 7-1]: "'Adrenin' is the natural secretion of the adrenal medulla; 'adrenalin' is a commercial extract of the adrenal glands" [underlines added] (7-20). Perhaps Walter B. Cannon recognized that the name epinephrine should not be used in research reports.

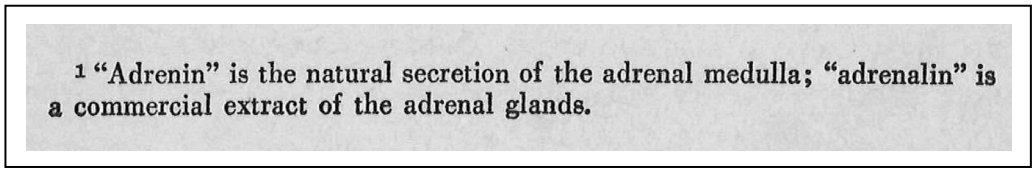

[1] "Adrenin" is the natural secretion of the adrenal medulla; "adrenalin" is a commercial extract of the adrenal glands.

Figure 7-1. The footnote on page 44 of the classic *The Wisdom of the Body* (7-20), which was the lifework of the American physiologist W. B. Cannon.

5. The letter that decided the name in the *US Pharmacopeia*

In 1926, the adrenal medulla hormone was listed for the first time in the *US Pharmacopeia* with the name "EPINEPHRINA Epinephrine." Why was the name "epinephrine" used? The answer can be found in a letter from that time that has been preserved. This was a business letter, dated November 19, 1921, from O. W. Smith, the president of Parke, Davis & Co., to Dr. Jokichi Takamine. The existence of this letter was referred to in an essay on Takamine's will that appeared in a magazine (7-21).

The letter has two paragraphs, the second of which reads,

"I might say, incidentally, that the revision committee of the U. S. P. expects to include Adrenalin Solution in the next edition. We have been asked to supply specifications. We have done so, but we have suggested to the sub-committee, of which Mr. Rosengarten is chairman, that the word "Adrenalin" is registered, is a valid trademark, and that under the circumstances the committee would probably use the word "Epinephrin" in the Pharmacopeia. We are afraid that if the word "Adrenalin" is used it may encourage manufacturers to use it also, whereas so far all of them have kept off the grass" [underlines added].

By this time, the trademark rights had already been transferred from Takamine to Parke, Davis & Co., and Adrenalin Solution had a monopoly of the market. This letter clearly shows that Parke, Davis & Co. still had the trademark rights to the name "Adrenalin," and the company refused to authorize use of the name in the *Pharmacopoeia* because it wanted to protect its monopoly. However, the company was not opposed to the name "Epinephrin" being used instead; as a result, this is the name that was adopted for use in the *US Pharmacopeia*.

In fact, even before this stage was reached there had been various discussions, which included exchanges of opposing views, aiming to find a generic name for the adrenal medulla principle that could be widely used regardless of any interests or rights. Let us look at these in chronological order.

First, there was an editorial in the *Journal of the American Medical Association* of March 25, 1911, titled "The Name 'EPINEPHRIN' versus the Name 'ADRENALIN,'" which was followed by the minutes of a heated discussion on "Proprietary versus Unprotected Names" (7-22). The latter article filled six A4 sized pages, and included downright antagonism between medical scientists and doctors on the one hand and Parke, Davis & Co. on the other. It is an engrossing read, but the contents are quite astonishing—what clearly emerges is that the culture, rules, and ethics of the academic and the business worlds were very different from what they are today.

On April 28, 1911, just 34 days after the publication of this journal, Judge Learned Hand ruled in favor of Parke, Davis & Co. in the lawsuit relating to the infringement of the patent for the manufacture of adrenalin that we saw in detail in Chapter 6. As a result, the company's monopoly of the sale of adrenalin became even more profitable [Note 7-1].

