A COMPARATIVE STUDY ON THE MAMMALIAN PITUITARY

I - THE DEVELOPMENT AND STRUCTURE OF THE PITUITARY BODY
IN THE RAT

By

ISMAIL MOHAMED NEGM.

M.B., Ch.B. (Cairo).

PART I

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" .....WHAT WE KNOW MAY INTERFERE WITH OUR LEARNING
WHAT WE DO NOT KNOW."

<div align="right">"CLAUDE BERNARD."</div>

".....the embryological record, as it is usually
presented to us, is both imperfect and misleading.   It
may be compared to an ancient manuscript, with many of
the sheets lost, others displaced, and with spurious
passages interpolated by a later hand ..... Like the
scholar with his manuscript, the embryologist has by a
process of careful and critical examination to determine
where the gaps are present, to detect the later
insertions, and to place in order what has been
misplaced."

<div align="right">"FRANCIS BALFOUR."</div>

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and

REVIEW

The existence of the pituitary body has been known since very early times. The Greeks, believed that the waste products of a certain chemical reaction in the brain flowed down the funnel-shaped infundibulum to the pituitary gland. From the gland, ducts were supposed to pass these waste products into the nasal cavity to form the "pituita" or nasal mucus.

This curious view was held from the time of Galen (130 A.D.), for the next fifteen centuries, till it was discredited in 1655 by Conrad Viktor Schneider. By dissection, he proved that there was no duct between the brain and the nose, and at the same time discovered the membranes in the nose, and the cribriform plate of ethmoid.

Theophile Bonet, J.J. Wepfer, and others, towards the close of the seventeenth century and the beginning of the eighteenth century, described pituitary bodies which were greatly enlarged, but they did not associate the enlargement with any pathological condition. (Singer and Underwood, 1962).

The function of the pituitary was unknown, until the last two decades of the nineteenth century. (Major, 1954).

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almost the close of the last century.

At that time the pituitary was thought by Luschka (1860) to be wholly derived from the brain, and he considered it a "nerve gland", in which the two parts were separated from one another by pia mater. Ecker (1851), on the other hand, held the view that both portions of the gland combined to form a unit that he termed a "blood vessel gland", while Reichert (1840), put forward a theory that the epithelial portion of the pituitary was mesodermic in origin, derived from the anterior end of the notochord.

Rathke (1838), was the first to describe the stomadeal evagination of the epithelium, and correctly assumed this to be the origin of the epithelial portion of the pituitary.

The posterior lobe of the pituitary was at first believed to represent the anterior extremity of the brain (Baer, 1828), but Mihalkovics (1875), Van Wijhe (1894), Kupffer (1893), and others demonstrated that the infundibulum is an outgrowth of the forebrain vesicle.

Notwithstanding the numerous studies to which the pituitary has been subjected since the beginning of this century, many problems remain unsolved. It has claimed the attention of anatomists, histologists, embryologists, and physiologists because it is, as has been stated by Sir Walter Brown (1870-1946), the "leader of the endocrine orchestra".

The morphology of the pituitary gland has been fully

established for relatively few mammals, and for even fewer birds and reptiles, but nevertheless, recent studies (see below) of the hypophysial anatomy in several mammals have revealed marked variations in its morphology.

Studies relating to the development of the pituitary body have been numerous, although in many of them the consideration of the hypophysis has been only incidental to the other interests of the observer, and no single investigator has given a complete account of the morphogenesis of the gland throughout the whole of its development.

Consequently, this study was undertaken in an attempt to trace the complete development of the pituitary body in a single mammal, namely the albino rat.

The albino rat (Mus norvegicus) was chosen because:

1) the animal can breed well in confined quarters,

2) it has a short gestation period (21 days),

3) it has large litters,

4) the pituitary of the adult animal has been subjected to extensive cytological and experimental work, and

5) so far as it has been recorded, no investigation, except Schwind (1928), has attempted to describe the development of the pituitary in the rat.

In particular, this present study is concerned with the morphogenesis of the pituitary body from the time of its first appearance during the embryonic life,

until the age of sexual maturity of the animal. Special

attention has been paid to the origin, topography, and

cytology, as well as the qualitative and quantitative

growth of its various lobes. The study also deals with

some related problems such as the development of the

cephalic end of the notochord in relation to the

developing gland, and the development of the surrounding

membranes, the nervous and blood supply, and the

functional activity of the pituitary as shown by

histological differentiation.

T E R M I N O L O G Y

With regards to the nomenclature of the parts of
the adult pituitary, it has been pointed out by Tilney
(1936) and others, that the terms "anterior and
posterior lobes and pars intermedia" are open to serious
criticism. They are applicable only to the human
subject, but not to all Vertebrates, in as much as the
neural process is frequently dorsal to the rest of the
pituitary, and in some species is actually anterior
thereto. Moreover, these terms are based exclusively on
topography, and indicate neither the function, nor the
origin of the parts, for "the pars intermedia" is only
intermediate in position and not in any other sense.

In early stages the use of topographical terms is
necessary, and accordingly, the parts of Rathke's pouch
are described as, "dorsal" i.e. on the side next to the
diencephalic floor, and "ventral" i.e. on the side next to
the pharyngeal roof, "rostral" or "anterior" towards the
snout, and "caudal" or "posterior" towards the hindbrain.

The "International Commission on Anatomical
Nomenclature", 1935, has recommended the following
classification.

The mammalian pituitary consists of 3 major
divisions: 1) lobus glandularis, 2) lobus nervosus,
and 3) the infundibulum or neural stalk.

For "lobus glandularis" and "lobus nervosus", there
are the following additional synonyms: "lobus

glandularis, lobus oralis, lobus buccalis, epithelial lobe and adenohypophysis"; "lobus nervosus, lobus cerebralis, neural lobe, and neurohypophysis".

"Lobe", is preferable for the major division, reserving "pars", to designate the subdivision.

Major Divisions and Subdivisions of the Mammalian Pituitary

Major Division		Subdivision
Adenohypophysis.	Lobus Glandularis	Pars Distalis (anterior lobe)
		Pars Tuberalis
		Pars Intermedia
		Posterior lobe
Neurohypophysis	Lobus Nervosus (neural lobe)	Infund. Process
	Infundibulum (neural stalk)	Infund.Stem. Median Eminence

Lobus Glandularis (Adenohypophysis)

The "pars distalis" was defined by Tilney (1936), as forming the major part of the glandular lobe and as being devoid of any contact or other distinct relation with the neural lobe.

"Anterior lobe" is employed as synonymous for the "pars distalis" and it is widely accepted in this sense.

The "intermediate lobe or pars intermedia", was defined by Atwell (1939), as the portion of the glandular lobe which has intimate relation with the neural lobe, and is separated from the anterior lobe proper by the

residual cavity of Rathke's pouch.

"Pars tuberalis" was defined by Tilney (1913), as a portion of the glandular lobe which is adherent to the median eminence of the tuber cinereum, and directly continuous with that part of the gland which partially surrounds the infundibular stem and process.

Neurohypophysis

The widely adopted usage regards the neurohypophysis as being divisible into two major divisions; i.e. the neural lobe, and the neural stalk.

Neural lobe (Lobus nervosus)

The neural lobe consists of the infundibular process excluding all or any parts of the neural stalk or glandular lobe.

The "posterior lobe"; As in gross dissection of the pituitary gland, the residual lumen forms a natural line of cleavage, so that the gland separates into an anterior lobe (pars distalis), a posterior lobe (neural lobe + pars intermedia), and the neural stalk. The term "posterior lobe" is applied to the infundibular process together with its mantle of pars intermedia. These terms are retained, only in this sense, although on embryological and functional grounds, objections to such usage can be advanced.

Neural stalk (Infundibulum)

No unanimity of opinion exists regarding the exact

definition of the infundibulum or neural stalk. It includes all of the neurohypophysis except neural lobe.

Should this term include the median eminence of the tuber cinereum? How many subdivisions does the neural stalk possess? What are the exact limits or boundaries of these subdivisions?

These matters are all open to debate. The literature is full of contradictions.

"Median eminence"; The median eminence can be defined as constituting the bulbous part of the infundibulum down to the point where the straight infundibular stem clearly commences. The upper dividing line between the median eminence and the hypothalamus proper, is said to be easily definable, while the dividing line between the former and the subjacent bulbous segment of the infundibular stem, is not definable on histological or cytological grounds. Some suggest that the term "infundibulum" should be applied to the whole neural stalk including the entire median eminence and the infundibular stem.

"Pituitary stalk"; refers to the infundibulum or neural stalk, together with its investing sheath consisting of portion of lobus glandularis (pars tuberalis).

"Epithelial pituitary stalk"; in view of the almost universal adoption of "hypophysial stalk" to mean the connection with the brain, the "epithelial stalk", seems preferable for the transitory, solid, embryological stalk of Rathke's pouch.

REVIEW OF LITERATURE

DEVELOPMENT OF THE PITUITARY BODY

A D E N O H Y P O P H Y S I S

O R I G I N

While a large amount of work has been done on the
embryology of the pituitary, it is apparent that
relatively little attention has been paid to the earliest
stages in its formation.   Perhaps because of this, there
is much ambiguity in the statements about the origin of
the pituitary, and there is doubt about;

1) whether the adenohypophysis is derived from either
   ectoderm or entoderm, or whether it is composed of
   elements derived from both of these germ layers;

2) whether the oral portion first appears in form of a
   solid ingrowth or hollow evagination; and

3) whether the formation of Rathke's pouch is due to an

   active proliferation of the oral epithelium, or to

   mechanical factors.

1) ECTODERM OR ENTODERM

Since the time of Rathke (1838), Dursy (1869),
Muller (1871), Goette (1874), Balfour (1874) and
Ostroumoff (1888), only a few authors have mentioned that
this portion of the gland is developed from entoderm
alone, while others have stated that the primary
ectodermal anlage is later augmented by a contribution

from the entoderm, (Kupffer, 1894; Saint-Remy, 1895; Valenti, 1897; Orru, 1900; Gregory, 1902; Smith, 1914; Atwell, 1915; Miller, 1916; and DeBeer, 1926); but it should be noted that the majority of them believe that, while entoderm enters into the formation of the pituitary, the main portion of the gland is ectodermal.

On an experimental basis Smith (1916), and Allen (1916, 1917), concluded that it was not possible for the entoderm to form the pituitary. Atwell (1918), supported this view and stated that, in the rabbit, no evidence can be found for believing that the entoderm contributes to the formation of the pituitary. This is supported by the recent studies on the development of the mammalian pituitary that have been carried out by Schwind (1928), in the rat; Nelson (1933), in the pig; Kingsbury and Roemer (1940), in the dog, and Oldham (1941), in the armadillo.

