

60 YEARS OF NEUROENDOCRINOLOGY

Celebrating the brain's other output-input system and the monograph that defined neuroendocrinology

Clive W Coen

Reproductive Neurobiology, Division of Women's Health, School of Medicine, King's College London, London SE1 1UL, UK

Correspondence should be addressed to C W Coen
Email
 clive.coen@kcl.ac.uk

Abstract

The brain's unimaginably complex operations are expressed in just two types of output: muscle activity and hormone release. These are the means by which the brain acts beyond its bony casing. Muscle-mediated actions (such as speaking, writing, pupillary reflexes) send signals to the outside world that may convey thoughts, emotions or evidence of neurological disorder. The outputs of the brain as a hormone secreting gland are usually less evident. Their discovery required several paradigm shifts in our understanding of anatomy. The first occurred in 1655. Exactly 300 years later, Geoffrey Harris' monograph *Neural control of the pituitary gland* launched the scientific discipline that is now known as neuroendocrinology. His hypotheses have stood the test of time to a remarkable degree. A key part of his vision concerned the two-way 'interplay between the central nervous system and endocrine glands'. Over the past 60 years, the importance of this reciprocity and the degree to which cerebral functions are influenced by the endocrine environment have become increasingly clear.

Key Words

- ▶ neuroendocrinology
- ▶ hypothalamus
- ▶ pituitary
- ▶ hormones
- ▶ neuroscience

Journal of Endocrinology
 (2015) 226, E3–E6

From Galen in the 2nd century AD, medical orthodoxy held that the brain–pituitary axis terminated in the nostrils and palate. Blood was allegedly endowed with vital spirit in the left ventricle of the heart and with animal spirit, the substance responsible for motion and sensation, after transport to the brain. The waste products of animal spirit were believed to pass through a funnel (*infundibulum*) to the pituitary (*pituita* means phlegm) and thence by ducts through the sphenoid bone and cribriform plate of the ethmoid bone into the nasopharynx. In 1655, Conrad Schneider of Wittenberg challenged this dogma with evidence that nasal discharge derives from nasal mucosa and not from the pituitary (Schneider 1655). During the following decade, Schneider's empirical studies

were extended by Richard Lower in Oxford. In a letter to Robert Boyle in 1663, Lower reported: 'Under the *glandula pituitana* in a calf's skull, there are commonly one or two holes, which receive vessels from the glandule, into which hole we syringed in milk, and immediately it came out of the jugular veins more slowly or fast, according as the milk was injected; but looking into the mouth, we could not discover the least drop of milk; whereupon we tried the same with ink ... so the old doctrine of catarrhs may be washed away'.

Three centuries later, it was irrigation of pituitary stalk portal vessels with ink that started the flow of ingenious studies culminating in what Lower might have called the new doctrine of neuroendocrinology. The paradigm-

shifting notion that blood passes down the portal vessels from the median eminence at the base of the hypothalamus into the anterior pituitary gland was finally confirmed when Green & Harris (1949) observed the direction of red blood cell movement in the living rat. Thus, the tripartite system linking the brain, anterior pituitary gland and blood stream had been demonstrated – but its functions remained unproven and controversial for many years.

