
Adrenaline Hunters: Past, Present and Future at 1900

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ABSTRACT

Adrenal gland was first described by the Italian anatomist Eustachio in 1564, but its physiologic role remained unknown for three centuries. Even after the report of Addison's disease in 1855, nobody knew its function. Oliver and Schäfer first discovered the blood pressure-raising property of adrenal extracts in 1894. Accordingly, in the late 1890's, highly motivated scientists had directed their attention to isolate active principle for the therapeutic utilization, but all failed. For instance, Abel's preparation 'epinephrine' was an inactive benzoylated derivative. In August 5, 1900 the Japanese industrial chemist Takamine and his young associate Uenaka settled in New York, succeeded to crystallize the adrenal extract by a procedure different from any yet employed. The active principle was isolated in the vacuum pan, crystallized with ammonia, and confirmed by the Vulpian reaction. 'Uenaka's Experimental Memorandum' describes that the novel crystal was coined 'adrenalin' (no "e") on November 7, 1900. Simultaneously, Takamine applied the US patent which was approved on June 2, 1903, and Parke, Davis & Company trademarked the name 'Adrenalin' to market worldwide. As a hemostatic during surgery and for treating heart failure, adrenaline has saved numerous lives. There are historical, etymological and practical justifications for using the term 'adrenaline'.

Keywords: Jokichi Takamine; Keizo Uenaka; Parke, Davis & Co.; Adrenaline; Epinephrin; Vulpian reaction; Adrenal medulla; Adrenalin Memorandum.

1. WHY WAS ADRENAL MEDULLA FOCUSED ON?

1.1 Anatomical description of adrenal gland by Eustachio in 1564

It is currently well known that the adrenal gland is comprised of two layers; an outer layer, cortex and an inner layer, medulla. To the question 'why is the adrenal gland composed of cortex and medulla that are distinct each other?', one can answer as follows. First, the adrenal cortex produces corticosteroids, while the adrenal medulla produces adrenaline and noradrenaline in the chromaffin cells. Second, the cortical hormones influence activity of the enzyme that converts noradrenaline to adrenaline. Third, the cortical hormones also influence the shape of chromaffin cells, somehow preventing them from extending processes, as do other postganglionic sympathetic neurons. The adrenal medulla behaves like 'a modified sympathetic ganglion' [1], and can be described as a 'knot' of the sympathetic nervous system [2]. The chromaffin cells in the medulla resemble neurons being devoid of axons [3]. These cells produce not only adrenaline but also a small amount (~20%) of noradrenaline, and secrete them into the bloodstream via the interconnecting ducts, muralium. When adrenaline is released into the bloodstream, it induces heartbeat, blood vessel constricting, and pupil dilating with the blood pumped toward the skeletal muscles, heart, and brain. In the brain noradrenaline is produced in larger quantities by the sympathetic neurons, while in the sympathetic nervous system it is usually used as an excitatory neurotransmitter. The enzyme phenylethanolamine *N*-methyltransferase, being produced in the chromaffin cells, adds a methyl group to noradrenaline for generating adrenaline. A rare tumor of the chromaffin cells is called pheochromocytoma, while insufficiency of the corticoid secretion causes Addison's disease.

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The history of adrenaline started with the anatomical discovery of an adrenal gland [4]. Italian anatomist, Bartolomeo Eustachio (Fig. 1-A) was born in 1524 in a little town, San Severino Marche. During teaching anatomy at the medical school of the Collegio della Sapienza at Rome, Eustachio could obtain cadavers for dissection from the hospitals of Santo Spirito and Consolazione. Most of his career was spent to prepare detailed copper plates of the human anatomy. He prepared splendid 47 copper plate engravings of anatomical illustrations, and published *Opuscula Anatomica* in 1564 with the aid of an artist Pier Matteo Pini. The first three tables depicted the external appearance of kidneys and their vascular connections to the aorta and inferior vena cava [5]. The copper plates, however, were never printed, since they were meant for a book that remained unfinished when Eustachius died in 1577. One and half century later, Giovanni Maria Lancisi, a successor to Eustachio in the chair of anatomy at the Sapienza, published the entire series of 47 engravings under the title: "*Tabulae Anatomicae Bartholomei Eustachi quas a tenebris tandem vindicatas*" (Anatomical Illustrations of Bartholomeo Eustachio rescued from obscurity) (Fig. 1-B), [6,4].

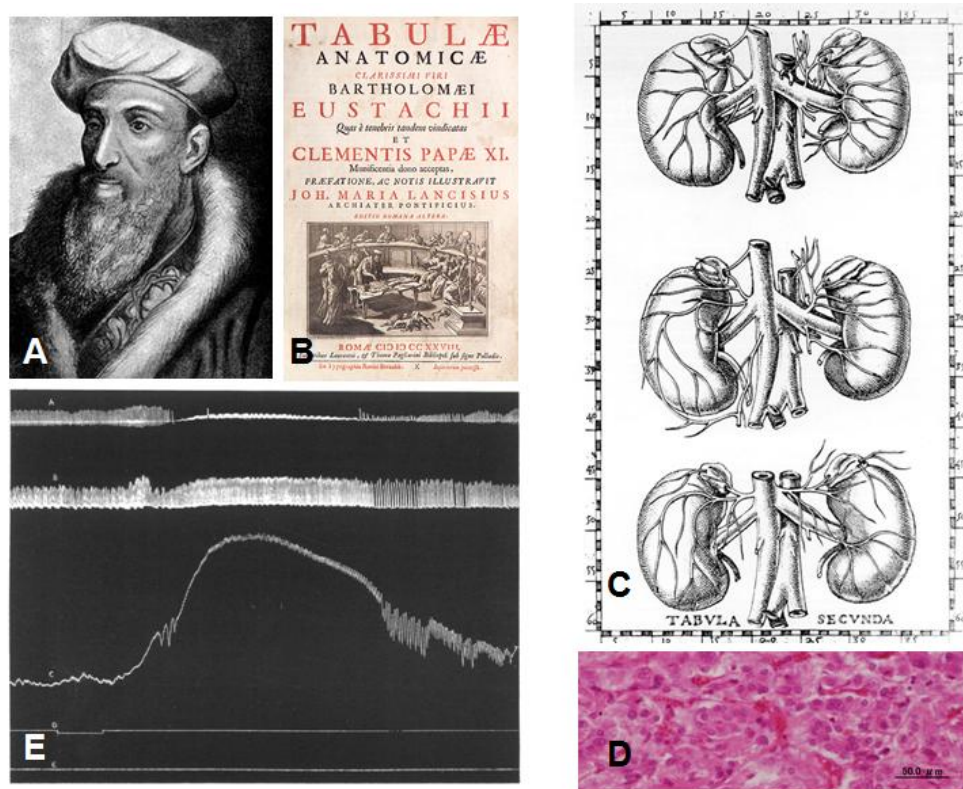


Fig. 1-A. Bartolomeo Eustachio, born in 1524 in San Severino Marche in the center of Italy, published 'Opuscula Anatomica' in 1564 to describe in detail the morphology of the kidney, ear, venous system and teeth

1-B. The title page of 'Tabulae anatomicae Bartholomeo Eustachi' shows an engraving of a dissection. This was discovered and published by Giovanni Maria Lancisi.

1-C. Eustachio's original legend of the tabula II, drawing 1 (the 47th plate). Please, note the anatomical variations supplying the adrenal gland; there are variations not only among the subjects but also between the right and left in the given individual

1-D. Light microphotographs of the chromaffin cells in the human adrenal medulla. Hematoxylin-eosin staining

1-E. Injection of 0.2 g adrenal watery extract to the 16 Kg dog provokes a sudden rise of the blood pressure in the femoral artery (C) with standstill of the auricle (A) and hypercontraction of the ventricle (B). Please, note that duration of the effect of the natural extract is very short, analysis of which led to the discovery of optical isomer.

(Cited from Journal of Physiology (London), 18: 230-276, 1895)

A portion of Book Five of *De Corporis Humani Fabrica*, published in 1543 by Andreas Vesalius (1514-1564), contained four excellent illustrations of the kidney, but none showed an adrenal gland at the upper pole of this organ [7]. Since Vesalius evidently overlooked this organ, its presence had been initially ignored by anatomists. Of particular interest was that in 1564, 20 years after publication of the *Fabrica*, Eustachio made an anatomical discovery. Presumably because he speculated that the adrenal gland functions as an accessory kidney, he termed '*glandulae renibus incumbentes*' (*Opuscula anatomicae*. Venice: V. Lucchino. [8] 1563-64. Reprinted in Leiden, 1707, and Delft, 1726). Eustachio is precisely describing anatomical variation of arteries supplying the adrenal gland (Fig. 1-C). In 1627, his finding was validated beyond all question by Casserius, professor of anatomy at Padua, the fifth successor of Vesalius [9]. The adrenal gland was depicted and labeled "*corpuscula reni incumbentia sive renes succenturiati*." Later, Jean Riolan named the adrenal gland '*capsulae suprarenales* (suprarenal gland)', a term equivalent to the modern one [10] (*Nomina Anatomica* (Fifth edition, 1983): *glandula suprarenalis*).

1.2 Anatomical Links between Nerve Plexus and Adrenal Gland

In 1656, Thomas Wharton [11], physician of St. Thomas' Hospital in London, pointed out the proximity of the adrenal gland with nerve plexuses, and postulated that it might take a substance from nerves to transfer into veins [12]. This was really a ground-breaking idea that suggests the emergence of endocrinology. He wrote in the chapter 16 of his text, '*Glandulae renales vel ad nerveum plexum abdominis sitae, earum usus*' as follows.

"Glandulae ad plexum, certo possumus statuere, non esse materiam plane excrementitiam, sed utilem, quia in venas perpetuo recipitur ... 'We may certainly believe (of the glands beside the plexus) that material is not completely excreted but is used since it is taken up continually by the veins' [11]."

Wharton was impressed by the large size of the nearby nerve plexus to such a small organ. He suggested that the adrenal gland receives certain substance from the nerves and passes it into the veins where it had some useful purpose. But, nobody could show its evidence until the beginning of the 19th century with the advent of achromatic lenses of the microscope. "*Quel est l'usage des glands surrénales?*" (What is the use of the adrenal glands?). In 1716, the Academie des Sciences de Bordeaux (the Academy of Sciences of Bordeaux) headed by the famous philosopher Montesquieu, at that time still 29 year-old Judge, offered a prize for an answer to such question [4]. However, no satisfactory answers were submitted, and no prize was awarded. Montesquieu concluded: '*Perhaps chance may some day effect what all these careful labours have been unable to perform*'.

Two centuries later, using an improved compound microscope, fitted with the latest in technology, achromatic lenses, Rudolph Albert von Kölliker, Swiss anatomist and physiologist, affirmed Wharton's earlier idea that the adrenal gland is functionally related to the nervous system [13]. He wrote: "*--- (the adrenal medulla), on account of its extremely abundant supply of nerves, must be regarded as an apparatus appertaining to the nervous system, in which the cellular elements and the nervous plexus either exert the same reciprocal action ---.*" (1854) Robert Remak [14] showed that the adrenal medulla developed in the embryo along with the sympathetic ganglia [14]. However, its function still remained unelucidated.

1.3 Report of Addison's Disease in 1855

Thomas Addison, describing the disease which bears his name, was educated at the University of Edinburgh and became physician of the Guy's hospital and lecturer on medicine. In 1849 he published a short note about the autopsy findings in three cases, entitled '*Anaemia-disease of the supra-renal capsules*' in the London Medical Gazette [15]. In 1855, three centuries after Eustachio's work, Addison asserted that the adrenal gland is indispensable for life. In his 43-page famous monograph published in London, "*On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*," Addison described 10 cases with the clinical syndrome of adrenal insufficiency [16]. The patients with 'a diseased condition of the suprarenal capsule', showed anemia, loss of weight, general weakness and fatigability, disturbances in the digestive apparatus, enfeebled heart activity, hypotension and a peculiar dark pigmentation of the skin. Pigmentation of the skin and

mucous membranes was the most characteristic sign. Addison said; it is '*the great distinctive mark of this form of anemia*'. The symptoms were caused by tuberculosis of the adrenal gland, especially of the cortex. His paper had an immediate impact in Paris; in August 1855 Armand Trousseau proposed at the meeting of the Academy of Medicine in Paris that it should be called Addison's disease [17].