2) SOLID INGROWTH OR HOLLOW EVAGINATION

Parker (1917), stated that the primordium of the hypophysis is a hollow evagination, but that in Teleosts and Amphibia it arises as a solid ingrowth of ectoderm; she concluded that the solid ingrowth is the most primitive form. DeBeer (1926), confirmed these facts, and found that it is also a solid ingrowth in Cyclostomes.

In mammals, the pituitary primordium is now recognized as a hollow evagination.

3) PROCESSES RESPONSIBLE FOR APPEARANCE OF THE POUCH

Most of the accounts concerning the development of the pituitary have indicated that the formation of Rathke's pouch is due to an active proliferation of the stomadeal ectoderm, resulting in an active invagination, which by its progressive growth meets an evagination from the floor of the neural tube.

Parker (1917), found that the position of the pouch is indicated at an early stage of development by a thickening of the epithelium of the stomadeum, immediately anterior to the oral plate. This thickened area becomes invaginated, and she considered that the development of Rathke's pouch is due to rapid growth of the differentiated epithelium of the hypophysial anlage, and not to mechanical force imposed by either the chorda or other structures. DeBeer (1926), observed that the extensive development of the forebrain and cranial flexure, only accentuates the stomadeal depression and causes the site of Rathke's pouch to come to lie within it. (stomadeal depression).

Other investigations tend to show that the "pituitary body" arises as a "single structure" whose development, in the early stages at least, is not brought about by an active proliferation of Rathke's pouch, but is dependent on its position in the median prochordal region of the head, the persisting adherence of the surface ectoderm to the neural tube, and upon a series of events attendant upon the development of the head as whole

(overgrowth and marked expansion of the neural tube and the development of mesenchyme between the ventral head ectoderm and the floor of the forebrain). (Frazer, 1915; Adelmann, 1922; Kingsbury and Adelmann, 1924; Haller, 1924; Schwind, 1928; Brahms, 1932; Nelson, 1933; Gilbert, 1934; and Kingsbury and Roemer, 1940).

M O R P H O G E N E S I S

It has long been customary to consider the pituitary as composed of two parts; the anterior lobe which is that portion derived from the ectodermal mouth invagination, and the posterior lobe that is developed from an outgrowth of the floor of the third ventricle of the brain. This concept is still sometimes used in some text books, but it is entirely inadequate for the description of the gland.

It was Herring (1908a) who first wrote of the epithelial investment of the neural lobe – which is separated from the rest of the anterior lobe by the residual lumen – as the "pars intermedia". The existence of a cleft in the epithelial portion of the gland dividing it into two unequal portions, had been previously noticed by Peremeschko (1867), and Lothringer (1886).

Recognition of a third distinctive epithelial portion of the gland, "pars tuberalis", that lies internal to the membranes of the brain in the region of the tuber cinereum, dated back to Tilney (1913).

Though this is considered now as the typical morphology of the gland, the absence of one or other of its epithelial portions has been encountered in some animals. (No pars tuberalis was detected in the two-toed and three-toed sloth and only questionably identified in the anteater). (Wislocki, 1938).

1) OUTGROWTHS OF RATHKE'S POUCH

In the region where Rathke's pouch narrows to form the epithelial pituitary stalk, which connects the pouch to the roof of the oral cavity, there arise outgrowths which may take the form of:

1) a median sprout, (Mihalkovics, 1875, in the rabbit; Kraushaar, 1885, in the rodents; Salzer, 1898, in the rabbit; Joris, 1907, in some mammals; Staderini, 1908, in the reptiles; Herring, 1908, in the cat; Bolk, 1910, in Macacus cynomolgus; and Wislocki and Geiling, 1936, in the whales),

2) two lateral outgrowths, (Chiarugi, 1894, in Cavia cobaya; Tilney, 1913, in the cat and chick; Woerdeman, 1914, in the pig; Baumgartner, 1916, in the reptiles; Miller, 1916, in the pig; Atwell, 1918, in the rabbit; Schwind, 1928, in the rat; Brahms, 1932, in the cat; Nelson, 1933, in the pig; and Oldham, 1941, in the armadillo),

3) a median and two lateral outgrowths, (Gaupp, 1893, in the lizard; Rossi, 1896, in the chick; Economo, 1899, in the chick; Staderini, 1908, in the reptiles; Tilney,

1911, in Aspidonectes; Bruni, 1914, in Amniotes; and
Brander, 1936, in man), or the

4) distinct proximal and distal lobes (relative to the
site of the epithelial pituitary stalk) separated by a
constriction which appears in that region. (Parker, 1917,
in Marsupialia).

These outgrowths may:

1) disappear (Parker, 1917),

2) grow up around the rest of the pouch until they come
in contact with the brain forming "pars tuberalis",
(Herring, 1908; Tilney, 1913; Atwell, 1918; Schwind,
1928; Brahms, 1932; Nelson, 1933; Wislocki and Geiling,
1936; and Oldham, 1941),

3) give rise to a layer of cells surrounding the main
epithelial portion of pituitary (Woerdeman, 1914; and
Miller, 1916), or

4) share in the formation of the pars tuberalis, and also
contribute to the main epithelial portion of the gland
(Baumgartner, 1916; and Brander, 1936).

The literature, concerning these outgrowths, is
very confusing, and the problem is still unsolved.

2) INTERMEDIATE PART AND ITS STRUCTURE

Two topographical criteria have been suggested for
identification of the pars intermedia during development
of the gland, namely, its intimate relation with the
neural lobe, and its separation from the anterior lobe
proper by the residual lumen of the pouch. (Atwell, 1939).

No "pars intermedia" has been found in the pituitary of certain species of animals such as the porpoise (Wislocki, 1929), the whales (Valso, 1934), the fin-back and sperm whales (Geiling, 1935), the armadillo (Wislocki, 1938a, and Oldham, 1941), the manatee (Oldham, McCleery, and Geiling, 1938), and the birds (Delwader, Tarr and Geiling, 1934, and Rahn and Painter, 1941).

In addition to the glandular cells and the small amount of connective tissue accompanying the very few blood vessels within the pars intermedia, a number of observers have noted certain distinctive cells, which have been variously interpreted; as nerve cells (Lothringer, 1886; Trautmann, 1909; and Cajal, 1911), sensory cells (Gemelli, 1905), glial cells (Retzius, 1894, Stendell, 1914; and Vazquez-Lopez, 1942), or supporting cells (Pirone, 1905; Herring, 1908; Miller, 1916; and Atwell, 1918).

Some investigators observed the presence of cysts in the intermediate lobe of the pituitary gland of certain mammals, (Romies, 1940, in the dog; Hanstrom, 1947, in the fox; and Anderson and Jewell, 1958, in the goat).

Recently, Ziegler (1963), making a light and electron microscope examination of the intermediate lobe of the pituitary of the rat, indicated the presence of dark and light areas within it, and attributed a functional significance to these areas.

3) RESIDUAL CAVITY

After the epithelial pituitary stalk (see
terminology) has become a solid structure the remains of
the original cavity of Rathke's pouch is known variously
as the residual lumen, the intraglandular cleft, or the
epithelial cleft. It serves to separate the pars
intermedia from the anterior lobe proper.

Some studies indicate that the residual lumen is
entirely lacking in later stages, but Brander (1936)
suggested that the statement that the cleft sometimes
disappears is highly misleading and that it persists,
although it may be inconspicuous.

As a rule the lining of the cleft, on both aspects,
is composed of the original cubical epithelium, but
these lining cells may undergo certain changes, and some-
times these cubical cells are ciliated.

4) EPITHELIAL PITUITARY STALK

Rathke's pouch is wide open to the mouth cavity at
the beginning of its growth, but constriction of the
opening leads to the formation of a short stalk
containing a narrow lumen joining the cavity of the pouch
with that of the mouth. The stalk later becomes solid,
elongated, and tapering from the gland to the epithelium
of the stomadeum.

The time at which the stalk becomes separated from
the gland or from the oral epithelium, is variable in
different animals, but it seems that the epithelial stalk

separates from the oral epithelium earlier than it does
from the gland.   (Atwell, 1918).

The stalk may either lose its connection with the
gland as the sphenoid becomes solid (Atwell, 1918; and
Tilney, 1936), or the connection may persist through a
foramen in the sphenoid (craniopharyngeal canal - see
below) (Brahms, 1932; and Kingsbury and Roemer, 1940).

An apparent migration of the points of attachment
of the stalk has been recorded.   This apparent
migration may be due to:
1) gradual forward dislocation and elongation of the roof
of the mouth. (Frazer, 1916),
2) changes in the glandular anterior lobe;
(a - rapid growth of the anterior lobe, b - bending of
the gland to form the intraglandular fossa, c - approx-
imation of the lateral lobes to the brain wall.
(Atwell, 1918),
3) degeneration and resorption of the cartilage (bone) of
the ventral wall of the canal through which the epithelial
stalk passes, and the formation of new cartilage (bone) on
the dorsal wall. (Brahms, 1932).

5) PHARYNGEAL HYPOPHYSIS

A number of investigations in the early years of
this century have established that a portion of the
epithelial stalk of Rathke's pouch persists throughout
life as a structure with histological features more or
less closely resembling those of the pars distalis of the

pituitary, and for that reason it has been called the "pharyngeal hypophysis".

Apart from man (Luschka, 1860; Froriep, 1882; Killian, 1888; Erdheim, 1904; Haberfeld, 1909; Arai, 1907; Tourneux, 1912; Frazer, 1916; Rudel, 1918; Atwell, 1926; and Romies, 1940), the only mammal in which a pharyngeal hypophysis has been reported as a regular finding is the dog. (Kingsbury and Roemer, 1940).

In other mammals there are only scattered observations relating to the possible presence of a pharyngeal hypophysis;   (Arai, 1907, in the cat and rabbit; and Atwell (1918) in the rabbit).

There are many authors on the other hand who found no substantial proof that any part of the epithelial stalk persists.   (Tilney, 1936, in man; Brahms, 1932, in cat; Haberfeld, 1909, Romies, 1940; and Boyd, 1956, in all animals examined including, rat, cat, mouse, guineapig, frog, toad, hedgehog, monkey and dog.)

6) CRANIOPHARYNGEAL CANAL

This is the name applied to the canal in the basisphenoid cartilage (bone), through which the epithelial stalk of Rathke's pouch connects the roof of the oral cavity with the pituitary gland.

