

## STARLING REVIEW

# Ernest Starling and 'Hormones': an historical commentary



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### Abstract

One hundred years ago Ernest Starling (1866–1927), almost surreptitiously, slipped the word 'hormone' into the English language. This review, beginning in the middle of

the nineteenth century, attempts to trace the growth of ideas in endocrinology up to this important moment.

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### Introduction

There is no magic date from which to begin a survey of endocrinology, for man has made use of endocrinological principles from time immemorial. Fuller Albright (1943) observed 'The earliest beginnings of endocrinology had as their *raison d'être* such ends as the procurement of a form of man-power safe for the harem, the salvaging of a male soprano voice for the choir, and the increased palatability that a rooster attains when he turns into a capon.' The middle of the nineteenth century finds an awareness of glands that had no ducts, glands that communicated only with blood vessels (Blütdruesen; blood-glands). But it was a purely anatomical description, and most authors of the time included the thyroid, lymph nodes, thymus, suprarenals and spleen in the collection of blood-glands. With a little imagination, it was possible to find a function for them: W B Carpenter, in his '*Cyclopedia of Anatomy and Physiology*' (1852), wrote that 'the products [of the glands] destined to be restored to the circulating current, apparently in a state of more complete adaptiveness to the wants of the nutritive function . . . glands concerned in the assimilation of the materials that are destined to be converted into organized tissues, instead of being the instrument of the matters which result from the disintegration or decay of the tissues.' This seems to be a sort of intuitive groping towards an endocrine control of intermediary metabolism.

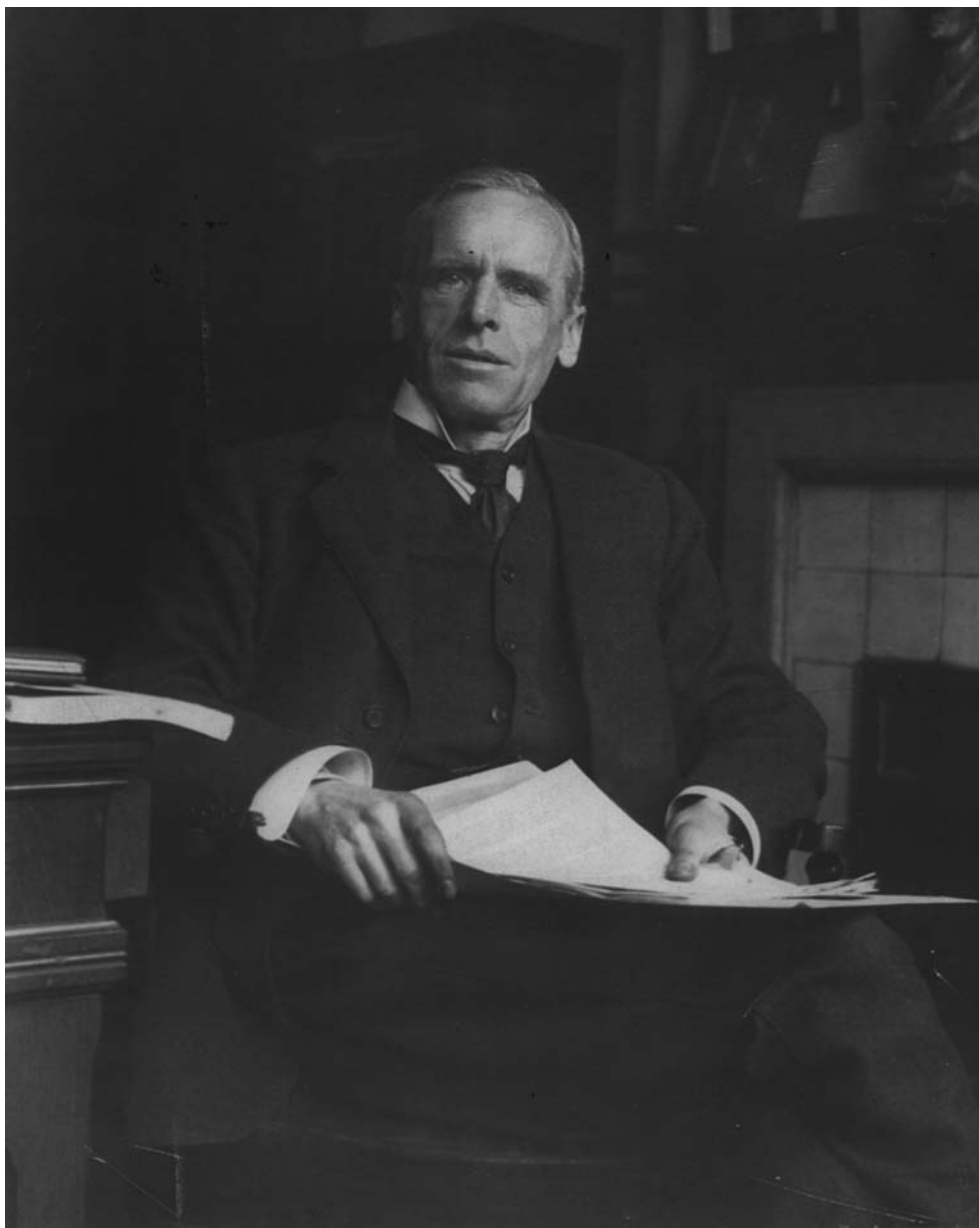
Claude Bernard, in 1855, is usually held responsible for the term 'internal secretion', a phrase that he used to describe the release of glucose from liver glycogen. It is likely that the phrase existed in the French and German literature long before Bernard (Medvei 1982), but Bernard's demonstration was so convincing and clear-cut

