60 YEARS OF NEUROENDOCRINOLOGY

**MEMOIR: working in the 'Huts' with
the professor: the first Maudsley
years****Seymour Reichlin**

Professor of Medicine, Emeritus, Tufts University, Boston, Massachusetts, USA

Correspondence
should be addressed
to S Reichlin
Email
seymourreichlin@gmail.com

During the first 2 years of Geoffrey Harris' tenure as Fitzmary Professor of Physiology, University of London (1952–1962), I was one of the four fellows in his laboratory based in the 'Huts', two prefabricated buildings on the grounds of Maudsley Hospital, South London. Peter Fawcett, a later collaborator, remarked, 'It was an enigma to me why this eminent man should be stuck in a bunch of ex-army huts in the grounds of a nuthouse' (Wade 1981). 'The Professor' was the way that my fellow graduate student Keith Brown-Grant referred to him. Harris had one secretary who handled all business of the laboratory, correspondence and manuscripts, one animal caretaker, one laboratory technician responsible for histological preparations and one machinist/instrument maker responsible for the fabrication of items such as electrodes and physiological equipment. There were no facilities for chemical analysis, or tissue or cell culture.

Fawcett should not have been surprised at the laboratory's modesty. In 1952, when Harris had moved from Cambridge, England was still struggling to recover from the ravages of World War II. It was in fact remarkable to find Harris' laboratory, arguably the leading neuroendocrine research programme in the world, functioning at all. The difficulties of doing research during the war, Harris once told me, were tremendous. He would buy rabbits for his studies in Cambridge from local farms, carrying them back to the laboratory in a basket on his bicycle. Microscope slides were in short supply, and he had to scrape and reuse them. Also, little was published due to restrictions on paper and supplies. The state of knowledge, and our research methods, was primitive by today's

standards. We worked before the dawn of molecular biology (Watson & Crick 1953), before any peptide had been sequenced (Du Vignaud *et al.* 1953a,b), before the term 'releasing factor' had been introduced (Saffran *et al.* 1955) and a decade before the invention of RIA which made it possible to measure moment-to-moment changes in blood hormone levels (Berson & Yalow 1960). Harris' landmark review of neuroendocrinology in 1948 (Harris 1948) had masterfully summarised the state of knowledge of the field, based on the methods available at the time, and was the precursor to the 1955 monograph, the subject of this special edition.

Harris had visited the USA for the first time 2 years before his move to London, and it was my good fortune that I had been a medical resident in New York City when he gave a public lecture at Long Island Medical College in Brooklyn. He reviewed the evidence for the hypophysial–portal hypothesis of anterior pituitary control based on his anatomical (Green & Harris 1947), pituitary stalk section (Harris 1950), transplantation (Harris & Jacobsohn 1952) and electrical stimulation studies (Harris 1937, Colfer *et al.* 1950). The novelty of Harris' approach, plus the clarity and elegance of his presentation and his charisma, excited me, and I decided on the spot to try to work with him. The content of the lecture was similar to a video he made for the BBC in 1971, the year of his death, available for viewing on YouTube ('Professor G W Harris' <https://www.youtube.com/watch?v=CWKH1sKnYvs>). At the end of his talk, I introduced myself – to my immense surprise he had read a paper I had written as a medical student on adrenergic control of adrenocorticotrophin release

(Ronzoni & Reichlin 1950) and he agreed to take me on as a fellow in his laboratory, provided of course that I could get fellowship funding on my own.

By 1952, when I joined the laboratory, Harris had begun to study the hypothalamic control of the thyroid gland with fellows, Keith Brown-Grant and Curt von Euler, utilising a collimated external Geiger counter to measure rate of release of radioactively labelled thyroid hormone from the gland (Brown-Grant *et al.* 1954a). Brown-Grant and I would meet with Harris in his office every morning to discuss our results and plan our work. If either of us had a different idea of how to do an experiment, or to propose a new experiment, or to propose a new interpretation of an experimental result, it took a great deal of discussion, usually not successful, to change Harris' mind. Not infrequently, one or more of the proposals or interpretations that Brown-Grant or I would have made, and immediately rejected by Harris, would be recycled and appear as a new suggestion by him weeks later: by then it was not always clear who was the father of the new idea. Brown-Grant and I also disagreed with each other at times on interpretation of results. Even though we were trying to prove the neurohumoral hypothesis of thyrotrophic regulation, Brown-Grant, to Harris' chagrin, took delight in supporting a contrarian view of the mechanism of hypothalamic median eminence involvement in thyrotrophin (TSH) regulation, namely the hypothalamic-filter hypothesis, which proposed that the median eminence might regulate TSH secretion by controlling the concentration of thyroxine presented to the pituitary (Brown-Grant 1957, 1966). When it came to time to write papers, the fellows wrote the first drafts; Harris was a marvellous critic of writing style, and a stickler for insisting that we include every relevant reference, giving due credit to the work of other scientists.

