Chapter 2

The Quest to Unravel the Mystery of the Adrenal Glands

The quest to unravel the mystery of the adrenal glands has a history that stretches back a very long time before Jokichi Takamine and Keizo Wooyenaka crystallized adrenaline from the aqueous extract of adrenal glands. Anatomical drawings from 16th century Italy accurately show the adrenal glands, so if we consider that period to be the starting point of the scientific history of the adrenal glands, then the quest has its roots in anatomy and pathology.

1. Searching in the dark

There is a considerable body of references and data relating to adrenaline; most of these begin with descriptions of Addison's disease. The story of Jokichi Takamine, which culminated in the successful crystallization of adrenaline, is no different.

Thomas Addison, who discovered this disease in the mid-19th century, made perceptive observations of anemia and diseases of the adrenal glands as a doctor, but he was not looking at the adrenal glands from the view point of endocrine physiology.

The first description of the adrenal glands appears in Leviticus 3:4 in the Old Testament. One theory holds that this was written around 333 BCE, during the time when Alexander the Great ruled over his empire (2-1); according to another theory, Leviticus was compiled much earlier, around 1,000 BCE (2-2).

The text describes the sacrifice of peace offerings, and the same description appears three times in Leviticus 3, once each for cattle, sheep, and goats, and once for calves in Leviticus 4: "Peace-Offering. The fat that cover the inwards, and all fat that is upon the inwards, and the two kidneys, and the fat that is on them, which is by the loins, and the *appendix* (see on iii. 4) upon the liver shall he take away. And the priest shall *burn* it upon the alter." (2-3). In this passage, "the fat that is on them, which is by the loins" is believed to refer to the adrenal glands (2-1).

Some scholars maintain that the next remaining record of the adrenal glands comes from around 200 years after the start of the Common Era. Claudius Galenus (L: Galenos in Greek, often called Galen) was the giant of medicine and pharmacy of the Greco-Roman era. He dictated his findings in Greek as he observed animal dissections, and these were recorded on papyrus. Seven of his treatises on dissection have been translated into German.

Galen gives these details of his observations of the veins in the vicinity of the kidney: “A twig from this not inconsiderable vein joins and connects with the spongy flesh (suprarenal gland) lying there. The second vein (renal) goes to this kidney itself.” Following this, he states that his findings from observation of the vicinity of the right kidney were clearly different from those of the left kidney (2-4, 2-5). While many of his ideas differ from present-day medical knowledge, Galen is recognized as the first person to describe the adrenal glands of mammals (2-1).

The first accurate illustration of the human adrenal gland that has been preserved was by the enigmatic anatomist Bartolomeo Eustachi [Figure 2-1], Professor of the Collegio della Sapienza in Rome (2-6, 2-7).

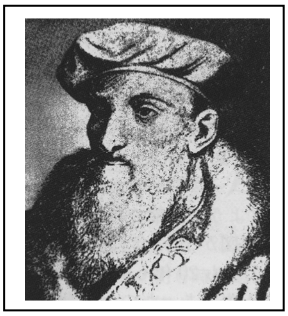

Figure 2-1. Bartolomeo Eustachi of Rome, the first person to accurately draw the adrenal glands. (Courtesy of the National Library of Medicine)

His human anatomy drawings, which he completed in 1552, include pictures of the kidney; blood vessels can be clearly seen connecting to a small gland tissue sitting on top of the broad bean-shaped kidney [Figure 2-2]. In his description, which was subsequently added in 1563, Eustachi appropriately named these the “*glandulae renibus incumbentes*” (glands lying on the kidneys), thus leaving for posterity his understanding that the adrenal glands are organs attached to the kidneys (2-1).

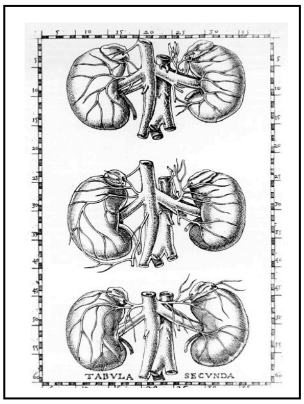

Figure 2-2. Bartolomeo Eustachi’s Figure 2. The blood vessels connecting to the kidney and the adrenal glands are clearly depicted (2-8). (Courtesy of HathiTrust).