Note 7-1.
The names of the non-prescription medications containing adrenal medulla principle that were given in the article in the journal were: Adnephrin (Frederick Stearns & Co.), Adrenalin (Parke, Davis & Co.), Adrin (H. K. Mulford & Co.), Supracapsulin (Cudahy Co.), and Suprarenalin (Armour & Co.) in the US; and Atrabilin, Chelafrinum, Epirenan, Hemostasin, Ischemin, Paranephrin (Merck), Renoform, Supranephran, Suprarenin (Hoechst), Suprarenin synthetic, Tonogen, and Vasoconstrictin in Europe and elsewhere. In addition, the article mentions that the same year in London the name "adrenine" was proposed for the *Yearbook of Pharmacy* in place of "adrenaline."

It is worth noting that the *Journal of the American Pharmaceutical Association* (7-23) published in 1915, four years later, discussed a similar ongoing problem with naming in relation to Aspirin (acetyl salicylic acid, an analgesic and antipyretic). This drug, which was produced by the German company Bayer A.G., was at the time a huge product on a scale comparable to Adrenalin.

The disputes over the name continued one after another, until 1920—this was the year in which the patent for the manufacture of Adrenalin expired. Adrenalin had grown since its launch to become a massive product, and there were 30 to 40 rival products of different quality containing adrenaline. The US government must have decided that it could no longer ignore the complexity of this competition or the confusion that it was causing in medical settings, and it took the opportunity to commence the preparations for listing the official name in the *US Pharmacopeia*.

The *US Pharmacopeia* is revised every 10 years, but the preparations for the revision begin several years earlier. The committee for drawing up the draft version of the 10th revision, which was to be made in 1926, released a detailed report on May 11, 1920, six years before the revision and, very aptly, the year in which the patent for the manufacture of adrenalin expired (7-24). The report proposed that adrenaline should be named "EPINEPHRIA (Latin name), Epinephrine (English name)." The members of the committee included Dr. Houghton, the project leader from Parke, Davis & Co. who had played an important part in the crystallization of adrenaline, and Frank O. Taylor from the same company. The final proposal was probably decided after they had put forward their company's position and come to a mutual agreement with the other members.

Let us return to the business letter to Takamine from O. W. Smith, the president of Parke, Davis & Co. This letter is dated November 19, 1921, one year after the draft for the 10th revision was submitted proposing "Epinephrine" as the official name. We will probably never know why Dr. Rosengarten, the Chairman of the Organic Chemicals Sub-committee, was trying once more to confirm the view of Parke, Davis & Co., because the Revision Committee members most likely had a duty of confidentiality. However, it seems to me that

with the expiry of the manufacturing patent, he probably wanted to check for the last time whether Parke, Davis & Co. would negotiate the use of adrenaline as a worldwide generic name without asserting trademark rights. Anyone in his position would have wanted to use the catchy name that was already firmly rooted in the medical profession as the name in the pharmacopoeia, so I sympathize with him.

Following the legal expiry of the manufacturing patent, the only way Parke, Davis & Co. could prevent products from other companies entering the market that it had monopolized was to protect its widely known trademark "Adrenalin" to the last.

There was no particular problem with this line of thinking, and the company certainly cannot be criticized for it. However, much of the ensuing confusion might have been avoided if Parke, Davis & Co. had suggested a name such as "adrenin(e)," which had been advocated by several other people (7-14 through 7-17, 7-20), instead of "Epinephrin," which was the name used for an inactive substance that was not the active principle.

6. The review that caused an unfortunate misunderstanding

In 1927, Abel published a long review titled, "Chemistry in relation to biology and medicine with especial reference to Insulin and other hormones" in the well-known scientific magazine *Science* (7-25). This review included two important descriptions.

The first of these is the following passage, in which he recollects how Takamine visited him at the time when he was struggling with his adrenal gland research: "After I had completed the above described investigation and while I was still endeavoring to improve my processes I was visited one day in the fall of 1900 (as I recall it) by the Japanese chemist, J. Takamine, who examined with great interest the various compounds and salts of epinephrine that were placed before him. He inquired particularly whether I did not think it possible that my salts of epinephrine could be prepared by a simpler process than mine, more especially without the troublesome and in this case wasteful process of benzoylating extracts of an animal tissue."

