

STUDIES ON THE PITUITARY BODY. I.

THE PHYLETIC OCCURRENCE OF PITUICYTES, WITH A DISCUSSION OF THE EVIDENCE
FOR THEIR SECRETORY NATURE.

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(Plate v; five Text-figures.)

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Bucy (1930, 1932), using Penfield's modification of del Rio-Hortega's silver carbonate technique (specific for oligodendroglia and microglia), demonstrated the presence of characteristic glial cells in the pars nervosa of the bovine pituitary gland. These he termed pituicytes. They are not numerous and are scattered throughout the nerve fibres and connective tissue which constitute the main mass of the gland. Ibáñez (1935) has described nerve fibres and embryonic glial cells in the partes nervosae of young dogs and cats. He distinguishes three types of nerve terminal. Previous to Bucy and Ibáñez, Berkeley (1894*a, b*) and Retzius (1894) succeeded in impregnating pituicytes. They used the inadequate and non-specific Golgi method. Cameron (1936) states that pituicytes constitute the bulk of the human pars nervosa, but gives no reference. I cannot find any description of the cytology of the human pars nervosa in the literature, published after the work of Bucy, except that of Trossarelli (1935). He used the Donnagio technique and described small cells and unmyelinated nerve fibres. Bucy considers that methods applicable to glial tissue other than silver carbonate impregnation are useless for showing the real cytological nature of the structure.

Recently it has been demonstrated by Geiling, de Lawder, and Tarr (1934) that it is the pars nervosa that elaborates pitressin (pressor, anti-diuretic principle) and pitocin (oxytocic principle), and not the pars intermedia as was thought by Herring (1908) and Cushing (1933). Herring (1908, 1913) stated that the pituitary of the skate (*Raja clavata*) exerts neither pressor nor anti-diuretic effects, but Hogben and de Beer (1925) have shown it to possess oxytocic properties. Hogben and de Beer also found no pressor activity in skate pituitaries, but quite marked pressor and oxytocic activity in Teleost pituitary extract. They deduce from the oxytocic properties of the two glands, that probably pitressin is not absent from Elasmobranchs but is present in small quantity. Pitressin and pitocin are formed in all classes of the Tetrapoda (Herring, 1913; Hogben and de Beer, 1925).

No research work has been carried out on the phyletic occurrence of pituicytes. This work was accordingly attempted with the view of supplying a comparative account of the cytology of the pars nervosa in the vertebrate series, and especially of providing a description of the conditions in Elasmobranchs, and to correlate, if possible, the presence or absence of pituicytes with the presence or absence of the hormones.

The anatomical nomenclature used in the various groups of Vertebrates is that given by de Beer (1926).

The writer wishes to take this opportunity to express his thanks to Professor W. J. Dakin for advice, and to Miss G. Burns for the preparation of the photographs.

Cytological Technique and Materials.

The technique used was Penfield's second modification of Hortega's silver carbonate method (quoted by Penfield and Cone in McClung, 1937). Instead of using the freezing microtome, sections were cut by the paraffin method.

The forms studied were.—Class Mammalia: *Sarcophilus harrisii* (Marsupial).—Aves: *Gallus domesticus* (Fowl).—Reptilia: *Tiliqua scincoides* (Skink lizard).—Amphibia: *Hyla aurea*, *H. coerulea* (Frogs).—Pisces: *Neoplatycephalus macrodon* (Teleost fish).—Elasmobranchii: *Raja australis* (Skate).

Cytological Observations.

Sarcophilus harrisii.—The pituicytes impregnate well with the silver carbonate. Large amounts of connective tissue, as seen in the infundibular process of the ox, are not evident. Many of the pituicytes possess a vascular process which ends on the connective tissue investment of a blood vessel, and indeed many of the cells are orientated so that the vascular processes are at right angles to the vessels (Plate v, fig. 1). At the periphery of the gland also the pituicytes take up a position at right angles to the connective tissue covering. In other parts they exhibit no particular orientation and are distributed indiscriminately throughout the collection of nerve fibres which make up the main mass of the pars nervosa. Blood vessels are fairly numerous, but the vascular processes of some of the more remotely situated cells are extraordinarily long (Text-fig. 1, cell 3).