The term was first used by Landzert (1868), and later by Greig (1924), and Brahms (1932).   Tilney (1936) offered serious objections to such a term namely;   the non existence of such structure, and that the pituitary is a derivative of the roof of the stomadeum not the pharynx.

N E U R O H Y P O P H Y S I S

Until the onset of the second World War studies on the morphogenesis of the pituitary gland were confined almost entirely to the epithelial portion.

The neural lobe is poorly developed in many of the lower Vertebrates, but attains a considerable size and importance in higher Vertebrates, where it forms a hollow or solid structure attached to the diencephalic floor by a narrow neck, the "pituitary stalk".

O R I G I N

Much discussion has taken place as to the nature of the factors which influence the formation of the neurohypophysis. (A) Is it produced by active proliferation of the infundibular region (Gronberg, 1901; Parker, 1917; Atwell, 1918; and Oldham, 1941)? (B) Are mechanical factors involved, such as: 1. The presence of the epithelial pouch against the wall of the forebrain (Mihalkovics, 1875; Herring, 1908; and Brahms, 1932). 2. Direct or indirect action of the cephalic end of the notochord (Giroud and Roux, 1959), or 3. The reaction of growth processes in the adjacent zones of the forebrain (optic and premammillary regions) on the inactive infundibular region. (Gilbert, 1935; and Kingsbury and Roemer, 1940)?

M O R P H O G E N E S I S

Usually the neural process appears as a hollow sac,

shaped like the finger of a glove.   The cavity of the

neural evagination usually disappears forming a solid

structure, but in some animals it is present in the most

proximal portion of the evagination (Schwind, 1928),

while in others there is a persistent lumen throughout.

(Brahms, 1932).

After the disappearance of the cavity of the neural

process, the process undergoes certain morphological

changes:

1) the original neural tissue of the lobe is much reduced

in amount, connective tissue is substituted, and the

process is considered as a connective tissue appendage of

the brain (Muller, 1871, in pig, man and sheep).

2) the tissue of the lobe is differentiated into the

three zones characteristic of the developing brain wall

(ependymal, mantle or nuclear, and marginal) and is

penetrated by connective tissue.   (Parker, 1917, in

Marsupialia).

3) its tissue is differentiated into a cortical and a

medullary layer.   (Atwell, 1918, in rabbit).

4) its cells are arranged in cords which are invested by

an infiltration of connective tissue and capillaries.

(Schwind, 1928, in rat).   or

5) its tissue is arranged in form of lobules outlined by

vascular connective tissue septa, and constructed around

branches of the hypothalmo-hypophysial tract.   (Bodian,

1951, and Roth and Luse, 1964, in opossum; Duncan, 1955,

and Payne, 1959, in birds).

The developing neural lobe undergoes certain degree of rotation, to acquire the "adult position" of the gland. These rotations are manifested in the changes which take place in the angle formed by the attachment of the neural lobe to the forebrain wall. (Atwell, 1918; and Schwind, 1928).

C O M P O N E N T S

Description of the several components of the neural lobe, cells, fibers and secretory substances, varies with different authors depending somewhat upon the species studied, the technique used, and upon the function attributed to each component. It may be preferable to review the most important components in the form of a table.

AUTHOR		COMPONENTS
Berkley	1894	nerve cells and fibers.
Retzius	1894	neuroglial cells and fibers.
Herring	1908	neuroglial and ependymal cells, fibers, and cellular islets from pars intermedia.
DeBeer	1926	same as Herring.
Bucy	1930,1932.	Pituicytes (first to introduce this term) and fibers.
Brahms	1932	neuroglial and ependymal cells and fibers
Geiling & Lewis	1935	(macrophages) and fibers.
Wislocki & Geiling	1936	Hyaline bodies (Herring bodies)
Gersh	1939	(paranchymatous glandular cells)

AUTHOR		COMPONENTS
Griffiths	1940	(2 types of protoplasmic astrocytes).
Oldham	1941	nerve cells and (ependymal cells).
Bargmann & Scharrer	1951	Bulbous secretory nerve endings (Herring bodies), and (modified supporting glial cells)
Hild	1951	
Bodian	1951	
Scharrer & Scharrer	1954	" " " " " "
Ranson & Clark	1959	" " " " " "
Vazquez-Lopez	1953	nerve fibers and endings, neuroglia, microglia, and reticular fibers.
Holmes	1959	nerve cells and fibers
Holmes & Knowles	1960	synaptic vesicles.
Lederis	1965	nerve fibers and endings, pituicytes, fibroblasts, and synaptic vesicles

The terms in brackets are the functional terms applied by different authors to the "pituicytes".

F U N C T I O N

As regards the function of the neural lobe there are three conflicting theories:

1) The posterior lobe of the mammalian pituitary is a "brain gland", not by virtue of tissue of brain origin, but by the growth into it of epithelial cells of ectodermic origin from the intermediate lobe. (Herring, 1908; DeBeer, 1926; and Bauer and Haugh, 1960).

2) The posterior lobe of the mammalian pituitary is a true "endocrine gland", as its paranchymatous glandular cells can produce and secrete hormones. (Gersh, 1939;

Wislocki and Geiling, 1936; Green and VanBreeman, 1955; and Payne, 1959).

3) The posterior lobe of the pituitary gland serves as an "<u>organ for storage and release</u>" of hormones elaborated by the neurons of certain hypothalamic nuclei, and carried down the axons of the hypothalamo-hypophysial tract into it. (Bargmann and Scharrer, 1951; Hild, 1951; Palay, 1953, 1955; Vazquez-Lopez, 1953; Scharrer and Scharrer, 1954; Duncan, 1956; Benson and Cowie, 1956; Wethington, 1958; Holmes, 1959; and Holmes and Knowles, 1960).

HERRING BODIES

Herring (1908a), however, did not define clearly the bodies which bear his name either from the standpoint of origin or structure and some confusion is still to be found in the literature.

Most authors, who are in accord with the neuro-secretory theory, believe that the Herring bodies are accumulations of secretory products which have their origin in the neurosecretory cells of the hypothalamus, and which move along the axons of these cells to their fiber endings.

NEUROEPITHELIAL CONTACTS

The relation of the intermediate lobe of the pituitary to the neural lobe tends to become more intimate, so "contacts" between the two portions of the gland have been described by different authors.

The phenomenon of invasion of the pars nervosa by

cells from the pars intermedia was first recorded by
Lothringer (1886), and later confirmed and expanded by
Herring (1908), DeBeer (1926), Guizzetti (1926, 1927),
Tilney (1936), Brander (1936), Wade (1938), Anderson and
Jewell (1958), and Bauer and Haugh (1960).

Atwell (1918) on the other hand interpreted these
"invasions" as growing processes from the neural lobe
into the intermediate lobe of the gland.

The function attributed to these neuroepithelial
contacts is open to discussion. It has been suggested
that they:

a - may have a secretory function in the pars nervosa,
    (Herring, 1908; DeBeer, 1926; and others),
b - may degenerate forming cysts of unknown function,
    (Anderson and Jewell, 1958),
c - may form a sort of mechanism for supplying ependymal
    and neuroglial elements to the intermediate lobe,
    (Atwell, 1918), or
d - may act to convey the secretion of the intermediate
    lobe through the neurohypophysis to the hypothalamus.
    (Bauer and Haugh, 1960).

MITOTIC ACTIVITY OF THE DEVELOPING GLAND

It has been noted that in any physiological or
experimental condition which results in an increase in
the total number of cells of the pituitary, mitosis must
play the sole role.

Numerous studies on the mitotic activity, index,

and number in the pituitary of immature and adult rats, under different physiological and experimental conditions, have been recorded.

No author, on the other hand, has confined himself to describe the mitotic activity of different regions of the developing pituitary, and in particular in the rat.

VOLUMETRIC DATA

The importance of the ductless glands in modern medicine has created a demand for more accurate data on these structures.

The need for quantitative facts is more urgent in the case of the pituitary, because this organ is composed of several parts which are more or less structurally, functionally, and embryologically distinct.

Quantitative data comprise but an exceedingly small portion of the principal contributions to our general knowledge of this gland.

Moreover, most of the reports are concerned with adult glands and there is little information on the quantitative growth of the gland in the prenatal period either in man (Covell, 1926), or in laboratory animals. (Francis and Mulligan, 1949, and Hewitt, 1950, in the dog; and Latimer, 1939, in the cat, and 1954, in the dog.)

CYTOLOGY OF THE PITUITARY GLAND

This topic has been exhaustively studied, and spectacular advances have resulted from the introduction of the recent histochemical and biophysical techniques.

(Bailey, 1932; Wolfe and Clivland, 1933; Severinghaus, 1933; Wolfe, 1935; Baillif, 1938; Pearse, 1952; Siperstein, Nichols, Griesbach and Choikoff, 1954; Knigge, 1957; McNary, 1959; Lever and Peterson, 1960; Pasteels and Herbant, 1962; and Barnes, 1962). taken by many investigators to be indicative of some influence the notochord may exert on the developing gland. The cephalic end of the notochord, which may be bifurcated (Grunwald, 1910; Keibel, 1889; Huber, 1912, 1917; and Oldham, 1941), has been said to:

1) present a causal relation to the head flexure of the embryo (Atwell, 1915),

2) to act mechanically in drawing out the infundibulum of the pituitary from the brain wall (Muller, 1868; and Dursy, 1869),

3) to form the entodermal diverticulum known as Seessel's pouch in a similar manner (Gage, 1906; Grunwald, 1910; Atwell, 1915; and Miller, 1916),

4) to make a larger or smaller contribution to the developing gland; a - whole pouch (Reichert, 1840), b - the vascular stroma of the hypophysis (Dursy, 1869), c - the connective tissues of the organ (Adelmann, 1922), or d - the entodermal portion of the gland (Miller, 1916, and Atwell, 1915),

5) to create a contact between notochord and pituitary, (Koelliker, 1879; Saint-Remy, 1896; Gage, 1906; Woerdeman, 1914; Baumgartner, 1916; Atwell, 1918; Aaser, 1931; and Nelson, 1933), or

6) to create a contact between notochord and foregut,

DEVELOPMENT OF THE RELATED STRUCTURES

DEVELOPMENT OF THE CEPHALIC END OF THE NOTOCHORD IN RELATION TO THE DEVELOPING GLAND

The close proximity of the cephalic extremity of the notochord to the hypophysis anlage has been taken by many investigators to be indicative of some influence the notochord may exert on the developing gland. The cephalic end of the notochord, which may be bifurcated (Grunwald, 1910; Keibel, 1889; Huber, 1912, 1917; and Oldham, 1941), has been said to:

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6) to create a contact between notochord and foregut.

