

## EARLY DEVELOPMENT OF THE HUMAN PHARYNGEAL HYPOPHYSIS — A PRELIMINARY REPORT<sup>1</sup>

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Most textbooks of Embryology and of Histology generally agree on the following more or less well-known facts: (1) the hypophysis or pituitary gland occupies a depression (the hypophyseal fossa) within the sella turcica which is located on the cranial aspect of the body of the sphenoid bone; (2) the hypophysis is a composite organ consisting of two main portions, an anterior and a posterior; (3) the anterior portion is further divisible into the pars distalis (or anterior lobe proper), the pars tuberalis and the pars intermedia, the posterior portion being designated usually as the neural lobe or pars neuralis; (4) three types of cells are recognizable in the anterior lobe; namely chromophobes, or reserve cells, which lack secretory granules, acidophiles, which contain alpha or acidophilic granules and basophiles, so-called because they contain beta or basophilic secretory granules; (5) the pars anterior is derived from the distal closed end of Rathke's pouch and the pars posterior arises from the infundibulum of the hypothalamic region of the diencephalon; (6) Rathke's pouch develops as a hollow epithelial diverticulum from the roof of the embryonic oral cavity or stomodaeum; (7) the original point of union of Rathke's pouch with the oral epithelium comes to be located well back on the roof of the primitive mouth, and still later when the palate separates off the nasal fossae from the oral cavity proper its site of origin lies at the postero-superior border of the nasal septum at its junction with the roof of the nasal pharynx; and (8) the distal end or hypophyseal portion of Rathke's pouch becomes separated from the stomodaeal epithelium by the obliteration of its original connecting duct or stalk.

Obliteration of the proximal connecting portion of Rathke's pouch with the oral epithelium is a gradual process. When the para-axial mesenchyme differentiates into embryonic connective tissue in the region of the future body of the sphenoid bone the connection of Rathke's pouch with its site of implantation to the epithelium becomes elongated and is gradually reduced to a narrow duct or stalk, which is termed the hypophyseal stalk or craniopharyngeal canal. When, later on, the process of chondrification takes place in the connective tissue, by means of which the cartilaginous body of the sphenoid is formed, the pharyngeal stalk is gradually compressed into a slender epithelial strand which is said to normally degenerate and disappear.

Most textbooks of embryology fail to give much detail concerning the origin and fate of Rathke's pouch and they dismiss the subject usually by merely stating that the stalk by which Rathke's pouch was attached to the stomodaeal epithelium completely disappears (2, 6, 10, 13, 14, 17, 18, 19, 21). On the other hand, some authors mention the occasional persistence of remnants of the connecting stalk of Rathke's pouch (1, 4, 7, 8, 11, 22, 24). Three typical sites of locations of these remnants have been described, namely "intracranial"—within the hypophyseal fossa adjacent to the hypophysis but separated from it by cranial dura mater, "interosseous"—embedded within the body of the sphenoid bone, and "pharyngeal"—within the soft tissue in the roof of the nasal pharynx. The term "pharyngeal hypophysis" is applied to the epithelial remnant in the roof of the nasal

<sup>1</sup>This investigation was aided by a grant from the Ohio State University Development Fund, for which the authors make grateful acknowledgment.

pharynx as opposed to the other two which are usually considered as a "persistent craniopharyngeal canal" (8, 22).