We first sought a model system in which thyroid function of the subject rabbit could be activated consistently. Then, the professor would cut the pituitary stalk, placing waxed paper between the cut ends of the stalk to block blood vessel regeneration, and repeat the release studies. Autumn was upon us and the days were growing chilly. In some experiments, therefore, we were able to expose rabbits to cold by simply placing them outside the doorway of the hut in an area protected from the wind or rain. In other experiments, the animals were placed in a cold room, and in still others, they were placed in the cold, and exposed to a breeze from a fan, or wet down in alcohol and then exposed to cold. Activation of the thyroid was observed in about half of the rabbits, but a third or more of rabbits exposed to more severe cold showed unexpected

thyroid inhibition. Our conclusion was that cold exposure did not produce a large enough, or consistent enough, increase in thyroid function to be a reliable model for testing the effect of pituitary stalk section, and that, in some cases, the stressful aspects of cold exposure may have inhibited thyroid hormone release.

This led us to determine the effect of stress alone (Brown-Grant *et al.* 1954b): simply tying the legs of the rabbit to the side of the cage with a cloth ribbon was stressful enough to bring about complete inhibition of thyroid hormone release. After Harris had cut the pituitary stalk, taking pains to block portal vessel regeneration, the baseline rate of release of radioactivity was found to be significantly reduced; restraint no longer inhibited the thyroid gland (Brown-Grant *et al.* 1957). At the time, we interpreted the stalk-section-induced inhibition of thyroid function to indicate loss of a postulated hypothalamic TSH-stimulating factor and the blockade of the stress-induced thyroid inhibition to suppression of this factor. None of us imagined that the thyroid-inhibitory effects of emotional stress that we observed in our restrained-stressed rabbits could have been due to the release, into the portal capillaries, of a factor that suppressed TSH secretion. This possibility only emerged after the discovery of somatostatin 20 years later (Brazeau *et al.* 1973), and the demonstration that it was released after stress (in the rat, (Arimura *et al.* 1976)) and was capable of inhibiting TSH secretion (Arimura & Schally 1976). The later discoveries concerning TSH control mechanisms are excellent illustrations of Ramon y Cajal's (1897) wise saying: 'Problems that appear small are large problems that are not understood.'

Life in the Harris laboratory followed a regular plan with two or three major projects underway with different fellows. Harris insisted on doing all surgical procedures such as stalk sectioning or electrode placement himself; the more difficult the problem, the more he enjoyed it. At one point in our studies it became necessary to adrenalectomise the rabbits – this too Harris insisted on performing himself. He genuinely enjoyed the surgical challenge, a measure of his fiercely competitive nature. Harris' qualifications as an experimental physiologist were prodigious: he devised succinct and simple experiments, and executed them elegantly. He kept meticulous, detailed laboratory notebooks, each operation being illustrated and described beautifully. When he did a new experiment, he planned it to be definitive, not just a pilot experiment. The results of autopsy and microscopic examination were similarly meticulously noted. These elegant records have now been deposited in the Bodleian Library in Oxford; they should be a worthy project for a medical historian.

