Neural Control of the Pituitary Gland

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by

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PREFACE

The suggestion of writing a monograph, under the auspices of the Physiological Society, was accompanied by the comments that such a monograph should—"not be written like a review article . . . giving an accumulation of all references . . . but it should be a book which will be particularly useful for the advanced student in Physiology. . . ." The following pages have therefore been based on a series of lectures given in the course on Physiology for the Part II of the Natural Science Tripos, Cambridge University. They have been written for the student who will, within the course of a few years, be standing on his own feet in the research field. The other worker in mind has been the specialist, in his own field, who is interested in physiology in general. For these reasons no attempt has been made to give a complete list of all the literature in this subject, except in isolated instances, as in Chapter 3, where the data have seemed to indicate a "negative" conclusion, or to present the material from an unbiased point of view. The attitude adopted has been rather to present the more important literature, and the points of view most likely to be found true in the light of future work—as it seems to the author.

I should like to express my sincere thanks to Mrs. E. M. Collen for her invaluable help and advice in preparing the manuscript, and to Mr. H. J. Campbell for his skilled aid in preparation of many of the illustrations. I am indebted to the following workers for their kind permission to reproduce various figures: Professor Sir Wilfred Le Gros Clark, F.R.S., Professor G. B. Wislocki, Professor E. B. Verney, F.R.S., Dr. W. J. Atwell, Dr. P. M. Daniel, Dr. J. D. Green, Dr. Dora Jacobsohn, Dr. Marjorie M. L. Prichard, Dr. H. Rydin, Dr. A. Westman, Dr. G. P. Xuereb; and to my co-workers Drs. K. Brown-Grant, J. G. Gibson, C. von Euler, S. Reichlin and A. C. R. Skynner, and to the editors of the following journals: the *Journal of Physiology*, *Journal of Endocrinology*, *Quarterly Journal of Experimental Physiology*, *Research Publications of the Association for Nervous and Mental Disease*, *American Journal of Anatomy*, *Acta Pathologica Microbiologica Scandinavica*, *Proceedings of the*

Royal Society, the Philosophical Transactions of the Royal Society, and *the Journal of Anatomy (London).*

I am greatly indebted to my wife for her patience and help.

In conclusion I should like to give the translation (for which I am grateful to Miss J. E. Shadwell) of a paper which may be taken as a model for the following reasons: (a) it is the first paper of any importance in the field of endocrinology, (b) it is brief and concise, (c) the work recounted is beautifully planned and economical in the use of animals, and (d) the results are clear.

"Transplantation of the testes" (*Arch. Anat. Physiol.,* 1894), by Professor Berthold, Göttingen.

On August 2nd this year I castrated six young cocks, i.e. a, b, c of three months, and d, e, f of two months. In some of these birds the wattle, the comb or the spurs were removed. Both testes were removed from a and d; these birds later showed the typical nature of the eunuch, behaved in a cowardly way, only occasionally, briefly or without energy fought with the cocks and emitted the well-known monotonous sounds of the eunuch. Comb and wattle became pale and developed only slightly; the head remained small. When these birds were killed on December 20th an insignificant, hardly perceptible cicatrix was found in place of the testes. The seminal conductors were seen to be thin, delicate little fibres.

Cocks b and e were castrated in the same way but only one testis was removed from the body, the other remained isolated in the abdominal cavity. In cocks c and f, however, both testes were removed from the abdominal cavity and then one testis of cock c placed in the abdominal cavity of cock f, and one testis of cock f in the abdominal cavity of cock c, in the bowels.

The four cocks (b, e, c, f) showed in their general behaviour the nature of uncastrated birds, they crowed quite audibly, were often fighting among themselves and other young cocks and showed the usual friendly interest for the hens; also their combs and wattles developed normally.

Cock b was killed on October 4th; the (one) testis had healed in its original place, had increased by more than half in size, numerous blood-vessels were present, the seminal canals were very clear and on cross section emitted a whitish liquid containing large and small cells but no spermatozoids.

The fairly well developed combs together with the wattles were removed from cocks c, e, f, and the abdominal cavity opened on the same day in order to examine the testis. In cock e I found the testis in the normal place as in the dead cock b; I detached it, drew it out of the abdominal cavity and found it to be similar to that of cock b. The abdominal wound soon healed, comb and wattle cicatrized but did not grow again. Instead of crowing as before the animal only made the usual eunuch sounds; it no longer bothered about the hens nor fought with other cocks but rather kept a measured distance from them and showed altogether the nature of a true eunuch.