Geoffrey Harris' research career had started in 1935 under the tutelage of Francis Marshall at the University of Cambridge. Marshall, a reproductive physiologist, 'drew attention to the ... variety of environmental factors, such as food, light, temperature, presence of a mate ... [that] are of importance in conditioning sexual periodicity. It is likely that the intrinsic sexual rhythm of many mammals is adjusted ... by such 'exteroceptive factors' as Marshall termed them' (Harris 1955). The mechanisms by which the central nervous system mediates these effects were unknown and became Harris' obsession. In his first two publications, he reported the induction of pseudo-pregnancy and ovulation by electrical stimulation of the head or hypothalamus (Harris 1936, 1937). These papers are like detective stories in which the crime has occurred inside a locked room. Harris characterised the enigma in his monograph: '(a) the hypothalamus [in the rabbit] forms part of a nervous reflex path by which the stimulus of coitus excites the secretion of gonadotrophic hormone ... [and yet] (b) the anterior lobe of the pituitary has at most a very scanty nerve supply'. Despite his focus on reproduction and the unsolved mystery about the route by which hormone-releasing signals access the pituitary gland, Harris was keen to tackle the full regulatory system from the start: 'There is no reason to doubt that the thyrotropic, adrenotropic, lactogenic, parathyrotropic and growth hormones are not similarly controlled' (Harris 1937). After the vascular link from the hypothalamus to the anterior pituitary gland had been demonstrated, Harris began to assess the role of the portal vessels by cutting the pituitary stalk; a positive correlation was found between the functional activity of the gland and the degree of vascular regeneration across the cut (Harris 1950). Further evidence for neurohumoral regulation via the portal vessels was obtained when Dora Jacobsohn and Harris grafted anterior pituitary tissue under the median eminence of female rats after the animal's pituitary gland had been removed; if the graft became vascularised by the primary plexus of the portal vessels, the animal exhibited normal reproductive functions (Harris & Jacobsohn 1952).

Harris' monograph of 1955 consolidated an extensive body of evidence into a coherent model – a model that showed his foresight by incorporating inhibition as well as stimulation of pituitary hormone release (see this issue: Grattan 2015, Murray *et al.* 2015): 'The most likely hypothesis is that nerve fibres from the hypothalamus liberate some humoral substance(s) into the capillaries of the primary plexus in the median eminence, and that this substance is carried by portal vessels to excite or inhibit the secretion of the gland cells in the *pars distalis* [anterior pituitary]' (Harris 1955).

This clearly stated hypothesis was to attract controversy for many years, as foreshadowed by the monograph's critical reception in *Nature* (Zuckerman 1956). 'An edifice of speculation' was the verdict of Solly (later Lord) Zuckerman, an influential zoologist, anatomist and sometime adviser to the British government on bombardment. According to Zuckerman, 'the pituitary-portal vessels are neither a sufficient nor a necessary explanation of this presumed control'. His observation that 'not even a single one [of the neurotransmitters involved in pituitary control] has yet been identified' was of course true, and remained so until November 1969, when Andrew Schally and Roger Guillemin published the structure of thyrotrophin-releasing factor within 7 days of each other (Boler *et al.* 1969, Burgus *et al.* 1969). Nevertheless, despite the protracted failure to isolate and characterise the releasing and release-inhibiting factors, pioneers such as Harris continued to elucidate the components of this novel physiological system and gather their findings into substantial volumes (Szentágothai *et al.* 1962, Harris & Donovan 1966). Their experiments were designed around ingenious surgical procedures, classic histological techniques, behavioural tests and, above all, bioassays that happened to be laborious and insensitive (the induction of ovulation remained Harris' favourite). The tools of this trade belonged to the tradition of direct observation as evoked by William Harvey's phrase 'through the use of my own eyes' (Harvey 1628).

By the end of the 1960s, radioimmunoassays were beginning to transform this field of research. The ability to assay small samples in great numbers revealed a novel phenomenon: the pulsatile release of pituitary hormones, as first seen with luteinising hormone (Midgley & Jaffe 1971, Nankin & Troen 1971). This pulsatility is now recognised as a vital feature in regulating reproduction, growth, adrenal cortex and posterior pituitary functions (see this issue: Plant 2015, Murray *et al.* 2015, Spiga *et al.* 2015, Leng *et al.* 2015). As Duke Ellington commented, 'It don't mean a thing if it ain't got that swing'. Neuroendocrinology and molecular

biology matured in parallel. Sensitive, automated hormone assays are now complemented by a vast range of molecular biological techniques for analysis or experimental intervention. These have been indispensable in, for example, elucidating circadian processes (see this issue: Johnston & Skene 2015) and the pathogenesis of pituitary adenomas and craniopharyngiomas (see this issue: Capatina & Wass 2015, Martinez-Barbera 2015). Molecular biological tools are also opening up new vistas in neuroendocrine neuroanatomy (see this issue: Watts 2015).