that he is given the credit for 'internal secretion'. Unfortunately, the rest of the world borrowed the expression, and used it for the passage of any molecule (including carbon dioxide) from tissues into blood (see information on Schäfer below).

Disordered function of the blood-glands was first described from careful clinical observation. Thus, Thomas Addison (1855) described a syndrome that he associated with disease of the suprarenal glands, with the patients suffering from weakness, vomiting and skin pigmentation. When the London Medico-Chirurgical Society would not publish his findings in its *Transactions*, poor Addison – a manic depressive – committed suicide. The Anglo-French-American physician, Charles Brown-Séquard (of whom more later) demonstrated that removal of the adrenals in experimental animals was invariably fatal; no distinction was drawn between adrenal cortex and medulla at that time.

In the 1870s, syndromes associated with over or under activity of the thyroid gland were described and a host of eponyms came into being, describing many aspects of human thyroid disease. But biochemistry hardly existed, so no chemical rationale could be offered for either adrenal or thyroid disorders.

Brown-Séquard (who was simultaneously on the staff of the Hospital for Nervous Diseases at Queen Square and a Professor of Medicine at the Collège de France) proposed that testicular extracts had a rejuvenating effect in man, for he had tried them on himself (he was 72 at the time). He went on to claim that almost any sort of illness would respond to testicular extracts; moreover, every organ in the body produced an agent with a possible therapeutic use. An article about him in the *British Medical Journal* was appropriately called 'The Pentacle of Rejuvenescence',



**Figure 1** Ernest Starling photographed in his office in UCL around 1921. The three-piece suit and the wing collar were his uniform throughout the 1920s.

‘Pentacle’ being a symbol used in magic (Annotation (anonymous) 1889). But Brown-Séquard’s bizarre ideas were made respectable by giving them a title, ‘organotherapy’, and it seemed to be welcomed by physicians on both sides of the Atlantic. In 1891, Victor Horsley, a pioneer neurosurgeon, and his pupil, George Murray, showed that hypothyroid (myxoedematous) patients could be successfully treated with thyroid extracts – a landmark in real endocrinology. Brown-Séquard saw this as a vindication of his ideas. He wrote in the *British Medical*

*Journal* in 1893: ‘The great movement in therapeutics as regards the organic liquid extracts has its origin in the experiments which I made on myself in 1889, experiments which were at first so completely misunderstood’[!] (Brown-Séquard 1893). In the market place, organotherapy extracts borrowed a ride alongside more respectable animal products, such as thyroid extracts, and tetanus and diphtheria antitoxins. Fortunately, by the turn of the century organotherapy had virtually disappeared (Borell 1976).

