

Links Between Nerves and Glands: The Story of Adrenaline



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After the discovery of adrenaline, the rudimentary ideas of neurotransmission were developed in the 20-year period 1890-1910. It is entwined with the concept of neural transmission by humoral substances initiated in 1656 by Thomas Wharton and by Glisson, who associated the adrenal glands with nerve plexuses. How this linkage functioned was unknown until Claude Bernard showed that adrenal glands produced 'secretions internes' affecting the milieu intérieur.

John Jacob Abel in 1899, and, independently, Jokichi Takamine in 1901, isolated a suprarenal extract that elevated blood pressure. Three years later Thomas Renton Elliott observed that from the adrenal medulla, a substance could be produced (i.e. adrenaline), whose effects resembled closely those of the sympathetic nervous system, thus echoing Wharton's conclusions. In the 20th century, George Oliver, Edward Schäfer and Henry Dale were to clarify the physiology and show the way for clinical applications of adrenaline.

So well known is adrenaline that the word has passed into common language as an inaccurate metaphor for a burst of anger, energy, or excitement. The discovery of adrenaline was entwined with the new but crucial concept of neural transmission by chemical (humoral) substances (Table 1). This discovery was the essential precursor of the modern neurotransmitter chemistry, necessary for the understanding of neural functions throughout the nervous system. First, the important historical background.

Anatomical links between glands and nerves

Thomas Wharton (1614-73) (Figure 1) was physician to St. Thomas' Hospital, London. In 1656 with remarkable prescience he associated the proximity of the adrenal glands with nerve plexuses: in Chapter 16 of his 1656 text, '*Glandulae renales vel ad nerveum plexum abdominis sitae, earum usus*' (p94), he writes:

"Glandulae ad plexum, certo possumus statueri, non esse materiam plane excrementitiam, sed utilem, quia in venas perpetuo recipitur ..."

Translated: ('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').^{2,3}

Wharton and Francis Glisson (1597-1677),⁴ reached similar conclusions concerning the glands and their functions: "*De actione et usu Lymphae ductuum sive canalium aquosorum*". His account that postulated the adrenals take a substance from nerves and transfer it to veins preceded

Table 1. Adrenaline: time line

1552	Eustachius published plates showing adrenal glands.
1656	Wharton associated adrenal glands with nerve plexus.
1852	Kölliker described microscopic anatomy: an apparatus appertaining to the nervous system.
1894	Oliver and Schäfer described pressor effect of adrenal medulla.
1896	Cybulski and Szymonowicz also described pressor effect.
1901	Epinephrine discovered independently by Abel and Takamine.
1901	John Newport Langley founded concept of 'receptors'.
1902	Alfred Kohn identified chromaffin cells.
1904	Stolz synthesized adrenaline.
1904	Elliott, showed sympathetic nerves produce their effects by liberating adrenaline.
1906	Henry Hallett Dale insisted on name 'Adrenaline'.
1910	Barger and Dale: sympathetic nerve stimulation more closely mimicked the effects of sympathomimetic primary amines than the effects of adrenaline.
1911	Walter B. Cannon and de la Paz showed that anger or fear are associated with adrenaline released in the blood from a cat's suprarenal vein.
1921	The transmission of the effects of nerve impulses, by the release of chemical agents, first became an experimental reality (Dale).

ed the neuroendocrine concept of the adrenal medulla as an anatomical-physiological nexus. Some 300 years later, at the beginning of the 20th century, it was generally thought that nerve impulses acted directly on the muscles or glands. Not until 1921, was it known how the stimulation of a nerve directed the workings of the tissues or organs it supplied.