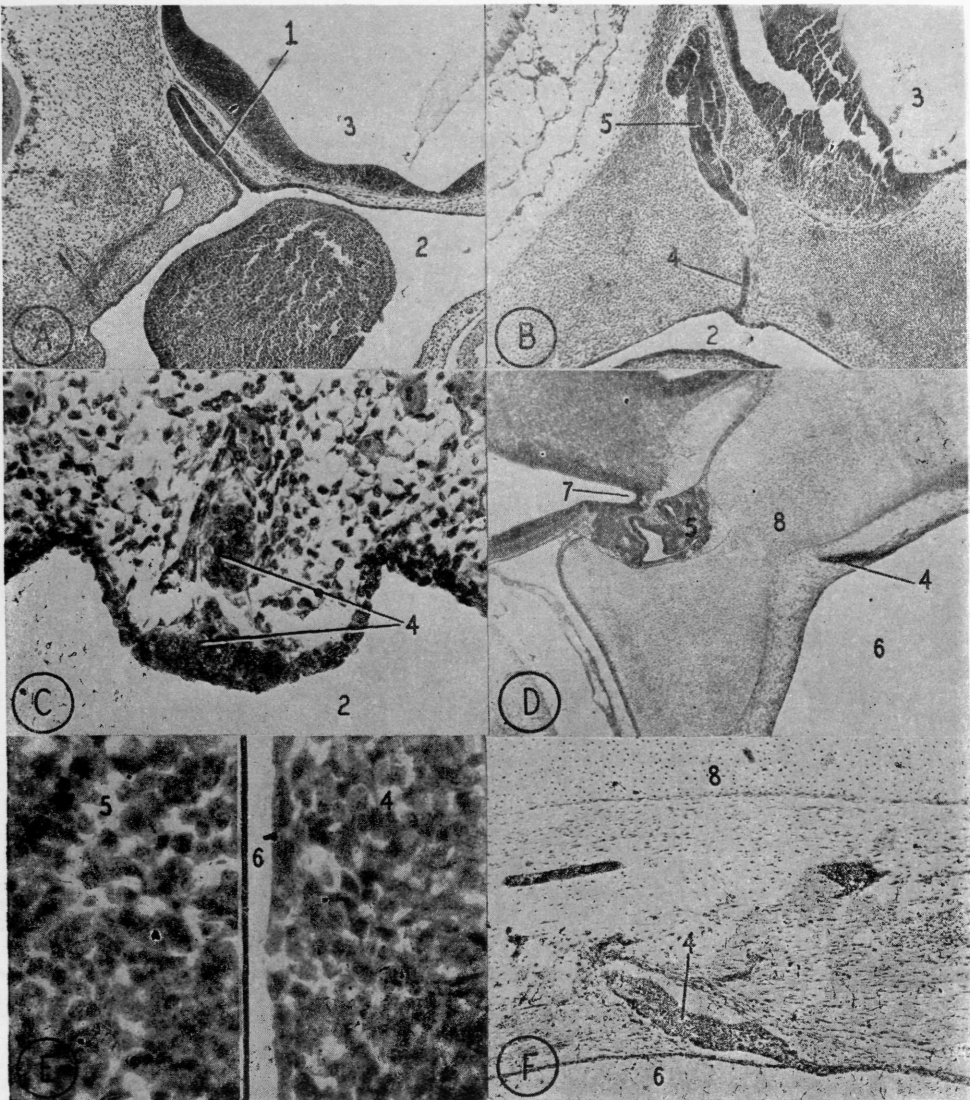
These epithelial remnants are generally considered to be anomalies or abnormalities. However, a few authors point out that the pharyngeal hypophysis is said to be constantly present (1, 4, 7, 22, 24). Thus, according to Smith and Copenhaver (24) "There occurs constantly in the vault of the nasopharynx, in man, a body of typical anterior lobe tissue. It has not been demonstrated in other species. This body lies in the midline and is elongated, its longitudinal axis being parallel to the sagittal plane of the body. It measures from 3.5 to 7 mm. in length by 1 mm. or less in diameter. The cells of the pharyngeal hypophysis are structurally identical with those of the anterior lobe and parallel them in their differentiation and development."

In view of the general agreement, among these outstanding embryologists and histologists, as to the constancy of occurrence of the pharyngeal hypophysis it seems strange that it is so frequently ignored in many textbooks of embryology, histology and human anatomy and that studies on its frequency of occurrence in the vertebrate series and on its histogenesis in man and other species have been so generally neglected. Aside from scattered reports in the literature concerning its involvement in neoplastic growths, which would appear very likely, surprisingly few papers bearing on its frequency in man and lower animals and on detail studies of its development have appeared. Haberfeld (9) reported the results of his studies on its development in a few human fetuses including the newborn; Christeller (5) reported its normal and pathological appearance in adults and in 1938 there appeared for the first time in the English literature a report of its occurrence in human autopsy material. This was by Melchionna and Moore (20) who found it in 51 out of 53 unselected autopsied bodies which they studied, ranging in age from the newborn to 69 years. These authors claimed its cellular constituents were histologically identical with those in the pars anterior of the hypophysis except the differentiated cells were relatively fewer. Hertwig (11) claimed that in many vertebrates, e.g. Selachians, the pharyngeal stalk is retained throughout life as a hollow canal which perforates the base of the skull and is united with the oral epithelium. Kingsbury (15, 16) made a detail study of it in the dog in which he claimed it occurred in almost 100% of the cases examined and mentioned that it had been reported seen in the cat (3) and rabbit. Its presence in the rat (23) and ox (12) however, has been denied.