In cocks c and f there was no sign of the testes in their usual place. Combs and wattles grew again, the birds retained their cock-like nature, crowed as before and also retained their former behaviour in respect of hens and other cocks. These two cocks were killed on 30th January 1849. There was no sign of the testes in their normal place; in cock c the testis was seen to have grown on the surface of the colon away from the back and bordered on both sides by the end of the caecum without however coalescing with the latter. In cock f the same thing had occurred but the site of adherence was further back towards the middle of the caecum. The testis was, in each bird, oval in shape, 15 lines long, 8 wide and 6 thick. Strong branches of the mesenteric vessels went up to the testis, penetrated in several places into the interior and could be traced to the seminal canals. As I dissected the testis a whitish milky liquid ran out which had exactly the same consistency and smell as normal cock semen. Under the microscope I recognized in this liquid very many small and large cells of 1/450–1/150 lines in diameter, and in addition numerous spermatozoids with the most beautiful ciliary movements, which increased considerably with the addition of a drop of water.

The following general physiological results emerge from these investigations:

(1) It is possible to transplant testes; they heal up after they have been removed from the body; the testis of one individual may be transplanted into another and it can heal in the same place whence it was removed or in quite a different place, i.e. on the walls of the bowels.

(2) The transplanted testis develops its characteristic features as a seminal organ, even in a different place, the seminal canals widen and become bigger and carry out their normal function while they secrete normal semen containing spermatozoids. The same occurs here as in plants, where the graft continues to grow with its own specific characteristics on the wild tree and brings forth its own fruit, not that of the wild tree.

(3) It is a known fact that severed nerves grow together again and that those parts, the nerves of which have been cut, regain feeling and movement when the nerves have healed. That the nerve fibres which belong together do not always unite in such instances, can be shown from the fact that skin from one part of the body can heal with that of another. From the fact that a detached testis heals on to quite a different part of the body, especially on to the intestine, and continues to develop as a semen-producing organ and secretes genuine semen, it is obvious that there are no specific seminal nerves and this is one of the chief arguments against the existence of specific trophic nerves, of which the sympathetic nervous system has until now been thought to consist.

(4) The remarkable consensual and antagonistic interaction of individual and communal life which develops at puberty and persists into an advanced age, is also evident when the testes are removed from their original place and from their nerves and have healed on to quite a different part of the body. With regard to voice, reproductive instinct, love of fighting, growth of the comb and wattle these birds remain true cocks. As the testes transplanted to a different place can no longer be connected with their original nerves, and as there are no specific nerves directing secretion as is clear from paragraph 3, it follows that the consensus in question is conditioned by the secretion of the testes, i.e. by their action on the blood and then by the consequent action of the blood on the whole organism of which, it must be admitted, the nervous system forms a very substantial part.

Arch. Anat. Physiol., 1849, 42–46.

CONTENTS

CHAPTER 1

INTRODUCTION

Meaning of the term hormone

The first demonstration of an internal secretion is to be found in the clear and precise experiments of Berthold in 1849. The significance of this work was overlooked for many years until Bayliss and Starling reported their results regarding secretin, in 1904. They emphasized the fact that a specific chemical substance may be produced in an organ or tissue, may be liberated into the blood-stream and carried to excite another organ, situated at a distance. Such substances are essentially chemical "messengers", and in searching for a name to characterize them this point was kept in mind. Eventually Mr. W. B. Hardy proposed "hormone", derived from ὁρμάω ("I arouse to activity"), and although the property of a messenger is not suggested by this term, it was finally adopted (see Starling, 1905, and Bayliss, 1915).

An essential feature of a hormone is the fact that it is secreted into, and carried by, the blood-stream. Nowadays there is some need for another term to represent the precursor of a hormone as it exists in the gland of origin. This precursor may, or may not, be the same chemical substance as the hormone itself, but a separate term would emphasize the dual nature of hormonal formation and secretion. An endocrine gland (such as the thyroid) subtracts simple substances from the blood-stream and builds them into more complex compounds which are stored in the gland for a variable period. This store is drawn upon according to the requirements of the organism. In many cases it seems that a mother molecule is split into simpler fractions, or changed in some way, before being liberated into the blood. This self-evident sequence of events is mentioned here for two reasons. Firstly the "hormone" content of a gland clearly varies with both the rate of formation and the rate of liberation of the hormone into the blood. Therefore the "hormone" content of a gland, by itself, gives no indication of the activity of the gland. Secondly the answer to the question—"How many hormones does a particular endocrine gland produce?"—may depend on whether the term hormone is taken to mean the active principles stored in the gland, or more correctly, the principles as liberated into the blood stream. The case of the adenohypophysis (anterior pituitary gland) is, in this respect, obscure. Six "hormones" are now generally ascribed to this gland on the grounds that it is possible to prepare six extracts from the gland with distinct physiological activities. However, it is not certain that these so-called hormones are liberated as such into the blood. It may be that only two or three compounds pass from the adenohypophysis into the blood, but that these compounds possess two or more of the activities usually attributed to the six "hormones". The ultimate test by which the number of substances secreted by a given endocrine gland will be decided is the qualitative and quantitative analysis of the hormones in the venous blood from the gland. The time when such tests are practical and accurate seems to be approaching for some glands such as the adrenal medulla and cortex, but it seems still remote for others such as the adenohypophysis.