These were groundbreaking ideas that contributed to the emergence of endocrinology: the control of peripheral organs and tissues by glandular secretions, which contribute to the maintenance of homeostasis. The concept of homeostasis began in 1855 when Claude Bernard postulated that all organs liberate special substances

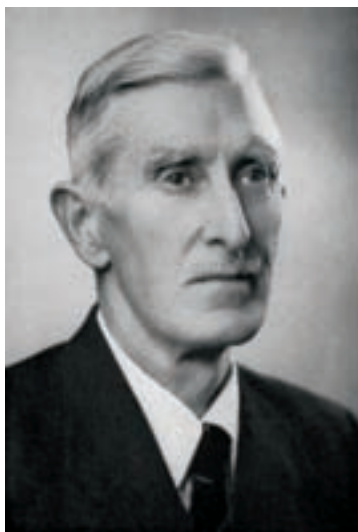


Figure 1. Thomas Wharton MD, FRCP (above left) and Thomas Renton Elliott, MD,FRS (above right).

into the tissue fluids – later called hormones (a word first suggested by Sir William Bate Hardy, a Cambridge physiologist.) – which maintained the constancy of what Bernard named, the *milieu intérieur*.⁵ Then came proof that endocrine glands secreted humoral substances that determined function or dysfunction in various tissues. Jacob Henle (1809-1885) in 1841 first recognised ‘ductless glands’, which secrete directly into the blood; this predated Claude Bernard who stated in 1855 that the adrenal glands produced ‘secretions internes’.^{6,7} In the same year Thomas Addison published his famous monograph: *On the constitutional and local effects of disease of the suprarenal capsules*,⁸ although, he did not mention a secretory role, nor any vital humoral factor stemming from the adrenals. It was the neurologist, Charles Édouard Brown-Séquard (1817–1894), who truly founded the vital function of the adrenal glands. On 25 August 1856 he reported to the Académie des Sciences in Paris that removal of both adrenal glands in cats, dogs, rabbits guinea pigs and mice was fatal, usually within 12 hours; but blood from a healthy animal injected into the veins of an animal deprived of its suprarenal bodies prolonged its survival.⁹ He had clearly demonstrated the vital humoral factor (cortisol) generated by the adrenals

Adrenal anatomy

The history of adrenaline started with the anatomical discovery of the adrenal glands in 1552 by Eustachius (?-1574). The Danish anatomist Caspar Bartholinus (1655-1738) called them *Glandulae renibus incubentis* and believed they were hollow and filled with black bile – *Capsulae atrabiliariae* – but George Frederic, Baron Cuvier (1769-1832) established in 1805 that they were solid and he distinguished the medulla from the cortex. Nagel in 1836 noticed that the human adrenal gland is composed of a cortical (Rinden) and medullary (Mark) substance;¹⁰ he provided

their name – adrenal glands. Rudolph Albert Von Kolliker (1817-1905), Swiss anatomist and physiologist, described their microscopic appearances in 1852.¹¹ He considered

“the cortical and medullary substances as physiologically distinct.... The former may, provisionally, be placed with the so-called ‘blood-vascular glands,’ and a relation to secretion assigned to it; whilst the latter, on account of its extremely abundant supply of nerves, *must be regarded as an apparatus appertaining to the nervous system, ...*” (my italics).

Thus, Kölliker confirmed and developed Wharton’s earlier ideas. In 1831, Philipp Friedrich Arnold (1803-90) thought that the adrenals developed from the embryonic mesonephros (Wolffian bodies), which they resembled. In a remarkable series of articles, Robert Remak (1815-1865) provided a vital link, showing that the adrenal medulla developed in the embryo along with the sympathetic ganglia.¹²

Chromaffin cells

In 1902, Alfred Kohn in Prague had identified the chromaffin cells, derived from the neural crest and intimately associated with the sympathetic nervous system.¹³ He found an unidentified substance in the adrenal medulla reacted with chromium salts to produce a brownish colour.¹⁴ He thus created the term chromaffin cells.¹⁵ A common sympathetic-adrenal progenitor cell for chromaffin cells and sympathetic neurons was postulated. Gradually the common embryology was demonstrated between chromaffinomas and the catechol-producing tissues of the adrenal medulla, sympathetic nerves, and ganglia. In 1904 Friedrich Stolz, and in 1905 Dakin synthesized adrenaline. Phaeochromocytomas were identified by Frankel in 1885, but were first named in 1912 by Ludwig Pick, who noted the diagnostic chromaffin reaction of the tumour cells.

