THE NEUROHYPOPHYSIS

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HELLER

Proceedings of the Eighth Symposium of the Colston Research Society held in the University of Bristol, 1956

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THE NEUROHYPOPHYSIS

Edited by

H. HELLER

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held in the University of Bristol
April 9th — April 12th, 1956

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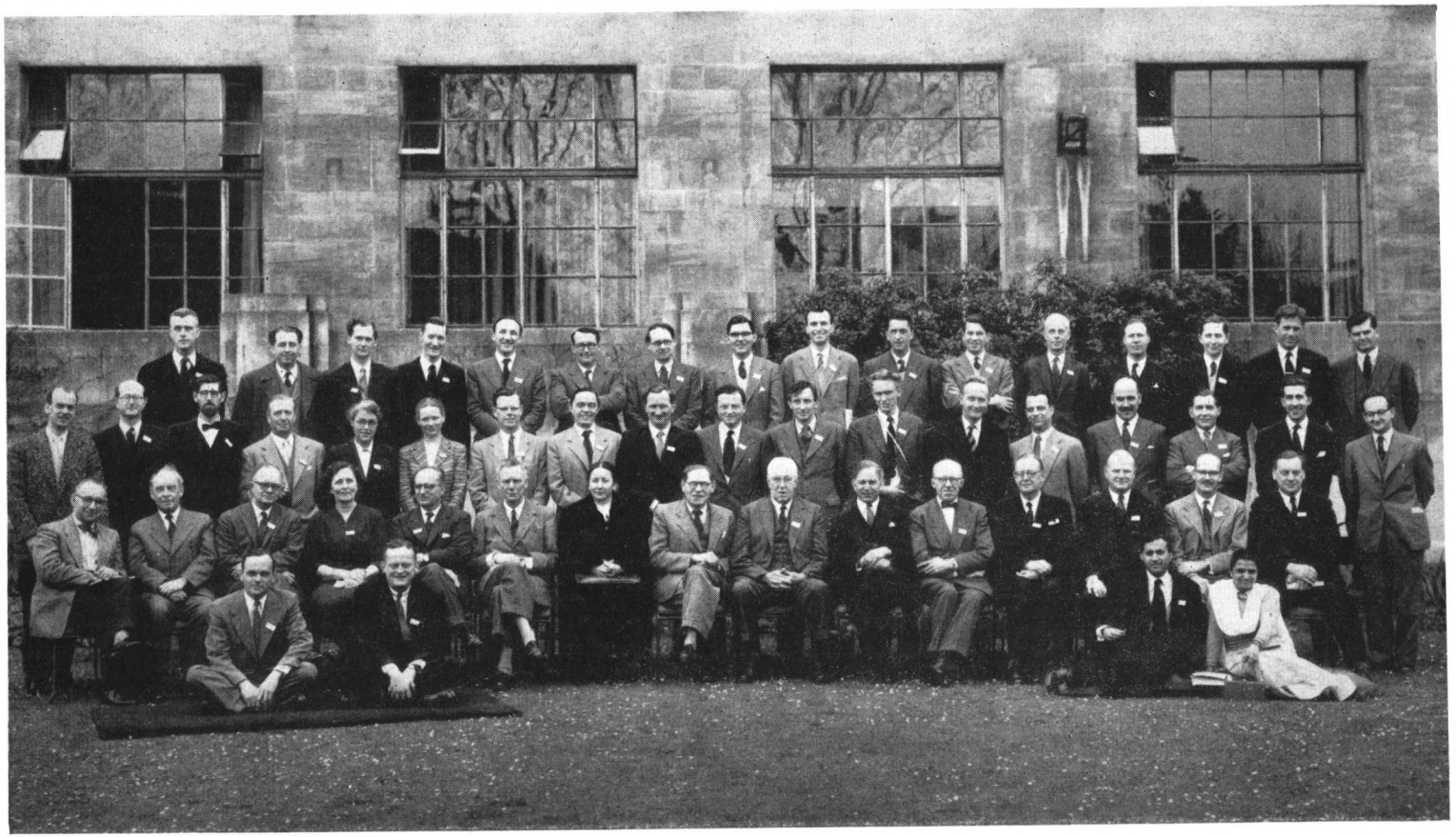

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Foreword

THE name of Edward Colston, the great seventeenth-century philanthropist and educationalist, is associated in Bristol with a number of scholastic and charitable institutions. It was adopted by a group of public-spirited citizens when, in 1899, they established the 'University College Colston Society', with the aim of fostering the young and struggling University College. For a decade it played a part in the movement which culminated in the institution of the University of Bristol in 1909.