(Dorello, 1900; Huber, 1912, 1917; Schwind, 1928; Nelson, 1933; and Oldham, 1941).

Some investigators denied these connections, and gave no support to the view that the notochord contributes to the developing gland (Mihalkovics, 1874, and Parker, 1917), while others stated that the connections are only through a strand of mesoderm which descends from the cephalic extremity of the notochord; "the prochordal plate". (Aasar, 1931; Schwind, 1928; and Oldham, 1941).

Recently, Giroud and Roux (1959) on an experimental basis, concluded that the notochord imposes, either directly or indirectly through the infundibulum, an inductive action on the development of the adenohypophysis.

THE MENINGEAL RELATIONS OF THE PITUITARY

The meningeal relations of the hypophysis have been investigated by few early workers on various adult animals and by a variety of methods. A survey of the literature up to 1924, reveals only vague, casual references concerning the arrangements of the leptomeninges in relation to the pituitary gland.

Embryological study of the membranes has received very little attention. (Wislocki, 1937a, in man; and Roussy and Mossinger, 1934, in cat and dog).

Great uncertainty exists regarding the arrangements of the meninges around the hypophysis, and opinions vary

widely in regard to the degree to which leptomeninges
extend around the epithelial and neural portions of the
gland, as it is clear from the following table.

AUTHOR		MENINGES
Lewis & Knavel	1913	archnoid spreads over the surface of the gland.
Stendell	1914	pia and dura around the neural, capsule and periosteum around the pars distalis.
Woerdeman (in pig)	1914	pia invests the neural lobe.
Parker (in Marsupialia)	1917	pia invests pars neuralis and distalis, dura surrounds the distalis.
Cowdry	1922	pia invests the neuralis, dura surrounds the whole gland.
Hughson (in pig)	1924	all meningeal envelopes surround the gland, and the subarchnoid space encloses the entire gland.
Bailey	1932	same as Hughson.
Brander	1932	no subarchnoid space around the neuralis or the whole gland, dura between the capsule and the periosteum of the sphenoid.
Dyke & Davidoff	1934	hypophysial subarchnoid space is continuous with the cisterna chiasmatis
Roussy & Mossinger (cat and dog)	1934	no subarchnoid space surrounds the hypophysis.
Schwartz (in dog)	1936	no subarchnoid space invests the hypophysis, dura extends throughout the sella and blends with the capsule.
Wislocki (in monkey)	1937	no subdural or subarchnoid spaces surround the body of the pituitary; subarchnoid space encircles the infundibular stalk; Capsule of gland, intrasellar dura, and adjacent periosteum constitute a continuous fused lamina.

AUTHOR		MENINGES
Wislocki	1937a	dura developing around the body of the hypophysis and forming the sellar diaphragm, fuses with the surface of the anterior and neural lobes, preventing the development of pia archnoid and subdural space around the body of the pituitary.
Sunderland	1945	no archnoid below the level of the dural aperture, no subarchnoid space into the pituitary fossa.
Boyd	1960	in prenatal stages the pituitary is surrounded by dura and a fibrous capsule which are closely applied to the surface of the gland precluding extension of the subarchnoid and subdural spaces around the gland.

NERVOUS SUPPLY OF THE PITUITARY GLAND

This matter cannot be regarded as being finally settled.

INNERVATION OF PARS NERVOSA

Although Cajal (1894) gave conclusive evidence for the presence of nerve fibers in the posterior lobe, the fact that the pars nervosa is largely nervous in nature has sometimes been lost sight of, as shown by the statement of Cowdry (1922) that nerve fibers are of rare occurrence in the pars nervosa.

Nevertheless Cajal's observations had been confirmed by Pines (1925), and Greving (1925), who recorded that some of the fibers arise from nuclei

bilaterally placed in the floor of the third ventricle, somewhat above and behind the optic chiamsa.

It is generally agreed that the supraoptic nuclei, and possibly to some extent the paraventricular nuclei are the sources of the supraoptico-hypophysial tract which converges in the tuber cinereum to the pituitary stalk through which it enters the neural lobe, where it forms an exceedingly complicated plexus of non myelinated nerve fibers which ramify to all parts of the lobe.

The manner of termination of the nerve fibers in the posterior lobe is not well understood, and it has been recorded that some fibers terminate:

1) as bulb or knob like swellings in the posterior lobe (Tello, 1912; Greving, 1925; Bucy, 1930; Ibanez, 1934; and Hair, 1938),

2) as pericellular nerve nets around the cells of the infundibulum (Cajal, 1911; Bucy, 1930; and Brooks and Gersh, 1941),

3) in the perivascular connective tissue (Tello, 1912),

4) in the walls of the blood vessels (Croll, 1928),

5) in the connective tissue of the capsule (Bucy, 1930),

6) in the zone between the intermediate and nervous lobes (Ibanez, 1934),

7) around the cells of the pars tuberalis (Hair, 1938),or

8) between the epithelial cells of the pars intermedia (Cajal, 1911; Tello, 1912; Pines, 1925; Croll, 1928; Ibanez, 1934; Hair, 1938; and Brooks and Gersh, 1941).

Electron microscope studies can give more definite

information on the termination of nerve axons in the pars
nervosa, and Vaquez-Lopez (1953) describes complicated
giant bulbs and menesci, but Holmes (1960) records the
presence of two types of vesicles; granular and synaptic,
whose presence is confirmed by Lederis (1965).

INNERVATION OF THE INTERMEDIATE LOBE

Many investigators report that some nerve fibers
pass from the neural lobe of the pituitary into the pars
intermedia.

While some observers record that the number of such
fibers is very small, and that they do not penetrate very
far in the pars intermedia (Cajal, 1911; in mouse;
Tello, 1912; Fisher, 1937; Rasmussen, 1938 and
Brooks and Gersh, 1938, 1941), others convey the
impression that they are plentiful (Truscott, 1944;
Berkely, 1894; Gentes, 1903; Gemelli, 1906; Trautmann,
1909; Cajal, 1911, in man; Pines, 1925; Roussy and
Mossinger, 1934; Bodian, 1937; Hair, 1938; and
Vaquez-Lopez, 1948).

The manner of termination of these nerve fibers in
the pars intermedia is not definitely known, but it is
recorded that these fibers terminate:
1) by very simple terminals (Berkely, 1894; and
Ibanez, 1934),
2) with terminal nerve net (Brooks and Gersh, 1941),
3) with small club or knob like formation on the surface
of the cells (Bucy, 1930; Truscott, 1944; Hair, 1938;
Vaquez-Lopez, 1948), or

4) with no definite nerve terminals (Rasmussen, 1938).

INNERVATION OF THE PARS ANTERIOR

The nerve supply of the anterior lobe of the pituitary has been demonstrated in a limited number of animals, but the source, nature, and manner of termination of these fibers is subject to considerable dispute.

While some investigations consider them as sympathetic filaments (Berkely, 1894; Tello, 1912; and Dandy, 1913), with secretory nature (Pines, 1925; and Croll, 1928), others suggest that they are parasympathetic fibers (Hair, 1938), but Harris (1960) states that experimental data argue against sympathetic and parasympathetic innervation of the pars distalis. Some studies record that the innervation of the anterior lobe of the pituitary is derived from the hypothalamic hypophysial tract (Brooks and Gersh, 1938, 1941; Rasmussen, 1938, Truscott, 1944; and Vaquez-Lopez, 1948).

Most of the observations indicate that the nerve terminals in the anterior lobe of the pituitary are of the knob like variety.

Harris (1960) states that Palay, and Farquhar and Rinehart have failed to find any nerve fibers in the pars distalis by the use of the electron microscope, which clearly differentiates between reticular fibers and nerve fibers.

DEVELOPMENT OF THE FUNCTIONAL ACTIVITY

Studies upon the beginning of secretory activity have been reported in a number of endocrine glands. Such studies which are of value in any of these organs, are of special interest in the case of the pituitary, because of its structural complexity, and the fact that a number of functions are attributed to it.

In the anterior lobe of the pituitary the acidophils and basophils have been presumed to be the source of the various hormones elaborated by this lobe, but in the last decade the application of new techniques in pituitary cytology, has led to a general belief that each pituitary hormone is contained within specific granules, that are produced by independent cell types. Accordingly, considerable attention has been given to studies on embryos to determine at what period these cells become differentiated.

Evidence derived from the histological appearance of the developing glands suggests that there may be secretion of pituitary hormones at an early stage of embryonic development.

The pioneer work of Phillips and Schmidt (1959) shows that the cytoplasm of a few cells located along the margins of the future residual lumen of the pituitary of the rat were selectively stained with "aldehyde fuchsin" on the 14th day of gestation.

In mammals, there is general agreement that cellular differentiation of the anterior lobe cells into

acidophils and basophils occurs during early developmental stages, although the sequence of differentiation is not always the same.

Direct evidences that the embryonic pituitary substances actually play a role during development has been provided through the removal of the pituitary by various methods. (Hwang and Wells, 1959; Kitchell and Wells, 1952; Coetzee and Wells, 1957; and Milkovic and Milkovic, 1962).

VASCULAR SUPPLY OF THE DEVELOPING GLAND

In view of the importance placed on the endocrine system in the last three decades, and the very great physiological significance of the pituitary, several studies have been made of the vascular supply of the pituitary glands of adult animals. (Herring, 1908a; Dandy and Goetsch, 1910-1911; Mudd, 1918; Brown, 1924; Fuchs, 1924, Nikolskaia, 1929; Popa and Fielding, 1930, 1933; Basir, 1932; Brander, 1936; Wislocki and Geiling, 1936; Wislocki, 1937b; Stevens, 1937; McConnel, 1953; Xuereb, Prichard, and Daniel, 1954; Daniel and Prichard, 1957; Jewell, 1956; Holmes and Zuckerman, 1959; Stanfield, 1960; Harris, 1960; and Farquhar, 1961a).

The study of the vascular supply of the pituitary of the adult rat has been limited to the observations of

Landsmeer (1951) on cleared material, observation of the direction of the flow of blood in the blood vessels of the pituitary of the living rat by Green and Harris (1949), and the study of the nature of the hypophysial blood supply by radioactive microspheres by Goldman and Sapirstein (1962).

The development of the vascular supply of the pituitary and of the hypophysial portal system, is nearly neglected, and a survey of the literature revealed only the papers by 'Espinasse (1934), Wislocki (1937a), and Niemineva (1950) in man; Glydon (1957) in rat; and Campbell (1966) in rabbit.

M A T E R I A L
and
M E T H O D S

P L A T E   I

P R E N A T A L   S E R I E S

1) $12\frac{1}{2}$ day rat embryo.