But not until 1946 did von Euler showed that purified extract of sympathetic nerves pro-

duced the same effects as demethylated adrenaline (Noradrenaline), which he deduced was the sympathetic transmitter.

The idea that chemical substances stimulated nerve transmission was indicated in the late 19th century. Du Bois Reymond’s¹⁶ in 1877 observed

“Of known natural processes that might pass on excitation, only two are, in my opinion, worth talking about: either there exists at the boundary of the contractile substance a stimulatory secretion in the form of a thin layer of ammonia, lactic acid, or some other powerful stimulatory substance; or the phenomenon is electrical in nature“

Adrenal extract: clinical significance

In 1895, nine years before Stolz synthesised adrenaline (C₉H₁₃NO₃) (Figure 2) in 1904,¹⁷ the pharmacological effect of adrenal extract had been shown by George Oliver MD, FRCP (1841-1915), a Harrogate physician, born in Middleton-in-Teeside. His experiments, remarkably conducted in a small Yorkshire spa town, using suprarenal glands obtained from his local butcher, led him to conclude:

The suprarenal capsules yield to water (cold or hot), to alcohol or to glycerine, a substance, which exerts a most powerful action upon blood vessels, upon the heart, and upon skeletal muscles... The effect upon the blood vessels is to cause extreme contraction of arteries, so that the blood pressure is enormously raised.¹⁸

He visited Edward Albert Schäfer FRS, (1850–1935), Professor of Physiology at Edinburgh, then at University College London, Carmichael recalls: “The classic story of this breakthrough puts George Oliver and Edward Schäfer at centre stage”.¹

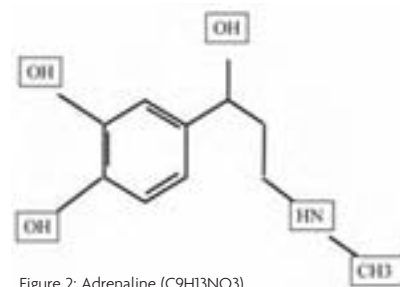


Figure 2: Adrenaline (C₉H₁₃NO₃).

Sir Henry Dale engagingly described the discovery of Oliver (1841-1915) and Schäfer:¹⁹

“Dr. George Oliver, a physician of Harrogate, employed his winter leisure in experiments on his family, using apparatus of his own devising for clinical measurements. In one such experiment he was applying an instrument for measuring the thickness of the radial artery; and, having given his young son, who deserves a special memorial, an injection of an extract of the suprarenal gland, prepared from material supplied by the local butcher, Oliver thought that he detected a contraction or, according to some who have transmitted the story, an expansion of the radial artery. Whichever it



Figure 3: left to right: JN Langley, FRS, Jokichi Takamine, Sir Henry Hallett Dale, MD, FRS.

was, he went up to London to tell Professor Schäfer what he thought he had observed, and found him engaged in an experiment in which the blood pressure of a dog was being recorded; found him, not unnaturally, incredulous about Oliver's story and very impatient at the interruption. But Oliver was in no hurry, and urged only that a dose of his supra-renal extract, which he produced from his pocket, should be injected into a vein when Schäfer's own experiment was finished. And so, just to convince Oliver that it was all nonsense, Schäfer gave the injection, and then stood amazed to see the mercury mounting in the arterial manometer till the recording float was lifted almost out of the distal limb.