Eustachi dedicated much of his life to producing copperplate engravings of the human anatomy, and in 1552 he completed 47 plates with the help of a relative, the artist Pier Matteo Pini. Of these, eight were published during Eustachi's lifetime. The remaining 39 plates were kept in the Vatican Library, and were published nearly 160 years later by Giovani Maria Lancisi as *Tabulae Anatomicae* in 1714 (2-8).

The beginning of the 17th century saw great advances in science, and these were accompanied by increased interest in discovering the functions of the kidney and the adrenal gland, which are organs shared by many higher animals.

First, in 1611 the Danish anatomist Casper Bartholin announced his findings that the adrenal glands were hollow organs filled with black bile, and he named them "*capsulae atrabiliarae*." The Bartholin family name is assured a place in medical history—Casper's son, Thomas, left a large body of work on the circulatory system, and Thomas' eldest son, Casper (the same name as his grandfather), discovered Bartholin's gland, a female genital organ.

The first anatomy book in Japan was the well-known *Kaitai Shinsho* (New Book of Anatomy), written in *kanji* characters and published in 1774. The author was Genpaku Sugita, who based his work on the *Tafel Anatomia*, an anatomy book that had been brought to Japan from the Netherlands, and which was itself a Dutch translation of the *Anatomische Tabellen* by the German Johann Adam Kulmus. Sugita had also referred to anatomy books by Casper and Thomas Bartholin, namely *Anatomicae Institutiones Corporis Humani* and *Historarium anatomicarum rariorum*.

Japan at the time was still in a state of national isolation, and trade was only permitted with a very limited number of countries. Because of this, the only clues to Western science, culture, and technology came from the cultural artifacts that were brought to Japan on Dutch ships. Few Japanese people understood European cross-wise writing, and Sugita even translated the names of foreign authors into *kanji* characters or the katakana syllabary (2-9).

Takamine and Wooyenaka, who were both born around a century later, must surely have read this book, deriving from it basic knowledge about the organ that they were to research and the scholars who had been pioneers in this field.

Incidentally, the way that "adrenal gland" is written in Japanese has changed with the times. The *kanji* characters that were used in the first edition of the *Kaitai Shinsho* had the meaning "small kidney," while the *kanji* used in the revised 1826 edition meant "side kidney." The *kanji* normally used today mean "auxiliary kidney."

Eventually in the West, medical scientists appeared who challenged the observation that the adrenal glands were hollow organs filled with black bile. These were the French anatomists Jean Riolan the Elder, and his son, Jean Riolan the Younger. They asserted that the adrenal glands were not hollow, but support groups of nerves on top of the kidneys (2-1).

An outstanding breakthrough of the time was the discovery of "the circulation of the blood" by the Englishman William Harvey in 1628. He made the discovery of an overall system in which blood courses through the whole body with the heart acting as a pump.

In 1656 the English anatomist Thomas Wharton finally announced a ground-breaking discovery. He was the first to make the connection between the function of the adrenal glands and the nearby nerve plexus. Wharton was greatly impressed by the fact that a small gland was provided with such a large nerve plexus, and he wrote that the adrenal glands receive some substance from the nerves, and pass this to the veins. This predated the present-day concept of neuro-endocrinology by about 250 years.

Numerous scholars, including Wharton's pupil, continued to research and discuss his discovery, but it was not until about 200 years later that Rudolf Albert von Kölliker gave the first complete description of the microscopic anatomy of the adrenal gland, as described later.

In 1785, about 130 years after Wharton put forward his idea, the German Johannes Christophorus Heino Schmidt described his view that endocrine principles were formed in the adrenal glands and were shed into the blood, aiding in the functioning of the heart (2-10). He wrote this penetrating insight in Latin—this was the *lingua franca* of European scholarship until the 18th century—and he passed away just two years later at the early age of 26. While the time in which he lived lacked the kind of rigorous experimentation we require today for a theory to be accepted, Schmidt has been hailed for his tremendous insight. Just four years after Schmidt's announcement, the revolution broke out in France (1785–), marking the start of republicanism.

2. The steady advance of anatomy and embryology

In 1805, a French scholar showed that the adrenal glands were tissues with solid interiors, and he discovered that they had a double-layer structure, with clear morphological differences between the central and outer regions. This was Georges Cuvier, who was a Professor of Animal Anatomy at the Muséum National d'Histoire Naturelle in Paris. Cuvier did not go as far as differentiating the adrenal medulla and the adrenal cortex with separate names, but he stressed that the functioning of the adrenal glands would likely be explained through comparative anatomical research.