The Society then changed its name and made its object more precise: it became the 'Colston Research Society' and devoted itself to the encouragement of original work in the University. It made grants for the purchase of apparatus and for the other expenses of research. As resources increased activities expanded and, notably, in the later thirties the Society financed a full-scale Social Survey of Bristol.

After the war a new reconsideration of policy led to the decision to devote the major part of the Society's efforts to the promotion of an annual symposium, the first being held in 1948. The rapid growth of the symposium as a means for the advancement of knowledge is one of the remarkable features of the intellectual life of recent years. Usually such meetings are fostered by bodies interested in one particular field of learning. As the list of titles (on the page opposite) shows, no such limitation applies to the symposia of the Colston Research Society. That the subject should be one at an interesting and active stage of development is the main factor in making a choice. The fact that the symposium is held in one of the younger seats of learning, with its home in an historic city, is a stimulus not only to the University but also, we believe, to the visiting guests who have come from many countries. The publication of the proceedings ensures the communication of the papers and discussions to wider circles.

As President of the Society for the year 1955-56 it was my privilege to preside over the eighth symposium, on 'The Neurohypophysis', the proceedings of which are printed in this, the eighth volume of the Colston Papers.

M. SKENE

Preface

THIS Symposium on the Neurohypophysis was the first international meeting devoted solely to the subject. It mirrors not only the diversity of aspects of the theme but also the rapid progress in recent years in the study of this involved endocrine system. This progress has been essentially twofold. Firstly, there is now strong suggestive evidence that the neurohypophysial hormones are elaborated not in the posterior pituitary lobe but in the hypothalamus and several of the papers read were concerned with the implications of this concept. Secondly, the chemical nature of the active principles—in some mammalian species at least—has been established. However, as Sir Henry Dale reminded us in his opening address, the physiological significance of the neurohypophysial hormones is known only incompletely. Admittedly, the regulatory role of the antidiuretic principle in the water metabolism of mammals (and most likely in that of 'lower' vertebrates) can no longer be doubted but the importance of the other pharmacologically demonstrable effects of posterior pituitary extracts is as yet based less securely. While, for example, there is strong evidence that oxytocin is normally implicated in the complex mechanism of lactation, its role in parturition is far from clear. Moreover, as is apparent from experimental results reported in this symposium, the neurohypophysis may have some further 'physiological' functions with which we are even less perfectly acquainted: vasopressin may in certain circumstances be concerned with the regulation of blood pressure; oxytocin may play a role in renal electrolyte excretion and may also be involved in the uterine mechanism for the ascent of spermatozoa.

There is another unsolved (or only partially solved) problem which was frequently mentioned, namely that of the estimation of the neurohypophysial hormones in body fluids. This has been achieved reliably when the concentration of exogenous or endogenous hormone is relatively high but the normal blood levels of the posterior pituitary hormones in animals or man have not been established. Until this has been done, clinical research on neurohypophysial function will obviously be severely handicapped. For this reason, and not only because of the limited time, papers on clinical aspects were deliberately excluded from the symposium. But as this volume shows, the subject was otherwise treated on a broad basis which included the comparative physiological approach.

There remains the pleasant duty to thank the individuals and organizations that made this symposium possible: First and foremost the Colston Research Society, and in particular its President, Professor M. Skene, and its Secretary, Mr. R. H. Brown, whose help has been invaluable. Secondly Sir Henry Dale and the Wellcome Trust for their generous grant which enabled us to invite speakers from the United States and Canada. I am also much indebted to Dr. S. J. Folley, Chairman of the Society for Endocrinology, and Dr. G. E. W. Wolstenholme, Director of the Ciba Foundation, for giving me their advice in the early stages of organizing the symposium, and

to Sir Lionel Whitby, Regius Professor of Physic and Master of Downing College, Cambridge, who accepted the onerous task of acting as Guest Speaker at the Reception of the Colston Research Society. Finally, I should like to express my sincere thanks to Dr. R. J. Fitzpatrick who acted as secretary to the symposium and who carried the main administrative burden, to Miss A. T. Walker and her staff who looked after the members of the symposium at Manor Hall, to Dr. M. Ginsburg who acted as Recorder, to Miss G. H. Pope whose secretarial services have helped so much in the preparation of the manuscripts, to Messrs. J. G. Lane and K. Lederis for technical help during and after the symposium and last but not least to the printers, Messrs. J. W. Arrowsmith Ltd.

