macrophages, while repressing proinflammatory cues. As such, the succinate/α-KG ratio within a macrophage appears to be a key controller of its functional fate. In addition to α-KG, ATP citrate lyase (ACLY)-mediated accumulation of the Krebs cycle metabolite acetyl-CoA was shown to support anti-inflammatory macrophage responses by promoting histone acetylation and subsequent transcription of IL-4-induced genes [15]. However, care is needed when interpreting these experiments since they used pharmacological compounds that are now known to show important off-target effects. Therefore, new genetic tools will be key to univocally address the role of the ACLY-derived immunometabolite acetyl-CoA in regulating macrophage responses.

Other future directions for follow-up research concern the ins and outs of immunometabolite transport and localization. How are these distinct immunometabolites transported out of the cell? Furthermore, once outside the cell, what is their actual fate? Which receptors, on which cells, do they target? Although distinct solute carriers (SLCs) were proposed as transporters for succinate and 2-hydroxyglutarate, no such transporter has yet been shown for itaconate. Single-cell metabolomics and other new high-end techniques that enable one to map the metabolic configuration of cells within complex microenvironments will be key to address these questions. Another important point to further investigate is the subcellular location of metabolites and their dynamics. Such spatiotemporal insight should help us to understand how immunometabolites translate metabolic rewiring into functional changes and disease progression. So far, most of our knowledge is derived from mouse models, but how could these data be translated to humans? Moreover, most studies have assessed the immunometabolism of immune cells in bulk; thus, how might this manifest at the single cell level? Finally, the million-dollar question is whether these immunometabolites or their derivatives could provide new therapeutic opportunities. For example, the effects of itaconate and other immunometabolites on macrophage function are mostly assessed by applying derivatives such as dimethyl-itaconate and 4-octyl-itaconate. While these compounds can have strong effects on macrophage function and potential therapeutic value, they do not fully recapitulate the endogenous effects of the 'real' immunometabolites that they mimic. Understanding their specific mode of action will be a key area of research and should clarify their applicability for future therapy. While waiting elucidation of these questions, we have also emphasized the importance of immunometabolites in regulating immune cell fate and disease outcome. Moreover, we stress the necessity of carefully defining them as metabolites that are generated within immune cells after activation, rather than as external metabolites that affect immune cell function.

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https://doi.org/10.1016/j.tem.2019.03.004

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Forum

The First Hormone: Adrenaline

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It is not often that three misconceptions are associated with one molecule for more than a century. This is the case with adrenaline. The aim here is to clarify that adrenaline was the first hormone, with the discovery of its activity and chemical purification being prior to secretin. Adrenaline is the correct name given by Jōkichi Takamine, epinephrine being its inactive benzoyl derivative.

While adrenaline is a well-known molecule, there have long been three misconceptions. It has not been recognized as the first hormone, its discovery is obscure,

and its names are confusing. This Forum aims to clarify the history of its discovery.

Secretin versus Adrenaline

Most textbooks state that secretin was the first hormone, discovered in 1902 by the British cousins William Bayliss (1860–1924) and Ernest Starling (1866–1927), at University College London (UCL).

In 1899, Bayliss and Starling followed up on one of Ivan Pavlov's observations published in 1898 that different kinds of substances in food, after digestion into chyme and movement into the duodenum, induced the pancreas to secrete different kinds of juices. Pavlov and others performed experiments and concluded that the effects of chyme on pancreatic secretion were due to nerves (the vagus, splanchnic, or local).

Bayliss and Starling made the novel discovery that this resulted from the chemical substance they called secretin, which was made by the mucous membrane of the upper parts of the small intestine and carried by the blood to the pancreatic gland cells. 'The crucial experiment' was performed on 16 January 1902, with all experiments finished by March 1902, published in a preliminary form as Bayliss and Starling (1902) [1] and in the full form in the *Journal of Physiology*.

Starling coined the term hormone in 1905 and acknowledged that the first hormonal activity was the increase of blood pressure by the injection of suprarenal extracts observed by Oliver and Schäfer [2].

