Geoffrey W. Harris †, 1913–1971

B.T. Donovan, Department of Physiology, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, England

The close of 1971 was marred for many of us by the death at a relatively early age of GEOFFREY HARRIS. An outstanding scientist and teacher, his experiments and writings contributed greatly to the foundation of neuroendocrinology as a discipline and stimulated researchers all over the world to engage in studies concerned with the interrelationships between the nervous system and endocrine activity. To mark our loss, the Editorial Board has invited BERNARD DONOVAN, an early pupil, to survey the career and achievements of this pioneer neuroendocrinologist.

66

Donovan

The lasting research interests of GEOFFREY HARRIS were aroused very early in his career, when, as a student at Cambridge, he came under the influence of the eminent reproductive physiologist F.H.A. MARSHALL, who had collated the information available on the environmental control of reproductive processes and was involved in the study of the physiological mechanisms involved. MARSHALL and E.B. VERNEY had shown in 1936 that diffuse electrical stimulation of the head of rabbits elicited ovulation and pseudopregnancy, and when MARSHALL suggested to HARRIS that it would be interesting to apply precisely localized electrical stimuli to different regions of the hypothalamus of oestrous female rabbits in an effort to trace the neural pathway involved in reflex ovulation the work was quickly undertaken. After examining the techniques available for this purpose with Dr. JOHN BEATTIE at the Royal College of Surgeons in London, and with Professor W.R. HESS of the University of Zurich, HARRIS found that stimulation of the tuber cinereum of the hypothalamus, the tegmental area and the anterior pituitary caused ovulation. At that time he believed that nerve fibres from the hypothalamus to hypophysis mediated this response. He had enjoyed a short spell in the summer of 1935 as a research assistant to Professor G.T. POPA, who with UNA FIELDING had described the hypophysial portal vessels in man, but it was then thought that the blood within them flowed up the stalk from the gland to the brain. The misleading findings that stimulation of the anterior pituitary caused ovulation probably resulted from the use of pulses of direct current which cause tissue damage and a seepage of gonadotrophin from the pars distalis.

After this first taste of research, HARRIS went as a Harmsworth Scholar to St. Mary's Hospital in London, where he proved to be an outstanding student and won prizes in bacteriology, ophthalmology and paediatrics. After qualifying in medicine in 1939, he spent a year as Resident Medical Officer at Hillingdon County Hospital before returning to Cambridge as Demonstrator in Anatomy in 1940. There he was kept busy teaching and had relatively little time, or money, for research. However, he was developing a remote control method of stimulating the brain, for in those days hormonal reactions were, in general, believed to be somewhat slow, and it seemed that a means of exciting the hypothalamus of conscious animals for many days or weeks would have immense experimental value. For this purpose, a pick-up coil consisting of 1,500 turns of enamelled fine copper wire

Donovan

67

formed into a coil 2 cm in diameter and insulated overall in bakelite varnish was fixed to the roof of the skull. From this a unipolar stimulating electrode of glass-insulated platinum wire ran vertically down into the brain while the secondary electrode was a silver plate placed beneath the scalp over the frontal bones. Stimulation was achieved by placing the coil, and animal, within a strongly fluctuating magnetic field. The technique was first tested by applying it to the study of the antidiuretic and oxytocic activities of the neurohypophysis, and formed the basis of a thesis submitted for the award of a MD degree in Cambridge in 1944. A more readily available report was later published in the Philosophical Transactions of the Royal Society in 1947. The later versions of this equipment, which could provide for the simultaneous stimulation of eight rabbits, could always be relied upon to impress visitors to his laboratory. Alongside that work, a study of the innervation and blood supply of the adenohypophysis of several species was undertaken in the early 1940's with J.D. GREEN, who was a fellow Demonstrator in Anatomy at that time. In an important paper in the Journal of Endocrinology in 1947, they suggested that, in the

absence of a well-marked nerve supply, the pars distalis was controlled by the brain through the portal system of vessels. Having written ‘Sufficient evidence is not available to prove neurohumoral control of the adenohypophysis, but we feel this theory has much to support it’, HARRIS set out to provide the necessary facts. The first momentous steps in that direction came in the form of experiments involving division of the pituitary stalk in rats. Similar studies had been performed by others but very varied results had been obtained, largely because vascular connections between the brain and pituitary gland were rapidly reconstructed. In HARRIS’ work, blood vessel reconnection was prevented by inserting a plate of waxed paper between the cut ends of the stalk, when hypofunction of the pars distalis ensued. In other animals in which a plate was not introduced and blood vessel regeneration allowed, normal endocrine activity was resumed. The use of waxed paper as a barrier permitted the preparation of serial sections through the operation site and so facilitated the demonstration of the presence, or absence, of vascular regeneration.