Cuvier was a natural historian, a comparative anatomist, and also the father of paleontology. He served in a number of important positions in the government of the Napoleonic era. One of his pupils, Marie J. P. Flourens, taught a scientist by the name of Alfred Vulpian—thus it was the pupil of one of Cuvier's pupils who would later make the most important discovery in the history of research into adrenaline (2-11). Some 30 years later, Dr. Nagel left a record of how Georges Cuvier was examining the adrenal glands of female snakes (2-12).

Swale Vincent of the Physiological Laboratory of University College, London, took on the ideas of Georges Cuvier, and published four papers on his anatomical research on the adrenal glands of fish, amphibians, and reptiles. He subsequently published reports of his work on the adrenal glands of elasmobranch fish (sharks, rays, etc.), teleosts, and ganoids (2-13).

Sometime after Cuvier's discovery, Friedrich Arnold, the famous Professor of Anatomy of Heidelberg University in Germany, was carrying out embryological research into adrenal glands. In 1831, he showed that the adrenal glands developed from the Wolffian (mesonephric) bodies through the formation of a fissure (2-1). Friedrich Arnold's son, Julius Arnold, continued after his father with a conspicuous career as Professor and Director of the Pathological Laboratory at Heidelberg University, and he also worked on research into the chemistry of adrenaline. Julius Arnold was one of the joint discoverers of the "Arnold-Chiari malformation," one of the causes of hydrocephalus.

Robert Remark and Henry Gray continued the microscopic anatomical research of the adrenal glands, and subsequently in 1836, Dr. Nagel of Germany clearly divided the tissue of the adrenal glands into two types, proposing the terms "cortex" and "medulla" for them. This became the scientific terminology that is still in use to this day [Figure 2-3]. In his 19-page paper on the subject, he wrote the following: "*Die menschlichen Nebennieren bestehen bekanntlich aus seiner Rinden- und einer Marksubstanz; das Verhältniss der ersten zur letzten ist wie 1:2*" (The human adrenal gland is made, as is known, from its cortex and medulla; the ratio of the first to the last is like 1: 2). From the way he expresses this, it looks as though the differentiation into two areas may perhaps have been common knowledge among researchers of the time (2-12).

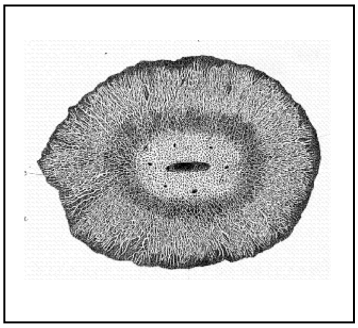

Figure 2-3. Diagram of an enlarged cross section of dissected sheep adrenal gland by Dr. Nagel (2-12).

It was the anatomist Rudolf Albert von Kölliker who announced an extremely important observation concerning the function of these two tissues, confirming the perceptive observations made by the anatomist Wharton some 200 years earlier (Wharton: 1656, Kölliker: 1852). Kölliker published his anatomical diagrams of the adrenal glands, made through microscopic observation, in 1852. In this work, he stated that the functions of the cortex and the medulla were clearly different—he confirmed that because the medulla is connected to a richly endowed nerve plexus, it must be an organ related to the nervous system. Kölliker had made an extremely important point here, but it appears that this was missed by Addison (2-1), a well-known researcher from the same period whom we shall introduce in the next section.

Kölliker, who was born in Zurich, Switzerland and educated in Germany, was later highly commended for his contribution to the field of anatomy, receiving the "Copley Medal" from Britain (see "In Brief 2-1"). The Copley Medal, which predates the Nobel Prize, honors natural scientists that have made a great contribution to their field [Note 2-1].

In Brief 2-1. The Copley Medal

The Copley Medal created by Sir Godfrey Copley is an award given by the Royal Society of London for "outstanding achievements in research in any branch of science, and alternates between the physical sciences and the biological sciences."

Medal-winners relevant to this book, and some others.