H. HELLER.

Bristol, 1956.

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Contents

Evidence concerning the endocrine function of the neurohypophysis and its nervous control

by

SIR HENRY H. DALE

THE 1891 edition of Michael Foster's then justly famous *Text-Book of Physiology*, which provided the basis for my own undergraduate studies of the subject when these began, in 1894, was curtly explicit in its account of the knowledge then available concerning the functions of the pituitary body. 'With regard to the purposes of the organ as a whole', it stated, 'we know absolutely nothing'—a statement which, you may imagine, was not without an aspect of reassurance, for a student with an examination in prospect. And, when the first evidence, to suggest a function for this previously mysterious organ, appeared a year later, in 1895, this was concerned, as was still later to be made clear, with only one of the parts of its composite structure, namely with its posterior lobe, the neurohypophysis, which is the subject to which our discussions in this symposium are to be limited—except, of course, in so far as some contributor may need to mention data which are more directly concerned with the anterior lobe—the adenohypophysis—or with the so-called 'pars intermedia', on account of light which they may throw indirectly upon the functions of the neurohypophysis and the mechanisms of their control, which are on this occasion to be our sole concern.

The first evidence, then, suggesting any function for the pituitary body, and for the neurohypophysis in particular, was presented in a short paper by George Oliver and E. A. Schäfer (1895). This was, in effect, a supplement to their main paper on the remarkable effect on the circulation of an extract of the suprarenal gland—a potent action which they had seen and reported briefly in the previous year, 1894, when Dr. Oliver, the enterprising physician from Harrogate, had first persuaded Professor Schäfer, inclined to be impatient and incredulous, to try the effect of injecting such an extract into a vein of an anaesthetized dog, at the end of an experiment which Schäfer had been making with a different object. And having, in their full paper in the following year, given an extended account of this astonishing activity of a suprarenal extract, and having shown that the substance responsible for it was obtainable only from the medulla, Oliver and Schäfer were naturally curious to discover whether other ductless glands contained any comparable, immediately active substances. They reported the results of this survey in the paper which directly followed that on the suprarenal extract, in the same number of volume 18 of the *Journal of Physiology*, published in 1895. And there you can find this first account of the activity, with intravenous injection, of an extract prepared from the whole pituitary body, this being the only one of the other glandular extracts which they tested, which showed a pressor, or, indeed, any other specific action on the circulation, comparable in intensity with that which they had observed with the suprarenal extract; the effect

of the pituitary extract, though it was much the more persistent, being the less impressive of the two, because it was wholly due to an intense vasoconstriction, and showed none of the cardio-acceleration which contributed so much to the suprarenal effect.

It was W. H. Howell (1898) who, some three years later, showed that the substance responsible for this pressor action of a pituitary extract was obtainable only from one part of the organ, and, rather surprisingly, only from its posterior, neural lobe. Howell also showed that, when the prolonged pressor effect of a substantial first injection had subsided, the animal was almost completely insensitive to the action of a further, similar, or even larger injection, and remained thus refractory for a period up to several hours, according to the size of the dose responsible for this 'tachyphylaxis'. In the following year, Schäfer & Vincent (1899) confirmed both these observations. They were puzzled, as were others later, by the finding, which they were nevertheless obliged to confirm, that such a powerful, immediate, pharmacodynamic activity should be due to something present only in the posterior lobe of the pituitary body. It would have been much easier, of course, to credit the anterior lobe, so obviously glandular in structure, with the production of something so highly and specifically active; whereas the posterior, neural lobe, from which alone the activity could be extracted, appeared to consist almost entirely of nerve-fibres and neuroglia, and to be, in fact, a kind of extension, through the infundibular stalk, from the grey matter of the floor of the third ventricle, though almost devoid of nerve-cells. Schäfer & Vincent ascertained, by experiment, that otherwise similar extracts, made from grey matter from other parts of the brain, did not, in fact, exhibit any activity of this kind. And this apparent anomaly, of the production from what looked like the almost purely nervous tissue of the posterior lobe, of an intensely active substance which no other nervous tissue yielded, with the suggestion that, nevertheless, this part of the pituitary body, like the suprarenal medulla, ought to have an important endocrine function, continued for a number of years to puzzle and to disconcert the minds of physiologists who became interested in the problem. It seemed to be difficult for them to reconcile such a finding with their sense of physiological propriety, so that they became too eagerly alert, perhaps, for any evidence which might appear to offer a plausible way of escape from so embarrassing a paradox. A key to its meaning seems now, at length, to be offered by the novel and highly suggestive lines of evidence which have been followed in recent years, concerning the relation of the structures of the posterior lobe to the nerve-cells of the hypothalamic nuclei, and the dependence upon this connexion of the hormonal content of the lobe. And this appears likely to be one of the most important subjects for our consideration at this symposium. Since my own part in our discussion can be little more than reminiscence and gossip concerning a phase in the evolution of its subject now long past, I can contribute little to the consideration of this recent development, except to emphasize the genuine difficulty which earlier investigators found in this idea, that a tissue, while it appeared to consist almost entirely of nerve-fibres and neuroglia, could also function as an endocrine gland—a difficulty which was certainly not diminished when it was found that the posterior lobe extract had other immediate physiological actions, comparable in interest and intensity to the pressor activity which had first been noticed.