In 1971, Harris received the Dale Medal from the Society for Endocrinology and delivered the Sir Henry Dale Lecture in London on May 27. On June 24, at the meeting of the Endocrine Society in San Francisco, Schally announced the structure of the releasing factor that is now called gonadotrophin releasing hormone. Later that year, Harris sent Schally a pre-publication copy of his Dale Lecture. It had been suitably updated to pay tribute to the releasing factor discoveries that 'will undoubtedly stand as a milestone in the history of endocrinology'. Schally's reply to Harris is quoted in *The Nobel Duel* (Wade 1981), an account of the decades-long rivalry between Schally and Guillemin (which seems like an embittered, endless Formula One race): 'I can't say I was pleased about this year's N.P. [Nobel Prize] award [which had just been announced]. So many people (not only neuroendocrinologists) thought that you should have gotten it ... we have no choice but to wait'. Schally's letter was written on November 29, but Harris never received it. He died that day, aged 58.

The Dale Lecture, which turned out to be Harris' valedictory review, appeared in print (Harris 1972) exactly 300 years after Lower published his evidence for the link between the pituitary gland and the circulatory system, *De catarrhis* (Lower 1672). The monograph with which the younger Harris had advanced 'the concept of neurohumoral control of anterior pituitary function' (Harris 1955) had been published 300 years after the study that inspired Lower's research (Schneider 1655). The *Journal of Endocrinology* is now celebrating the 60th anniversary of Harris' monograph – a work that launched the scientific discipline now known as neuroendocrinology. Although that term had appeared in the French title of a treatise in 1946 (Roussy & Mosinger 1946), it was used only sporadically prior to 1963. In that year, Ernst and Berta Scharrer (co-founders of the concept of neurosecretion) produced a book called *Neuroendocrinology* (Scharrer & Scharrer 1963) and Seymour Reichlin used the term as the title for a series of review articles in the *New England Journal of Medicine* (Reichlin 1963a,b,c). By 1965, *Neuroendocrinology*, the first journal dedicated to this discipline, had been founded.

Although the term neuroendocrinology may appear to grant primacy to neuronal mechanisms, Harris' exposition of this physiological system left no such ambiguity: 'It is clear that the interplay between the central nervous system and endocrine glands ... is one of reciprocity' (Harris 1955). In 1655, tobacco smokers may have comforted themselves by choosing to believe that Schneider had shown the brain to be impermeable. But 360 years later our science must accommodate the vast range of exteroceptive and interoceptive factors known to converge on the brain, including the hormones that enter it by diffusion or active transport (see this issue: Joseph-Bravo *et al.* 2015).

Fifty years ago, in the introduction to the inaugural issue of *Neuroendocrinology*, written only a few days before his accidental death by drowning, Ernst Scharrer posed an existential question: 'Should we anticipate the development of a permanent community or are we constructing a future ghost town?' (Scharrer 1965). The articles published in this issue of the *Journal of Endocrinology* leave the answer beyond doubt. They bear witness to a flourishing community, one that owes its origins to Harris and his colleagues, three of whom provide their personal reflections on this anniversary (see this issue: Raisman 2015, Reichlin 2015, Fink 2015). The review articles are presented in a sequence similar to the one adopted by Harris when setting out his case for this novel physiological system in 1955.

Brains are normally embodied organs. If neuroscience is to do justice to that condition, the integrative perspectives of neuroendocrinology will be indispensable. As we celebrate the 60th anniversary of the monograph that defined neuroendocrinology, it seems that vanishingly few cerebral functions are impervious to the endocrine environment (see this issue: McEwen *et al.* 2015). Harris' legacy has become the lifeblood of neuroscience.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this editorial.