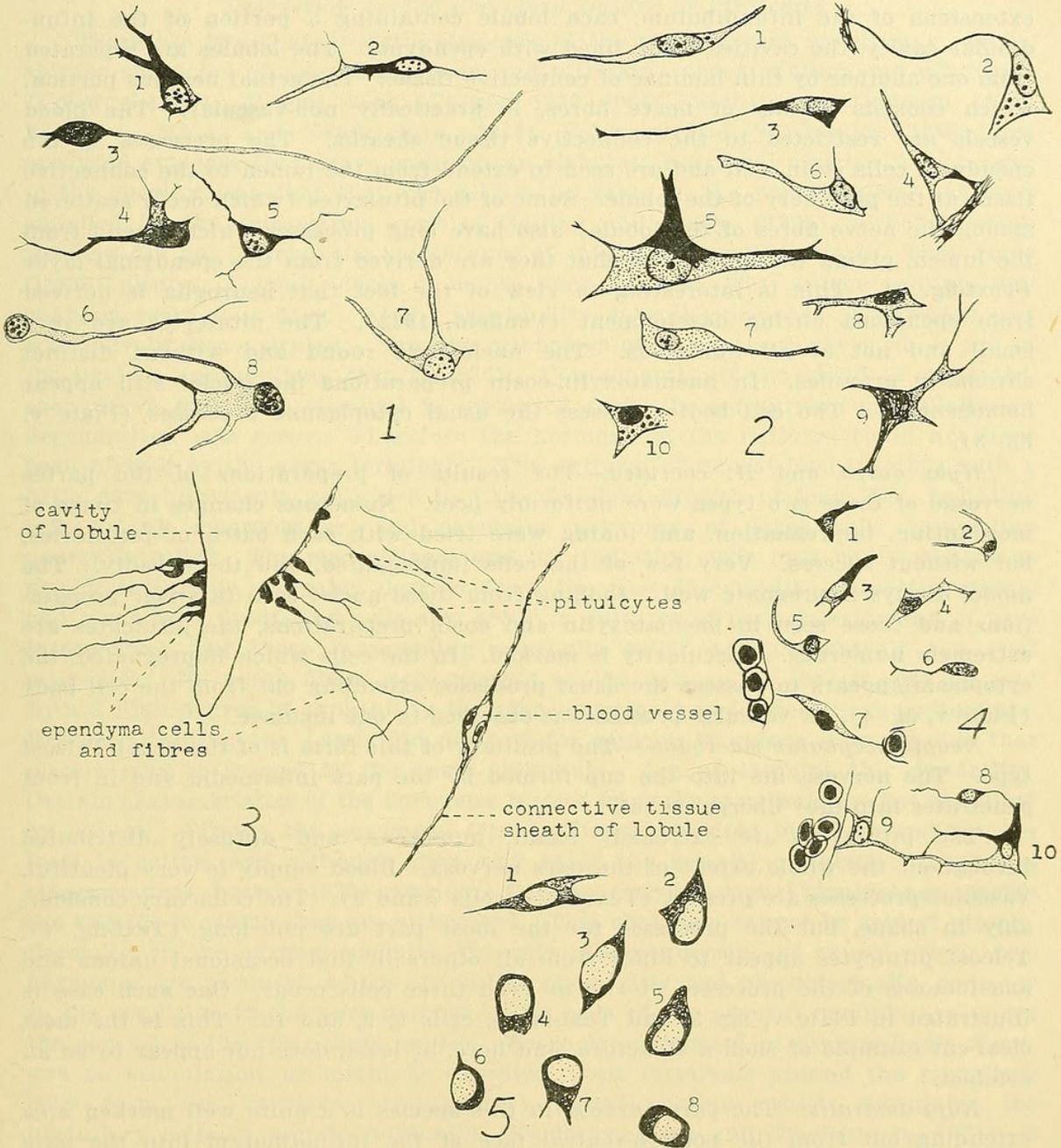
The cells vary greatly in shape (Text-fig. 1); some have several processes arising from the cell body; others, and by far the most frequent, are unipolar or bipolar. The cytoplasm in some cells is finely granular, in others appears a dense black, or both conditions may occur in one cell. Coarse cytoplasmic pigment granules, which occur in some of the bovine pars nervosa elements, were not observed in my preparations.

The nuclei, in general, are spherical or oval in shape. The chromatin is moderate in amount and diffusely distributed. Nucleoli were not seen. Some of the nuclei stain so intensely that they appear homogeneous and the chromatin granules cannot be made out.