Inasmuch as so few studies have been made of this structure, and in view of its possible involvement in pathological conditions of the hypophysis and possibly other endocrine organs, the authors have launched upon a research program to investigate its frequency of appearance in man and other vertebrates, its histogenesis and fate and eventually to determine whether or not pathological conditions or experimental procedures may affect it in any way. The present report on its early development in man is the first to come out of this projected study.

In a six mm. (about four weeks) human embryo Rathke's pouch is well defined (Fig. A). It appears in a sagittal section as a finger-like epithelial diverticulum in close relation to the floor of the fore-brain and with a narrow, slit-like lumen opening inferiorly into the oral cavity. However, in a transverse section at this stage it is, in reality, wide and flattened.

By the 12 mm. stage (about five weeks) the continuity of Rathke's pouch throughout its length is broken, its distal free end, which is destined to differentiate into the pars anterior of the hypophysis, is enlarged and its proximal end persists for some distance and retains its connection with the oral epithelium (Fig. B). Condensation of the mesenchyme in the area intervening between the remaining portions of Rathke's pouch (4 and 5) indicates the beginning of chondrification of the future body of the sphenoid and may explain the constriction of the neck of the



Photomicrographs of sections of human embryos showing stages in development of the pharyngeal hypophysis.

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|--|---------------------------------|
| A. 6 mm. Human—Sagittal section—Mag. 84×—H. & E.           | 5. Pars anterior of hypophysis. |
| B. 12 mm. Human—Sagittal section—Mag. 81×—H. & E.          | 6. Nasal pharynx.               |
| C. 22 mm. Human—Cross section —Mag. 387×—H. & E.           | 7. Infundibulum.                |
| D. 25 mm. Human—Sagittal section—Mag. 44×—H. & E.          | 8. Basisphenoid.                |
| E. 50 mm. Human—Sagittal section—Mag. 778×—H. & E.         |                                 |
| F. 80 mm. Human—Sagittal section—Mag. 84×—Hem. & Orange G. |                                 |
| 1. Rathke's pouch.   |                                 |
| 2. Oral cavity.  |                                 |
| 3. Fore-brain.   |                                 |
| 4. Pharyngeal hypophysis.                                  |                                 |

pouch. The persistent site of implantation of the proximal end of the pouch is the primordium of the pharyngeal hypophysis.

Figure C shows a magnification of the pharyngeal hypophysis (4) in a 22 mm. (about eight weeks) human embryo. The epithelial cells composing it are undifferentiated, although they exhibit evidence of elongation and proliferation at the site of implantation on the free surface of the oral epithelium. The persistent stalk is surrounded by mesenchyme with the exception of its periphery where a connective tissue capsule is differentiating and an embryonic blood vessel is making its appearance at its free distal extremity.

In an embryo 25 mm. in length (about 10 weeks) the future body of the sphenoid is cartilaginous, the sella turcica is outlined and is occupied by the future hypophysis, the pars anterior of which shows vesicle-formation, and the pharyngeal hypophysis is well marked and distinguishable from the surrounding cells, its original direction with respect to the differentiating pars anterior of the hypophysis being maintained. By this stage the palate has formed and the original site of attachment of the pharyngeal hypophysis to the epithelium of the primitive, oral cavity has shifted caudally (rather the head has grown forward from that point) so that it now lies in the roof of the nasal pharynx, where its presence has been described in the adult stage (5, 9, 20).

No evidence could be found in the present series of human embryos of the beginning of cellular differentiation in either the future hypophysis or the pharyngeal hypophysis until the 50 mm. stage (about 12 weeks), at which time (Fig. E) the cellular constituents of both (4, 5) were almost identical and consisted of two types, one type having an oval, vesicular nucleus with relatively sparse, more or less colorless cytoplasm and the other type having a smaller, rounder and more darkly staining nucleus with more abundant, and slightly acidophilic, cytoplasm.

The oldest human embryo included in the present study was an 80 mm. (about 14 weeks) stage (Fig. F). As can readily be seen from the photomicrograph the pharyngeal hypophysis is well marked and, in comparison with previous stages, has undergone considerable hypertrophy and is quite vascular when examined under high magnification. Cellular differentiation in the pars anterior and in the pharyngeal hypophysis showed little advancement over the 50 mm. stage. A cursory examination of stages 115 mm. (about 4 months), 138 mm. (about 4½ months) and 160 mm. (about 5 months) revealed its presence and to be undergoing continued hypertrophy and increased vascularity.

Further studies of the fate of the pharyngeal hypophysis in older human embryos are in progress and will be reported in the future.

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