It is possible that Brown-Séquard's obsession with tissue extracts actually had some benefit. Thus in 1893, George Oliver, a spa physician working in Harrogate, was making extracts of adrenals, believing that they might raise blood pressure and be of use in patients with low blood pressure. (It is not clear *why* Oliver believed there to be a connection between the adrenals and blood pressure – an important gap in the story.) He gave some extract to his own son, and using a device of his own invention (an 'arteriometer') showed that his son's brachial artery narrowed under the influence of the injection. Unfortunately, Oliver did not have a blood pressure measurer, so he took some of his extract to Edward Schäfer, Professor of Physiology at University College, London (UCL). We have a description of the meeting from Henry Dale: 'Oliver went 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 adrenal 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 manometer 'til the recording float was lifted almost out of the distal limb . . .' (Dale 1948).

Schäfer was perhaps the first serious laboratory scientist to involve himself with the endocrine system. He and Oliver studied, in detail, the effects of adrenal extracts on blood pressure; it was the adrenal medulla (not the cortex) that gave rise to the pressor effect. They went on to show (in 1895; Schäfer 1895) that extracts of the pituitary caused a rise in blood pressure, and thyroid extracts caused a fall. Schäfer was sceptical about clinical observation as a basis for the science of endocrinology, and had little time for Brown-Séquard's fantasies.

In an important address to the British Medical Association in 1895, he gave a contemporary review of all that was known about internal secretions. But it seems that organotherapy had somehow kept its hold, for we find: 'Every part of the body does, in fact, take up materials from the blood, and does transform these into other materials. Having thus transformed them, they are ultimately returned into the circulating fluid and in that sense every tissue and organ of the body furnishes an internal secretion.'

He went on to give precise summaries of what was known of the internal secretions of the pancreas, liver, thyroid, pituitary, and (naturally) adrenals. He made no mention of the testes or ovaries. Schäfer was, incidentally, known as a man with rather a short fuse, and his 'Internal Secretions' address must have been given in rather a strained atmosphere, for a footnote says: 'Professor Schäfer intended to illustrate his address by lantern slides, but the hall being unsuitable for this, he gave his audience a good idea of his meaning by tracing the curves with his finger.'

## The arrival of Starling

In 1899, Schäfer left UCL for the chair of physiology at Edinburgh. It is not clear why he did this, although it might be relevant that the change more than doubled his salary. The new professor at UCL was Ernest Starling, then aged 32. Starling had just been elected to the Royal Society for his work on the formation of lymph; he showed that the outward hydrostatic forces in the capillary were opposed by inward osmotic forces brought about by plasma proteins ('Starling's Principle'). Figure 1 is a formal portrait of him, taken some years after the research described here.