Thus the extremely active substance formed in one part of the suprarenal gland, and known as adrenaline, was discovered. And in due course there came to light the curious correspondence between the effects produced by this potent substance and those produced by nerves of the so-called sympathetic system; and Professor TR Elliott, then a post-graduate research student in Cambridge, was led to make the brilliant suggestion that these sympathetic nerves produce their effects by liberating small quantities of adrenaline at the points where they end in contact with muscle fibres and gland cells.⁷

Carmichael 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."⁷

Oliver and Schäfer collaborated, to show that when the suprarenal extract was injected into anaesthetised animals there was a marked vasoconstrictor effect which caused a rise in blood pressure. They presented their results to the Physiological Society²⁰ and raised the possibility of using adrenaline to achieve haemostasis, and in Addison's disease.²¹ However, the extract had no name until John Jacob Abel (1857-1938) at Johns

Hopkins' prepared adrenal extracts in 1897 and called them 'epinephrin',^{22,23} whilst others used the term 'suprarenin'.

An important parallel discovery was made by Napoleon Cybulski (1854-1919)²⁴ at Krakow, who in 1896 published the effects of extirpation of the adrenal glands in anaesthetised dogs. His assistant, Wladyslaw Szymonowicz (1869-1939) removed the left adrenal of a dog on 17 December 1894, and 12 days later removed the other adrenal. The dog's "blood pressure fell from a control value of 145/98 to 12/3 in the next 10 hours." When Szymonowicz injected an aqueous extract of adrenal glands, the blood pressure rose to 130/104 and the heart rate fell.²⁵ This complemented the clinical experiments of Oliver and Schäfer. Davenport²² perhaps surprisingly, attributed this massive fall in BP to acute hypoglycaemia resulting from acute adrenalectomy.

The discovery of Suprarenal extract

In parallel with these physiological discoveries, John Jacob Abel (1857-1938) in 1899, and independently, Jokichi Takamine (1854-1922) (Figure 3) in 1901 isolated a suprarenal extract that elevated blood pressure. In 1900 the Japanese chemist Takamine, after visiting Abel's laboratory, with Keizo Uenaka purified the extract,²⁶ since he realized Abels' preparation was contaminated by a benzoyl derivative whose physiological actions were not those of pure adrenaline. Takamine patented his techniques with Parke, Davis & Co. who marketed the pure crystalline substance as Adrenalin. His patent application on November 5, 1900, was entitled "Glandular extractive product on a blood pressure raising principle". He named the crystalline substance "Adrenalin" But commercial controversy was to erupt. Walter Dowson, Director of Wellcome Physiological Research Laboratories, founded in 1895, suggested instead that the word Epinephrine should be used. The recently appointed Henry Hallett

Dale (1875-1968) became inextricably involved. Dale had been at University College as Sharpey Scholar for only six months before he was appointed as pharmacologist to the Wellcome Laboratories in 1904, where he became Director in 1906. But Dale insisted that British physiologists used the name adrenaline to describe the active principle of the adrenal glands, and did not imply a specific commercial preparation. He considered epinephrine inappropriate and inaccurate, and refused to use it instead of Adrenaline.²⁷ After protracted debate in which Wellcome's commercial interest was questioned, Dale prevailed: adrenaline was the name to be established in Britain.

Meanwhile, in 1904, Thomas Renton Elliott (1877-1961), MD, FRCP, FRS (Figure 1) later, Professor of Medicine at University College, London, advanced understanding of the mechanism. In a series of animal experiments on contraction of the ileocolic sphincter and bladder, he observed that from the adrenal medulla, a substance could be produced (i.e. adrenaline), whose effects resembled closely those of the sympathetic system. Elliott, in keeping with Wharton, deduced that the impulses in the sympathetic nerves released adrenaline in the nerve endings, which would then be the real vehicles of the stimulation effect.²⁸ For a detailed biography and account of Elliott's experiments see Henry Dale's Obituary notice in Biographical memoirs of Fellows of the Royal Society, Volume 7 - 1 Nov 1961; Pages 52-74.

Physiology and pharmacology

These salient physiological and pharmacological observations were made before the clinical significance of adrenaline was fully elucidated. (*vide infra*).