Funding

This piece is an overview of more than three centuries of research by many scientists. As such, it did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

- Boler J, Enzmann F, Folkers K, Bowers CY & Schally AV 1969 The identity of chemical and hormonal properties of the thyrotropin releasing hormone and pyroglutamyl-histidyl-proline amide. *Biochemical and*

- Biophysical Research Communications* **37** 705–710. (doi:10.1016/0006-291X(69)90868-7)
- Burgus R, Dunn TF, Desiderio D & Guillemin R 1969 Molecular structure of the hypothalamic hypophysiotropic TRF factor of ovine origin: mass spectrometry demonstration of the PCA-His-Pro-NH₂ sequence. *Comptes Rendus Hebdomadaires Des Séances De L'Académie Des Sciences. Série D: Sciences Naturelles* **269** 1870–1873.
- Capatina C & Wass JAH 2015 60 YEARS OF NEUROENDOCRINOLOGY: Acromegaly. *Journal of Endocrinology* **226** T141–T160. (doi:10.1530/JOE-15-0109)
- Fink G 2015 60 YEARS OF NEUROENDOCRINOLOGY: MEMOIR: Harris' neuroendocrine revolution: of portal vessels and self-priming. *Journal of Endocrinology* **226** T13–T24. (doi:10.1530/JOE-15-0130)
- Grattan DR 2015 60 YEARS OF NEUROENDOCRINOLOGY: The hypothalamo–prolactin axis. *Journal of Endocrinology* **226** T101–T122. (doi:10.1530/JOE-15-0213)
- Green JD & Harris GW 1949 Observation of the hypophysio-portal vessels of the living rat. *Journal of Physiology* **108** 359–361. (doi:10.1113/jphysiol.1949.sp004339)
- Harris GW 1936 The induction of pseudo-pregnancy in the rat by electrical stimulation through the head. *Journal of Physiology* **88** 361–367. (doi:10.1113/jphysiol.1936.sp003446)
- Harris GW 1937 The induction of ovulation in the rabbit by electrical stimulation of the hypothalamo–hypophysial mechanism. *Proceedings of the Royal Society B* **122** 374–394. (available at: <http://www.jstor.org/stable/81989>)
- Harris GW 1950 Oestrous rhythm. Pseudopregnancy and the pituitary stalk in the rat. *Journal of Physiology* **111** 347–360. (doi:10.1113/jphysiol.1950.sp004484)
- Harris GW 1955 *Neural Control of the Pituitary Gland. Monographs of the Physiological Society*. London, UK: Edward Arnold Ltd.
- Harris GW 1972 Humours and hormones. The Sir Henry Dale Lecture for 1971. *Journal of Endocrinology* **53** (Supplement) ii-xxiii. (doi:10.1677/joe.0.053000I)
- Harris GW & Donovan BT 1966 *The Pituitary Gland*. London, UK: Butterworths.
- Harris GW & Jacobsohn D 1952 Functional grafts of the anterior pituitary gland. *Proceedings of the Royal Society of London. Series B, Biological Sciences* **139** 263–276. (doi:10.1098/rspb.1952.0011)
- Harvey W 1628 *Exercitatio anatomica de motu cordis et sanguinis in animalibus*. Frankfurt, Germany: William Fitzer.
- Johnston JD & Skene DJ 2015 60 YEARS OF NEUROENDOCRINOLOGY: Regulation of mammalian neuroendocrine physiology and rhythms by melatonin. *Journal of Endocrinology* **226** T187–T198. (doi:10.1530/JOE-15-0119)
- Joseph-Bravo P, Jaimes-Hoy L, Uribe RM & Charli J-L 2015 60 YEARS OF NEUROENDOCRINOLOGY: TRH, the first hypophysiotropic releasing hormone isolated: control of the pituitary–thyroid axis. *Journal of Endocrinology* **226** T85–T100. (doi:10.1530/JOE-15-0124)
- Leng G, Pineda R, Sabatier N & Ludwig M 2015 60 YEARS OF NEUROENDOCRINOLOGY: The posterior pituitary, from Geoffrey Harris to our present understanding. *Journal of Endocrinology* **226** T173–T185. (doi:10.1530/JOE-15-0087)