Starling and his brother-in-law, William Bayliss, were compulsive experimenters. At UCL, in the first years of the century, they investigated the innervation and movements of the small intestine, and made the first serious descriptions of peristalsis. While investigating the innervation of the pancreas and duodenum (Bayliss & Starling 1901, 1902) they were repeating Pavlov's experiments on the nervous control of the gut (he was awarded a Nobel Prize for this work in 1904). Pavlov believed that pancreatic secretion was solely controlled by the vagus; when acid gastric contents passed into the duodenum, vagal afferents in the duodenal wall passed to the brain, and vagal efferents returned to the pancreas, stimulating the secretion of pancreatic juice into the duodenum. Bayliss and Starling carefully dissected away all the nerves that accompanied the vessels supplying the pancreas and duodenum. They then put acid into the duodenum, and pancreatic secretion occurred in the normal way. So it was possible (but not certain) that some other mechanism was responsible for pancreatic secretion in response to acid in the duodenum. Working on the hypothesis that acid caused the release of something from the duodenum into the blood, they scraped some mucosa from the duodenum, added acid to it, ground it up with sand, filtered it and injected it intravenously into an anaesthetized dog. Pancreatic secretion followed a few seconds later. The elegance of this manoeuvre made it quite irrelevant as to whether they *had* removed all the nerves in the first experiment. The agent released from the duodenum was christened secretin, and when Pavlov read Bayliss and Starling's paper, he told an assistant to repeat the experiment. It worked, and Pavlov famously remarked: 'Of course they are right. It is clear that we didn't take out an exclusive patent for the discovery of the truth.' (Babkin 1951). But in his heart, Pavlov believed he *had* taken out such a patent, for when he came to give his Nobel Lecture in 1904, Bayliss and Starling's discovery did not even get a mention (Pavlov 1904). Pavlov still believed that pancreatic secretion was entirely controlled by the nervous system; after all, that was a significant part of his Nobel research.

Bayliss and Starling did not seem to bear any grudge against Pavlov. When the Bolshevik revolution of 1919

# The Croonian Lectures

ON

## THE CHEMICAL CORRELATION OF THE FUNCTIONS OF THE BODY.

*Delivered before the Royal College of Physicians of London  
on June 20th, 22nd, 27th, and 29th, 1905,*

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### LECTURE I.

*Delivered on June 20th.*

#### THE CHEMICAL CONTROL OF THE FUNCTIONS OF THE BODY.

MR. PRESIDENT AND GENTLEMEN,—From the remotest ages the existence of a profession of medicine, the practice of its art and its acceptance as a necessary part of every community have been founded on a tacit assumption that the functions of the body, whether of growth or activity of organs, can be controlled by chemical means; and research by observation of accident or by experiment for such means has resulted in the huge array of drugs which form the pharmacopocias of various civilised countries and the common armamentarium of the medical profession throughout the world.

These chemical messengers, however, or “hormones” (from *ὀρμῶν*, I excite or arouse), as we might call them, have to be carried from the organ where they are produced to the organ which they affect by means of the blood stream and the continually recurring physiological needs of the organism must determine their repeated production and circulation through the body.

Figure 2 The beginning of Starling’s lecture, and the important sentence which appears a page later in the lecture. It was given on June 20 1905, and published in *The Lancet* on August 5th.

threatened to make his life impossible in Russia, the two Londoners went to great lengths to help him and his family move to England or America. But Pavlov’s subsequent research (conditioned reflexes) turned out to be so in keeping with the principles of dialectical materialism that he was allowed to stay in Russia, living a life of comfort, until his death in 1936. Incidentally, it can be argued that Pavlov’s abrupt change of direction in his

research was a direct consequence of the discovery of secretin (Todes 2002).

Starling and his colleagues at UCL investigated (as best they could, for biochemistry was a very young subject) the nature of secretin. The working hypothesis was that the substance existed in the wall of the small intestine as a precursor (‘pro-secretin’) which released secretin under the influence of acid. The concentration of pro-secretin

diminishes steadily as one moves down the intestine. Bayliss and Starling showed that it was a universal stimulant – secretin from one species would stimulate the pancreas of any other species. ‘The evolution of this mechanism is, therefore, to be sought at some time anterior to the development of vertebrates’ wrote Starling. (We must remember that the literature still existed without using the word ‘hormone’.) It is also worth pointing out that secretin, a significant internal secretion, came from the wall of the intestine and not from a recognized internally secreting gland.