Levels of endocrine activity

(*a*) *Autonomous activity.* When deprived of their "physiological stimulus" the level of activity of the various glands becomes markedly decreased or disappears entirely. Thus the denervated neurohypophysis ceases to secrete and undergoes atrophy, and the denervated adrenal medulla shows a very reduced activity and becomes relatively inexcitable to direct electrical stimulation. In hypophysectomized animals the ovaries and testes atrophy and reproductive activity ceases, although the initial stages of oogenesis and spermatogenesis still occur in some species, such as the rat; the adrenal cortex atrophies though some secretory action, sufficient to maintain life, is maintained; and thyroid activity is greatly reduced though not abolished. Similarly if the anterior pituitary is deprived of its "physiological stimulus", that is if the pituitary stalk is cut or if the gland is transplanted to a site remote from the sella turcica, then gonadal atrophy occurs, growth ceases and the thyroid and adrenal cortex undergo atrophy. Since the reduction in activity of the thyroid and adrenal cortex is not so complete, according to some accounts, in the pituitary transplanted as in the hypophysectomized animal, it appears that residual secretion of thyrotrophic and adrenocorticotrophic hormones still occurs. It might be pointed out also that there is not the same tendency to hypoglycaemia after stalk section as after hypophysectomy.

It may be said, then, that some glands, although atrophic, retain a residuum of activity when deprived of the main stimulus to their normal function, though others, such as the posterior pituitary gland, become completely inactive.

(*b*) *Normal activity.* The central nervous system is ultimately responsible for maintaining the activity of most endocrine glands at normal levels and, to a large extent, for regulating their activity according to the requirements imposed by a varying environment.

Inter-relationship between the nervous system and endocrine glands

In general, a reciprocal relationship exists between the central nervous system and the endocrine glands. Firstly the nervous system regulates, directly or indirectly, the functional activity of the adenohypophysis, neurohypophysis, ovaries, testes, thyroid, adrenal cortex and adrenal medulla. Secondly the hormones derived from these glands, or the actions they exert peripherally, react back on the nervous system and thereby produce a variety of neurological effects.

(*a*) *Neural control of endocrine glands.* In 1925 Starling and Verney described two extreme methods used in physiological investigation; firstly the synthetic method whereby a particular organ is studied in isolation, the normality of the environment being sacrificed to obtain simplicity and a higher degree of experimental control; and secondly the analytic method whereby the organ is studied in a relatively intact animal, thus sacrificing much control of the variable conditions in order to obtain a more normal environment. Most organs and systems were first studied in the more or less isolated state, and their intrinsic properties investigated, before being studied in the more intact animal in which their functions relative to other systems, and relative to the animal as a whole, were matters of concern. Much is now known regarding the anatomy and histology of the endocrine glands and the biochemistry and physiological properties of the compounds they secrete, but still only little is known as to the manner in which the activity of the different glands is co-ordinated with that of the other systems of the body, or the way in which this activity is varied according to changes in the environment. It is clear that environmental factors exert a profound effect on the secretory activity of these glands, but the mechanism by which these effects are produced is known only in outline. For example, trauma to a limb may result in a flexor reflex response in that limb, and also to a discharge of hormones from the adrenal cortex. Much could be said of the sequence of events starting in trauma and ending in contraction of the flexor muscles, but until recently very little could be said about the mechanism linking trauma and discharge of the adrenal cortical hormones. The synthetic approach has been studied in detail but the analytic method has hardly been applied to the glands of internal secretion.