1731: Stephen Gray（English, electrical experiment）
1753: Benjamin Franklin（American, lightning rod）
1843: Jean Baptist Dumas（French, chemistry）
1864: Charles Darwin（English, the theory of evolution）
1874: Louis Pasteur（French, microbiology and stereochemistry）
1875: August Wilhelm Hofmann（German, organic chemistry）
1876: Claude Bernard（French, experimental physiology）
1892: Rudolf Virchow（German, medicine）
1897: Rudolf Albert von Kölliker（German, medicine）
1892: Rudolf Virchow（German, medicine）
1897: Rudolf Albert von Kölliker（German, medicine）
1902: Joseph Lister（English, disinfection before operation）
1919: William Bayliss（English, physiology）
1924: Edward Albert Sharpey Schäfer（English, physiology）
1927: Charles Sherrington（English, physiology）
1937: Henry Dale（English, physiology）

Note 2-1.
When Rudolf Albert von Kölliker was Professor of Histology at the University of Würzburg, he attended an academic meeting of anatomy in Berlin in 1889. There he heard a presentation by Santiago Ramón y Cajal (2-14) on anatomical findings of the cerebellum. He was so impressed by Cajal's specimens that he escorted Cajal back to his hotel and is reported to have said, "You discovered neuron synapses, and I discovered you."
Kölliker also had great respect for Camillo Golgi, who is famous for the Golgi staining method. Cajal and Golgi shared the Nobel Prize in 1906, "In recognition of their work on the structure of the nervous system. "

3. Addison's disease

Pathological research into the adrenal glands began in 1849. Thomas Addison was then a doctor at Guy's Hospital, a London hospital established by Sir Thomas Guy in 1712 on par with the celebrated St. George Hospital; at the request of the president of the South London Medical Society, he presented a paper titled "Anæmia: Disease of the Suprarenal Capsules" at a meeting of the society (2-15).

Addison presented three cases in which symptoms of languor had gradually become severe. He made no report of the specific symptoms of deposition of pigment in the skin and hypotension, and in fact did not know how to measure blood pressure. Nonetheless, during autopsies following death due to pulmonary tuberculosis, he noticed that there was disease of the adrenal glands, located immediately above the kidneys. However, he did not present any connection between anemia and abnormality of the adrenal glands. His report was published in the *London Medical Gazette* that year. This was an age in which pulmonary tuberculosis was greatly feared as an incurable disease.

Three hundred years after Eustachi first clearly showed the adrenal glands in his anatomical drawings in 1552, the glands were now shown to be important organs for the maintenance of human life. The date of this academic meeting, March 15, 1849, was seen as a historic moment for the science of endocrinology.

At this time, Britain was at the forefront of modern science. A generation or two before Addison's time, John Hunter, who had a checkered career as an anatomist, and his associates went as far as stealing dead bodies from the cemetery of well-known hospitals in their efforts to create the foundations of anatomy (2-16). Hunter's pupil, Edward Jenner, discovered that smallpox could be prevented with cowpox vaccinations, thus founding the field of immunotherapy (2-17).

Addison became completely convinced that this anemia was a unique syndrome six years after his initial presentation. Encouraged by his peers, he presented a comprehensive scientific report in 1855, titled *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*. His review described in detail 11 cases, of which six were patients that had contracted tuberculosis (2-18).

This was a momentous report, and while it stirred up considerable debate in England, and Scotland, it was given a very poor reception. John Hughes Bennett of Edinburgh, Scotland was opposed to recognizing this syndrome as a disease.

However, the famous clinician Armand Trousseau of the Hôtel-Dieu hospital in Paris judged the descriptions in Addison's work to be flawless, and named the syndrome Addison's disease (maladie d'Addison, morbus Addisonii) (2-19).

Meanwhile in Japan, in 1855, the year of Addison's scientific report, Jokichi Takamine was one year old. That year, his mother took him from his birthplace in Takaoka, Ettchu Province (present-day Toyama Prefecture), to Kanazawa, Kaga Province (the south of present-day Ishikawa Prefecture), where his father was a doctor working at a public clinic.

That same year, the Universal Exposition was held in the Champs-Élysées in Paris, attracting some 5.16 million visitors. This was a year in which modern civilization and culture were making great leaps.

The discovery of Addison's disease was of enormous importance from the point of view of the history of pathology. However, this disease was caused by abnormality of the exterior "cortex" of the adrenal glands; it had nothing to do with the interior "medulla" of the adrenal glands, which has completely different function from the cortex. It is the medulla that secretes the adrenaline with which we are concerned in this book [Note 2-2].