Addison first proved that the adrenal gland is a vital organ, however, he apparently missed the physiological distinction of the medulla and cortex within the same small organ. In 1852, using microscopy, Albert von Kölliker recognized a histological distinction between the cortex and medulla (1852). He stated clearly; "*I consider the cortical and medullary substances as physiologically distinct.*" He showed that the adrenal cortex is formed first and is subsequently invaded by the sympathetic neural elements.

1.4 Discovery of Vulpian Reaction in Adrenal Medulla in 1856

The year 1856 ushered in an era of applying histochemistry to the adrenal medulla, which provided a definitive proof that the medulla is a distinct and special part of the adrenal gland. Alfred Vulpian in France, still 30 year-old, showed that ferric chloride stains tinted the adrenal medulla green without coloring the cortex [18]. An aggressive worker Vulpian started his work from 4 am., and observed that the same reaction occurs in samples of venous blood leaving the adrenal gland, but not in the arterial blood entering the gland. To account for these observations, Vulpian accurately speculated that the adrenal medulla releases a distinctive substance into the blood. Since the stain did not color other organs, he thought that the adrenal medulla is releasing something special. Accordingly, Cloez and Vulpian challenged to isolate the substance, and could observe various crystals although eventually failed. It is noteworthy, however, that they recommended to avoid oxidation- and photo- injuries during isolation [19]. The Vulpian reaction was confirmed by Prof. Rudolf Virchow of the Berlin University in 1857 [20]. Simultaneously, the chromaffin reaction, the most famous histochemical reaction associated with adrenal medulla, was first noted by Bertholdus Werner as a brownish deposit after fixation in chromic acid or dichromate salts [21].

Everybody thought that the material giving these reactions should be related to the function of the adrenal medulla. With the new techniques of microscopy and histochemistry coming into general use, there was a significant increase in interest in the adrenal medulla. Chromaffin granules were first noticed by a microscopist Manasse in 1894 [22]. The term "chromaffin granules" indicates catecholamine- containing organelle of the adrenal chromaffin cell. During the last half of the 19th century, the basic anatomy, histology (Fig. 1-D), histochemistry, and embryology of the adrenal medulla were understood. Such concepts were established that the adrenal medulla is histologically and functionally distinct from the cortex, and is somehow associated with the nervous system, specifically with the sympathetic nervous system.

2. IDENTIFICATION OF THE ADRENAL FUNCTION

2.1 Fatal Effect of Adrenalectomy Confirmed by Brown-Séquard

Addison's monograph attracted immediate attention of the physiologist Charles-Edouard Brown-Séquard [23]. By showing an unfailingly fatal result after removing adrenal glands of dogs, cats, rabbits, and guinea-pigs, Brown-Séquard clearly demonstrated that certain humoral factor (i.e. cortisol) is generated by the adrenal gland. After 60 extirpation experiments of various animals, on August 25, 1856 he reported at the Académie des Sciences in Paris that removal of bilateral adrenal glands in these experimental animals was fatal usually within 12 hours, but injection of the blood from a healthy animal into the adrenal-deprived animal can prolong its survival [24]. He concluded that the adrenal gland is essential to life.

The symptoms of experimental animals following the adrenal removal were similar to those of patients with Addison's disease, but more acute and without the pigmentation. Although Brown-Séquard could not precisely understand function of the adrenal gland, he speculated that the cause of death on its

removal is the accumulation of toxic substances in the blood. He considered that its function should be to modify a substance which is endowed with the property of being easily transformed into pigment.

2.2 Pharmacological Effect of Adrenal Extract

The abundant breakthrough in the latter half of 19th century put George Oliver and Edward Albert Schäfer at center stage [25]. Since one characteristic of Addison's disease is a remarkable feebleness of the heart's action, Oliver and Schäfer independently hypothesized that the adrenal gland continuously discharges into the blood something essential for the maintenance of vascular tone [26,27]. They knew that arterial blood pressure is low in Addisonian patients. If destruction of the adrenal gland is the cause of Addison's disease, it is obvious to look for a blood pressure-raising principle in the glands. Oliver and Schäfer were thinking about treating Addison's disease when they were doing their experiments.

Oliver was the son of a Yorkshire physician, and obtained his own medical education at the University College London. He particularly admired William Sharpey, the professor of physiology, and late in life he endowed the Oliver-Sharpey Lectures. As a rural medical practitioner of spa town Harrogate in England, Oliver devoted his spare time to the original physiological research in the private laboratory. In the 1890's, only very few university-based clinicians worried about blood pressure, but he was one of very few physicians of general practice who knew about blood pressure. He had been making a number of clinical observations upon the effect of various organ extracts such as adrenal gland, thyroid gland, brain etc., upon the circulation, but was unable to obtain any definite conclusions [28]. He employed winter leisure in designing an instrument for measuring internal diameter of the radial artery. He had an instrument maker construct an original arteriometer to estimate the diameter of an artery under the skin. When doses of a glycerin extract of adrenal glands from the sheep and cow supplied by the local butcher were given by mouth to his young son of twenty-year-old, Oliver could detect a change in the diameter of the radial artery.

At that time, Prof. Schäfer and his colleagues were studying the effects of injecting extracts of various glands in the body. They found that, with the exception of the suprarenal and pituitary extracts, all of the extracts caused a more or less pronounced fall of the arterial pressure. When Oliver visited Department of Physiology at University College London to verify his findings in 1893, Schäfer was engaged in an experiment of recording the blood pressure of a dog. By the special request, however, he injected a dose of the adrenal extract which Oliver produced from his pocket, into the vein of a dog, and then stood amazed to see the mercury immediately climbed in the arterial manometer until the recording float lifted almost out of the distal limb. Of course, Schäfer agreed to the collaboration, and they started to examine the effects of adrenal extracts on the cardiovascular system. A series of experiments were done during the winter of 1893-1894 [29]. For example, the injection caused an enormous rise (from 2 to 4 times above normal) of blood pressure (Fig. 1-E), although it entirely passed off after a few seconds. During this time, the auricles came to an almost complete standstill while the ventricles augmented with the heart-beat greatly accelerated (Fig. 1-E).

Saturday, March 10, 1894, was a day of note for medicine. In this afternoon, at the physiological laboratory of University College London, Oliver and Schäfer demonstrated the action of the intravenous injection of a small dose of watery extract of the adrenal extract in front of the fellow members of the Physiological Society. At that time Henry Dale was still 18-year-old student, and Charles Scott Sherrington was 37-year-old physiologist. Both, the future Nobel Laureate, were impressed greatly by this experiment. This open experiment initiated a scientific vista, leading to the discovery of adrenaline, and was later regarded by historians as a breakthrough in physiology and endocrinology. Their abstract in 1894 was heralded as the first demonstration of a hormonal effect. Oliver and Schäfer [29] later published a long paper, reporting that intravenous injection of an aqueous or glycerol extract of the adrenal medulla into an anesthetized animal produces a remarkable rise in the arterial blood pressure, and the active principle is confined to the medulla of the gland. They raised the possibility of using the adrenal extract to achieve hemostasis and to treat Addison's disease [30]. To the question 'is the active principle of the gland contained in the cortex or in the medulla?', Oliver and Schäfer concluded that 'it is only in the medulla'.

Schäfer [31,32] said, 'In the autumn of 1893 there called upon me in my laboratory at University College a gentleman who was personally unknown to me, but with whom I had a common bond of interest-seeing that we had both been pupils of Sharpey, whose chair at that time I had the honour to occupy. I found that my visitor was Dr George Oliver, already distinguished not only as a specialist in his particular branch of medical practice, but also for his clinical application of physiological methods. Dr Oliver was desirous of discussing with me the results which he had been obtaining from the exhibition by the mouth of extracts of certain animal tissues, and the effects which these had in his hands produced, upon the blood vessels of man, as investigated by two instruments which he had devised-one of them the haemodynamometer, intended to read variations in blood pressure, and the other, the arteriometer, for measuring with exactness the lumen of the radial or any other superficial artery. Dr Oliver ascertained, or believed he had ascertained, by the use of these instruments, that glycerine extracts of some organs produce decrease in calibre of the arteries and increase of pulse tension, of others the reverse effect.

.... With the suggestion that we should undertake such an investigation Dr Oliver promptly agreed, and it was then and there arranged to devote that winter to a thorough examination of the physiological effects of such extracts. The result of this conjunction of effort, brought about by the fortunate chance foreseen by old Montesquieu, speedily showed that, whilst many of the extracts which had been dealt with clinically by Oliver were inert or at any rate not specific in their action, the suprarenal capsules, and to a lesser extent the pituitary body, yielded to glycerine and to water and to saline solutions principles which have an extraordinary effect upon the tone of the heart and arteries, transcending that of any known drug' [33].

Oliver and Schäfer gave two presentations to the Physiological Society in London, and their publication about the discovery of active principle and its therapeutic possibilities in hemostasis and in adrenal deficiency (Addison's disease) stimulated the search for a pure extract of the active principle. Carmichael (<http://iscb12.webs.ull.es/ChromaffinCell/History.html>) states that: "Their publication in 1894 resulting from their subsequent experiments is heralded as the first demonstration of a hormonal effect. Many historians regard this study of the adrenal medulla as a milestone in endocrinology." But, they did not give the active principle of adrenal gland a name.

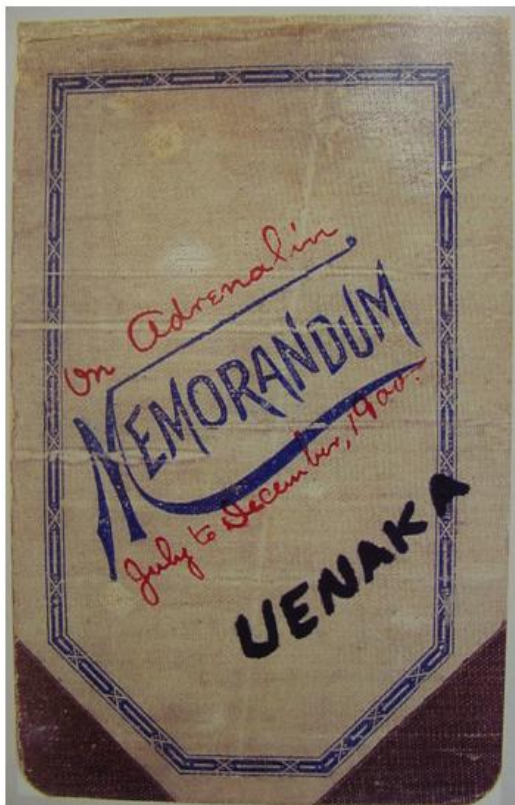
2.3 Pathological and Physiological Aspects of Adrenal Medulla

In 1886, Felix Fränkel reported the first case of a tumor (pheochromocytoma) of the adrenal medulla in an 18 year-old girl [34]. She died suddenly of collapse, and her clinical history and autopsy findings pointed to the relationship between the adrenal medulla tumor and a severe hypertensive crisis. This is the first evidence which indicated a relationship between the adrenal medulla and blood pressure. Alongside the studies of the adrenal medullary pathology, physiologists were carrying out the classic studies on the function of the adrenal medulla. George P. Dreyer in 1898 [35] and M. Lewandowsky in 1899 [36], independently, noted the correspondence between the effects of stimulation of postganglionic sympathetic nerves and the effects of adrenal extracts.

Krunkenberg (Virchow's Arch. f. path. Anat., 1885, ci, 542) in 1885 paid attention to the similarity between the color reaction of the adrenal extract and that of a small molecule, pyrocatechol. He suggested that the stained material in the adrenal medulla might be related to a catechol; a kind of polyphenol [37]. Brunner [38] in 1892 confirmed Krunkenberg's conclusions in reference to the similarity between the color reaction of some substances in the glands and those of pyrocatechol. The German chemist Fraenkel suggested that the active principle is a substituted catechol, probably a benzoyl derivative, which he called spymogenin [39].

By the end of 19th century, it became widely accepted that the adrenal gland is essential to life, and should possess a marvelous therapeutic value. For example, Bates, a famous ophthalmologist in New York, showed a hemostatic effect of the adrenal extract during the eye surgery [40]. Furthermore, Solis-Cohen, Professor of the Jefferson Medical College, demonstrated its effect in the treatment of hay-fever in 1898, because he himself was suffering from this disease [41]. The 'suprarenal therapy' using animal glandular extract became increasingly popular, and the marvelous therapeutic value of the suprarenal extract was being established. However, because the natural extract was prone to

deteriorate very rapidly, it was necessary to prepare the fresh extract each time before use. Accordingly, isolating and unmasking the active principle of adrenal glands presented a challenging biomedical problem that attracted ambitious scientists.