   (3·5 m.m. crown rump length) X 13·3

2) $13\frac{1}{2}$ day rat embryo.

   (6 m.m. crown rump length) X 8·5

3) $14\frac{1}{2}$ day rat embryo.

   (7·5 m.m. crown rump length) X 8

4) $15\frac{1}{2}$ day rat embryo.

   (12 m.m. crown rump length X 5

5) $16\frac{1}{2}$ day rat embryo.

   (15 m.m. crown rump length) X 4

6) $17\frac{1}{2}$ day rat embryo.

   (18 m.m. crown rump length) X 4

1

2

3

4

5

6

Plate. 1.

P R E N A T A L   S E R I E S

7) 18½ day rat embryo.

    (22 m.m. crown rump length) X 3·5

8) 19½ day rat embryo.

    (24 m.m. crown rump length) X 3

9) 20½ day rat embryo.

    (27 m.m. crown rump length) X 2·7

7

8

9

Plate. 1.

TEST ANIMALS

The animals used in this study were Albino rat
(Mus norvegious), Wistar Institute strain.

The animals were bred in Anatomy Department, from
adults obtained from a dealer.   They were maintained in
the animal house under normal conditions, and adequately
fed on M.R.C. pellet diet 41B, with sufficient tap water.

The female animals were marked, recorded and put in
separate cages.

SELECTION OF THE SERIES STUDIED

The selection of the members of the series studied
was dependent on some biological events which mark out the
main developmental highlights.

The youngest embryo of the series was taken at $9\frac{1}{2}$
days of embryonic life, because the origin of the
pituitary does not become evident until cellular
specialisation has established the differences between
somatic and neural ectoderm (Tilney, 1936), and the
development of the germ layers in the rat embryo takes
place on the 8th - 9th day of the gestation period.
(Griffith, and Farris, 1942).

The last prenatal animal of the series was taken at
$20\frac{1}{2}$ days of embryonic life, as the average length of
gestation in the rat is 21·8 days (Long and Evans, 1922).

The spermatozoa of the male rat became mature
between the 36th - 40th day after birth, at about the

time of descent of testes, (Pomerat, 1941), and the vagina
of female Wistar rat opens between 35-50 days after birth
(Shay, unpublished), so the last postnatal animal in the
series was taken 6 weeks after birth.

PRENATAL SERIES

The prenatal series consists of embryos which were
taken at: $9\frac{1}{2}$, $10\frac{1}{2}$, $11\frac{1}{2}$, $12\frac{1}{2}$, $13\frac{1}{2}$, $14\frac{1}{2}$, $15\frac{1}{2}$, $16\frac{1}{2}$, $17\frac{1}{2}$,
$18\frac{1}{2}$, $19\frac{1}{2}$ and $20\frac{1}{2}$ days of embryonic life; i.e. the age
difference between successive members of the series was
one day. (Plate 1).

POSTNATAL SERIES

The postnatal series consists of animals which
were sacrificed at, 0-12 hours (birth), one week, two
weeks, three weeks (weaning), and six weeks (puberty),
after birth.

D E T E R M I N A T I O N   O F   A G E
TIMING OF EMBRYOS

Several techniques have been used to secure
adequate approximation to embryo age. The "vaginal
smear" method was proved to be the most satisfactory one.
The primary requisites to the approach to the embryo are
a study of the estrous cycle of the female, and an
adequate knowledge of the physiology of fertilization.
Only by this knowledge, can an adequate timing of embryo
age be achieved.

ESTROUS CYCLE

The cellular contents of the vagina undergo cyclical changes. The cycle is characterised with five (Long and Evans, 1922) or four (Hupe, 1900) different stages, each is recognised by periodic histological changes in every portion of the reproductive tract which are identified by the vaginal smear. (see below).

Each of these stages is approximately of constant length. The average total length of estrous cycle in the rat is 4·8 days. (Long and Evans, 1922).

The vaginal smear of the "estrus or heat" period is characterised by cornified non nucleated epithelial cells with no leucocytes as shown in the following table correlating Hupe's classification with that of Long and Evans.

STAGE		VAGINAL SMEAR	LENGTH	REMARKS
L. & E.	HUPE.			
1. P R O E S T R U S.		Nucleated round cells	12 H.	
2. ESTRUS		cornified non nucleated	12 H	
	ESTRUS	epithelial cells alone		Ovulation & Mating
3. METESTRUS, I			15–18 H	
4. METESTRUS, II.	POSTESTRUS	non nucleated cornified cells + leucocytes	6 H	
5. D I E S T R U S		leucocytes + a few epith. cells	60 H	

Duration of estrus or heat period ranges from 1–28 hours with average of 13·7 hours (Cooley and Slonaker, 1925).

The estrus usually begins at 4-10 p.m. (Blandau, Boling, and Young, 1939).

Periods that start early in the evening tend to run somewhat longer than ones that start later. (Cooley and Slonaker, 1925).

There are certain external signs which associate the estrus stage and help in its diagnosis. (see below).

Ovulation occurs spontaneously during estrus in the rat whether mated or unmated. It commonly occurs in the Wistar strain approximately 9 hours after the onset of estrus, but may occur as early as $7\frac{1}{2}$ hours, and as late as $12\frac{1}{2}$ hours after the onset of estrus. (Boling, Blandau, and Young, 1939).

Immediately after ovulation the eggs are found in the upper part of the oviduct. (Snell, 1942).

The whole maturation process of the ovum requires not less than 4 hours nor more than 15 hours, (Kirkham and Burr, 1913; and Long and Mark, 1911), and the extreme limit of its viability is approximately 12 hours. (Blandau and Young, 1939; and Blandau and Jordan, 1941).

MATING

The albino rat males are capable of copulating at any time of the day or night, but are most active at night (Long and Evans, 1922), and they attempt copulation 15-70 times in 15-20 minutes with 1-2 ejaculations providing the female is in active heat. (Griffith and Farris, 1942).

Sperm reach the upper end of the uterus almost at

once after mating, and the ovarian end of the oviduct where

fertilisation occurs within 15 minutes of mating (Florey

and Walton, 1932, Hartmann and Ball, 1930; Lewis and

Wright, 1935; and Rossman, 1937).

Sperm retain their fertilising ability in the

oviduct for 6 hours. (Snell, 1942).

FERTILISATION

Sperm penetrate the coverings of the ovum quite

rapidly, and reach the vitellous in less than two hours,

this penetration of the vitellous may be regarded as the

actual moment of fertilisation. (Lewis and Wright, 1935).

Fertilisation of the ova must take place within

these indicated periods, as the interval between

ovulation and fertilisation is prolonged, there is

progressive decrease of the number of pregnant animals,

rapid reduction in litter size, and an increase in

number of abnormal pregnancies which are terminated by

the death and resorption of embryos. (Blandau, Boling

and Young, 1939).

THE PROCEDURE ADOPTED (Plate 2-A).

1) 9 a.m. the separated, marked females were examined

for the following external associated signs of

estrus:

a - COPULATORY RESPONSE

Pelvic digital stimulation of the female produces

lordosis. (Blandau, Boling and Young, 1941).

b - EAR QUIVERING

One of the earliest signs of heat in the Wistar strain female albino rat is ear quivering elicited by stroking her gently on the head or back. (Griffith, and Farris, 1942).

c - ESTRUS EXCITEMENT AND RUNNING ACTIVITY

Estrus is evidenced by increased running activity which begins at the onset. (Farris, 1941). The estrous cycle changes and the changes in spontaneous activity of the female rat parallel each other. (Wang, 1923).

d - APPEARANCE OF THE SUPERFICIAL GENITALIA

The vagina appears dry, lusterless, and whitish blue with swollen, congested lips. The vaginal orifice is gaping and surrounded with small radiating ridges. (Long and Evans, 1922). During estrus period there is usually a disagreeable odour attached to the vaginal secretion.

Vaginal smears were taken by the pipette or lavage method which is preferable to spatula or curette method and cotton swab method, as it is less upsetting (Emery and Schwabe, 1936, 1938), and it was carried out by inserting a fine pointed pipette containing a few drops of physiological saline, smoothly into the vagina, the saline ejected and immediately sucked again.

The contents were then transferred to a marked slide for staining. Wright's stain was used because of its

simplicity and clear diagnostic differentiation.
(Nicholas, 1942).

2) 10 a.m. females in estrus were taken to the male cages
   for mating.   Copulation usually took place within the
   first 30 minutes, but the females were left there for
   6 hours to have a sure chance of successful
   fertilisation.

3) 4 p.m. the females were separated and taken back to
   their cages.   This time was considered to be the onset
   of embryo age timing.

4) 9 a.m. (following morning) the presence of copulation
   plug - which is a convenient sign of mating as
   copulation is accompanied by its formation - was
   secured.

   COPULATION PLUG.   It is formed by a mixture of the
   secretion of the vesicular and coagulating glands of
   the male.   It appears at 8-20 hours after copulation
   and persists for 18-24 hours, sometimes as long as 48
   hours.   A plug is always unaccompanied by the presence
   of sperm.   (Long and Evans, 1922;   and Snell, 1942).

5) 24 hours later, a vaginal smear was taken to detect
   the diagnostic picture of pregnancy;   cornified, non
   nucleated epithelial cells, leucocytes, and large
   quantity of mucus.   (Plate 2-B)

6) At the appointed date, the pregnant mother was
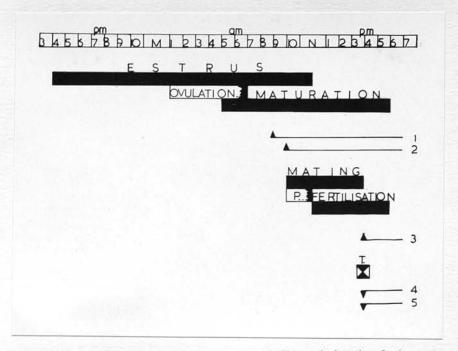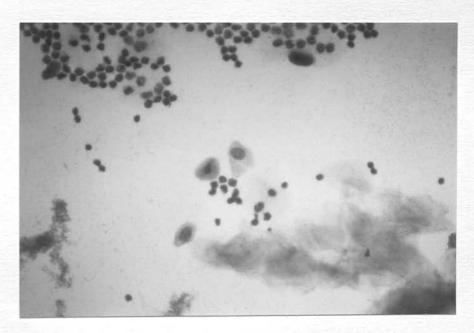   sacrificed and the litters were extracted.

Plate. 2. A. Timing of embryos. Physiological data.

Steps of procedure.