The adrenal gland (or suprarenal capsule) is a small gland above the kidney. In 1855, Dr Thomas Addison (1793–1860) of Guy's Hospital in London discovered what was later called Addison's disease, caused by damage to the adrenal glands [3]. Soon researchers were interested in finding what was in the glands. Removal of adrenal capsules from animals often resulted in death.

George Oliver (1841–1915) was an English doctor with a home laboratory who may have even experimented with his son, feeding him adrenal extracts. Edward Albert Schäfer (1850–1935) was then a professor of physiology at UCL, whose contributions included the proposal of the term 'endocrine' for ductless glands. In 1893, Oliver went to Schäfer, suggesting that they collaborate on the physiological effects of adrenal extracts. Oliver and Schäfer published two abstracts in 1894 and a full paper in 1895, showing the effects of adrenal extracts, including that of increasing the blood pressure and the heart beat [2]. They determined that the active principle was from the medulla, not the cortex of the adrenal glands.

As detailed below, adrenaline was purified in 1901 by Takamine (Box 1). Secretin was not purified until 1961 and determination of its primary structure would take another decade (1970).

Thus, the first hormone was clearly adrenaline, because both the discovery of its activity in 1895 and its chemical purification in 1901 predated those of secretin in 1902 and 1961.

Purification of the Active Principle from Adrenal Glands

In 1895, Schäfer asked two of his colleagues at UCL to study adrenal extracts chemically. In 1897, Sigmund Fränkel (1868–1939) of Germany extracted from the adrenal capsules what he called spygmogenin [4]. From 1897 to 1901, John Abel of Johns Hopkins University published a series of papers on what he called epinephrin from 1898 onwards [5–7]. The molecular formula of epinephrine was $C_{17}H_{15}NO_4$ [6]. In 1900, the Austrian scientist Otto von Fürth (1867–1938), then working at Strasbourg University, after pointing out that epinephrine was inactive, purified what he called suprarenin, with the molecular formula $C_5H_9NO_2$ [8]. In 1901, Abel offered a rebuttal to von Fürth, claiming that his principle was active, although it was not the native principle, but might contain an extra benzoyl [7].

The pharmaceutical company Parke-Davis in Detroit, MI suggested that Takamine purify the active principle from the adrenal gland. In 1900, Takamine and his assistant Keizo Uenaka (1876–1960) had purified a highly active principle with the molecular formula $C_{10}H_{15}NO_3$. In January 1901, Takamine reported his findings to the Society of Chemical Engineering in New York and published in the *American Journal of Pharmacy* [9]. In December 1901, Takamine reported adrenaline to the British Physiological Society, and he published in the *Journal of Physiology* in 1902 [10].

By the summer of 1900, Thomas Aldrich of the Department of Biology of the Scientific Laboratory of Parke-Davis had purified adrenaline, and he published his results in 1901. He recognized the priority of Takamine's report to the Society of Chemical Engineering. He compared the physical and chemical properties and concluded that he and Takamine had isolated the same molecule, with the same molecular formula: $C_9H_{13}NO_3$ [11]. The correct formula was closer to that deduced by Takamine than those by Abel and von Fürth.

Adrenaline versus Epinephrine

Adrenalin was the name on the patent of Takamine and Parke-Davis. After a lawsuit filed by Abel, Takamine won. Both the British and the European Pharmacopoeia used adrenaline but the US Pharmacopoeia used epinephrine.

In 1927, 5 years after Takamine died (and 25 years after losing the patent fight), Abel claimed that Takamine visited him and modified his method to purify adrenaline. A research note by Uenaka was later found and its mixed Japanese and English

Box 1. Jōkichi Takamine (1854–1922)