Adrenaline isolation by Uenaka

macerate ~700 bovine adrenal glands (9 Kg)
in 80~95° C warm water

↓ add acetic acid, agitate

aqueous extract in CO₂ gas

↓ remove albumin at 90°C and press
extracted fluid

↓ avoid air, add 2~3 volume of alcohol
to remove contaminations

mixed liquid

↓ evaporate alcohol in the vacuum pan
add ammonia to precipitate

yellow precipitate of crude adrenaline

↓ dissolve in acid
refine with alcohol and ether, and dry

white crystalline adrenaline precipitates (7 g)

check Vulpian reaction by ferric chloride

Fig. 2-A. Portrait of Dr. Jokichi TAKAMINE in his early 60s and his signature, appearing in the book described by K. K. Kawakami in 1928.

2-B. His young associate, Dr. Keizo Uenaka (or Wooyenaka) in the mid-20s.

2-C. Photo of the Takamine laboratory in the 109th street in Manhattan, presumably taken around 1960. The Takamine laboratory was located at the underground (rectangle) of the janitor's building.

2-D. The small (around 15 m²) experimental room where Uenaka worked in 1900 for the adrenaline crystallization, was located between the Central Park and Hudson river. The large glass bottle in the right lower appears to be a vacuum pan he utilized.

2-E. Parke, Davis & Co. (later division of Warner-Lambert Company) in Detroit. Dr. Takamine earned royalty from this large company after patenting Taka-Diastase and Adrenalin.

3. ADRENALINE HUNTING RACE

3.1 Competitive Hunting Race in 1890's

Late 19th century, Benjamin Moore in London, John Jacob Abel in Baltimore, and Otto von Fürth in Straßburg, were independently challenging to isolate and purify the biological compound involved in the adrenal gland. For instance, von Fürth [42,43,44] used iron to precipitate a substance that he named 'suprarenin' (The Latin word, *supra*, means "above," while *ren*, "kidney." Here, one must note that Addison's book in 1855 used the phrase "supra-renal capsules" in its title). Moore, a junior colleague of Schäfer's laboratory at University College London with a background of chemistry, found the compound to be identical with a powerfully-reducing substance in the adrenal medulla, that was

first described by Vulpian [18]. He determined that catechol itself was not the substance because it cannot raise blood pressure. Accordingly, he used the cumbersome phrase "physiologically active extract of the suprarenal gland" [45]. Moore [45] also concluded that the active principle is the reducing substance, and later [46] discovered that oxidation of a solution containing the reducing substance destroyed its pressor activity. He (Proc. Physiol. Soc., London, xiv ; Jour. Physiol., 1895, xvii) concluded that the physiologically active body must be identical with the reducing body which gives a green color reaction with the iron salts. Fraenkel [47] suggested that the reducing body is a substituted catechol, probably a benzoyl derivative. This later ironically became a cause of Abel's failure, although Moore claimed this is not true.

Almost immediately after the publication of Oliver and Schafer's paper in 1895, John Jacob Abel of Johns Hopkins University undertook to isolate the active principle. P. D. Armour and Company of Chicago supplied Abel with a very generous amount of sheep adrenal glands. In 1897, Abel and his colleague Albert Crawford isolated benzoate and sulphate derivatives from the glands. Using benzoyl chloride, they precipitated an amorphous yellow material that had some ability to raise blood pressure, although less active than the crude extracts [48]. In 1898, Abel reported that the most purified material had the composition $C_{17}H_{15}NO_4$ [49]. In 1899 he published a paper announcing an extract which he named "epinephrin" (the Greek word, *epi*, means "close by," while *nephros*, "kidney"). He stated in the summary of this paper; '*die Formel $C_{17}H_{15}NO_4$ ausgedrückt wird und welche Ich Epinephrin nenne (I will coin the name epinephrine to the substance expressed by the chemical formula $C_{17}H_{15}NO_4$.)*' Although the name of "epinephrin" well indicated certain active principle by the terminal "-in", this provoked a series of troubles, because inactive substance was designated as if active. His method [50] was much more complicated than Takamine and Uenaka's relatively simple method (Fig. 3-right). Abel was simply bogged down by the complicated procedure using benzoyl chloride. Although two benzoyl groups had been removed, one still remained, and Abel now referred to this compound as mono-benzoyl epinephrine [51,52]. Abel's final extract was a mono-benzoyl derivative, from which he later produced a crystalline, epinephrine-hydrate, which he believed to be identical to the gland extract but was physiologically inactive. 'Benzoylation' was responsible for much of Abel's troubles and failure.

Nearly two years before Parke, Davis & Co. offered 'Adrenalin' for sale, the active principle of the suprarenal gland, as prepared by Abel, was in the hands of clinicians in the form of a salt and in solution with the name "Epinephrin", becoming the subject of experiment and report to medical societies [53]. However, von Fürth claimed that Abel's epinephrine is not pure, being merely an inactive foreign matter. The methods which Abel developed for its extraction and purification, have been overthrown by others and were not accepted also by his scientific competitors. von Fürth ascertained isolation by different methods in the form of iron compound and named it 'suprarenin'. Neither of them obtained their product in the pure form. Abel and von Fürth sharply debated each other's results, while Jokichi Takamine remained outside the fray.

Takamine described in the November issue, 1901 of Am J. Pharmacy [54] that '*J. J. Abel's investigation on the subject has no doubt thrown some light on the chemical side; unfortunately for him, however, he was not working with the active principle but a somewhat modified substance, or the benzoyl-compound which withstood his autoclave treatment. I have tried it with different solvents in view of crystallizing but thus far in vain, and concluded that this portion of the benzoyl compounds is not crystallizable*'. Furthermore, he mentioned as follows; '*Last summer I devoted my attention to this subject and am pleased to announce that I have succeeded in isolating the active principle in a pure, stable, crystalline form, the base itself. I do not by any means desire to usurp the credit due to the pioneer investigators, yet in view of the fact that neither of the authors (indicating Abel and von Fürth) quoted above have obtained the active principle in a pure form, and that there may exist some room for controversy, I have, therefore, termed my substance, as I isolated, Adrenalin.*

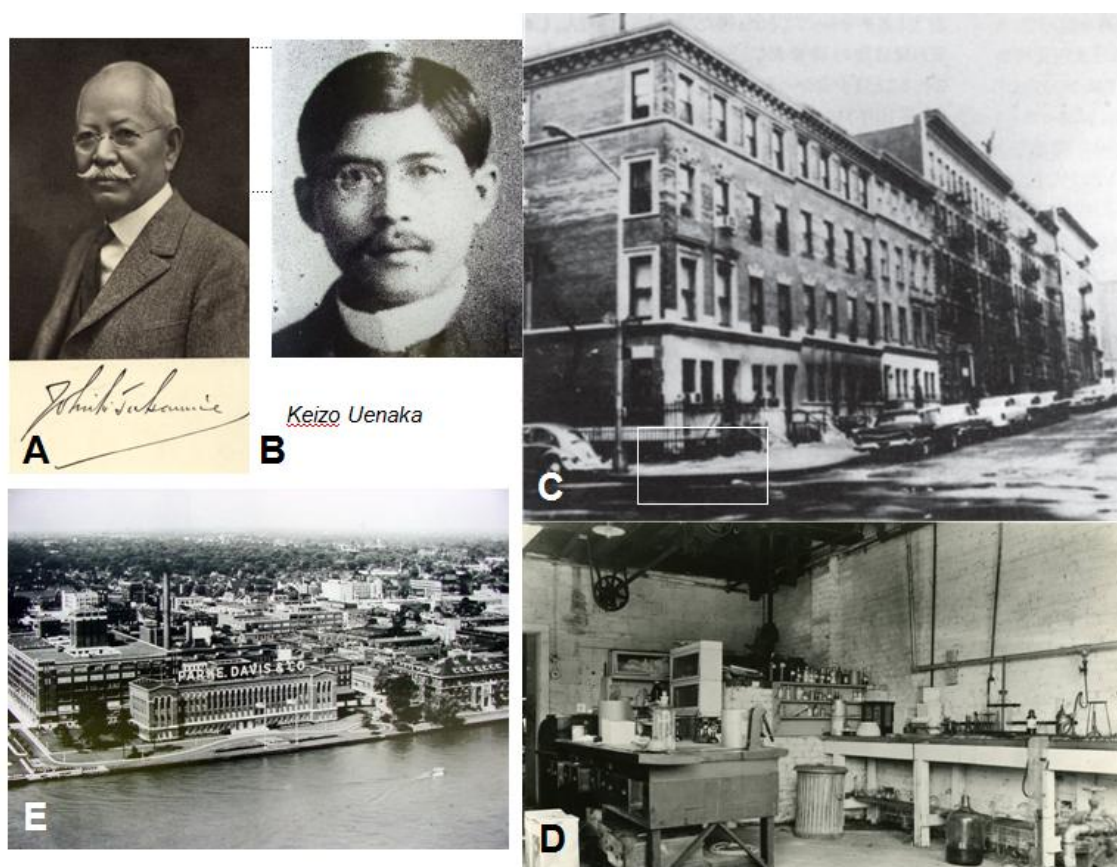


Fig. 3. 'On Adrenalin Memorandum' (98 x 152 mm) described by Uenaka. Uenaka wrote at the 1st page as 'Investigations for Active Principle of Suprarenal Gland. July, 1900'. He wrote in the cover page as 'July to December, 1900', but actually the eight series of his isolation experiments were completed until November. In December, Drs. Takamine and Uenaka visited Detroit to instruct Parke, Davis & Co. to manufacture adrenaline at the factory level. Since the naming of Adrenalin was done on November 7 and this memorandum contains no descriptions about this visit in December, Uenaka presumably later wrote the red letters of 'On Adrenalin, July to December, 1900' around November, 1900. It is intriguing to note that his signature is not the American style 'WOYENAKA' but the Japan style 'UENAKA'. Uenaka didn't know the spelling of 'UENAKA' cannot let Americans pronounce like 'WOYENAKA' from his arrival to New York, February until the start of this memorandum, July, 1900. This indicates he was in this period concentrating in experiments without communicating American people. The right shows a process of adrenaline isolation being developed by Uenaka within a couple of months

Takamine modestly stated that he had no interest in taking credit from earlier investigators, presumably because he was well aware of the bitter dispute between Abel and von Fürth. Takamine's naming way showed a remarkable contrast with Abel: The former called the active principle 'my substance', while the latter called 'die Formel $C_{17}H_{15}NO_4$ '. As $C_{17}H_{15}NO_4$ was later shown to be inactive, the term 'epinephrine' became actually nonsense.

3.2 Successful Isolation by Two Japanese in August 5, 1900

Takamine already developed an enzymatic extract of aspergillus he called 'Taka-diastase' that rapidly converted starch to sugar, and Parke, Davis & Co. sold it for many years as a relief for dyspepsia [55, 56]. Takamine was accustomed to the commercial practice with its patents and registered a trademark. Parke, Davis & Co. had well recognized the success of 'Taka-diastase', and was ready to cooperate

with him in both investigative and financial aspects. Around 1897, William Warren, its general manager asked Takamine to purify the blood pressure-raising substance from the adrenal medulla. Takamine (Fig. 2-A) was a modest Japanese with splendid creative ability, but for more than two years thereafter he floundered in the dark for a process of isolation. However, this experience of floundering had urged Takamine to ask Prof. Nagai in Tokyo send an appropriate young colleague to New York. And, the superb research experience of Keizo Uenaka (sometimes written in English as Wooyenaka: Fig. 2-B) could invite Takamine to a fortunate success in this challenging project. The procedure of crystallizing the active principle of the adrenal gland was much more simple (Fig. 3), compared with that of Abel [57]. The secret of success was essentially at the incidental similarity between ephedrine and adrenaline [58].