Plate. 2. B. Vaginal smear. Pregnancy. (cornified, non nucleated epithelial cells, leucocytes, and mucus).

POSTNATAL

The pregnant females which were let to go to full
term, were repeatedly examined at 2 hour intervals in the
last 2 days of gestation for signs of parturition, and
any new arrival was recorded, and its age was easily
determined to the nearest hour.

HISTOLOGICAL PROCEDURES

ANAESTHESIA

Light chloroform, in a bell jar, followed by intra-
peritoneal injection of 35% chloral hydrate (0·1 c.c./100
grams body weight).

OPERATIONS

1. PREGNANT ANIMALS

A median incision of the anterior abdominal wall of
the pregnant mother was made.   The gravid uterus was
clearly exposed, and embryos were extracted and
immersed in the fixative at once.   They were kept
in the solution, either within their membranes ($9\frac{1}{2}$,
$10\frac{1}{2}$ and $11\frac{1}{2}$ day embryos), as a whole ($12\frac{1}{2}$, $13\frac{1}{2}$, $14\frac{1}{2}$,
$15\frac{1}{2}$ and $16\frac{1}{2}$ day embryos), or as skinned heads ($17\frac{1}{2}$,
$18\frac{1}{2}$, $19\frac{1}{2}$ and $20\frac{1}{2}$ day embryos) depending on their age.

2. POSTNATAL ANIMALS

The chest of the animal was opened and the heart
was clearly exposed.   With a 5 c.c. syringe equipped
with (32G) needle, the left ventricle was perfused

with the recommended fixative.   After decapitation

and skinning of the heads, they were immersed in the

fixative for the suitable time.

3. INDIAN INK PERFUSION

A mixture of equal volumes of Indian ink and

physiologic saline was perfused to study the vascular

bed.

Under Baker dissecting microscope, with 2 c.c. syringe,

equipped with the fine "32G" needle, 1-2 c.c. of the

solution was perfused, through the umbilical vein of

young embryos, or through the exposed left ventricle

of the heart of old embryos and postnatal animals.

The Indian ink solution was circulated by the

pulsations of the heart to virtually all the

capillaries of the animal.   The animals or their

skinned heads were immersed into the fixative.

FIXATION

1. Bouin's fixative was used as the standard fixative in

this study, as it keeps well, penetrates rapidly and

evenly, and causes little shrinkage.   The perfused

tissues were kept in the solution for 24-48 hours

depending on the age and size.

2. Fixatives recommended for each silver impregnation

method were used.

a - Alcohol-formol-acetic; in Peters' protein-silver

mixtures method. (formol 5 c.c., glacial acetic acid

5 c.c., 50% alcohol 90 c.c.).

Time recommended for fixation; similar to Bouin's

b - Ammoniated absolute alcohol; in Rasmussen

modification, pyridine silver method. (absolute

alcohol 100 c.c.; 6 drops of ammonia hydrate).

Time of fixation 5 days.   The original technique

gives 3 days, but the pieces used were larger.

c - 5% Gluteraldehyde in M/10 phosphate buffer, for

perfusion, and 25% gluteraldehyde, 1 part, added to

2·5% potassium dichromate 4 parts for immersion;   in

Golgi - Kopsch modification.

Time recommended for immersion, a week.

DECALCIFICATION

For proper cutting, the heads of animals above 10

days old, had to be decalcified. After proper fixation

these heads were put in the E.D.T.A. solution (50 grams

of disodium salt of ethylene diamine tetra acetic acid in

350 c.c. water, adjusted to pH 7), for 6 weeks or less

depending on the age till proper decalcification took

place.   This method was recommended as it causes very

little shrinkage in the tissues.

The decalcified tissues were washed, overnight,

under running tap water.

DEHYDRATION AND CLEARING

After proper fixation and decalcification, the

standard methods of dehydration and clearing were adopted.

After dehydration and clearing, the specimens were

processed in one of two ways: 1) serial sections.

2) whole cleared preparations.

SERIAL SECTIONS

EMBEDDING

Methods employed for embedding the tissues were:

1. Paraffin wax embedding method.

2. Celloidin embedding method, for 100µ sections.
   (Culling, 1957).

   a - Standard celloidin method, for unstained sections
   for the study of the blood supply.

   b - Low viscosity nitrocellulose method (L.V.N.) for

   Golgi - Kopsch modification stained sections.

3. Double embedding method.   The following method was
   used as standard in this study.

   After proper dehydration, the tissues were transferred
   from absolute alcohol to the following successive
   solutions:

   a - a mixture of equal volumes of absolute alcohol and
   methyl salicylate, for 3 hours.

   b - pure methyl salicylate, till they clear. (usually
   24-36 hours).

   c - 1% celloidin in methyl salicylate, for 2-4 days;
   depending on the size of the tissues.

   d - 3 changes of benzene each for one hour.

   e - a mixture of equal volumes of benzene and wax,
   kept at 37°C for 3 hours.

   f - impregnation in 3 changes of wax at 56°C, each for
   one hour.

   g - wax embedding, and section cutting as ordinary
   paraffin sections.

STAINING

The stains used were:

1) Harris's alum haematoxlin and eosin. (Culling, 1957).

2) Mallory's trichrome stain:

   a - Crossmon's modification. (Crossmon, 1937).

   b - Crooke-Russell modification. (Culling, 1957).

3) Southgates mucicarmine. (Culling, 1957).

4) Chrome alum haematoxlin phloxine. (Gomori, 1941).

5) Combined aldehyde fuchsin and periodic acid Schiff

   stain (Elfman, 1959).

6) Combined aldehyde thionin and periodic acid Schiff

   stain. (Paget and Eccleston, 1960).

7) Silver impregnation methods:

   a - protein-silver mixtures stain. (Peters, 1958).

   b - pyridine-silver method. (Rasmussen, 1938).

   c - Golgi-Kopsch modification method. (Colonnier,

   1964).

SECTION CUTTING

All the tissues were cut sagittally.

The thickness of the section:

6μ for ordinary stains;

15μ for silver impregnation;

20μ for stained, Indian ink - injected material;

100μ for Golgi-Kopsch modification, and unstained,

Indian ink - injected material.

L.V.N. EMBEDDED SECTIONS

The sections according to Morest (unpublished)
were made on a sliding microtome, and collected in serial

order in 70% ethanol, and passed through; one change of
95% ethanol, 2 changes of 100% butanol, and 2 changes of
cedar wood oil, for 10 minutes in each change. They
were rinsed in toluene before mounting with Permount.

WHOLE CLEARED PREPARATIONS

For whole cleared preparations, Landsmeer (1951)
method modification was used.

In some injected specimens, the head was dissected,
leaving the pituitary intact with the brain, in others,
the dorsal half of the skull and the brain, was cut off.

These specimens were processed, through the same
steps described - above - for the modified double
embedding method.

The specimens were transferred from 1% celloidin in
methyl salicylate solution, to anisi oil, where they were
kept and examined.

QUANTITATIVE GROWTH

In order to ascertain the total volume of the
pituitary gland and the relative volume of its various
lobes at different prenatal stages, the "paper weight"
method used by Hammar (1914), Jackson (1917), Rasmussen
and Herrick (1922), and Covell (1926) was used.

Every section of the series was projected by means
of a Leitz projection apparatus, onto paper of standard
weight (8·747 - 8·7466-m.g./sq.cm.). A magnification of
about 300 times was used. The areas of the lobes of the

gland were then outlined by means of a sharp hard pencil. The outlined areas were then cut out with a small pair of scissors, and the various parts were weighed.

The relative proportion which each lobe forms of the total paper weight is comparable to that of the fresh gland providing the shrinkage of each lobe has been about the same.

Jackson (1917), Rasmussen and Herrick (1922), and Covell (1926) found sufficiently close agreement between the glandular and neural lobes in this respect.

The relative weight of each lobe was determined by dividing the paper weight of each lobe by the sum of the paper weights for the three lobes.

It was possible to ascertain the absolute volume of the whole gland or of any of its lobes, by dividing the total paper weight (of the whole gland or of certain lobe) by the weight of 1 sq. cm. of the paper (8·747 m.g.), then further dividing by the magnification squared (300 x 300), and finally multiplying the result by the thickness of the section (reduced to centimeters).

Volume of gland or any of its lobes =

$$\frac{\text{Total paper weight (of gland or of a certain lobe)}}{\text{Weight of sq.cm. of paper}} \times \frac{\text{Thickness of section (reduced to centimeters)}}{(\text{Magnification})^2}$$

In order to show the changes which occur in the hypophysis, the data representing the growth changes in volume were treated by graphic reconstruction, and making of tables.

MITOTIC ACTIVITY

The previous methods used to represent the mitotic activity of the pituitary gland are entirely unsatisfactory for the following drawbacks;

1) Almost all the investigations carried out on this topic were based mainly on the count of the number of mitoses either in a selected number of sections of each gland, or even in a limited number of microscopic fields, and wrongly this limited sample was interpreted as an actual representative of the case.

2) Some observations considered the "mitotic index" as the number of mitoses per standard square area $(m.m.^2)$, neglecting the depth of the field, represented by the thickness of the section, which is usually not the same in different investigations.

3) Most of the investigations recorded were concerned with the number of mitoses "per gland" to detect the effects of various drugs or different physiological conditions, and no attempt was tried to report the mitotic state of the different lobes or portions of the gland.

4) No record, including drawings to represent the distribution of the mitotic activity of the different regions of the gland, was discovered.

To overcome these difficulties, a new technique by which the approximate number of mitoses found in every region of the gland in every prenatal stage, could be counted per volume and represented by drawings, was

introduced:

1. The serial sections of the pituitary gland in each
   embryonic stage were examined, and the successive
   sections which are almost of the same shape and nearly
   of the same surface area, were assorted into groups of
   6, 9 or 12 sections.

2. The most representative section of each group was
   projected onto duplicated sheets of paper with a carbon
   paper in between, a magnification of about 300 times
   was used. The areas of the lobes of the gland were
   outlined by means of a sharp hard pencil.

3. All sections of that certain group were projected onto
   the same duplicated papers, at the same magnification,
   and made to coincide with the already drawn outline of
   the chosen section. With the point of a blunt needle,
   the sites of the cells undergoing mitosis in every
   section were indicated, the mark being recorded by
   the carbon paper on the underneath sheet. A special
   mark (dots, circles, crosses, ..) was used for each
   section. After projecting and marking by this way
   all sections forming one group, the front paper was
   removed, and the underlying one was taken and the
   mitoses of every projected section could be checked
   under the microscope.

4. This process was repeated with each group of sections,
   ending with a certain number of drawings representing
   the sites of mitoses in every section of the gland
   throughout all the embryonic life.