Harris held tenaciously, and it must be admitted, somewhat rigidly, to his views about how to do neuroendocrine research. Early on, he was adamant that studies of endocrine function should be carried out on unrestrained, unanaesthetised animals, a viewpoint that had led him to develop the elaborate remote electrical stimulating methods that had proved so successful in his stimulation studies of ovulation and pituitary–adrenal activation. Yet, this dictum in the end impeded progress in the field: electrical stimulation of the hypothalamus in anaesthetised animals, carried out by others, allowed the delineation of specific hypophysiotrophic areas for the release of luteinizing hormone (LH) (Critchlow 1957), growth hormone (GH) (Frohman *et al.* 1968, Martin 1972) and TSH (Martin & Reichlin 1970). Trained as an anatomist, Harris was most comfortable with phenomena that could be visualised anatomically and that could be demonstrated in living animals. This outlook was reflected in his work in several ways. One example was his approach to the isolation of releasing factors. When Roger Guillemin visited the Harris laboratory in 1954 to get some ideas from Harris as to how he should set up his new laboratory at Baylor, he outlined his plans to try to isolate corticotrophin-releasing factor utilising a pituitary tissue culture assay, Harris showed 'polite skepticism' (Wade 1981). Later, when Harris finally mobilised a programme to isolate gonadotrophin-releasing factor, he laboriously assayed hypothalamic extracts by injecting samples prepared by his London-based chemical collaborators into the pituitaries of rabbits under stereotaxic control taking ruptured ovarian follicles as his measure of biological activity (Fawcett *et al.* 1968). His main competitors, groups associated with Schally and Guillemin, were using the rapid and economical Parlow ovarian ascorbic acid depletion rat ovary assay and could test many more samples a day. To be fair, it should be pointed out that the American laboratories had access to many more slaughterhouse hypothalami than could be made available in England, and the driven intensity of the two major laboratories of Schally and of Guillemin to isolate the releasing factors would have been hard to match.

Similarly, Harris' insistence on concrete, anatomically valid endpoints impeded his efforts to study the hypothalamic control of GH secretion. He was slow to recognise the value of immunoassay: Frederick C Greenwood, who had pioneered the development of RIA of GH in England, told me in 1968 that he had proposed to Harris that they collaborate in a study of the hypothalamic control of GH secretion in monkeys with an immunoassay cross-reactive with human GH, but Harris told Greenwood that he was

not convinced that RIA was really measuring meaningful hormone levels and turned down the idea (F C Greenwood personal communication, 1968).

Harris was also slow to accept Ernst Scharrer's concept of neurosecretion (Scharrer & Scharrer 1940), which is now recognised as an essential feature of hypophysiotrophic neuronal function. It is true that most of the leading neuroscientists at the time shared Harris' scepticism (Scharrer 1978), but in my view Harris ignored Scharrer's work because Scharrer believed that the neurohypophysis with its established neuronal control was somehow involved in anterior pituitary regulation, a view strongly rejected by Harris because it contradicted his hypophysial–portal hypothesis.

Despite the modesty of his surroundings in the 'Huts', those early years in London were of critical importance in Harris' career. With junior collaborators, he established the importance of the hypophysial–portal blood system for the control of thyroid and adrenocortical function, demonstrated the site of oestrogen feedback in the brain and initiated the search for LH-releasing hormone (LHRH). He established the Endocrine Curriculum at the Institute for Psychiatry, wrote the Neural Control monograph, emerged as the most influential neuroendocrinologist of his time and successfully defended himself against his severest critic, Sir Solly Zuckerman, Professor of Anatomy at the University of Birmingham who was determined to disprove Harris' theory about the role of the hypophysial–portal vessels in anterior pituitary regulation.

The Zuckerman–Harris controversy is the stuff of legend (Wade 1981), reaching its climax in 1954. Zuckerman asserted dogmatically that if a single exception could be found in which an animal could be shown to have ovulated in the absence of an intact hypophysial–portal system, Harris theory was completely invalid. A junior associate, A P D Thomson, cut the pituitary stalk in a group of female ferrets, which normally come into heat in response to increasing ratios of light to darkness. Following the operation, two of the ferrets in the study, Zuckerman triumphantly reported, came into heat in the absence of portal vessel connections as shown by Indian ink vascular perfusion (Thomson & Zuckerman 1953). Faced with this challenge, Harris accompanied by Bernard T Donovan, then one of his research fellows, visited Birmingham to examine histological preparations of the stalk region for themselves. They returned to the Maudsley Laboratory in an exultant state; Harris, an experienced histologist, recognised at once that the portal blood vessels had regenerated in the two key ferrets that had

ovulated. Apparently, histological preparation methods in Birmingham (paraffin embedded, 10 μ sections) had washed the Indian ink out of the vessels. In contrast, Harris' more laborious technique (celloidin embedding, 100–200 μ sections) preserved the perfused vessels. [Donovan & Harris \(1954\)](#) carried out their own series of ferret studies and confirmed the Harris hypothesis: no portal vessel regeneration – no ovulation; their report was bluntly critical of the Thomson–Zuckerman methods of stalk section and histological preparations.