Note 2-2.
Two famous people are reported to have contracted Addison's disease: one was the English female author Jane Austen, the other was US President John F. Kennedy, who was assassined in 1963 (2-20). Jane Austen, who is famous for works such as *Pride amd Prejudice*, passed away aged 41 in 1817, when Addison had just started as a doctor in London; The presumed diagnosis for Austen is based on her symptoms. There have been differing opinions in recent years, and the cause of death is not definite.

4. What happens if the adrenal glands are removed?

Following on from Addison's discovery, the Frenchman Charles-Édouard Brown-Séquard carried out research aimed directly at the function of the adrenal glands. He presented a total of seven papers—two each in 1856 and 1857, one in 1858, and then later one each in 1892 and 1893—detailing research in which he showed the effects of removing the adrenal glands of animals. He demonstrated plainly that this organ has an important role in supporting the life of the organism (2-21 through 2-27).

The parts directly relating to adrenal glands in his papers can be summarized as follows. In his experiments, Brown-Séquard used dogs, cats, rabbits, mice, and marmots as experimental animals, removing the left, the right, or both adrenal glands. In one experiment, he used 66 rabbits to show that mortality was not an indirect result of the operative procedure. His experiments were on a massive scale, and with a level of detail that had hardly been seen to date. He showed that removal of the two adrenal glands resulted in death more quickly than removal of the kidneys on both sides.

Brown-Séquard performed this research while working under the physician Pierre Rayer, and he went about it with tremendous vigor. This approach to his work can be seen in his life history and in the following anecdote about him. This was at a time when Brown-Séquard was struggling to find work, traveling between France and the United States. In May1854 he returned to his birthplace, Port Louis in Mauritius, to find a massive outbreak of cholera that had claimed 8,000 victims—he immediately helped organize a response at a hospital. To determine whether or not opium was effective for treating cholera, he ingested material vomited by patients, and apparently nearly died from the dose of laudanum he took (2-28).

Brown-Séquard was born on April 8, 1817 on the island of Mauritius in the Indian Ocean. His father, Charles Brown, was an Irish-American naval officer from Philadelphia, and his mother, Charlotte Séquard, was a cheerful French woman. Unfortunately, his father died fairly soon after marrying when his ship sank. Like the great French physiologist Claude Bernard, Brown-Séquard first aimed to be a playwright, but realizing that he would be unable to gain recognition for his talents, he set his eye on becoming a doctor. He worked under the two greatest clinicians of the time, Armand Trousseau and Henri Louis Roger, until 1842, after which, like Bernard, he chose the path of physiological research rather than continuing his clinical training (2-29).

Even today, Brown-Séquard has a place in the history of medicine for his discovery of Brown-Séquard syndrome, a loss of sensation and motor function (paralysis and anesthesia) caused by the lateral hemisection (cutting) of the spinal cord. This rather strange but earnest character came to take an important part in our story some 33 years later, when he appeared in Paris.

Sometime after Brown-Séquard's research, the Italian Guido Tizzoni, who was Professor of General Pathology at the University of Bologna, published "Ueber die Wirkungen der Exstirpation der Nebennieren auf Kaninchen (On the Effects of Removal of the Adrenal Glands of Rabbits)" in a German journal of pathological anatomy in 1889. This paper was a huge research thesis with a tremendous amount of detail, running to 100 pages with 68 microscopic images of dissected organs in cross section (2-30). This paper included descriptions of the works of other Italian researchers in the same field, including Philippeaux, Foà, Pellicani, and Marino-Zuco.

It was a lengthy journey from Brown-Séquard's conclusion that the adrenal glands were essential to maintaining life until the final proof. Following on from Brown-Séquard's work, some 14 leading physiologists carried out experiments under a great variety of experimental conditions—different animal species were used, the glands were removed at different ages or different times, and left, right, or both glands were removed—and there was considerable dispute among the researchers over the interpretation of the results. In one experiment, it was found that if the lower part of the left adrenal gland of rabbits was ligated, a compensatory action came into play and the rabbit would become obese, sometimes almost doubling its body weight (2-31).

The final determinant was apparently a scientific report by Strehl and Weiss in 1901, which described experiments using 114 animals. This was 45 years after Brown-Séquard's paper was first published (2-32).

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The tiny organs on top of the kidneys had puzzled people since ancient times. Medical scientists and physiologists noticed that these organs were likely linked to disease, and they established that removing these organs had a more lethal effect than removing the far larger kidneys. The spirit of enquiry that had led these researchers in their earnest quest to discover the function of the adrenal glands was starting to bloom.

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