On every one of these drawings, the magnification,
the number of constituent sections, and the thickness
of the section were recorded.

The mitotic index per cubic millimeter in any
region of the gland at any of its prenatal stages can be
easily calculated:

a - Count the number of mitoses (on the drawing) in a
definite surface area (m.m.^{2}).

b - Calculate the volume by dividing the surface area by
the magnification squared, and multiplied by the
recorded thickness (reduced to millimeter).

c - Mitotic index; number of cells counted/volume
calculated in m.m.^{3}.

OBSERVATIONS

SECTION I.

 Development of the pituitary body:

 Morphogenesis, cytology, and mitotic and

 functional activities.

SECTION II.

 Volumetric growth of the prenatal pituitary.

SECTION III.

 Development of the cephalic end of the notochord

 in relation to the developing pituitary gland.

SECTION IV.

 The meningeal relations of the developing pituitary

 gland.

SECTION V.

 The development of the vascular supply of the

 pituitary gland.

SECTION I

DEVELOPMENT OF THE PITUITARY

In sets of serial sections of $9\frac{1}{2}$ day embryos no traces of the pituitary body could be detected.

At the $10\frac{1}{2}$ day stage, however, Rathke's pouch is apparent as a very small evagination of the roof of the stomadeum.

Consequently, it may be considered that the pituitary gland of the albino rat appears for the first time, at least in this study, in the interval between $9\frac{1}{2}$ - $10\frac{1}{2}$ days of pregnancy.

STAGE I

$10\frac{1}{2}$ day embryo

In the $10\frac{1}{2}$ day embryo, the primordium of Rathke's pouch (Fig. 1) is represented by a finger like evagination, in the midline of the roof of the stomadeum.

This evagination projects in an anterodorsal direction and its anterior wall (rostral) is in close proximity to the rounded posteroventral wall of the forebrain vesicle (Fig. 2) and no mesenchyme tissue intervenes between the two structures, though this tissue is present elsewhere around the periphery of the pouch.

There is a direct communication between the stomadeal cavity and that of the pouch (Fig. 3) through a small circular orifice at the base of the pouch.

At this embryonic stage, there is no indication of

any neural evagination to form the neurohypophysis
(Fig. 2) and the wall of the forebrain vesicle in the
region opposed to the pouch shows no sign of thickening.

Fig. 3, representing a midsagittal section, shows
that the posterior (caudal) wall of the pouch and the
roof of the stomadeum meet each other at an angle, while
the anterior wall (rostral) of the pouch is in line with
the roof of the stomadeum and forms a gradual sloping
curve with it.

The cause underlying such asymmetry in the shape of
the pouch is most probably the persistent adherence of the
neural ectoderm and the stomadeal epithelium in the
region of the evagination. This is suggested by: 1) no
mesenchyme tissue intervenes between the two structures,
and 2) the site of evagination is found at the region
where the forebrain vesicle is closest to the surface
ectoderm. The anterior wall of the pouch has the same
shape as the adjacent zone of the forebrain vesicle.

The walls of the pouch (Fig. 2) have a fairly
uniform thickness (12μ), and are formed essentially from
a single layer of cells except at the base of the
anterior wall of the pouch where there is a slight
thickening in which the cells form two layers.

No clear histological differences are present
between the cells forming the roof of the stomadeum and
those forming the defined base of the pouch (Fig. 3),
but there are differences present within the pouch itself.
The cells of the anterior (rostral) wall of the pouch

(Fig. 6) tend to be rounded in shape with centrally located nuclei, while those of the opposite posterior (caudal) wall (Fig. 5) are elongated with their long axes arranged obliquely to the axis of the pouch and their nuclei lying away from the luminal end of the cells.

More than one third of the cells of the anterior wall of the pouch and less than one fourth of those of its posterior wall are in one or other of the mitotic stages (Fig. 147).   In general the mitotic figures occur in all regions of the pouch but are most frequently observed in the zone adjacent to the lumen of the pouch. The greatest number of mitoses can be seen in the basal portion of the anterior wall of the pouch.

The cells of the lateral walls of the pouch (Fig. 4) show characteristics intermediate between these two extremes; some being elongated and others are rounded, but all of them having centrally located, rounded nuclei.

The roof of the stomadeum (Fig. 7) near the site of the pouch is formed of a single layer of rounded or cuboidal cells with central spherical nuclei, and very infrequent mitotic figures.

The cells of the wall of the forebrain vesicle (Fig. 6) are arranged in two or more layers.   The cells are mainly columnar having their nuclei either at the ends of the cells or centrally located.   Some of the cells of the forebrain vesicle adjacent to the tip of Rathke's pouch are in one or other of the mitotic

stages (Fig. 7).

No remnants of the oral membrane can be detected at this stage and the surrounding mesenchyme is still undifferentiated.

The linear anteroposterior and lateral dimensions of the cavity of the pouch are almost equal; each is 35µ, while the linear dorsoventral dimension representing the depth of the pouch is 80µ.

(The measurements of each of the three diameters represents the maximum dimension of the cavity of the pouch in the plane in which they were measured.)

STAGE II

$11\frac{1}{2}$ day embryo

The stomadeal evagination (Fig. 9) is a wide, wedge shaped diverticulum having a centrally depressed fundus with surrounding raised edges. A finger like evagination of the posteroventral wall of the forebrain vesicle (Fig. 9) representing the primordium of the infundibulum and the neurohypophysis, projects in a posteroventral direction, and its ventral aspect is in close proximity to the indented central portion of the fundus of the pouch with no mesenchyme tissue intervening between the two structures.

The mesenchyme tissue, filling the very narrow space between the pouch and the forebrain vesicle except along the midline, and separating the "whole" forebrain vesicle from the surface ectoderm of the head, is present elsewhere around the periphery of the pouch and the neural evagination. The separation of the pouch and the forebrain vesicle observed in this stage, is most probably due to growth of the two structures and the surrounding mesenchyme tissue.

The change of the shape of the stomadeal evagination may be due to: 1) marked increase in the dorsoventral axis of the pouch evident by the presence of a great number of mitotic figures in the tip and basal portions of the pouch, and 2) posteroventral growth of the developing neural evagination, contacting the pouch in the midline and indenting it.

The direct communication between the stomadeum and the cavity of the pouch still persists but through an oval, anteroposteriorly compressed orifice having its widest dimension in the midline and situated at the base of the pouch.

The neural evagination (Fig. 9) has a more or less symmetrical appearance, and it lies at right angles to the wall of the forebrain vesicle to which it is connected. There is a direct communication between the cavity of the neural evagination and the cavity of the forebrain vesicle through a small circular orifice at the base of the neural evagination.

The neural evagination, being relatively thick walled (30μ), its cavity occupies only the intermediate third of its whole thickness. The walls of the neural evagination are uniformly thick, and their cells are arranged in two or more layers of elongated cells with basal or centrally located nuclei. The cells of the neural evagination show mitotic divisions, but these are less numerous than in the pouch. The cells undergoing mitosis are most frequently observed in the zone adjacent to the cavity of the evagination.

The total width of the neural evagination related to that of the stomadeal evagination is in the proportion: 3:4.

The walls of the pouch are increased in thickness (24μ), and are formed of two layers of cells except:

1) at the base of the anterior wall of the pouch where

there is slight thickening in which the cells form more than two layers, and 2) at the fundus of the pouch where the cells are arranged in a single layer.   The cells of the fundus of the pouch are similar to the cells of the posterior wall of the pouch.

There is an increase in all the linear dimensions of the stomadeal evagination.

The linear dimensions of the cavity of the pouch in this stage are as follows:

Anteroposterior: 55μ width: 70μ, and the vertical or dorsoventral depth: 110μ.

STAGE III

12½ day embryo

The stomadeal evagination represented by a wedge shaped diverticulum, has its anterior wall completely separated from the posterior wall of the forebrain vesicle by mesenchyme tissue, while its fundus is in close proximity to the developing neural evagination with no such tissue intervening between them. (Fig. 11).

There is still a direct communication between the stomadeal cavity and that of the pouch through the small oval orifice situated at the base of the pouch (Fig. 11) which is greatly reduced anteroposteriorly. This reduction in the anteroposterior diameter of the orifice is obviously not caused by thickening of the basal portions of the walls of the pouch; the responsible factor is outside the structure of the pouch itself.

The surrounding undifferentiated mesenchyme is growing actively as indicated by the presence of mitotic figures through it.

The neural evagination although elongated, still retains walls of uniform thickness and its symmetrical shape (Fig. 11). The direct communication between the cavity of the forebrain vesicle and the cavity of the neural evagination persists through the circular orifice found at the base of the evagination.

The relation between the width of the neural evagination and that of the stomadeal evagination is in

the proportion: 2:3.

The walls of the pouch are of almost uniform thickness (27μ) except in the fundus where the thickness is slightly less than elsewhere.

The walls of the pouch are formed from approximately two layers of cells. The cells of the inner layer, lining the cavity of the pouch, are rounded in shape with central nuclei. (Fig. 14). The cells of the outer layer show histological differences; those of the anterior wall tend to be rounded in shape with centrally located nuclei, while those of the opposite posterior wall are elongated with their long axes arranged obliquely to the axis of the pouch and their nuclei lying away from the luminal end of the cells.

The cells of the neural evagination (Fig. 11) are arranged in two or more layers. They are mainly columnar having their nuclei either at their ends or centrally located, except for the cells in the apical zone of the neural evagination (Fig. 13) which tend to be rounded with centrally located spherical nuclei.

The roof of the stomadeum near the site of the pouch is formed of a single layer of rounded or cuboidal cells with central spherical nuclei (Fig. 15).

There is a marked increase in the linear dimensions of the cavity of the pouch except its antero-posterior diameter which, on the contrary is reduced (see above), and these linear dimensions can be represented by the following figures: Anteroposterior: 35μ (previous stage: 55μ), width: 95μ, and the dorso-ventral depth: 150μ.

STAGE IV
13½ day embryo

Rathke's pouch (Fig. 21) is an elongated, ovoid, incompletely closed sac, connected in the midline to the roof of the stomadeum. The anterior wall of the pouch is close to the rounded posteroventral wall of the fore-brain vesicle but is separated from it by a narrow space (Fig. 19) filled with mesenchyme tissue, while the dorsal portion of the posterior wall of the pouch is in direct contact with the anteroventral aspect of the neural evagination (neural process), with no intervening mesenchyme tissue (Fig. 20), although this tissue is present elsewhere around the periphery of the pouch and the neural process.