For more than 5,000 years, the Chinese people have used the stems of *Ephedra vulgaris*, under the name of má huáng (麻黄), as a medicine of a diaphoretic, a circulatory stimulant, a sedative in cough and an antipyretic. Nagayoshi Nagai, after studying in Germany under instructions of famous chemists Profs. Liebig and Hoffmann, became a legendary professor of chemistry and pharmacy at the University of Tokyo. He was a leading figure in the chemical research on natural products and a noted leader in Japanese pharmacology in the 19th century. Nagai had organized the Tokyo Chemical Society in 1887 with the aid of Takamine. He first isolated from 'Ma huang' (a medical herb used in China) a derivative of phenylethylamine and named it ephedrine [59]. Uenaka was trained as a student of Prof. Nagai in his laboratory. Ephedrine was closely related in structure and physiological action to adrenaline [58]. Ephedrine contains two asymmetric carbon atoms as compared with one carbon of adrenaline. Furthermore, adrenaline differs only in containing two phenolic hydroxyl groups in the ortho-position to each other, making it much more susceptible to oxidation than ephedrine. The similarity of adrenaline with ephedrine produced a miracle of Uenaka (Figs. 2-B, 3), although he was presumably not aware of this issue during his assiduous work. Uenaka had a strong foundation from his highly relevant research experience to take on the challenge of isolating adrenaline.

At the age of 83, Uenaka (1876-1960) talked in his interview in Japan to the science journalist as follows (translated by the author).

I was born in 1876, and studied at two-year training course of Pharmacy of the Tokyo University, in the laboratory chaired by Prof. Nagai. After graduation at the age of 22, I was engaged in the development of the agent necessary for covering fluorescence plate of X-ray in Tokyo University for a couple of month. For the subsequent 18 months, I experienced analysis of copper ions in the stool of Ashio mineworkers to elucidate the cause of poisoning, and isolation of nicotine from the tobacco as an insect repellent in the Tokyo Hygiene Institute. I decided to leave Japan and seek out Dr. Takamine in New York, because the step-up was hardly possible in Japan for the two-year course graduates. I thought the free atmosphere in the United States might provide more opportunities for advancement.

I arrived at New York in February of 1900 at the age of 24. In the Takamine laboratory at the small (about 15 m²) underground room (Fig. 2-D) of the janitor's building located on East 103rd street (Fig. 2-C), I utilized the simple procedure. Briefly, bovine adrenal tissues supplied by the Parke, Davis & Co. (Fig. 2-E) were macerated in the 60~70 % alcohol to obtain the precipitates, the filtered fluid of which was evaporated in the vacuum pan. Finally, I confirmed the active principle by the Vulpian reaction. As adrenaline was relatively simple substance, I could fortunately isolate it without difficulties. On July 21, I first identified crystals of the active principle at the bottom of a test tube. Thereafter, I utilized the watch glass, because I was trained as such by Prof. Nagai.

To identify chemical reactions, Prof. Nagai usually used it; he arranged many 10 cm dishes over the white paper, and put the tested material into the dish. Then, he added to each watch glass various concentrations of the test agents gently and slowly from the tip of thin tube. He carefully observed the color when the test agent is sinking to the bottom, and determined the optimum concentration. I learned this procedure, and just imitated. Furthermore, after coming to New York, the book of chemical isolation I bought indicates that the state of the crystals at the bottom of the dish is helpful to determine the nature of alkaloid. This instruction was also helpful to modify Prof. Nagai's procedure. I noticed that the adrenaline crystals appeared at the marginal stream of the sinking agent. To tell the truth, I wondered why previous researchers had failed to isolate them (smiles). Adrenaline should

have been crystallized by the previous researchers, if the Vulpian reaction was properly utilized for the confirmation of the final product. Although there were no special reference papers and data accumulated, utilization of the Vulpian reaction, watch glass, vacuum pan, and ammonia was a mother of my success. I was convinced of the final success around my birthday in August 1900.

I sent to von Fürth one gram of the purified substance, and he replied me; 'Thank you for sending me something very valuable. Congratulations of your success!. The Parke, Davis & Co. intentionally advertised our success for the promotion of its business. I suppose von Fürth might have achieved his goal, if such a simple idea of ammonia utilization for the final precipitation emerged. It is as if he had left us some space for work with such an idea not emerged'

About the physiological properties of the final products, Takamine described in the November issue, 1901 of Am J. Pharmacy [54] that *'The physiological activity of adrenalin thus isolated is astoundingly strong. A fraction of one drop of aqueous solution of adrenalin or its salt in strength of 1:50,000 blanches the normal conjunctiva within one minute. It is the strongest hemostatic agent known. The result of three intravenous injections of 1 c.c. of the solution of adrenalin chloride of 1:100,000 into a dog weighing 8 kilograms raised the blood pressure corresponding 30 millimeters of mercury.'*

Many experiments in science work, because someone made a very small change in methods. Sometimes just a small change in the pH of the buffer made all the difference for no apparent reason. Uenaka conceivably did not make so profound insights in the purification science or chemistry. Just simply repeating what he had learned from Prof. Nagai, Uenaka got the conditions right and his experiment worked, and deserve credit for being successful. Abel came close, but his experiments were not successful in the end; that is what he is saying, mixed in with his own deep passion and profound regret. He became very depressed by his being unsuccessful. Most scientists use the work of others to develop new things. That is the normal course of progress. Takamine very appropriately read the works of Abel, Moore, and von Fürth carefully in order to instruct Uenaka (Fig. 3). For example, Takamine conceivably instructed as, the author speculates, *'please, be careful to use the vacuum pan because the active principle is prone to oxidation, and use the Vulpian reaction for the final confirmation of the crystal !'*.

3.3 'On Adrenalin Memorandum' written by Uenaka

Uenaka described an experimental notebook (Fig. 3-left) in the classic-style Japanese sentences about the eight series of experiments from July 20 to November 15 in 1900 for isolating active principle of the suprarenal gland [60]. For fear of affecting Takamine's reputation, however, Uenaka dared not disclose presence of his memorandum both before and after Takamine passed away. After Uenaka's death, in 1966 his son Mioji Uenaka informed of its presence and gave photocopy to Prof. Aiko Yamashita who deciphered the illegible document carefully and later introduced it (Fig. 3-left) in the science history journal [60]. Then, the process of the adrenaline discovery became thoroughly clear.

In the last page of November 15, 1900, Uenaka described, ***'Prior to conclude (means END of experiments) the present experiments at the Takamine laboratory, Dr. Takamine and myself will visit Parke, Davis & Co. in Detroit in the early December. The details of our procedures were described in the laboratory notebook.'*** This description is crucial because indicating three issues; One is that there existed an official experimental record for the Takamine laboratory other than the personal experimental memorandum of Uenaka (Fig. 3-left). However, nobody knows its outcome until now. Another is that Uenaka had succeeded very quickly for the isolation; presumably within two weeks if his experiment started on July 20, or within a few months after his arrival in New York in February, 1900. The other is that Drs. Takamine and Uenaka, after convinced of their final success, visited Parke, Davis & Co. for three weeks in December 1900 for the full-scale production of adrenalin at the factory. In the Takamine laboratory in New York, they isolated only 7g of the crystal from 8~20Kg of the adrenal tissues (Fig. 3-right), while in Detroit the company (Fig. 2-E) could isolate about 200g of the crystal by the instruction of Uenaka.

Here, one must note that Takamine has finished to apply for a United States patent on his "Glandular Extractive Product" on Nov 5, 1900 by the single name (Table 1). The fact that Takamine could summarize the isolation procedure into the patent application presumably during a couple of months, suggests that he could by himself understand details of the isolation procedure from the official experimental record, along with observing the on-going experiments of Uenaka. This is easily speculated from the fact that concerning the patent application nothing is described in the Uenaka's memorandum. This was done by Takamine himself, independent to Uenaka.

Table 1. Summary of Takamine's patents on adrenalin. The famous Judge Learned Hand of the Circuit Court of the Southern District of New York decided (189F.95) that H.K. Mulford Company was infringing on the Takamine's patents; No. 730,176 (9 out of 16 items) and No. 753,177 (4 out of 8 items)(as shown by underlines)

Patent No.	Date application filed	Date divided application filed	Date approved	Title	Content
730,175	Nov 5, 1900		June 2, 1903	Process of obtaining products from suprarenal glands	describes in detail isolation procedure of the active principle of adrenal gland
730,176	Nov 5, 1900	Jan 14, 1903	June 2, 1903	Glandular extractive product	describes properties of the adrenal gland extract, and deduced formula was $C_{10}H_{15}NO_3$
730,196	Nov 5, 1900	Nov 26, 1900	June 2, 1903	Process of isolating the active principle of the suprarenal glands	modifies the procedure by using ammonium hydroxide
730,197	Nov 5, 1900	Nov 26, 1900	June 2, 1903	Process of isolating the active principle of the suprarenal glands	modifies the procedure by using a 'fixed caustic alkali'
737,198	Nov 5, 1900	Jan 8, 1901	June 2, 1903	Process of preparing extracts of the suprarenal glands	describes certain new and useful improvements
753,177	May 12, 1903		Feb 23, 1904	Glandular extractive compound	describes improvement for creating more stable solutions by using hydrochloric acid
945,638	Feb 4, 1904		Jan 4, 1910	Glandular compound and process of producing same	describes a new iron-containing derivative (ferrous compound)
1,460,832	Dec 27, 1920		July 3, 1923	Process for the recovery of the active principle of the suprarenal glands	describes more efficient extraction procedure, done by Uenaka and approved after Takamine's death

Uenaka's Experimental Memorandum (translated by Aiko Yamashita [60], and modified by the author) describes;

July 20, 1900: It actually indicates the start of this project, and throws doubt on the previous researcher's method using sodium hydroxide.

'Dr. Takamine returned from the New York Branch of Parke, Davis & Co. with aqueous extract of the adrenal tissues, and directed me to isolate an active principle from the extract, according to the previous method. I added sodium hydroxide carefully to make it slightly alkaline, Took some of the extract, and studied its reaction to ferric chloride as reported by Dr. Vulpian. However, in the presence of the protein and other contaminations, a bright color was not obtained, but a dark green color appeared, It was clear that the active principle was oxidized during

vaporization, although some remained. Prof. Abel of Johns Hopkins University and associate Prof. von Fürth of the Physiological Research Institute of Straßburg, are at present the most authoritative chemical researchers of the adrenal gland principle. Throwing doubt on their studies, I had decided to conduct (means START) the above experiment, and confirmed that the alkaline extracts, as they reported, showed no extraordinary reactions, though emitting an amine-like odor'

July 21, 1900: It indicates success of confirming the active principle by the Vulpian reaction and necessity of the fresh adrenal tissues for developing his original procedures.

'In the early morning, looked into the test tube containing the alkaline extract prepared yesterday, and found on the round bottom of the tube a small watery crystalline mass. Washed the crystals once with water, moistened with a drop of dilute hydrochloric acid, and added ferric perchloride: a vivid green color appeared at last by the Vulpian reaction. Encouraged by the promising findings, asked Dr. Takamine to provide an abundant quantity of fresh adrenal glands.

July 30, and thereafter: It indicates an original experimental procedure using the adrenal tissues, not aqueous extract.

'The first package of 20 pounds of the bovine adrenal tissues arrived from the Parke, Davis & Co. The material was equally divided into two parts, extracted without using sodium hydroxide, and filtered.

(A) To 4Kg of the material, three fold volumes of water were added. The mixture was macerated at 75~85°C for 8 hours.

(B) To another 4Kg of the material, two fold volumes of 95% alcohol were added. The mixture was macerated at about 82°C for 6 hours.'

August 4, 1900: It indicates a confirmation of the activity of the new crystals.

' The alkaline liquid was stood overnight until the crystals were precipitated in the liquid. The crystals were filtered with a paper, washed with water, and dried to generate a slightly brownish crystalline powder. It showed a characteristic green color by the addition of ferric chloride. A drop of an acid solution of the newly produced crystals was put in the eye of a mouse, and its color faded immediately to white. This test was done, because I remember such report that the adrenal extract shows a vasoconstrictive effect.'

This description suggests that presumably introduced by Takamine, Uenaka was informed of this information from the paper published by the ophthalmologist in 1896 [40].

August 5, 1900: It indicates a success of adrenalin crystallization.

'The previous researchers failed to isolate the active principle of the adrenal gland. However, since our new crystals revealed Berlin blue in the presence of ferric perchloride, I am now convinced that isolation of the active principle of adrenal glands was successful in the Takamine laboratory.

August 21, 1900: It indicates that the new crystals are distinct from Abel's epinephrine.