Jōkichi Takamine was born in Japan to parents who had hoped for him to study medicine, but he liked chemistry and graduated from Tokyo University before studying for his PhD in Glasgow, UK. After returning to Japan, he established the first fertilizer factory in Japan [16]. While attending the 1884 World Cotton Exposition in New Orleans, he fell in love with Caroline Field Hitch, a daughter of his landlord. He worked in Japan for a few years before returning to New Orleans to fulfill their engagement. After marriage, Takamine and his wife went to Japan, where he discovered an amylase, capable of degrading starch, which decreased both the time and the cost for fermentation. His mother in law suggested that he go to Chicago and apply the enzyme to whiskey manufacturing. From then on, Takamine and his wife settled in the USA, first establishing the Takamine Ferment Company in Peoria, near Chicago. There they met local resistance, with the factory burnt down by arson and dissolution of his company by stockholders. Then the situation got worse when he suffered from a severe liver disease requiring immediate hospitalization. During the months of hospitalization, he noticed that the main meal was starch and two-thirds of patients had digestive problems (dyspepsia). He showed that his enzyme was effective in treating dyspepsia. He named the enzyme Taka-Diastase and sold his patent to Parke-Davis, with sales exceeding US$ 30 million. This was a major contribution to early biotechnology.

With a handsome income from Taka-Diastase, Takamine was able to establish his own laboratory in New York in 1897. In 1900, he hired Keizo Uenaka (1876–1960) as his assistant. Uenaka had excellent training in chemistry with Nagayoshi Nagai (1844–1929) at Tokyo University, who discovered ephedrine from the Chinese herb medicine Mahuang. Together, they purified adrenaline.

text showed that Takamine and Uenaka had purified adrenaline before the date of Takamine's presumable visit claimed by Abel [12].

Abel was the first chairman of the first department of pharmacology in the USA, one of the two cofounders of the *Journal of Biological Chemistry* in 1905, and the founder of the *American Journal of Pharmacology and Experimental Therapeutics* in 1908. His influence was far greater than that of Takamine.

Thus, although historians had argued for Takamine, it remains that for a long time American scientists believed more in Abel than in Takamine. For example, in 1982 the American physiologist Horace Davenport believed that Abel discovered the principle, although he changed his mind by 1991 to recognize the discovery of Takamine. Although there have been repeated arguments for the usage of adrenaline, epinephrine is still used in US textbooks and by US scientists. Most assume that there had been priority disputes between US and European scientists, whereas the truth was that both names were proposed by scientists working in the USA, although one was of Japanese origin and the other was of European origin.

Experts' Agreement: Adrenaline

In 1903, Hermann Pauly (1870–1950), then at the University of Bonn, determined the structure of adrenaline. He also believed the principle purified by Takamine to be active, whereas that by Abel to be inactive [13]. In 1904, the German chemist Friedrich Stolz (1860–1936) became the first scientist to synthesize what he also called adrenalin [14]. The British chemist Henry Dakin (1880–1952) also credited Takamine and Aldrich for discovering adrenaline [15]. In 1906, Henry Dale, the British pharmacologist who would later win a Nobel Prize in 1936, insisted that adrenaline was the correct name, with epinephrine as the name of the inactive principle.

Because Takamine and Parke-Davis patented adrenalin, Henry Wellcome (1853–1936), the US founder of the British pharmaceutical company Burroughs-Wellcome, was reluctant to use the name, even trying to block Dale, who was working in the Wellcome research laboratories, from using adrenaline. Dale pointed out that British scientists believed that adrenaline was the active principle while the epinephrine of Abel was inactive, insisting on the use of adrenaline in his papers. Because Parke-Davis patented adrenalin, scientists use adrenaline. After Abel passed away, Dale wrote an obituary for Abel, still politely noting that Abel's epinephrine was 'a monobenzoyl-derivative of the active principle'.

Credit Long Overdue

Adrenaline was important for both basic research and medical applications. In basic research, it was not only the first hormone, it also helped in the discovery of the neurotransmitter noradrenaline, which is the precursor in the biological synthesis of adrenaline. In medicine, adrenaline was used almost immediately and it is still in use today, a record not matched by many molecules. One wonders whether racial and other biases resulted in the award of the first Nobel Prize to a Japanese biologist in 2012 rather than 100 years earlier.

Takamine has won respect and awards from Japan, including the gift of cherry trees by the Japanese emperor, but is not well recognized by the rest of the world. Using the term adrenaline, instead of epinephrine, is a right step forward for credit long overdue.

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https://doi.org/10.1016/j.tem.2019.03.005

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