The controversy did not end there, but was brought up again in a spring 1954 meeting, at the Ciba Foundation in London in which Harris and Zuckerman squared off after Zuckerman's presentation of his data on ferrets. Everyone was acutely aware of the tension between the two men and anticipated a keen debate. Harris was an accomplished speaker, but Sir Solly was by far a more cunning and skilful debater and spoke with deliberate and practised authority summarising his objections to Harris' theories ([Zuckerman 1955](#), [Wade 1981](#)). Although by training an anatomist, he has been described 'as one of the most influential figures in the nebulous and powerful network, sometimes call the Establishment, which lies at the heart of much of Britain's national decision making' ([Chalfont 1993](#)). Among innumerable other appointments, he had been Scientific Advisor, Combined Operations Headquarters of the British Defense Service, 1939–1946, and Chairman, Defence Research Policy Committee, had been knighted, and later made a Life peer. Harris, challenged, became more and more tense, his face reddened, and as he spoke, the pitch of his voice gradually rose until it was almost a squeak. But Harris won the debate, then, and in posterity.

Zuckerman, for his part, stubbornly unconvinced of the validity of the hypophysial–portal hypothesis, never accepted that Harris was correct. His last iconoclastic arguments are recorded in an article he published as late as 1978 ([Zuckerman 1978](#)), written despite the elucidation of the structures of thyrotrophin-releasing hormone ([Burgos et al. 1969](#), [Folkers et al. 1969](#)), LHRH ([Matsuo et al. 1971](#)) and somatostatin ([Brazeau et al. 1973](#)), and the exponentially increasing literature that had demonstrated unequivocally their presence in nerve endings in the median eminence and of several releasing factors in portal vessel blood. To the community of neuroendocrinologists, Sir Solly's implacable pronouncements have been inexplicably equivalent to the rejection of Galileo's view of the relationship between the Sun and planet Earth.

Despite the fact that Harris was only 11 years older than me, it took me many years, long after I was an independent worker, to address him by his first name. He maintained a

distinct British reserve that did not encourage that kind of intimacy. Despite this formality, however, Harris encouraged us at the end of the day to join him at a local pub where we could talk about our projects, or anything else in science. In many of his other pursuits, like playing squash, he savoured life, and was intensely competitive. He could be playful as well. One of the highlights of my tenure in his laboratory was a kind of lark that took us to Dorking, Surrey, to capture wild rabbits, which were alleged to develop thyrotoxicosis due to the stress of captivity ([Reichlin 1993](#)). This finding contradicted the results of our own studies indicating that restraint stress inhibited thyroid function in domestic rabbits. In a rustic meadow, Harris and his large white bulldog, Lemuel, and I watched as the rabbits came leaping out of their burrows into set up nets after the professional rabbit catcher had dropped his trained ferret into their burrows.

In preparing this note, I have been aided immeasurably by informative biographical accounts of Harris' career by former colleagues and collaborators ([Fortier 1971](#), [Vogt 1972](#), [Raisman 1997](#)). Marthe Vogt's comprehensive review of Harris' life and contributions in the Proceedings of the Royal Society, is particularly poignant, because she had been elected to the Royal Society just a year before Harris, had been its emissary chosen to 'vet' Harris' laboratory in the huts while he was being considered for election, and as the most junior fellow in the laboratory I had been assigned to show her around and to accompany her to the train station on her way back to Edinburgh. Despite the 'humbleness' of our research 'Huts', Harris survived Dr Vogt's inspection and was, in fact, elected to the Royal Society in 1953 at the unusually young age of 40. In that one domain, Zuckerman beat out Harris – Sir Solly had been elected at the age of 39.

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