The Cambridge physiologist, John Newport Langley, FRS (1852-1925) (Figure 3) between 1905-12, gave the first scientifically founded concept of receptors. He cut the preganglionic sympathetic fibres in a cat and allowed them

to degenerate. He saw that

"application of warm 1 p.c. nicotine to the deafferented ganglion produces effects like those produced by brief stimulation of its pre-ganglionic fibres, ... it follows, I think, that nicotine does not stimulate nerve-endings of pre-ganglionic pilomotor fibres, and it is probable that it does not stimulate the nerve-endings of any pre-ganglionic fibres.

"In other words, nicotine, and by extension other drugs, act directly upon the cells of the ganglion."

He then cut the nerves to leg muscles of chickens. After axon endings on the muscles had degenerated, injection of nicotine still caused the muscles to contract and injection of curare blocked the action of nicotine. He concluded:

"all cells contain two constituents: (1) substances concerned with carrying out the chief functions of the cells, such as contraction, secretion, the formation of special metabolic products, and (2) receptive substances especially liable to change and capable of setting the chief substance in action. Further, that nicotine, curare... as well as the effective material of internal secretions produce their effects by combining with the receptive substance, and not by an action on axon-endings if these are present, nor by a direct action on the chief substance."²⁹

Adrenergic and cholinergic transmission

Ten years after Elliott's researches, Sir Henry Dale (1875-1968) (Figure 3) played a crucial role in developing adrenaline.³⁰ With his friend

Otto Loewi (1873-1961), Dale also investigated acetylcholine, which they found related closely to the effects of the parasympathetic stimulation – succinctly summarised in Loewi's Nobel lecture – *The Chemical Transmission of Nerve Action*. Until that time, acetylcholine had not been isolated and could not be considered as a transmitter of nerve impulses. Dale and Loewi later demonstrated its crucial neurotransmitter role, for which they shared the Nobel Prize of 1936. Dale proposed the terms "cholinergic" and "adrenergic" to describe fibres by the kind of chemical (rather than the chemical itself) they might use... "to assist clear thinking".³¹

Further clarification came when in 1948, Raymond Ahlquist (1914-83), an American pharmacologist, writing about adrenergic nervous transmission,³² proposed that different receptors, not different molecular modifiers, caused different tissue responses. These specific receptors for epinephrine and norepinephrine, he localised to different tissues; they were named alpha and beta-receptors.

Transmission of nerve impulses

In his Nobel Lecture, December 12, 1936, entitled: *Some Recent Extensions of the Chemical Transmission of the Effects of Nerve Impulses*, Sir Henry Dale elucidated its physiology:

"The transmission of the effects of nerve impulses, by the release of chemical agents, first became an experimental reality in 1921. In that year Otto Loewi published the first of the series of papers from his laboratory, which... established all the principal characteristics of

this newly revealed mechanism, so far as it applied to the peripheral transmission of effects from autonomic nerves to the effector units innervated by them."³³

Dale's own work had been principally concerned with ergot alkaloids but his move to Wellcome laboratories prompted his immediate involvement with adrenaline. But by 1910, Barger and Dale showed that sympathetic nerve stimulation more closely mimicked the effects of sympathomimetic primary amines than the effects of adrenaline,^{34,35,37} they just missed identifying noradrenaline as the sympathomimetic transmitter. Dale went on to become a world-renowned clinical pharmacologist, rewarded by the FRS in 1914 and with Loewi, by the Nobel Prize in 1936.

Walter B Cannon (1871-1945) and de la Paz³⁴ developed the physiological studies of adrenaline, highlighting its role in the "subjugation of the viscera to sympathetic control" and "the emotion of anger or fear associated with the appearance of adrenaline in the blood from a cat's suprarenal vein."

In summary, the story of adrenaline highlights the fundamental principles of neural transmission by humoral substances. The isolation and physiology of adrenaline by Abel, Takamine Stolz, and Elliott in the brief period: 1890-1910 followed the concept of neural transmission initiated in 1656 by Thomas Wharton. The clinical physiology, elegantly revealed by George Oliver and Edward Schäfer was further investigated and developed by Sir Henry Dale and others, who showed the way to its widespread clinical utility. ♦

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