It is clear that the central nervous system is largely responsible for correlating endocrine activity with that of the other systems of the body, and with the varying requirements of the organism due to environmental change. In the case of two endocrine glands, the neurohypophysis and the adrenal medulla, it is easy to understand how such control can be mediated for both of these glands are richly innervated. The neurohypophysis receives a direct nerve supply from the hypothalamus, known as the hypothalamo-hypophysial tract, whilst the adrenal medulla is connected to the hypothalamus by descending tracts in the brain stem and spinal cord and by the final supply which passes in the splanchnic nerves and lumbar sympathetic chain. On the other hand the control exerted by the nervous system over the adenohypophysis, thyroid, adrenal cortex, ovaries and testes has been difficult to understand. These endocrine glands are clearly under neural control and yet they have a very scanty innervation, if any at all. The few nerve fibres that have been traced to some of these glands are in all probability vasomotor in nature, and not secreto-motor. The problem as to how these glands are influenced by nervous processes in the absence of a secreto-motor nerve supply, would be clarified if it could be found how the adenohypophysis is brought under neural control; for the thyroid, adrenal cortex and gonads would then be brought indirectly under similar control via the action of the anterior pituitary eutrophic hormones. There is now much evidence that the hypothalamus controls the activity of the adenohypophysis, and thereby the gonads, thryoid and adrenal cortex, through the hypophysial portal vessels of the pituitary stalk, and some such sequence of events as illustrated in Fig. 1 may be envisaged as relating the hypothalamus functionally with these glands, as well as with the neurohypophysis and adrenal medulla. The greater part of what follows (Chs. 2–12) is an attempt to analyse the

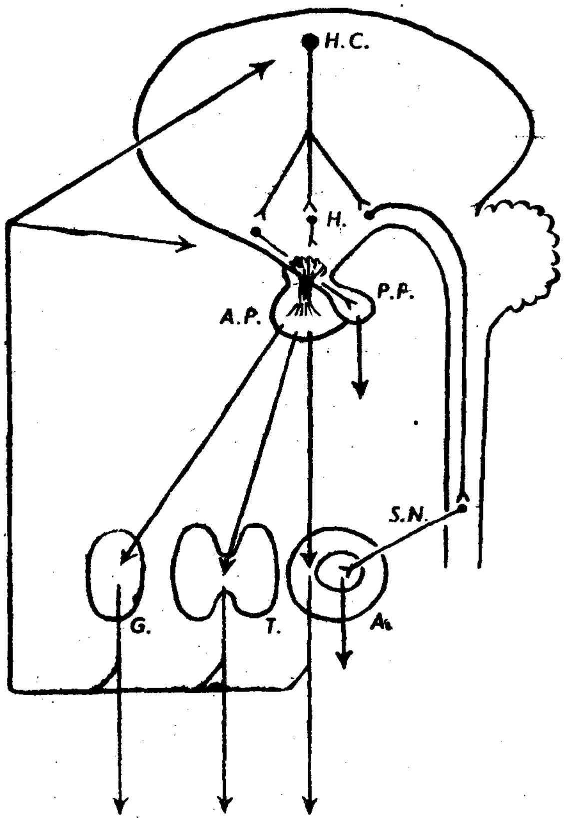

Fig. 1. Diagram to illustrate the reciprocal relationship between the central nervous system and endocrine system.

A., adrenal gland; *A.P.*, anterior pituitary; *G.*, gonads; *H.*, hypothalamus; *H.C.*, "higher centres"; *P.P.*, posterior pituitary; *S.N.*, splanchnic nerves; *T.*, thyroid.

mechanism by which the central nervous system, and the hypothalamus in particular, controls and integrates the activity of these glands.

(*b*) *Hormonal control of the nervous system.* It is clear that the interplay between the central nervous system and endocrine glands (at least the adrenal cortex, thyroid, ovaries and testes—the so-called pituitary target organs) is one of reciprocity (see Fig. 1). The target organ hormones seem to exert two main actions on the central nervous system. By means of a type of feedback mechanism they appear to exercise a fine control over their own secretion. For example, a rise in the blood oestrogen level depresses pituitary gonadotrophic secretion and so ovarian secretion of oestrogens. Whether this effect of a rise in concentration of a target organ hormone in the blood is due to an action on some cerebral mechanism such as the hypothalamus, which in turn affects pituitary secretion, or to a direct action on pituitary cells, or both, is uncertain—though the former possibility should be kept in mind. However the secretion of a particular trophic hormone is affected by other factors as well, and the final pituitary output seems to depend on the summation of effects produced by many stimuli, both humoral and neural.