Gallus domesticus.—During the course of development of the pituitary complex in the chicken, finger-like processes grow out of the distal portion of the infundibulum (de Beer, 1926). These persist in the adult, surrounded by a thin sheath of connective tissue, but much of their lobular character is disguised owing to the presence of masses of interstitial tissue, composed of nerve fibres, connective tissue, and blood vessels. Each lobular extension contains a portion of the infundibular cavity. The cavities of the extensions are all lined with ependyma. The ependyma cells can easily be identified in both haematoxylin-eosin, and Penfield preparations, being always arranged with their long axes at right angles to the border of the lumen. In silver carbonate preparations each cell has a long process which extends into the gland, away from the lumen. Connective tissue septa and blood vessels are plentiful. The pituicytes are distributed amongst the nerve fibres of the lobules and the interstitial masses, being most numerous in the latter. They are much smaller than those of *Sarcophilus*, as can be seen in Plate v, figs. 1 and 2.

Vascular processes are frequent, terminating on the connective tissue septa and on the blood vessels (Text-fig. 2, cells 2 and 4).

As usual, the pituicytes vary greatly in shape (Plate v, fig. 2, and Text-fig. 2). The cytoplasm is granular in some cases, stains intensely black in others.



Text-fig. 1.—*Sarcophilus harrisi*. Pituicytes, showing variety of forms assumed. Not to scale.

Text-fig. 2.—*Gallus domesticus*. Pituicytes, showing variation in form. Not to scale.

Text-fig. 3.—*Tiliqua scincoides*. Distal portion of lobule of pars nervosa. Showing two bipolar pituicytes among the ependyma processes. $\times 240$.

Text-fig. 4.—*Neoplatycephalus macrodon*. Pituicytes, showing usual lack of uniformity in shape. Cells 8, 9, 10 reveal anastomosis and union of the cytoplasmic processes. Not to scale.

Text-fig. 5.—*Raja australis*. Pituicytes, showing fairly uniform shape, and absence of long cytoplasmic processes. Not to scale.

Occasionally coarse granules occur in the cytoplasm but do not resemble those found in bovine pituicytes, being much smaller and less numerous (Text-fig. 2, cells 2 and 10). Nuclei vary from a flattened oval shape to spherical. The chromatin is distributed as small granules. Nucleoli are seen occasionally.

Tiliqua scincoides.—The pars nervosa here consists of a few large lobular extensions of the infundibulum, each lobule containing a portion of the infundibular cavity, the cavities being lined with ependyma. The lobules are separated from one another by thin laminae of connective tissue. The actual nervous portion, which consists mainly of nerve fibres, is practically non-vascular. The blood vessels are restricted to the connective tissue sheaths. The processes of the ependyma cells stain well and are seen to extend from the lumen to the connective tissue at the periphery of the lobule. Some of the pituicytes (which occur scattered among the nerve fibres of the lobule) also have long processes which extend from the lumen, giving the impression that they are derived from the ependymal layer (Text-fig. 3). This is interesting in view of the fact that neuroglia is derived from ependyma during development (Penfield, 1932). The pituicytes are very small and not at all numerous. The nuclei are round and without distinct chromatin granules. In haematoxylin-eosin preparations the nuclei still appear homogeneous. The cell bodies possess the usual cytoplasmic processes (Plate v, fig. 3).

Hyla aurea and *H. coerulea*.—The results of preparations of the partes nervosae of these two types were uniformly poor. Numerous changes in times of mordanting, impregnation, and toning were tried with each batch of pituitaries, but without success. Very few of the cells impregnated, and these badly. The nuclei always impregnate well. Judging from these nuclei seen in silver preparations and those seen in haematoxylin and eosin preparations, the pituicytes are extremely numerous. Vascularity is marked. In the cells which impregnated, the cytoplasm appears to possess the usual processes extending out from the cell body (Plate v, fig. 4). A vascular process was observed in one instance.

Neoplatycephalus macrodon.—The pituitary of this form is of the usual Teleost type. The nervosa fits into the cup formed by the pars intermedia and in front penetrates into the "Übergangsteil".

The pituicytes are extremely small, numerous, and diffusely distributed throughout the whole extent of the pars nervosa. Blood supply is very plentiful. Vascular processes are present (Text-fig. 4, cells 7 and 9). The cells vary considerably in shape, but the processes for the most part are not long (Text-fig. 4). Teleost pituicytes appear to differ from all others in that occasional unions and anastomoses of the processes of two or even three cells occur. One such case is illustrated in Plate v, fig. 5, and Text-fig. 4, cells 8, 9, and 10. This is the most clear-cut example of such a structure, and here, at least, does not appear to be an artefact.

Raja australis.—The pars nervosa in this species is a quite well marked area extending out from the postero-ventral face of the infundibulum into the pars intermedia.