' Our new crystals were dissolved in a small amount of sodium hydroxide, and shaken after adding a drop of benzoyl chloride. An oily liquid produced was undoubtedly not the same substance as Abel's epinephrine. As far as my experiment is concerned, our new crystals are obviously distinct from the product of Prof. Abel; epinephrine.

October 13, 1900: It indicates an optimal dilution of new crystals.

' A drop of 1:1,000 acid solution of the new crystals was placed in one of my eyes, while a drop of the aqueous extract of the Parke, Davis & Co. in another eye. Then, the new crystal showed a stronger discoloration than the aqueous extract. So, it was concluded that the optimal dilution of new crystals for practical use should be 1:1,000.'

October 18, 1900: It indicates activity of a 1:4,000 dilution.

'There was no difference in an eyelid decolorizing effect between Parke-Davis aqueous extract and a 1:40,000 dilution solution of our new crystals. So, I was convinced more and more of the activity of new crystals.'

November 6, 1900: It indicates that ammonia is appropriate to precipitate crystals.

'In order to determine which is more effective for precipitating new crystals, a single use of ammonia (A) or a combination of sodium hydroxide and ammonium chloride (B), (A) generated 1.4 ‰, while (B) 0.8 ‰. Then, the ammonia method proved better for the precipitation.

(November 5, 1900: Date of Takamine's United States patent application filed)

November 7, 1900: It indicates a naming episode.

' The free intramolecular exchange occurs within the new crystals, but other researchers failed to isolate the same crystals as ours. The new crystals were named 'adrenalin' as recommended by Dr. Wilson, a friend of Dr. Takamine.

November 15, 1900: It indicates end of the research in the Takamine laboratory, as well as transition to the main stage of industrial production from New York (Fig. 2-C, D) to Detroit (Fig. 2-E).

'An eighth or last package of the adrenal tissues has arrived. Further study will be conducted on the industrial level at the factory of Parke, Davis & Co.'

The Uenaka's memorandum does not mention the research activities prior to July 21 as well as after November 15, 1900. There are two possibilities explaining this; one is that it might be a personal memorandum only of the Uenaka's adrenalin experiments, while another is that there is a formal laboratory memorandum including Takamine's preceding experiments. The latter possibility is likely, because Uenaka described at the end of the memorandum: *'For further detail, please refer to the laboratory diary*'. Although this suggests that the record was kept separate from his personal memorandum, in spite of eager search by the Uenaka family, one could not so far find out a trace of the *Takamine Laboratory Experimental Note* [60]. The author speculates that it was long preserved in the Takamine laboratory, and only the Takamine family had responsibilities for its outcome.

If summarizing briefly, Uenaka's procedure was as follows (Fig. 3-right); adrenalin, constituting only 0.1 percent of the weight of the adrenal glands, was extracted from the adrenal exudates in the vacuum pan for preventing oxidation, dissolved in alcohol, and crystallized by ammonia or sodium hydrate, finally checked by the Vulpian reaction.

- 1) Finely-disintegrated adrenal gland tissues are **macerated in 50~80°C warm water bottle being put in the boiled water** for 5 hours.
- 2) Raise 90~95°C for 1 hour to coagulate albumin and remove it.
- 3) Avoid exposure of liquid to the air by floating fat membrane and/or circulating carbon dioxide gas.
- 4) Press the tissue to extract the liquid containing the active principle.
- 5) To avoid contact with atmospheric air, evaporate water in **a vacuum pan**, and condense the extracted fluid.
- 6) Add 2~3 volume of alcohol to the condensed fluid to remove the contaminated substance.
- 7) Evaporate alcohol in **a vacuum pan**.
- 8) **Add ammonia** to the residual liquid for precipitation until becoming distinct alkaline, and wait for several hours.
- 9) Yellow-brownish precipitate formed is crude adrenalin.
- 10) Filter, wash and dry this precipitate.
- 11) Adrenalin precipitates **in a light yellowish tomato-like form or in needles**.
- 12) Instead of ammonia, a small amount of sodium hydrate can be used.
- 13) For purification, dissolve the crude adrenalin in acid, then add alcohol and ether.

- 14) Separate the precipitate by decantation and filtration.
- 15) White crystalline precipitate of adrenalin will be obtained.
- 16) Wash with water and alcohol, and dry.
- 17) Addition of ferric chloride to the crystal produces a beautiful emerald green, while iodine produces pink coloration (**Vulpian reaction**).

3.4 Coining the Name 'Adrenalin' and Patent Application

Norton Wilson, a well-known otolaryngologist and a friend of Takamine, visited his laboratory in November 1900, and suggested the name of 'adrenalin'. Since the Latin word 'ad', means "near" while 'renal' means "kidney" i.e., 'adrenalin' means the substance coming from glands near the kidneys. Accordingly, Takamine used the word 'adrenalin' at the presentation in London in 1901 and in his paper in the Journal of the American Medical Association in 1902 [61]. The word 'adrenalin' soon became incorporated into the English language. Unlike the more academic researchers, he first wanted to patent his method earnestly, instead of publishing the scientific papers in the academic journals. Before Takamine published his papers on adrenalin, he had finished to apply for five patents on November 5, 1900 (Table 1). On January 22, 1901, he applied for an English patent that was granted in July of that year (English patent 1467; 22 Jan 1901). Takamine was interested more in the commercial advancement than the basic scientific aspect of research. In his patent application, Takamine was represented by lawyers from the New York office of Knight Brothers, a highly experienced legal firm. His patent application had a rigorous review by James Littlewood, a highly capable examiner who had a medical degree from the Georgetown University. He believed that the natural product that was simply separated from other substances, without any changes, could not be patented. Littlewood quickly decided, based on the established criteria from other cases, that because adrenalin was a naturally occurring substance, it could not be patented. Having absolutely nothing to do with Takamine, the American Medical Association Code of ethics for 1903 strongly objected to patenting drugs (Principles of Medical Ethics, by American Medical Association, [62]). This was true at the end of the 19th century as well.

As the examiner immediately refused Takamine's application about the 'product', Takamine was obliged to divide the patent into five categories, four of which were revised to claim 'process', not the 'product itself' (Table 1); i.e. 'process of obtaining', 'process of isolating', 'process of preparing', etc. He changed the wording of the original patent so that it could cover the wider field. Only one described the properties of the active principle itself. Three 'process' applications were submitted again from November 26, 1900 to January 8, 1901, within 2 months after the initial application, and the final application of the 'product' was submitted two years later, on January 14, 1903 (Table 1). After considerable back- and -forth with Littlewood, Takamine's lawyers claimed that the purified adrenalin was not exactly the same substance found in the adrenal extracts, and that it was much more chemically stable than adrenaline in a gland extract. After more than two years of skirmishes, Littlewood finally relented, and all the five patents were approved for patenting in June 2, 1903 (Table 1).

If his first application on November 5, 1900 was immediately accepted, Takamine would have the rights to adrenaline, exclusively. In response to the prompt rejection, he arranged for Parke, Davis & Co. (designated 'Parke-Davis' after becoming a division of Warner-Lambert Company) to market the pure crystalline substance as 'Adrenalin', being spelt with a capital "A" and without a terminal "e". On April 16, 1901, Takamine was given the right to use the word Adrenalin as a trademark (USA Trade Mark 86,269, 1901). Later, on May 14, 1906, the trademark was transferred to the Parke, Davis & Co. (Affidavit, State of New York, County of New York, May 14, 1906) which first offered the pure adrenalin and the solution adrenalin chloride for sale to the medical profession and the drug trade. It is conceivable that this later affected Parke, Davis & Co. to refuse the proposal of the United States Pharmacopoeia (USP) to adopt 'adrenalin' as a generic (approved) name.

E.M. Houghton, Director of the Parke, Davis Research Laboratories in Detroit confirmed by the pharmacological assay that action of the crystalline product was 600 to 800 times as strong as that of the freshly-prepared aqueous extract [63,52]. Houghton's extremely precise pharmacological assay using many dogs was a great supporter of Takamine and Uenaka. They could not so quickly isolate

the adrenal extract without the support of Houghton. During his 8 series of isolation experiments, Uenaka could carefully plan the next procedure by confirming Houghton's assay data of the previous extraction experiment. This showed a remarkable contrast with Abel who had no supporters for the biological assay. At the 52th American Medical Association held on June 4~7, 1902 in Minneapolis, Houghton delivered a lecture about the history of adrenal gland by introducing 37 investigators including Addison, while Takamine talked about the crystallization of adrenaline; both papers were published in the same issue of JAMA [63,61].

In the early 1901, Parke, Davis & Co. delivered these 'Adrenalin' products (later found to be contaminated with noradrenaline) to many clinicians for the clinical trial. 'Adrenalin' moved almost immediately from the laboratory into the hospital, where it was used by surgeons as a local hemostatic and by physicians to treat many diseases such as allergies, asthma, and heart failure. The otolaryngologist Dr. Emil Mayer [64] reported its marvelous effects upon nasal hemorrhage of 35 patients in New York on March 27, 1901. It is amazing that the clinical effects of adrenaline was demonstrated within three months after manufacturing at the Parke, Davis & Co. Favorable results were reported also by Drs. Wilson, Bates, Reichert, Ingals, Stucky, Chambers, Curtis, Swain, and others [54]. Also amazing was that in the April, 1901 issue of *'Homoeopathic news'*, the advertisement of *'Solution, Adrenalin Chloride'* appeared as Astringent, Hemostatic, Cardiac and Vasomotor Stimulant by Parke, Davis & Company [65]. The trademark of 'ADRENALIN' was registered on April 16, 1901 by Takamine, and was transferred to the Parke, Davis & Co. on May 14, 1906. As the biological activity of adrenaline was distinct according to the species extracted and the age of animals, it took up to 5 years after the success of crystallization for Park, Davis & Co. to supply the perfect and stable solution of adrenaline.

When Takamine presented a communication to the Physiological Society of London in 1901, he spelled the word with a lower case "a" and made no reference to any commercial associations. Since 'Adrenalin' was trademarked in the United States in 1906, no other corporate entities could use the term. This brought a whiff of scandal not only to the pharmaceutical industry but also to the scientific community which was to last for many decades in USA. On the cover page of the pamphlet published by Park, Davis & Co. in London, the trade name around 1907~1909 was 'Adrenalin (Takamine)'. There should have been some debates concerning the trade name of 'Adrenalin' or 'Adrenalin (Takamine)' versus the very similar generic name 'adrenalin' and 'adrenaline'. The word 'adrenalin' or 'adrenaline' began to achieve widespread recognition not only in America but also in Britain, Germany, and France as representing the active principle of the suprarenal gland. The term thus spelled took its place in the scientific nomenclature and be descriptive both of its origin and character.

Takamine's next patent (No. 753,177) was applied on May 12, 1903 and approved on February 23, 1904, which described utilization of hydrochloric acid (HCl) to obtain more stable salt. Takamine received a 5 percent royalty on the wholesale price of 'Adrenalin'. His 7th patent (No. 945,638) was applied on February 4, 1904 and approved on January 4, 1910, which described a new iron-containing derivative. The last patent application (No. 1,460,832) was done by Uenaka on December 27, 1920 and approved on July 3, 1923, after Takamine's death, which was the longest patent describing the more efficient extraction of the active principle (Table 1).

At the end of the 19th century, the Manual of Patent Examining Procedure states '*a thing occurring in nature, which is substantially unaltered, is not a manufacture*'. It was a common sense at that time that a natural product is not patentable. However, the first of the legal cases to define the patentability of the natural product was in 1909 that claimed aspirin as a 'manufacture'. The second legal case, occurring two years later, was that of adrenalin. H.K. Mulford Company in Philadelphia was producing and marketing 'Adrin', a crystalline substance similar to 'Adrenalin', using a slightly different procedure than Takamine's process. Parke, Davis & Co. (Fig. 2-E) argued that H.K. Mulford Company was infringing on the Takamine's patents; No. 730,176 and No. 753,177. On the contrary, H.K. Mulford Company claimed that Takamine's patent 730,176 was not valid, because the product is a naturally produced substance. On April 28, 1911, a decision was handed on this legal case by the famous Judge Learned Hand of the Circuit Court of the Southern District of New York (189F.95, Hand, [66]). He referred to the aspirin case, and decided that H.K. Mulford Company was infringing on the patents. Hand stated that '*considering the similarity of the processes, the use of each substance practically,*

and the approximation of result physiologically, the two are near enough to be an infringement one of the other'. While the battles about nomenclature and patents were going on, adrenalin was exploited by physicians to treat a wide range of diseases around the world.