The other important description is almost unnoticeable, but it should not be overlooked. On page 341 of the review, toward the bottom of the left-hand column, it says, "[…] their secretory product, adrenalin or epinephrine (U.S.P.)." Thus, Abel wrote "adrenalin" first, followed by "or epinephrine." He must have confirmed that it had been listed for the first time in the *US Pharmacopeia* under the name "epinephrine" the year before the review was published, and then written "adrenalin" before "epinephrine." Abel clearly harbored no ill

will toward Takamine when he wrote this review.

Unfortunately, Abel's review was to lead to a major misunderstanding, which he could surely never have imagined. "Epinephrin(e)," which was written by Horace W. Davenport, a professor at the University of Michigan who had made the study of the sympathetic nervous system his life's work. This was published in 1982, over half a century since both Abel and Takamine had passed away. Davenport had great respect for Abel, who had been the first professor of the Department of Pharmacology at the University of Michigan. "When I was young," he begins, going on to reminisce about the past, "I was taught to say adrenalin only when I specified the Parke, Davis product. Otherwise, I should say epinephrine. In addition, a faint air of scandal seemed to hang over adrenalin, something about a stolen secret. No one seemed to know the facts. Tracing the origin of the scandal, if there were one, added piquancy to my investigation." (7-26)

This passage served to spread the baseless rumor widely among researchers in the field that Takamine had stolen the experimental procedure from Abel, who was ahead of him in the isolation race.

While it is something of a postscript, entry no. 3650, Epinephrine, in the well-known *Merck Index* (13th Edition, 2001) lists the following names: adrenaline, levorenin, Bronkaid Mist, Epiglaufrin, Eppy, Glauposine, Primatene Mist, Simplene, Sus-phrine, and Suprarenaline, besides Epinephrine. Even today adrenaline remains as just one of the 10 alternate names. In spite of this, the references cited for "isolation from animal adrenal glands" are one work each from Takamine and Aldrich, which are the very works cited in Chapter 4 of this book (4-55 and 4-25). Despite the fact the entry is a listing of Epinephrine, Abel, who named it, is not mentioned and his work is not cited.

Davenport's review (7-26) contains a significant factual error. One paragraph starts, "Takamine never gave the source of his starting material." This is simply untrue. In US patent 730,175 of November 5, 1900, Takamine gives examples of the animals used: "The clean suprarenal glands or capsules of animals such as cattle, sheep, &c." He then describes the extraction process. (This patent was later divided, and the same is recorded in patent 730,176, which was the mother patent).

It may have been difficult for Davenport as an academic to get hold of the patent specifications, but I include this detail for the sake of Takamine's good name. In addition, Vulpian's 1856 paper on the color reaction lists the names of many animal species in which he discovered secretions showing the color reaction, and it had been clear for over half a century that if the animals were readily available domestic animals, there was no need to

specify the species.

Davenport attempts to verify his theory of Takamine's plagiarism by comparing Abel as an academic and researcher, largely on the basis of Abel's recollections, with the conduct of Takamine as a businessman. However, he ends without obtaining any positive evidence. Considering that Abel did not have a method that could successfully crystallize adrenaline, and consequently there was nothing to steal, the whole idea of a "motive to steal" is thus utterly illogical and indeed incomprehensible.

Among the Japanese researchers who read Davenport's review, some felt very unhappy for the suspicion against Takamine and the exclusion of adrenaline from the Pharmacopoeia, and raised blames towards Abel. After everything became clear, however, this really was a great shame (7-27).