Another effect of circulating hormones on the central nervous system results in modification of the behavioural reactions of the animal. As examples of this action might be quoted the psychological changes that occur throughout the different phases of the sex cycle, and the effect of disturbances in the blood level of the thyroid hormone. "A pinch too little of thyroxine spells idiocy, a pinch too much spells raving delirium" (Hoskins, 1941). It is very likely that such changes in the overt pattern of behaviour are directly due to the influence of the various hormones on the central nervous system, but little work has been performed in an attempt to analyse the detailed mechanism by which such effects are produced. This subject is discussed further in Chapter 13.

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CHAPTER 2

NERVE SUPPLY AND BLOOD SUPPLY OF THE ADENOHYPOPHYSIS (ANTERIOR PITUITARY GLAND)

In discussing questions involving the detailed anatomy of the pituitary gland the standardized nomenclature, suggested by Rioch, Wislocki and O'Leary (1940), will be used (Fig. 2). The *neurohypophysis* is described by these authors as consisting of three parts—the *median eminence of the tuber cinereum*, the *infundibular stem* and the *infundibular process* (lobus nervosus or neural lobe). The first two parts may be collectively referred to as the *infundibulum* or *neural stalk*. The *adenohypophysis* or *lobus glandularis* is likewise divided into three parts—the *pars tuberalis*, the *pars intermedia* and the *pars distalis*. The neural stalk, together with its sheath of portions of the lobus glandularis, is designated the *hypophysial stalk*.

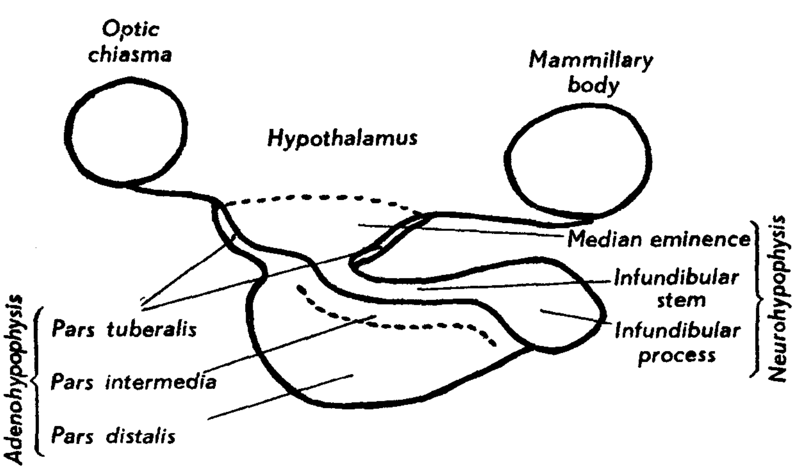

Fig. 2. Diagram of a sagittal section through the pituitary gland of a rabbit, to illustrate the terminology of Rioch, Wislocki & O'Leary, 1940.

MAJOR DIVISIONS AND SUBDIVISIONS OF THE MAMMALIAN HYPOPHYSIS
(after Rioch, Wislocki and O'Leary, 1940)

Adenohypophysis	*Lobus glandularis*	1. *Pars distalis*	anterior lobe
		2. *Pars tuberalis*	
		3. *Pars intermedia*	posterior lobe
Neurohypophysis	*Lobus nervosus* (*neural lobe*)	1. *Infundibular process*	
	Infundibulum (*neural stalk*)	1. *Infundibular stem*	Neural stalk together with sheath of portions of lobus glandularis, designated as *hypophysial stalk*
		2. *Median eminence of the tuber cinereum*	

The nerve supply and blood supply of the anterior pituitary gland, or more accurately, the adenohypophysis, refers to the supply of the three parts of the pituitary gland which are derived from Rathke's pouch of the embryo.

THE NERVE SUPPLY OF THE ADENOHYPOPHYSIS

Over a hundred years ago a nerve supply to the pituitary gland, originating from the sympathetic plexus around the carotid artery, was described by Bougery (1845). He suggested that the pituitary gland formed a link between the brain and the sympathetic nervous system, that is between the mind and the viscera. Since the time of Bougery, and especially since about 1920 when light was first thrown on the hormonal activities of the adenohypophysis by Philip Smith, H. M. Evans and others, the nerve supply of this part of the pituitary has been the subject of investigation by many workers. It has been suggested that it receives secreto-motor nerve fibres from three sources—sympathetic fibres from the plexus around the internal carotid artery, parasympathetic fibres from the petrosal nerves, and hypothalamic fibres from the median eminence and infundibular stem. [For further references to the literature on this subject see Harris (1948).]