3.5 Chemical Formula Determination by Aldrich in 1901

T.B. Aldrich left the department of pharmacology at the Johns-Hopkins University, and joined the biological laboratory of the scientific division of Parke, Davis & Co. in Detroit from July 10, 1898 for the adrenal research. He, although a former associate of Abel, described at the head of his paper in Am J. of Physiology in 1901 as follows [67].

'THE most recent and in many respects the most important contribution to our knowledge of the active principle of the supra-renal gland, although not exhaustive, is from Dr. Jokichi Takamine who has isolated the blood-pressure-raising principle of the gland in a stable and pure crystalline form, by a method which he claims to be entirely different from any yet employed. To this body which is very active in raising the blood pressure, he has given the name "Adrenalin".'

Since Takamine's chemical formula; $C_{10}H_{15}NO_3$ differed very little from the right one proposed by Aldrich; $C_9H_{13}NO_3$, he presumably described 'although not exhaustive', as he admitted the priority of Takamine in the crystallization of adrenaline.

In the summer of 1900, almost simultaneously with Takamine and Uenaka, Aldrich succeeded in obtaining a semi-crystalline substance that gave the characteristic color reaction with ferric chloride. A few months later, he obtained a larger quantity of the same substance, and could confirm in the beginning of 1901 that it is identical with Takamine's "adrenalin" [67]. Aldrich could obtain a sample of Takamine's adrenalin, because Takamine had a continuing relation with Parke, Davis & Co. Using both Takamine's product and that prepared by himself, Aldrich finally determined the precise chemical formula.

In the same paper, Aldrich discussed as follows.

'It is interesting to note in this connection (indicating Abel's publication in 1901) that if we subtract a benzoyl residue (that means C_7H_5O) from Abel's formula for "epinephrin"— $C_{17}H_{15}NO_4$ — we obtain a formula $C_{10}H_{10}NO_3$ which is not very far removed from that of adrenalin — $C_9H_{13}NO_3$ — a difference that can be readily explained if we suppose either of the substances (indicating Adrenalin and Epinephrin) to be contaminated with other bodies.

.... Abel has isolated at least the salts of "epinephrine" in an apparently pure form, but in very small quantities; Takamine and myself have isolated what at the present time appears to be the active principle in quantities sufficiently large for an exhaustive investigation'.

Aldrich's formula for adrenalin turned out to be the correct one, because his preparation had a greater purity. von Fürth, Hermann Pauly, Gabriel Bertrand, Hooper Jowett, and George Barger with Arthur Ewins, all confirmed Aldrich's formula. Aldrich showed the composition $C_9H_{13}NO_3$; that is, the substance contained atoms for carbon (C), hydrogen (H), nitrogen (N), and oxygen (O) in a ratio of 9:13:1:3 (Fig. 4-A). Takamine and Uenaka, at the time of isolation of active substance from the adrenal gland, did not know that their active substance is not absolutely pure, because of containing a little bit noradrenaline. Similarly, Abel also did not know that his "epinephrine" represents merely the monobenzoyl derivative of the native principle, being far from the pure and active adrenalin. In epinephrine, the retained benzoyl group was strongly attached to the imide nitrogen of the side chain of the molecule; an unusual circumstance in any event. Intriguingly, Aldrich properly indicated future of adrenalin research, and failure of Abel's isolation procedure.

No less than four formulas for the active principle of the suprarenal glands were proposed by Abel from time to time. It would certainly be a distortion of the truth, therefore, to apply the name "epinephrin" to the substance which has a different chemical constitution. However, Abel [68] (Bulletin of the Johns Hopkins Hospital. 13: 29-36, 1902, American Journal of Physiology. 8: xxix-xxx, 1903)

also claimed that the Takamine's adrenal extract is not chemically pure. This claim was somehow reasonable because in adults, adrenaline accounts for approximately 80% of adrenal medulla catecholamine content, while noradrenaline makes up most of the remaining [69]. Another forty-five years would pass before the discovery that approximately one-third of the ostensibly-pure adrenaline obtained from the adrenal medulla was actually noradrenaline, $C_9H_{12}NO_4$.

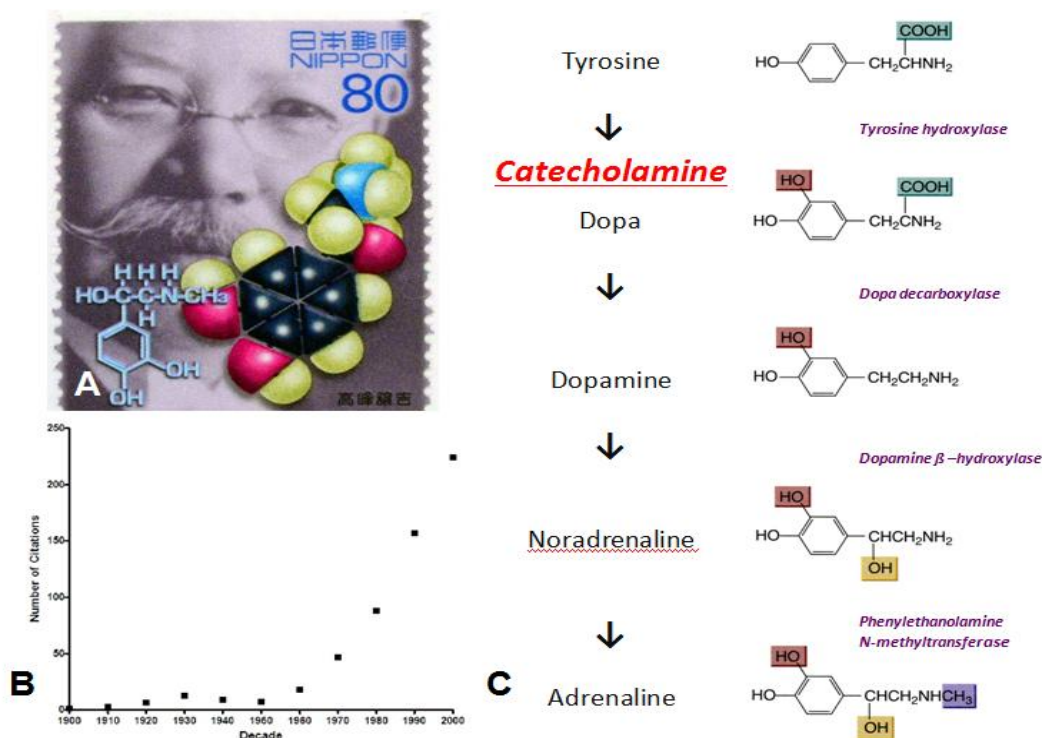


Fig. 4. 4-A. A commemorative stamp of Dr. Jokichi Takamine made in 2004 by the Japan government.

4-B. A remarkable increase of citations of the word 'Adrenaline' in the New York Times (Cited from ADRENALINE by B.B. Hoffmann published by Harvard University Press in 2013)

4-C. The synthesis of catecholamines. Tyrosine hydroxylase, being activated after stimulation of sympathetic nerves or adrenal medulla, hydroxylates tyrosine to form 3,4-dihydroxyphenylalanine (dopa). This hydroxylation is generally regarded as the rate-limiting step in the biosynthesis of catecholamines. Dopa is decarboxylated to form dopamine through the catalysis of dopa decarboxylase. Dopamine β -hydroxylase hydroxylates dopamine to form noradrenaline. Noradrenaline is N-methylated by phenylethanolamine N-methyltransferase to form adrenaline. As tyrosine can be synthesized from phenylalanine, not only tyrosine but also phenylalanine can become a precursor of adrenaline

In 1903, Abel, epitomizing an academian of the time, (Berichte der Deutschen Chemischen Gesellschaft zu Berlin, 36: 1839-1847, 1903) [70] formally admitted in the German chemical journal that 'The important observation that the substance can be precipitated in crystalline form from concentrated gland extracts by the aid of ammonia and other alkalis we owe to Takamine'. (original: Die wichtige Beobachtung, da ß die Substanz in krystallinischer Form mittels Ammoniak und anderen Alkalien aus dem concentrierten Drüsenextracte auszufällen ist, verdanken wir Takamine.) Considering a schism between academia and industry at that time, 'verdanken wir Takamine' is extremely intriguing. Nothing could be more explicit. In 1903 and 1904, Pauly insisted on the priority of Takamine in crystallizing biologically active principle of the adrenal gland. He claimed that by adding benzoyl chloride to a solution containing the active substance, Abel produced benzoyl compounds that have the slightest biological activity [71,72].

4. ADRENALINE VERSUS EPINEPHRINE

4.1 Takamine Versus Abel: Bitter Disputes about Priority

Takamine's work stimulated both commercial and academic interest. However, Abel, as a professor of the pharmacology department of the Johns-Hopkins University, basically did not approve of pharmacological research with any sort of commercial connection. Five years after Takamine's death, Abel stated at the Willard Gibbs Lecture, and left it in the 'Science' paper in 1927, as follows [73].

'The (adrenal) medullary hormone is called by various names, as adrenin, suprarenalin, suprarenin, adrenalin and epinephrine, the latter having been adopted by the United States Pharmacopoeia as the official designation. This name was coined by me thirty years ago at a time when I supposed that the form in which I had succeeded in isolating it represented the base as it actually exists in the capsules.

After I had completed the above described investigations 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. He remarked in this connection that he loved to plant a seed and see it grow in the technical field.

.... Takamine prepared suprarenal extracts more concentrated than mine, and without first attempting to separate the hormone from its numerous concomitants by benzoylating or otherwise, simply added ammonia -the reagent that I had so long employed- to his concentrated extracts, whereupon he immediately obtained the native base in the form of burr-like clusters of minute prisms in place of my amorphous base.

.... Takamine's success was due to the employment of ammonia on very highly concentrated, though impure, extracts.'

In fact, Abel claimed that Takamine tried to "plant a seed" about what would work; that is quite complimentary. However, almost from the beginning Abel was engaged in controversy with von Fürth, and the controversy intensified when Takamine and Aldrich independently published their papers on adrenalin. Abel was critical of Aldrich's formula, $C_9H_{13}NO_3$, and of Takamine's $C_{10}H_{15}NO_3$. He actually accused Takamine of stealing his technique of using ammonia at the final process of precipitation, and suggested that Takamine's achievement was not an original work but essentially a copy of his experimental procedure. Abel would like to say 'Dr. Takamine should have been successful only after his visit to my laboratory'. Here, one must note that Takamine and Uenaka's success was not in 'the fall' but in August 5. In November 7, they already coined the term 'Adrenalin', and applied the US patent on November 5 (Table 1). Furthermore, based on Abel's published papers, both before and after 1900, there is no reason to believe that Takamine obtained any information from Abel about these procedures. Abel had admitted his failure by confessing '*the blunders of a pioneer*' [73]. He gave full credit to Takamine until 1922, but obviously changed his policy after Takamine passed away. The '*coining Epinephrine*' is done by Abel; it's true. But, '*I had succeeded in isolating it*' is obviously not true. Throughout Abel's paper he is utilizing and advertising the name of 'epinephrine'.

Abel failed to extract active principle of the adrenal gland, nonetheless, he is often remembered as the discoverer of adrenaline; he would make an important contribution some 30 years later when he crystallized insulin. Later, William de Bernier MacNider [74] pointed out the hidden human cost of the adrenaline research:

".... Such a statement would however be only a part truth if mention were not made of the great disappointment at times almost of an incapacitating character experienced by Professor Abel in not having actually carried the epinephrine work to its final point by obtaining the crystals and determining their structural formula. The indomitable spirit of the man overcame this disappointment to go forward

for years to a variety of important discoveries which culminated in his isolation with the aid of Geiling of crystalline insulin."

Ever after his retirement at the age of 75, Abel continued to publish his first author papers until 77 and coauthor papers until 81; his age at death [74]. This is amazing. In the twenty-first century, Abel is remembered in the United States as a great pharmacologist, or as a pioneer of American pharmacology.

4.2 Adrenaline Versus Epinephrine in Britain

Burroughs, Wellcome & Co. was the company that had delivered the adrenal extract as '*Supra-renal Tabloid*' (Dr. Solis-Cohen used this for treating hay-fever). In 1894, this company established quasi-independent laboratories, the Wellcome Physiological Research Laboratories (WPRL) in London. Physiologists and pharmacologists employed were engaged in the basic research such as isolation, identification, and synthesis of new chemotherapeutic compounds such as anti-toxins. The WPRL was unique at that time in Britain, because no other pharmaceutical manufacturer had developed scientific research programmes, and the explicit associations between trade and academe were virtually non-existent. The contractual obligations regarding communication and publication were strict as follows.