Davenport's review caused the misunderstanding by running contrary to what were probably Abel's true intentions, and contained expressions that Abel would perhaps not have wanted. Nine years after this review was published, Davenport once again touched on the subject of adrenaline, this time in a comprehensive scientific history titled, "Early History of the Concept of Chemical Transmission of the Nerve Impulse" (7-28). Curiously, Abel's name does not appear in the text, and not one of the 84 works cited was by Abel. Takamine is mentioned in five places; and one of these, a short sentence of just seven words, is quite clear: "The man who succeeded was Jokichi Takamine." It looks as though Davenport had come to realize with the passage of time that in the history of adrenal gland chemistry, it was not Abel whose achievements should be trumpeted [Note 7-2].

Note 7-2.
At the start of this latter review, Davenport writes that one reason for his interest in epinephrine was the fact that the leading American physiologist Walter B. Cannon, whose lifework was the sympathetic nervous system, had tried to prove in his final work that the adrenergic nerve transmitter was epinephrine but had been unsuccessful; Davenport wanted to discover the reason for this (7-28).

It was the Swedish physiologist Ulf von Euler who later succeeded, and he was honored with a Nobel Prize for his work. In a commemorative lecture titled "Twenty Years of Noradrenaline," von Euler praised Cannon for his huge achievements in this field (7-29).

7. The name of the adrenal medulla hormone in different Pharmacopoeias

So far we have looked at the reasons for, and the background of, the five names given to the active principle of the adrenal glands. We have already seen that only two of these names —adrenaline and epinephrine—have survived, and Table 7-1 shows which of these names is currently used in the respective pharmacopoeia of various major countries.

England is proud of its ground-breaking discovery that the blood pressure-raising

principles are secreted from the adrenal glands. Jeffrey K. Aronson of the Department of Clinical Pharmacology, University of Oxford, who gives a thorough guide to the naming of the adrenal medulla hormones to date in a paper published in 2000 (7-30), states, "There is […] clear historical and etymological evidence that epinephrine is an inappropriate name to use."

He goes on to conclude, "Assuming that you don't want to call it dihydoroxy-phenylmethylaminoethanol, which name should you use—adrenaline or epinephrine? All the arguments and evidence suggest that you should prefer adrenaline." This reaffirms the "validity of adrenaline" that Thomas Maben had emphasized nearly 100 years earlier (7-12).

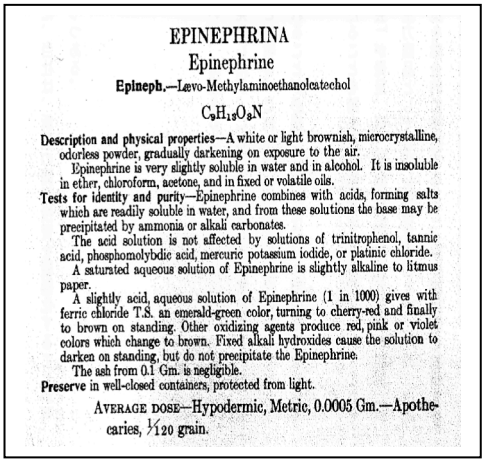
In the United States, however, which was the land where adrenaline was crystallized, there has been no change in the listing in the pharmacopoeia from when it first appeared in 1926 as "epinephrine" up to the present day [Figure 7-2]. The name "adrenaline" has never appeared together with "epinephrine.

Table 7-1. Names of suprarenal medulla hormone in several pharmacopoeias

Country	**Adrenal medulla principle**	**Other names**
USA	Epinephrine	No description
Japan	アドレナリン Adrenaline	Epinephrine
Britain	Adrenaline/ Epinephrine	No description
European*	Adrenaline （Adrenalinum）	No description
P.R. of China**	腎上腺素	Epinephrine
WHO international	Epinephrine	Adrenaline
Cf.Merck Index13th ed.	Epinephrine	Adrenalin[Parke-Davis] Adrenaline

* The *European Pharmacopoeia* is published by the European Directorate for the Quality of Medicines & Health Care (EDQM) of the Council of Europe/Strasbourg.