Sympathetic supply

Dandy (1913) was the first to give a detailed description of the sympathetic pathway to the gland. He used the intravitam methylene blue method of staining these fibres in the dog, and observed nerve fibres leaving the sympathetic plexuses around the vessels of the circle of Willis, and passing down the pituitary stalk with the arterial supply to the gland. Hair (1938), working on the cat, likewise found a rich innervation passing with the vessels of supply to the gland, as did Truscott (1944) who studied the rat. Rasmussen (1938) in a detailed study of the innervation of the human hypophysis, supplemented by observations on the rat, guinea-pig, rabbit, cat, dog and monkey, found some sympathetic fibres passing from the cavernous plexus to the pars distalis, but in view of the fact that large areas of the pars distalis were found to be free of nerve fibres, he drew the conclusion that these fibres were most likely connected with the vascular system. Green (1951*a*) studied the innervation of the pituitary gland in seventy-five species of vertebrates from cyclostomes to man, and found perivascular fibres in the pars tuberalis, but not in the pars distalis of the hypophysis.

It may then be taken as established that sympathetic nerve fibres pass to the pituitary gland from the surrounding perivascular plexuses, but it is not yet clear whether the main secreting mass of the adenohypophysis, the pars distalis, receives any of these fibres, or what the nature (secreto-motor or vasomotor) of such fibres might be. It is very likely that the sympathetic innervation is destined mainly for the pars tuberalis, and that the pars distalis receives few, if any, fibres. This view is in accordance with that expressed by Green (1951*a*) after his comprehensive investigation of the problem, and it would indicate that the fibres are vasomotor in nature, for the pars tuberalis is the most vascular region of the pituitary gland, and as far as is known has no definite endocrine function.

Experimental data concerning the relationship between the cervical sympathetic system and anterior pituitary function is clear in its implications. Although many fragmentary claims have been made that stimulation or removal of the cervical sympathetic chain affects the secretion of gonadotrophic or thyrotrophic hormones, the fact that complete sympathectomy does not prevent normal reproduction in female cats (Cannon, Newton, Bright, Menkin and Moore, 1929), and does not cause any very significant change in the metabolic rate of cats (Cannon et al., 1929) or rats (Lee and Bacq, 1933) demonstrates that a sympathetic innervation of the pituitary plays no appreciable part in the control of secretion of the gonadotrophic and thyrotrophic hormones. The observations of Phillips (1942) that action potentials may be recorded from the pars distalis during electrical stimulation of the cervical sympathetic trunk, of Collin and Hennequin (1936*a* and *b*) and of Popják (1940) that histological changes in the pituitary and hypothalamus follow removal of the superior cervical ganglion, might be explained on a sympathetic vasomotor innervation of the hypophysial vessels. Two easily observable reactions that have been much used in investigating the effects of nervous stimuli on pituitary secretion are the pseudopregnancy response of the rat and the ovulation response of the rabbit, both elicited by sterile mating or some form of artificial stimulation. There is much evidence that in these reactions the anterior lobe of the pituitary gland is activated by a nervous reflex. Some workers have found that partial sympathectomy in the rat abolishes or reduces the pseudopregnancy response to artificial stimulation of the vagina or uterine cervix, and others (Friedgood and Cannon, 1936) have produced maturation of ova in the rabbit by electrical stimulation of the cervical sympathetic system. But again it is possible that these minor changes are due to vasomotor effects, since pseudopregnancy still follows sterile coitus in the partially sympathectomized rat (Vogt, 1933; Friedgood and Bevin, 1938) and ovulation still follows sterile coitus in the partially or completely sympathectomized rabbit (Haterius, 1934; Brooks, 1935). There is no sound evidence that a sympathetic innervation of the anterior pituitary gland plays any part in regulating the activity of this gland.

Parasympathetic supply

In 1932 Cobb and Finesinger, and Chorobski and Penfield, described a parasympathetic innervation of pial vessels in the cat and monkey. Nerve filaments were found to run from the greater superficial petrosal branch of the facial nerve to the carotid plexus and these were described as carrying vasodilator fibres. Following this discovery, Hinsey and Markee (1933) suggested that secreto-motor fibres might reach the anterior pituitary gland over a similar pathway, and Zacharias (1941) reported that in the rat a branch from the Vidian ganglion, situated at the junction of the greater superficial and great deep petrosal nerves, runs to at least the capsule of the pituitary gland. There then followed a