The pituicytes, treated with silver carbonate, present the typical staining properties of those in other classes, but are peculiar morphologically. They are variable in size, but mostly very large, fairly uniform in shape, possessing only one or two cytoplasmic processes (Text-fig. 5, and Plate v, fig. 6). Occasionally processes are absent. The nuclei in general are very large relative to the cytoplasm, and often are curiously indented. This occurs after formalin or Bouin fixation. Chromatin is scanty. Nucleoli are often present. The cytoplasm is very finely

granular and stains darkly. The pituicytes, owing to their lack of fine processes, stand out well in sections lightly stained with haemalum and eosin, the outlines of the cells agreeing well with those seen in silver preparations. Blood vessels are not numerous.

Discussion on the Secretory Nature of Pituicytes.

There are two characteristic elements of the pars nervosa which may reasonably be suspected of secreting pitocin and pitressin—nerve endings and pituicytes (Cowdry, 1934). Recent work (Parker, 1932, 1934; Feldberg and Gaddum, 1934; Feldberg, Minz, and Tsudzimura, 1934; Feldberg and Vartiainen, 1935) has produced evidence that nerve endings can elaborate hormonal agents. The answer to the question, whether they can secrete pitressin in the pars nervosa, has been supplied by the interesting work of Geiling and Lewis (1935), although these workers did not indicate the significance of this aspect of their work. They made tissue cultures of small pieces of mouse pars nervosa. The culture medium was changed every four days. At the end of fifty days the presence of pitressin was conclusively demonstrated. Now the cell-bodies of the nervosa nerve fibres are in the nucleus supraopticus (Clark, 1936). Consequently, if the gland is explanted, each nerve fibre and terminal is separated from its perikaryon, and Wallerian degeneration will occur. Therefore the hormone in the cultures could not have been formed by the nerve terminals. The cultures of neural lobe together with a little pars intermedia gave rise to "An abundant growth of long, flat, radiating cells, many macrophages, and extensive networks of large cells resembling neuroglia cells". The macrophages and flat radiating cells may be discounted as non-characteristic, probably derived from the pars intermedia, connective tissue and blood cells (radiating cells also occur in cultures of pars anterior and of pars intermedia), but those "resembling neuroglia cells" are undoubtedly the glial pituicytes. No nerve fibres were present in the culture, so that it may be said with a high degree of probability that the hormone was formed by the pituicytes. However, Geiling and Lewis did not test for pitocin, therefore it is possible that pitocin may be formed by the nerve terminals. Let us examine this possibility. Certain characteristics of the hormones formed by nerve terminals are not exhibited by pitocin. Firstly, the hormones (transmitters) liberated by nerve endings are local in action, and although they may enter the general circulation in special circumstances, Loewi (1935) considers they have no functional significance outside the effector in which they are elaborated. This obviously cannot be said of pitocin. Secondly, in the adrenal medulla, the only other endocrine of neural origin, two hormones are produced which are unlike chemically and physiologically, contrary to the condition in the pars nervosa. The cells of the adrenal medulla are under the control of the splanchnic nerves. These are composed of preganglionic fibres, and on stimulation, as might be expected, their terminals around the medullary cells form the hormone (transmitter) acetyl choline, which stimulates the medullary cells to secrete adrenalin (Feldberg, Minz and Tsudzimura, 1934)—a hormone of different chemical composition and diametrically opposed physiological properties. But pitocin and pitressin have similar solubilities, are related to one another chemically (both are amines, Kamm et al., 1928) and, although in some instances they reveal opposed physiological action, they can also produce similar effects, as seen in the following table:

<i>Structure or Substance Affected.</i>	<i>Effect of Pitocin.</i>	<i>Effect of Pitressin.</i>
Uterine musculature of guinea pig.	Causes contraction.	Nil.
Uterine musculature of rabbit.	Causes contraction.	Causes contraction. (Robson, 1933, 1934.)
Mammalian blood vascular system.	Nil.	Vasoconstrictor.
Avine blood vascular system.	Vasodilator (?). (Morash and Gibbs, 1929.)	Vasoconstrictor. (Morash and Gibbs, 1929.)
Capillaries in web of frog's foot.	Vasoconstrictor.*	Vasoconstrictor.*
Insulin (in mammal).	Antagonizes and produces hyperglycaemia. (Geiling and Eddy, 1928.)	Antagonizes and produces hyperglycaemia. (Geiling and Eddy, 1928.)