** P.R. of China adopted 'Adrenalinum Adrenaline (Epinephrine)'in English, in 1992.



EPINEPHRINA

Epinephrine

Epineph.—Lævo-Methylaminoethanolcatechol

$C_9H_{13}O_3N$

Description and physical properties—A white or light brownish, microcrystalline, odorless powder, gradually darkening on exposure to the air.

Epinephrine is very slightly soluble in water and in alcohol. It is insoluble in ether, chloroform, acetone, and in fixed or volatile oils.

Tests for identity and purity—Epinephrine combines with acids, forming salts which are readily soluble in water, and from these solutions the base may be precipitated by ammonia or alkali carbonates.

The acid solution is not affected by solutions of trinitrophenol, tannic acid, phosphomolybdic acid, mercuric potassium iodide, or platinic chloride.

A saturated aqueous solution of Epinephrine is slightly alkaline to litmus paper.

A slightly acid, aqueous solution of Epinephrine (1 in 1000) gives with ferric chloride T.S. an emerald-green color, turning to cherry-red and finally to brown on standing. Other oxidizing agents produce red, pink or violet colors which change to brown. Fixed alkali hydroxides cause the solution to darken on standing, but do not precipitate the Epinephrine.

The ash from 0.1 Gm. is negligible.

Preserve in well-closed containers, protected from light.

AVERAGE DOSE—Hypodermic, Metric, 0.0005 Gm.—Apothecaries, 1/120 grain.

Figure 7-2. The page of the *US Pharmacopeia* released on January 1, 1926, showing the entry for "Epinephrine." The name has not changed since then.

Table 7-2 shows the names used in successive pharmacopoeias in Japan, the homeland of Takamine and Wooyenaka, the scientists who successfully crystallized the active principle of adrenal glands and called it adrenalin.

Table 7-2. Names in the Japanese Pharmacopoeia

Revision	Year	Name	Other names
5th - 7th	1932 - 1961	Epirenamine	—
8th	1971	Epinephrine	Epirenamine
9th - 12th	1976 - 1991	Epinephrine	Epirenamine, Adrenaline
13th - 14th	1996 - 2001	Epinephrine	—
15th	2006	Adrenaline*	Epinephrine
16th	2011	Adrenaline	Epinephrine

* On December 14, 2001, a request for the adoption of Adrenaline as the Pharmacopoeia name, was submitted to the Ministry of Health, Labour and Welfare of Japan.

We can see that the name was changed twice following the first listing in 1932, and by 2006 had finally settled with "adrenaline."

I will close this chapter by mentioning one work that shows how the isolation of adrenaline is seen in the specialized field. This is the *Handbook of Physiology*, a major work published by the American Physiological Society. The only researchers that are recorded as having extracted adrenaline from the adrenal glands are Takamine and Aldrich (7-31).

◇ ◇ ◇

The history of naming the adrenal medulla hormone must surely be more convoluted than that of any other principle of the living body. No less than five names have been proposed over the course of the century and a half since the isolation race began and two of these—adrenaline and epinephrine—have lasted.

In the Prologue, I showed three photographs illustrating how widely the word "adrenaline" has come to be used in fields other than medicine in the US. Returning to use of the official name of the hormone would inevitably cause a considerable degree of chaos. No one is going to buy a bottled soft drink advertising blood pressure-raising activity from a vending machine, and no one is likely to imagine that buying a drink that says "Epinephrine" on the label will make them feel livelier.

The name "adrenaline," given to a hormone—an organic compound—was born in the United States of America. For me, it is a great shame that this name will probably never be

used again in the fields of either government administration (the pharmacopoeia) or science in the land of its birth.

Nonetheless, I am pleased to be able to show the disputes over the trademark and the generic name, and the events through which the *US Pharmacopeia* came to use the name "epinephrine," as clear historical facts through the letter in this chapter. I am also happy to be able to show through some of the writings left by Abel and Takamine that there was no ill feeling between these two men, with regard to either their work or the naming of adrenaline.

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