The special importance for pituitary function of blood derived from the median eminence was next established in work with DORA JACOB-SOHN, who with Professor A. WESTMAN in Lund, had published many

68

Donovan

papers on the effects of transection of the pituitary stalk in rats and rabbits between 1937 and 1945. Work on the consequences of transplantation of pituitary tissue away from the sella turcica was begun by HARRIS and JACOBSON in Cambridge in 1949. Although preliminary findings were published later that year the definitive results were first reported during a famous meeting at the Ciba Foundation in London in 1951, when it was shown that, if pituitary tissue taken from newborn young was transplanted to the median eminence or to the surface of a temporal lobe of the hypophysectomized mothers, only those grafts in contact with the median eminence showed good cellular differentiation and functioned in a normal manner. Clearly the median eminence produced some factor essential for hormone production by the anterior pituitary gland.

The attractive simplicity of the neurohumoral concept, and the explanation it provided for many contradictory observations in the literature, as well as convergent work in other laboratories, led to its wide adoption by endocrinologists. R.O. GREEP predicted in 1961 that the neurovascular hypothesis ‘will likely go down as one of the most important conceptual formulations ever made in the endocrine field’. However, some remained quite unconvinced. Professor S. ZUCKERMAN of the University of Birmingham (now Lord ZUCKERMAN) was a notable sceptic and, with A.P.D. THOMSON, argued that the hypophysial portal vessels were not essential for normal gonadotrophin secretion in the ferret. This work was repeated, but not confirmed, by HARRIS and DONOVAN and the resultant controversy over the interpretation of experimental observations was of more than local interest.

HARRIS did not limit his researches to the function of the hypophysial portal vessels. During his Cambridge years he was examining the hypothalamic control of ACTH secretion with H. COLFER and J. DE GROOT, and of TSH secretion with K. BROWN-GRANT and C. VON EULER, whilst study of neurohypophysial function was sustained with B.A. CROSS. Such studies were characterized by a meticulous surgical technique and elegant experimental design. Alongside his experimental work, HARRIS published a major survey of the information relating to the neural control of the pituitary gland in *Physiological Reviews* (1948), and less extensive accounts in the *British Medical Journal* and *British Medical Bulletin*. These enhanced his reputation as a scientist and tended to define the area of study coming to be known as neuroendocrinology. Indeed, he applied this name to his

Donovan

69

new department upon moving to the Fitzmary Chair of Physiology at the Institute of Psychiatry in the University of London in 1952.

For the next ten years HARRIS was happily occupied in fostering the development of his speciality. In collaboration with visiting workers from many parts of the world he explored various facets of the control of adrenal, thyroid and ovarian function. Continuing efforts were made to isolate and purify luteinizing hormone releasing factor and his group was one of the first to obtain an active extract. The wider aspects of the feedback action of target hormones upon the brain were not neglected and studies on the action of testicular hormones during sexual differentiation of the brain and of the hypo-thalamic locus of action of oestrogenic hormones in promoting sexual behaviour were profoundly influential.

Because of his wide interests and warm personality he was a welcome participant in research conferences on both sides of the Atlantic and a splendid ambassador of British science. In 1953 he was elected a Fellow of the Royal Society and in 1955 published his classic monograph on the Neural Control of the Pituitary Gland, which quickly sold out. Though often urged to prepare a new edition, he took greater pleasure in active research and had to be prised out of his laboratory. Nevertheless, he was persuaded to edit a treatise on The Pituitary Gland [Butterworths, London 1966] in which the controlling mechanisms were treated exhaustively. This task, as I can testify, proved to be more burdensome and exasperating than expected but the prolonged gestation eventually proved fruitful.

The eminence of GEOFFREY HARRIS as a scientist and teacher prompted a number of attempts to wean him from the Institute of Psychiatry, but only that from the University of Oxford proved irresistible and in 1962 he succeeded Sir WILFRED LE GROS CLARK as Dr. LEE’s Professor of Anatomy and Head of the Department of Human Anatomy. There he was able to develop his interest in the teaching of preclinical subjects and, appropriately, was concerned to promote interdisciplinary co-operation. He also encouraged the application of the hormone assay techniques developed in his Neuroendocrinology Research Unit (financed separately by the Medical Research Council) to the variety of endocrinological, gynaecological and psychiatric problems facing the clinicians in the local hospitals. In Oxford, as in London, many honours came to him. Last summer he was awarded

70

Donovan

the Dale Medal of the Society for Endocrinology and his review lecture on Humours and Hormones makes fascinating reading.

GEOFFREY was a sociable character and enjoyed company. Not the least of the benefits accruing to those privileged to work in his laboratory were the opportunities for meeting the succession of top flight teachers and investigators who came to visit him. Many an enthralling endocrine, or other, topic was explored over a glass of beer. Though pleased, he was always faintly embarrassed by the position he came to occupy as a father-figure to neuroendocrinologists. He felt that such status was accorded only to the old and infirm and that he fell into neither category. Nevertheless, it is fitting that he was so recognized during his lifetime. He died at the early age of 58, after a short illness, on the 29th November 1971.