'.... It is also understood that before publishing any communications upon physiological matters or upon any work connected with the laboratories you are first to submit same to and obtain the approval of the Director.'

Henry Dale, a Cambridge-trained biologist, was offered a position at the WPRL, and studied on the physiological and pharmacological effects of ergot of rye, which included experiments using 'adrenalin'. In 1906, he prepared a paper for publication, and passed the manuscript to his Director, Walter Dowson, for approval in accordance with his contract. During the latter part of the 19th century, the custom of distinguishing trade names and branded goods had developed as commercial markets and press and poster advertising expanded [75]. Furthermore, Parke, Davis & Co. was a rival company which has a branch in London. Accordingly, Dowson objected to the use of the word 'adrenalin', because 'Adrenalin' had been a registered trade-name of the rival company. Instead, he suggested that the word 'epinephrine' should be used, as it is actually the same chemical substance. However, Dale refused this proposal, because the British physiological community used the term 'adrenaline' to describe active principle of the adrenal gland, and this term did not imply a specific commercial preparation. He proposed to adopt the term 'adrenaline', because the added "e" making the term indicates a basic substance conformably to the practice of chemists, and the term thus spelled would take its place in the scientific nomenclature and be descriptive both of its origin and character.

There was a big debate between the physiological and chemical societies. Physiologists considered Abel's 'epinephrine' physiologically inactive, owed nothing to Abel's work, and did not recognize the substance by any other name except for 'adrenaline'. In contrast, chemists insisted that the word epinephrine is scientifically correct, and published papers on 'epinephrine'. For example, Jowett in England said in his paper [76]: '*As this author (Abel) was the first to isolate the substance, although in an impure condition, it would seem that the name originally assigned by Abel, to the active principle, should be the one adopted.*' Dale emphasized that the major, definitive physiological paper on the subject published in the Journal of Physiology, by Elliott in 1904, had been entitled '*On the action of adrenalin*' [77]. He stated that if the term 'adrenaline' could not be employed, his paper would not be published in the Journal of Physiology. Dale enclosed an authoritative statement by the Editor of the Journal of Physiology, J.N. Langley, that 'adrenaline' is now the scientific name, becoming so rooted that it is futile to try and make scientific people adopt an alternative name which has been failed [78]. In response to this, Wellcome accepted that the use of "adrenaline" in physiological publications is unavoidable. However, within twenty-four hours, he withdrew his permission to use the term 'adrenaline', by reconsidering the chemists' argument for 'epinephrine'. They thought it was time to correct the erroneous use of "adrenaline" also in the physiological literature. Furthermore, there was a risk of legal problem, if WPRL used the rival trade name. Dale emphasized again that the chemical designated 'epinephrine', isolated by Abel and used by chemists, is not physiologically identical to the crude extract of adrenal gland. As a physiologist, he could not describe the substance 'epinephrine'

with which he has been working as 'adrenaline'. At last, Wellcome agreed, on 8 March in 1906 that, subject to the inclusion of an explanatory footnote below differentiating the preparations used, Dale could submit his paper.

'In accordance with physiological custom the name 'adrenaline' is used throughout this paper to denote the active principle of the supra-renal gland, in whatever form administered. Simple extracts of the gland, commercial preparations issued under various 'brand' names, and solutions of the pure base, without preservative, were all used, and all give the effects describe.'

Dale, as a director of Wellcome Laboratories, proposed to adopt the term 'adrenaline', because both the initial "a" and the final "e" may indicate a basic substance conformably to the practice of chemists. The word 'adrenalin' was used as an official name in a general sense in Germany, and two famous professors said as follows.

Professor Pauly [71] of the University of Bonn:

"The credit of first, precipitating and isolating from the suprarenal gland of the therein contained blood-pressure-raising principle as a chemical individual belongs to Takamine. It has the name 'adrenalin,' given to it by its discoverer, which name, among the many trivial names given to it, possesses the best scientific claim."

Prof. von Fürth [79]:

"Abel and his pupils employ the name of epinephrin to designate the active principle as contained originally in the gland, instead of adrenalin or suprarenin. As the substance described and analyzed by Abel under the name epinephrin is certainly different from the original body in the adrenal glands, I shall avoid using the same, since it necessarily leads to a misunderstanding."

4.3 Adrenaline Versus Epinephrine in the United States

We now know that Takamine was indeed the first to isolate the active principle of adrenal extracts, and was a discoverer of 'adrenaline' (Yamashita, 2001: Yamashima, [56]). Abel failed to purify the active principle, nonetheless, he is often remembered as a nomenclator, receiving even Nobel Prize nominations. In 1901, Thomas Maben maintained that since Abel's original 'epinephrine' was not the right chemical, 'adrenaline' should be an appropriate name [80]. However, the USP has for a long time utilized the term 'epinephrine'. This is probably due to the following reasons.

1) Although being far from the belief of physiologists in London that the physiologically-inactive substance like 'epinephrine' is nonsense, a court judge Hand, (189F.95) considering Abel's benzoyl derivative stated that *'Takamine cannot claim to have been the first to discover a stable and pure salt having the physiological activity of the suprarenal gland'*.

2) In those days, the industrial science was despised by the academia, and pharmacologists working for the drug companies were looked down by their academic colleagues. Abel was the first Prof. of Pharmacology in both Michigan (1891-93) and Johns Hopkins (1893-1932). As a father of US Pharmacology, he played a major role in the founding of the American Society for Pharmacology and Experimental Therapeutics (ASPET). When it was founded in 1908, commercial pharmacologists were not allowed to join. In 2008, one hundred years after its establishment, the ASPET honored Abel as its founder. Accordingly, he could affect to the decision of the USP at that time, but Takamine could not. As Abel failed in isolation, he stuck politically to leave only the name; 'epinephrin'.

3) At the beginning of the 20th century, the university-based scientists generally did not patent their inventions, and many people opposed patenting drugs. Abel was strongly against making a profit on the scientific discoveries, and believed that the results of his scientific work should be the property of humanity. In contrast, Takamine was an industrial chemist, considered patents more important than scientific papers, and made a huge profit by patents.

4) In 1911, the Journal of the American Medical Association published a lengthy editorial concluding that the correct scientific name for the active substance of the adrenal gland should be 'epinephrin' (without the last 'e')(The Propaganda for Reform, JAMA, 1911). The editorial emphasized the importance of Abel's contributions and noted that Abel had done his work for the public good, without receiving any personal financial reward. Accordingly, in 1925 Abel received the Research Corporation of America's first annual research prize for "*having done more to promote human enjoyment of life than any other living American scientist.*"

5) Lastly, "epinephrin" was the only name for the substance which has not been monopolized at that time. Around 1900, Abel said 'epinephrin', but Abel 'writing in 1927 about 1900, he wrote 'epinephrine' [73]. Eventually, epinephrine with a terminal "e" became the accepted generic name in America.

Two decades later, when the patents of 'Adrenalin' were becoming invalid, another reason of using 'epinephrine' occurred in the Parke, Davis & Co. side. The background of this was described in detail in the following business mail dated November 19, 1921 (Table 2), from its president Mr. O.W. Smith to Takamine (page 165, Hormone Hunters, by Mitsuo ISHIDA, [81]).

**Parks, Davis & COMPANY
DETROIT, MICH.**

November 19, 1921.

Office of the President.

**Dr. Jokichi Takamine,
180 Broadway, New York City.**

Dear Dr. Takamine:-

A discussion developed yesterday in my office on the subject of the Adrenalin trademark. On the one hand it was urged that every trademark is perpetual, and on the other hand it was declared that the registration of Adrenalin expires within a year or two and that some months ago you recommended to Mr. Bartlett that it be renewed when the time came. Which view is correct? I am very much interested in the whole question and I wish it might be possible for me to see a copy of either your original application or a copy of the letter of registration granted you by the Patent Office. Won't you please have a copy made and sent to me ? Of course you understand I am not talking about the patent on the product, but solely about the registration of the name "Adrenalin" as a trademark.

I might say, incidentally, that the revision committee of the U.S.F. 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.

Very truly yours,

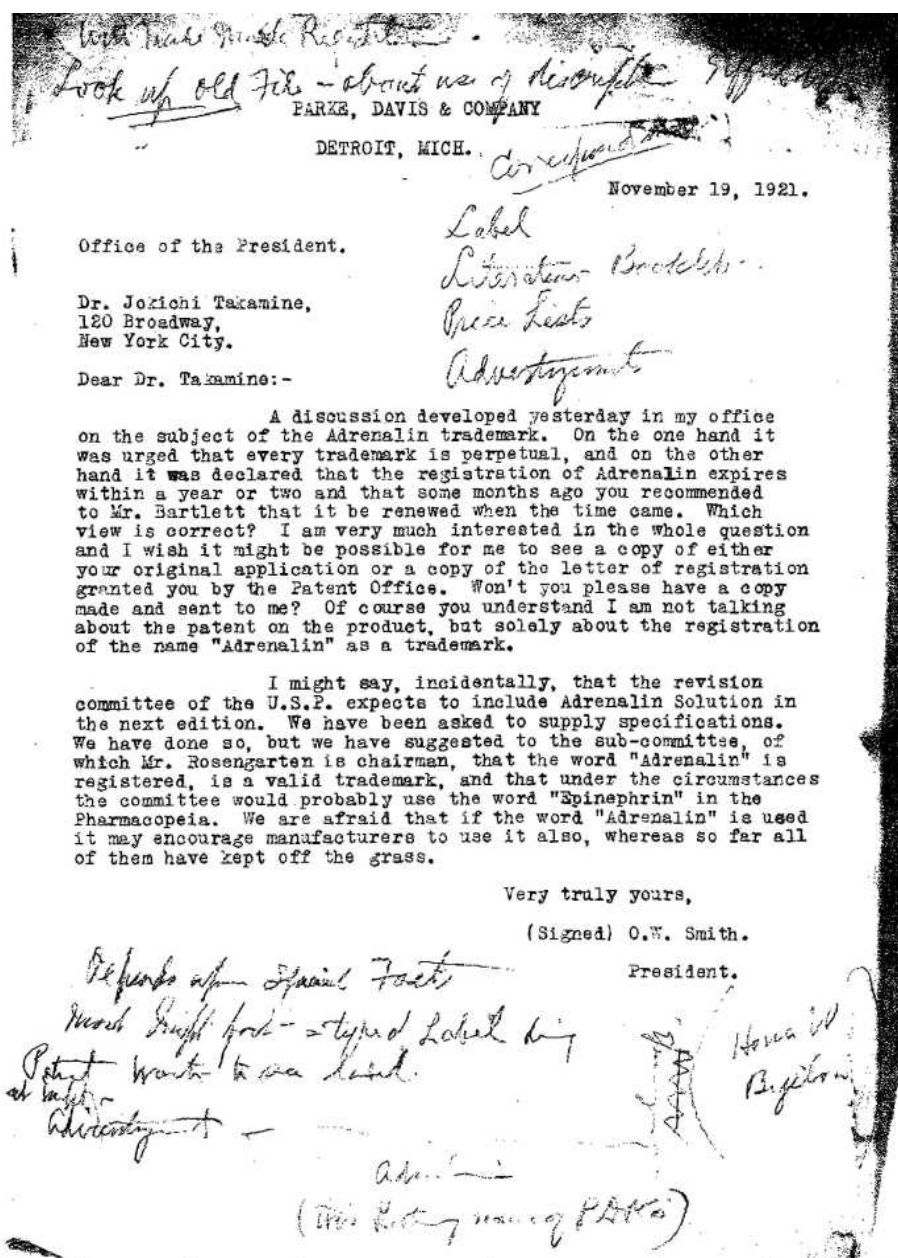
(Signed) O.W. Smith.

President.