So, in the first decade of the twentieth century, physiologists had two internal secretions of scientific respectability – adrenaline (adrenin, epinephrine) and secretin. The word ‘endocrinology’ appeared at this time (there seemed to be no need for the term ‘exocrinology’). Probably because of the discovery of secretin, Starling was asked to give the Croonian Lecture to the Royal Society in March 1904 (Starling 1904). The lecture, ‘The Chemical Regulation of the Secretory Process’, updated Schäfer’s internal secretion lecture of nine years before. Starling concentrated on the two obvious substances. ‘This evidence, slight though it is, points to secretin being a body of relatively small molecular weight and not a colloid. It may be compared to the active principle of the suprarenal glands, adrenalin, which has been obtained in a crystalline form and the chemical constitution of which has been approximately determined. This is indeed what one would expect of a substance which has to be turned out into the blood at repeated intervals in order to produce in some distant organ or organs a physiological response proportional to the dose.’ (This quantitative thinking seems more sophisticated than that from any other contemporary writer on the subject).

Physiologists seemed particularly impressed with secretin as an internal secretion with a ‘drug-like’ action (we have to resist using the word ‘hormone’). Secretin’s precise origin and action seemed more intellectually satisfying than adrenalin’s rather poorly defined role (Cannon’s ‘fight-or-flight’ function for adrenalin did not come on to the scene for another ten years or so).

In 1905, Starling was invited to give the Croonian Lectures of the Royal College of Physicians (Starling 1905a–d) (this is slightly confusing for – as we have seen above – he had given a Croonian lecture to the Royal Society in the previous year). There were four lectures in which he reviewed the whole endocrinological scene including a lot of his own work. Lecture 1 was ‘The Chemical Control of the Functions of the Body’. He begins by outlining nervous control, but points out that chemical control – of which little is known – is probably more extensive than nervous control, and is the only means of internal communication in plants and lower animals. Then, out of nowhere, comes the sentence: ‘*These chemical messengers, however, or hormones (from ὁρμάω, I excite or arouse) as we might call them, have to be carried from the*

organ where they are produced to the organ which they affect by means of the blood stream and the continually recurring physiological needs of the organism must determine their repeated production and circulation throughout the body.’ (my italics) (see Fig. 2).

The rest of the first lecture is devoted to discussing internal secretion, and deals at length with carbon dioxide as a signalling molecule for respiration. Quoting the work of Haldane and Priestley, he says ‘This simplest of all examples of a co-ordination by chemical means of widely separated organs gives a clue as to how more complex correlations may have evolved.’ But he does not use the word ‘hormone’ again. Nor does the word appear in lecture 2 (secretin, ‘gastric secretin’ (the work of J S Edkins)) or lecture 3 (the control of pancreatic secretion). But in the fourth lecture (thyroid, ovaries and testes) he suddenly remembers his new word, and finding it rather useful, uses it no less than seventeen times!

So where did Starling get the word in the first place? We have one remarkable clue. Joseph Needham, distinguished Cambridge biochemist and Chinese scholar, wrote a book of essays in 1936 entitled ‘*Order and Life*’. On page 80, he uses the word ‘hormone’, and refers to it in a footnote. It seems that Starling was dining in Caius College, Cambridge (where Needham was a fellow) and was in conversation with William Hardy, who had invited Starling to dinner. Hardy was a distinguished biologist, and the two decided that they needed a word for an agent released into the blood stream that stimulated activity in a different part of the body. They turned to a classical colleague, W T Vesey (an authority on the Greek poet, Pindar) and asked him. He produced the Greek verb for ‘excite’ or ‘arouse’ (ormao) and, to quote Needham ‘The deed was done.’ Starling presumably jotted it down in his pocket-book and the word made its first appearance in his Croonian lecture, as we saw above. The exact interval between the dinner in Caius College and the appearance of ‘hormone’ is not known, for Needham gives us no date in his footnote. In fact, the footnote implies that Needham was not actually there himself on the evening, but had heard the story from one of the diners. And that is all we know of the origin of the hundred-year-old word that we take so much for granted.

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