Magnus & Schäfer (1901) observed that an intravenous injection of the pituitary posterior lobe extract into an anaesthetized animal produced also, after a latency, a conspicuous increase in the rate of the secretion of urine; and, a few years later, this observation was confirmed and extended by Schäfer & Herring (1906). It is, of course, now generally recognized that this effect, definite and striking though it is, and regularly as it can be reproduced under the given conditions, is, in fact, an anomalous and artificial result, due to the depressed kidney function produced by the anaesthesia, and to the use of the intravenous route for administering the pituitary extract in relatively large doses. It was later recognized that the truly physiological, *anti*diuretic effect, now accepted as the genuine, hormonal action on the kidney, could only be reproduced artificially if the extract was injected hypodermically, or in very small doses intravenously, and into unanaesthetized animals.

Before we discuss further this natural, antidiuretic effect, however, I ought to make brief mention of another action of the posterior lobe extract, on the plain muscle of the wall of the uterus, which I first described incidentally (Dale, 1906), having come across it almost by accident, when I recorded the already known pressor action for another purpose. I was studying a now familiar, but then newly discovered, action of certain alkaloids of ergot—what has since been termed a 'sympatholytic' action—in which augmentor actions of adrenaline, and corresponding effects of sympathetic nerves, transmitted as we now know by the release at their endings of adrenaline and its primary homologue, are suppressed, or replaced by inhibitor effects. In a female cat, at an early stage of pregnancy, I happened to be recording the arterial blood-pressure and the activity of the muscular wall of the uterus; and, by a previous dose of an ergot preparation, the actions of adrenaline on both of these had been so reversed, that each injection of it now produced a fall of the arterial pressure, in place of the normal rise, and a relaxation of the uterus, in place of the previous contraction. I thought that it would be of interest to know whether the pressor effect of the pituitary posterior lobe extract would also be reversed, like that of adrenaline, or, as I expected, unchanged. When, accordingly, I injected an appropriate dose of the pituitary extract, I observed that it had not only retained its normal pressor action, in contrast to the reversed, depressor action of adrenaline, but that it also produced a powerful, contractile response of the uterus, not hitherto described. Other experiments, made then to study this action deliberately (Dale, 1909), showed that it was produced on the uterus in all species and in various physiological conditions, even in those in which the natural effects of adrenaline were to produce simple inhibition of the organ's tone and rhythm. It was clear, then, that these peripheral actions of the pituitary posterior lobe extract, unlike those of adrenaline, had no relation to the effects of impulses in the sympathetic or any other autonomic nerves. And I took the opportunity to see also for myself the diuretic action on the anaesthetized animal, of which a full description had then recently been given by Schäfer & Herring (1906); also to make some observations on the nature of the substance, assumed then to be only one, which was responsible for all these actions, showing it to be excreted in the urine, stable to peptic digestion and to boiling at a mildly acid reaction, but readily destroyed by tryptic digestion or by hot alkalis, and to have, accordingly, the characters of a relatively simple polypeptide. For the time being, it seemed to me natural to suppose, in default of good