* That vasoconstriction in the web of a frog's foot can be caused by pituitary extract was demonstrated by Krogh (1922) and Schneider and Asher (1926), but their work contains no indication as to which of the hormones operates here. The writer finds that intramuscular or intravenous injections of 0.2 c.c. of either pitocin or pitressin cause marked and prolonged constriction of the capillaries and arterioles in the web of *Hyla aurea*. The venules are unaffected.

The above two points can scarcely be dignified with the title of evidence, but they hint that pitocin is not formed by nerve terminals. The following offers something more concrete.

It has been proved (Loewi, 1935, Cannon and Rosenblueth, 1937) by numerous experiments that the nerve fibres of the autonomic system are either adrenergic (i.e., secrete an adrenaline-like body) or cholinergic (secrete acetyl choline). Those of the parasympathetic are cholinergic, while sympathetic fibres generally are adrenergic, but some are cholinergic. The cell bodies of the nervosa nerve fibres are in the nucleus supraopticus. This is sympathetic in character (Kappers, 1928; Ranson, Kabat, and Magoun, 1935; Crouch and Elliott, 1936). In view of this, there is no reason to doubt that the nervosa nerve terminals are either adrenergic or cholinergic and that their function is to control secretion by pituicytes, of pitressin and pitocin. Conclusive evidence that pitocin is not secreted by nerve fibres would be its demonstration in a culture of pars nervosa.

If pituicytes are to be regarded as the elaborators of pitocin and pitressin, correlation of their presence with the presence of the hormones is obviously essential. As has been seen, pituicytes occur throughout the vertebrate series. Pitocin also occurs in all classes of the Vertebrates, but in small quantities in Elasmobranch pituitaries (Hogben and de Beer, 1925). The writer found that intramuscular injections of one dose each (equivalent to 120 mgm. of dried gland each) of *Raja australis* pituitary, into two frogs (*Hyla aurea*) brought about slight constriction of the small capillaries in one case, but had no effect in the other. Control injection of 1.0 c.c. of 0.25% acetic acid had no effect. The constriction was possibly due to pitocin, as Hogben and de Beer could not demonstrate pitressin in skate pituitary by injecting a dose equivalent to 50 mgm. of dried gland into the jugular vein of a cat. They are of the opinion, however, that possibly pitressin is present in such a small amount that it is undetectable in such a dose. It seems from these scanty data that pitressin may be produced, and that pitocin is produced

in small quantity. At any rate the presence of pitocin and pituicytes in Elasmobranchs, pitressin, pitocin and pituicytes in all the other classes, agrees with the view that pituicytes are the secretors.

SUMMARY.

1. The presence of pituicytes has been demonstrated in all the classes of Vertebrates.

2. It has been thought that the pars nervosa hormones may be secreted by nerve endings or pituicytes. Evidence from tissue culture experiments shows that pitressin cannot be formed by nerve endings, and that it is formed by pituicytes.

3. No work has been done to demonstrate pitocin in pars nervosa cultures, but as the nerve terminals of the autonomic nervous system are either adrenergic or cholinergic, and as the pars nervosa nerves are sympathetic, it is reasonable to assume that they are also adrenergic or cholinergic and that the pituicytes are responsible for the secretion of both pitressin and pitocin.

4. Pituicytes and pitocin occur in Elasmobranch pituitary; pituicytes, pitocin, and pitressin occur in all the other classes of Vertebrates. This is also in accordance with the suggestion that the pituicytes are secretory.

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EXPLANATION OF PLATE V.

- 1.—*Sarcophilus harrisi*, pars nervosa. Showing pituicytes arranged with their long vascular processes extending towards the blood vessel in the lower part of the figure. $\times 460$.
- 2.—*Gallus domesticus*, pars nervosa. Showing unipolar pituicytes in an interstitial mass. $\times 620$.
- 3.—*Tiliqua scincoides*, pars nervosa. Multipolar pituicyte with one long process extending towards lumen of lobule on the left. On the right the connective tissue sheath of the lobule may be seen. $\times 620$.
- 4.—*Hyla aurea*, pars nervosa. Showing poorly impregnated pituicyte. $\times 620$.
- 5.—*Neoplatycephalus macrodon*, pars nervosa. Three pituicytes exhibiting union and anastomosis of their cytoplasmic processes. Also cell on left can be seen giving off two vascular processes to the blood vessel. $\times 1,000$.
- 6.—*Raja australis*, pars nervosa. Showing the peculiar pituicytes with their short cytoplasmic processes. $\times 620$.



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