In the early 1900s', there were many trade names for the products of the active principle of adrenal glands, i.e. in USA; Adnephtrin (Frederick Stearns & Co.), Adrenalin (Parke, Davis & Co.), Adrin (H. K. Mulford & Co.), Supracapsulin (Cudahy Co.), and Suprarenalin (Armour & Co.), while in Europe; Atrabalin, Chelafrinum, Epirenan, Hemostasin, Hemisine, Ischemin, Paranephrin (Merck), Renoform,

Supranephran, Suprarenaden, Suprarenin (Hoechst), Suprarenin synthetic, Tonogen and Vasoconstrictin. The name 'Suprarenin' later became one of the proprietary trade names for adrenaline marketed in a number of European countries. The editorial of the American Medical Association described as follows (The Propaganda for Reform, JAMA, [53]).

Table 2. Letter from the president O.W. Smith of the Parke, Davis & Co. to Dr. Jokichi Takamine on November 19, 1921. Handwritten letters by Dr. Takamine can be appreciated among the typewritten letters. (by the courtesy of Mr. Yutaka Yamamoto)



'Some years ago the Council on Pharmacy and Chemistry decided that it was necessary to adopt, in each instance, a generic term to designate those products that are on the market under two or more

proprietary names. When it came to the consideration of the various preparations of the blood-pressure-raising principle of the suprarenal gland which were on the market, it was necessary to establish some name that should be common to all of them. The name adopted was "epinephrin." This was selected in part because it was the name under which the preparation was first called to the attention of the profession of this country by Professor Abel, as will be mentioned later. Further, the name is one which is as appropriate for the preparation as any adopted by the various manufacturers, and is, in addition, easily learned. We doubt if any one will deny that the Council on Pharmacy and Chemistry, representing as it does the American Medical Association and the medical profession of the United States, has as much right to adopt a name for the preparation as has" any manufacturing firm.

.... When there are several, however, the adoption of one proprietary name as a generic term for that whole class of products is an injustice to all the other products in that class. Moreover, in the inevitable confusion that results, science is sacrificed to commercialism....

.... When the same substance is actually marketed and used under several distinctive trade-names, it becomes necessary to use a generic name when speaking of properties of the substance which are common to all "brands." This is the intent of most scientific and medical writers on the suprarenal base, and when the word "adrenalin" is used by medical writers, it is generally meant in the generic, and not in the distinctive sense. Since the name "adrenalin" is protected, it should not, and properly cannot, be used in this way. The name "epinephrin," since it is not monopolized, is not only the best, but also the sole name which can be rightly applied to the suprarenal base, in the generic sense.

The general manager of Parke, Davis & Co. protested against this unfair manner of the editor. ' He knows, you know, that there is no such thing on the market as epinephrine, and that Dr. Melland used our product, adrenalin; that over 90 per cent. of all clinical work done with the active principle of the suprarenal gland is done with our preparation, adrenalin, and that it is equally unfair to your readers and unfair to the manufacturer to deliberately substitute any other name—just as wrong as it would be for a druggist to substitute any other product. You know that there is no such thing on any market as epinephrin. And yet you try to deprive us of the credit which is fairly ours.'

Currently, both the WHO non-proprietary name and the United States approved name are 'epinephrine'. On the other hand, its approved name in other Western countries is 'adrenaline'. In 2004, Japan issued a commemorative stamp showing his face with a superimposed representation of the adrenaline molecule (Fig. 4-A). In 2006, in honor of Takamine, Japan (Nippon) decided to change its official name for the drug from 'epinephrine' to 'adrenaline'. Nowadays, the word "Adrenaline" is widely used in the United States to connote excitement, danger, thrills and emotions. "Epinephrine" is simply a drug. It is likely that 99.99% of Americans would not know that adrenaline and epinephrine represent the same chemical. Fig. 4-B [82] illustrates that the word 'Adrenaline' now appears frequently in a serious newspaper in this country, the New York Times. Up until the 1960s, adrenaline appeared in this newspaper only a few times each year; since that time, the number of citations has grown considerably without any indication of leveling off. The frequency of the word dramatically increased starting in the 1960s in stories about sports, emotions, mountain climbing etc, which has nothing to do with Takamine. Although very little is known to millions of visitors who have attended the annual National Cherry Blossom Festival in Washington, D.C., Takamine played a major role for presenting more than 3,000 cherry trees to the United States from Japan. As he did not want to offend anyone by offering a private donation, Takamine made all financial arrangements behind the scenes [83,56].

5. DISCOVERY OF SYMPATHETIC NEUROTRANSMITTER

5.1 Elliott's Original Hypothesis in 1904

Adrenaline, noradrenaline, and dopamine are all derived from the amino acid tyrosine, and are currently known as catecholamines, as they contain a catechol moiety and an amine side-chain (Fig. 4-C). In neurons catecholamines are confined to the vesicles, while in adrenal medulla they are stored in the chromaffin granules (Fig. 1-D). Due to the advent of electron microscope, it is currently well

known that about one fifth of the secretory granules in the adrenal medulla contains noradrenaline. But, in the early decades of the 20th century, nobody knew this. The prevailing view at that time was that of Oliver and Schäfer who maintained that adrenal medulla secreted tiny quantities of the active principle continuously [26]. In due course there came to light the curious correspondence between the effects produced by adrenaline and those produced by nerves of the sympathetic system.

After Adrenalin[®] became commercially available in 1901, British and American physiologists and pharmacologists used it for their experiments. One of the first and most thorough was Lan Thomas Renton Elliott, a postgraduate research student in Cambridge. He was able to conduct an extensive analysis of the comparative effects of Adrenalin[®] and sympathetic nerve stimulation. In his famous abstract published in 1904, he used the term 'Adrenalin' [77], which was gradually replaced in the scientific papers. After examining a variety of smooth muscle preparations and glandular tissues, he noticed the similarity between the pharmacological actions of adrenalin and the effects of sympathetic nerve stimulation. In a preliminary communication to the British Physiological Society in May 21, 1904, Elliott [77] introduced the concept of 'chemical transmission' into scientific lore, by concluding: *"Adrenalin might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery."* He made such brilliant suggestion that the sympathetic nerves produce their effects not directly, but by liberating a small quantity of adrenalin at the points where they end in contact with gland cells and muscle fibers. This suggestion was far in advance of the knowledge and the ideas at that time.

5.2 Consolidating Elliott's Seminal Hypothesis

After the structure of adrenalin had been determined to be rather simple, comprising of only 9 carbon atoms, a large number of chemists, physiologists, and pharmacologists studied the blood pressure-raising property of various sympathomimetic amines that are related to adrenalin. One of the compounds collected by George Barger, Dale's colleague in the WPRL, was *d,l*-aminoethylcatechol [84]. It had been synthesized by Stölz in 1904 [85], and was marketed under the trade name of 'Arterenol' by Farbenwerke Hoechst A.G. Years later it was called 'Noradrenalin'. Stölz succeeded to synthesize also 'adrenalin', and used this term in the paper although Hoechst company had already started to sell the adrenal active principle that was developed by Fürth [42-44] as '*Suprarenin*' from 1900 [85]. At the time noradrenaline was already available commercially and did not require its synthesis for the experiments. Studying the biological effects of various sympathomimetic drugs, Barger and Dale [84] found that adrenaline did not mimic all the actions of sympathetic nerve stimulation as one might expect if it were the transmitter, and that in fact certain amines of the ethanolamine series showed closer similarity in this respect. They overlooked the most physiologically relevant derivative noradrenaline, and missed identifying noradrenaline as the sympathomimetic transmitter. More than thirty years later, the concept of neurotransmission by Barger and Dale led to the discovery of noradrenaline by Ulf Svante von Euler.

Although Elliott failed to consolidate his early scientific contributions into a lasting legacy, his seminal work became a paradigm for the later studies in neuroscience. It was only later that Dale realized that Elliott had been correct in principle. This oversight permitted a major discovery in the chemical transmission to elude him. Until 1921, the physiological mechanisms involved in the transmission of signals across synapses were a subject of debates. The discovery of noradrenaline, as the sympathetic neurotransmitter, was a particularly important breakthrough in the early part of 20th century (Fig. 4-C). In the second decade of the 20th century, Dale lamented the "opportunities missed" to examine the analogs of adrenaline [86]. Used in the pharmacological experiments afterward, work went on for four decades before scientists realized that noradrenaline is a major neurotransmitter.

5.3 Discovery of Noradrenaline as a Neurotransmitter

Nowadays it is well-known that adrenaline and noradrenaline are the main actors of the human adaptation to the environment. In the last century, many scientists challenged to elucidate the role of noradrenaline in the sympathetic nervous system. However, it was not until the mid-1940s that von Euler used various pharmacological and chemical assays to differentiate noradrenaline from adrenaline, since both compounds were involved in the adrenal extracts. Because blood pressure of

the cats and rectal caecum of the chicken responded much more strongly to adrenaline than noradrenaline, von Euler used these two bioassay systems. A fluorometric technique, being developed in his laboratory, was also useful to independently measure adrenaline and noradrenaline. He observed that extracts of sympathetic nerves and organs innervated by such nerves acted differently from adrenaline but closely mimicked noradrenaline. Although many before postulated it, he was the first to demonstrate that noradrenaline is the main neurotransmitter in the sympathetic nervous system [87]. Three years later, he showed that noradrenaline is a constituent of the adrenal medulla [88].

The discovery of noradrenaline as the neurotransmitter at postganglionic sympathetic nerve endings positioned von Euler at the frontier of research in biogenic amines. Stimulation of the sympathetic nerves is nowadays well known to be closely related to the “fight or flight” response, which results in the secretion of corticosteroids by the adrenal cortex as well as the release of adrenaline and noradrenaline by the adrenal medulla and sympathetic nerves [89]. Cooperating with adrenaline and corticosteroids, noradrenaline helps to coordinate different body part responses for stresses. Noradrenaline is a neurotransmitter present in both the peripheral and central nervous system to regulate mood, arousal, learning and memory, blood flow, and metabolism [90,91]. von Euler’s contributions to the field of pharmacology [92,93] were recognized with the Nobel Prize in 1970, which was 70 years after the success of adrenaline crystallization by Takamine and Uenaka, and 66 years after the Elliott’s seminal hypothesis.

6. CONCLUSION

Since Parke, Davis & Co. in Detroit used the proprietary (trade or brand) name ‘Adrenalin’, epinephrine became the generic (approved or official) name in USA on the incorrect assumption that Abel’s extract was the same as Takamine’s adrenaline. Nowadays, however, neurons with adrenaline and noradrenaline as neurotransmitters are generally called adrenergic and noradrenergic neurons. Furthermore, the receptors on which adrenaline and noradrenaline act are classified internationally as adrenoceptors. The name adrenaline is preferred to epinephrine in most parts of the world. There is clear and abundant historical evidence that epinephrine is an inappropriate name to use. Furthermore, adoption of ‘epinephrine’ in the clinical practice will increase the risk of accidental misuse of ampoule labeled ‘ephedrine’ in emergencies. Accordingly, we should urge the World Health Organisation to change the international non-proprietary name epinephrine to adrenaline [94].

COMPETING INTERESTS

Author has declared that no competing interests exist.

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He is a clinical neuroscientist specialized in neuronal death, Alzheimer's disease, and adult neurogenesis. In 1975, he graduated from Kanazawa University Faculty of Medicine. In 1979, he completed his research diploma in the Kanazawa University Graduate School Medical Research Course (Doctor of Medicine). He then studied abroad in Germany and Sweden, including neuropathology and brain science. He became Chief of Medical Staff at Kanazawa University Hospital, Associate Professor of Kanazawa University Medical Faculty, and Director of Restorative Neurosurgery at Kanazawa University Graduate School of Medical Sciences. At present, he is the CEO of the Arimatsu Medical and Dental Clinic in Kanazawa city, and heads a special "higher brain dysfunction" outpatient clinic. In 1998, he proposed the "Calpain-Cathepsin Hypothesis" as a mechanism of neuronal cell death. He also discovered that the causative agent responsible for Alzheimer's disease is not amyloid β , but hydroxynonenal derived from ω -6 fatty acid-rich "cooking oil". He is the author of 210 published scientific papers in English, and 75 papers and 15 books in Japanese. He is also known to be an author of 'Cooking Oil makes Genius or Alzheimer!' which was published from Austin Macauley Publishers, London in 2017 (<http://www.austinmacauley.com/book/cooking-oil-makes-genius-or-alzheimer>). It is now ranked No. 2 of the worldwide Dementia Books. Recent researches with young physicians of Kanazawa University Hospital have led him to conclude that hydroxynonenal is also the real culprit of diverse lifestyle-related diseases such as obesity, type 2 diabetes, non-alcoholic steatohepatitis, etc.

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