- Lower R 1672 *De catarrhis*; addendum to the 1672 edition of *Tractatus de corde*. London, UK: J. Redmayne.
- Martinez-Barbera JP 2015 60 YEARS OF NEUROENDOCRINOLOGY: Biology of human craniopharyngioma: lessons from mouse models. *Journal of Endocrinology* **226** T161–T172. (doi:10.1530/JOE-15-0145)
- McEwen BS, Gray JD & Nasca C 2015 60 YEARS OF NEUROENDOCRINOLOGY: Redefining neuroendocrinology: stress, sex and cognitive and emotional regulation. *Journal of Endocrinology* **226** T67–T83. (doi:10.1530/JOE-15-0121)
- Midgley AR Jr & Jaffe RB 1971 Regulation of human gonadotropins. X. Episodic fluctuation of LH during the menstrual cycle. *Journal of Clinical Endocrinology and Metabolism* **33** 962–969. (doi:10.1210/jcem-33-6-962)
- Murray PG, Higham CE & Clayton PE 2015 60 YEARS OF NEUROENDOCRINOLOGY: The hypothalamo–GH axis: the past 60 years. *Journal of Endocrinology* **226** T123–T140. (doi:10.1530/JOE-15-0120)
- Nankin HR & Troen P 1971 Repetitive luteinizing hormone elevations in serum of normal men. *Journal of Clinical Endocrinology and Metabolism* **33** 558–560. (doi:10.1210/jcem-33-3-558)
- Plant TM 2015 60 YEARS OF NEUROENDOCRINOLOGY: The hypothalamo–pituitary–gonadal axis. *Journal of Endocrinology* **226** T41–T54. (doi:10.1530/JOE-15-0113)
- Raisman G 2015 60 YEARS OF NEUROENDOCRINOLOGY: MEMOIR: Geoffrey Harris and my brush with his unit. *Journal of Endocrinology* **226** T1–T11. (doi:10.1530/JOE-15-0049)
- Reichlin S 1963a Neuroendocrinology. *New England Journal of Medicine* **269** 1182–1191 contd. (doi:10.1056/NEJM196311282692206)
- Reichlin S 1963b Neuroendocrinology. *New England Journal of Medicine* **269** 1246–1250 contd. (doi:10.1056/NEJM196312052692306)
- Reichlin S 1963c Neuroendocrinology. *New England Journal of Medicine* **269** 1296–1303. (doi:10.1056/NEJM196312122692407)
- Reichlin S 2015 60 YEARS OF NEUROENDOCRINOLOGY: MEMOIR: working in the 'Huts' with the professor: the first Maudsley years. *Journal of Endocrinology* **226** E7–E11. (doi:10.1530/JOE-15-0034)
- Roussy G & Mosinger M 1946 *Traité de Neuro-Endocrinologie*. Paris, France: Masson and Co.
- Scharrer E 1965 Neuroendocrinology: its past, present and future. *Neuroendocrinology* **1** 1–3. (doi:10.1159/000121653)
- Scharrer E & Scharrer B 1963 *Neuroendocrinology*. New York, NY, USA: Columbia University Press.
- Schneider CV 1655 *Liber de osse cribriformi, et sensu ac organo odoratus*. Wittenberg, Germany: Mevius & Schumacherus.
- Spiga F, Walker JJ, Gupta R, Terry JR & Lightman SL 2015 60 YEARS OF NEUROENDOCRINOLOGY: Glucocorticoid dynamics: insights from mathematical, experimental and clinical studies. *Journal of Endocrinology* **226** T55–T66. (doi:10.1530/JOE-15-0132)
- Szentágothai J, Flerkó B, Mess B & Halász B 1962 Hypothalamic control of the anterior pituitary: an experimental-morphological study. Budapest, Hungary: Akadémiai Kiadó.
- Wade N 1981 The nobel duel: two scientists' 21-year race to win the world's most coveted research prize. Garden City, New York, NY, USA: Anchor Press/Doubleday.
- Watts AG 2015 60 YEARS OF NEUROENDOCRINOLOGY: The structure of the neuroendocrine hypothalamus: the neuroanatomical legacy of Geoffrey Harris. *Journal of Endocrinology* **226** T25–T39. (doi:10.1530/JOE-15-0157)
- Zuckerman S 1956 Control of pituitary function. *Nature* **178** 442–443. (doi:10.1038/178442a0)

Received in final form 5 June 2015
Accepted 11 June 2015