The direct communication between the cavity of the pouch and the stomadeum is a mere slit-like orifice (Fig. 24) within a narrow stalk of cells, connecting the basal portion of the pouch to the roof of the stomadeum in the midline. This connection (Fig. 23) is called the "epithelial pituitary stalk".

The walls of the pouch are of almost uniform thick-ness (36μ), (Fig. 26) except at two places in the midline: 1) in the dorsal region of the posterior wall of the pouch (Fig. 20), (?previous fundus of the pouch - see below) which is in contact with the neural process, 2) the other in the basal portion of the anterior wall of the pouch (Figs. 23 and 24).

The basal portion of the anterior wall of the pouch, in its intermediate region (nearly half of its width), can be divided into three equal zones; two prominent, dorsolateral knob like projections - Gl - (Fig. 22), and an intermediate basal ridge like growth - T - (Fig. 24) connected to the epithelial pituitary stalk (Fig. 23). The latter (T) projects mainly into the lumen of the pouch (Fig. 24).

The pouch is an ovoid elongated sac, and no longer flattened. The fundus of the pouch is still there, but most probably is incorporated into the posterior wall of the pouch, suggested by the following facts:

1. The dorsal portion of the posterior wall of the pouch (extending from the dorsal end of the pouch to a very slight projection on the posterior aspect of the pouch) is in contact with the neural evagination and is slightly thinner than the rest of the walls of the pouch. The fundus of the pouch in stages II and III is also thinner than the rest of the walls of the pouch (Figs. 20, 11 and 9).

2. The reduction in the ventral angle between the neural process and the forebrain vesicle (Fig. 21) suggests change in the direction of the neuroectodermal contact between the neural process and the fundus of the pouch, moving the latter nearly in line with the posterior wall of the pouch.

3. If the walls of the pouch grow at a uniform rate,

then a comparison of the linear dorsoventral measurements
of the anterior and posterior walls of the pouch at this
stage with the corresponding walls of stage III, should
show a greater increase in the posterior wall than the
anterior wall. If the fundus of the earlier stage has
been added to the posterior wall, it is evident from
Table I, that the posterior wall of the pouch at the $13\frac{1}{2}$
day stage could include both the expected increase due to
its intrinsic growth and the fundus of the pouch of the
previous stage ($12\frac{1}{2}$ day) with its intrinsic growth.

TABLE I

Age day	Ant. wall d.v.	Post. wall. d.v.	Fundus. a.p.	Post.w.+Fundus
$12\frac{1}{2}$ (III)	190μ	117μ	90μ	207μ
$13\frac{1}{2}$ (IV)	350μ	376μ	-	376μ

The neural evagination (process) is a solid mass of
cells (Fig. 18) and its cavity is restricted to the most
proximal portion of the evagination (Fig. 17). The
distal half of the neural process is related to the
dorsal portion of the posterior wall of the pouch (Fig.
20), while its proximal half which is connected to the
forebrain vesicle is free and surrounded with mesenchyme
tissue (Fig. 29). This mesenchyme tissue not only
invests the neural evagination, but it also infiltrates
its tissue dividing it into lobules (Fig. 29).

The ventral angle between the neural process and
the wall of the forebrain vesicle is greatly reduced.

The relation between the width of the neural process and that of the pouch is in the proportion: 1:2.

The cells of the neural process (Fig. 18) are irregularly arranged, essentially ovoid in shape, and small in size (relative to the size of the cells of the pouch).

The cells of the pouch (Figs. 27 and 28) are arranged in approximately three layers, except in the basal portion of the anterior wall of the pouch (Fig. 24) where many layers of cells are found.

The cavity of the pouch is nearly fusiform in shape (Fig. 26) and its dorsoventral diameter is approximately double its width. The linear dimensions of the cavity of the pouch are as follows: Anteroposterior: 60µ; Width: 170µ; and the dorso-ventral: 340µ.

The linear measurements of the diameters of the epithelial stalk of the pituitary are: Anteroposterior diameter: 20µ; transverse: 30µ; and its dorsoventral length is 50µ.

STAGE V
14½ day embryo

The pouch is represented by a closed, oblique, kidney shaped sac (Fig. 35), connected in the midline to the roof of the stomadeum by the epithelial pituitary stalk, and directed anterodorsally with its dorsal end occupying the interval between the neural process and the posteroventral wall of the forebrain vesicle, while its anterior wall is widely separated from the forebrain vesicle.

The direct communication between the cavity of the pouch and the stomadeum no longer exists, and the epithelial stalk is a solid cord of cells (Fig. 41) which connects the expanded basal portion of the pouch to the epithelial roof of the stomadeum.

The epithelial stalk is expanded dorsally where it is continuous with the middle basal growth (T) of the anterior wall of the pouch (Fig. 41), while it tapers ventrally to meet, at right angle, the cuboidal epithelium of the roof of the stomadeum, and is surrounded throughout its course by the prochondral mesenchyme condensation. The epithelial stalk is double the length of that at the previous stage.

The growth of the pouch is confined to the triangular area bounded by the roof of the stomadeum on one side, and the angle between the neural process and the forebrain vesicle on the other.

The vertical dorsoventral diameter of this confined space is found (Fig. 47) to be almost unchanged through the three successive stages; $13\frac{1}{2}$, $14\frac{1}{2}$ and $15\frac{1}{2}$ day stages.

This fact plays most probably a significant part in the changes of the direction and shape of the developing pouch, as at this stage, the prochondral condensation in the ventral zone of this confined area, not only reduces the available space for the growing pouch but it also appears to:

1. shift the pouch dorsally as is clear from the elongation of the connected epithelial stalk (Fig.47).
2. change the direction of the developing pouch (Fig.47) so that the long dorsoventral axis of the pouch remains in $13\frac{1}{2}$ day stage, almost parallel to the vertical axis of the confined space, but at the $14\frac{1}{2}$ day stage it becomes oblique with the dorsal end of the pouch in the angle between the neural process and the forebrain vesicle, while the ventral extremity of the anterior wall of the pouch is separating from the wall of the forebrain vesicle, and to
3. change the shape of the pouch as the main growth becomes in its width.

However, the change in shape of the pouch is effected also by the rapid growth of the basal portion of the anterior wall of the pouch shifting the inferior part of the pouch forwards, and by the marked increase in the size of the neurohypophysis invaginating the dorsal portion of the posterior wall of the pouch which is in contact with it (Fig. 39). This is shown by the marked

difference between the concave shape of the wall of the pouch in contact with the neural process and the convex shape of the regions of the pouch lateral to this contact.

The walls of the pouch are of a fairly uniform thickness (40μ) (including the dorsal portion of the posterior wall), except its basal portion which is three times the thickness of other regions.

The thickening of the basal portion of the anterior wall of the pouch, though greatly increased, is still restricted transversely to the intermediate zone of the wall (nearly $\frac{1}{2}$ its width), and does not extend dorsally further than its centre (Fig. 34).

Fig. 34 shows that the middle ridge like outgrowth of the anterior wall of the pouch (T) is greatly enlarged and expanded in all directions. It is in contact with the medial aspects of each of the dorsolateral knob like projections (GI), and continues anterodorsally, anterior to the dorsolateral projections (GI), in a form of tongue like process which reaches the upper limit of the projections. The tongue like process leaves a fossa like interval between it and the anterior aspect of the pouch, and this is filled with mesenchyme containing blood vessels. (artery to the trabecula – see the development of the vascular supply) The two dorsolateral outgrowths (GI) have expanded in all directions, and are separated by a narrow median space which is an extension of the interval between (T) and (GI) and like it is filled with vascular mesenchyme.

The neural process is enlarged (Fig. 37), but the part of its ventral wall which is not connected to the pouch is greatly reduced most probably due to the growth of the dorsal portion of the pouch.

The relation between the width of the neural process to that of the pouch, at this stage, is in the proportion of 2:5.

The cavity of the pouch has its transverse diameter markedly increased, its dorsoventral diameter reduced, and its anteroposterior diameter unchanged. The linear dimensions of the cavity of the pouch are as follows: Anteroposterior: 60μ; width: 260μ; and dorsoventral depth 240μ.

Application of differential cytological methods to pituitary tissue at this stage (Gomori chrome alum haematoxlin phloxine, combined aldehyde fuchsin and periodic acid Schiff, and combined aldehyde thionin and periodic acid Schiff) reveals the presence of faintly stained granules in the cells around the cavity of the pouch and the cells of the outgrowths of the pouch (Figs. 43-46).

STAGE VI
$15\frac{1}{2}$ day embryo

Rathke's pouch (Fig. 48) resting on the newly laid down cartilage, is represented by an inverted S shaped sac, connected by a long epithelial stalk passing through a canal in the cartilage to the roof of the stomadeum. The dorsal end of the pouch and the dorsal portion of its anterior wall are in close proximity to the posteroventral wall of the forebrain vesicle, but are separated from it by a very narrow interval filled with mesenchyme.

The thin prochondral mesenchyme condensation found in the ventral zone of the area available for the growth of the pouch, is replaced by thick cartilage (Fig. 68).

The vertical height of the neural process (Fig. 55) is greatly increased and it becomes conical in shape with a dorsal rounded apex and a base in contact with the dorsal portion of the posterior wall of the pouch. It is separated from the pouch (Fig. 55) by a single layer of cells, which is in continuity with the mesenchyme tissue at its edges.

The neural process (Fig. 55) lies at right angles to the wall of the forebrain vesicle, and appears as though sitting on the dorsal portion of the posterior wall of the pouch by its whole base (Figs. 53 and 67).

The cavity of the pouch (Fig. 48), greatly increased in width, is sigmoid in shape with anterodorsal (Fig. 52) and posteroventral parts (Fig. 51).

The superior part of the original posterior wall of the pouch (Fig. 66) is in contact with the neural process, while the inferior part (Fig. 63) is free. Both of these portions are of the same uniform thickness (40μ) as in the previous stage, except at their junction where there is a slight thickening (Fig. 65), the cells of which are undergoing mitosis.

In a similar manner the anterior wall of the pouch (Fig. 64) consists of a small, anterodorsal portion (Fig. 52) which is of similar thickness to the posterior wall of the pouch, and a very markedly thickened basal portion (Fig. 50). The thickening of the basal portion of the anterior wall, not restricted as previous stages to the intermediate region, extends over the whole width (Fig. 68).

The two dorsolateral projections of the anterior wall of the pouch (GI) expand greatly in all directions (Fig. 56), and each of them comes in contact with the middle basal outgrowth (T). Fig. 72 shows that dorsal to these dorsolateral outgrowths (GI), there are two similar separate outgrowths (GII) reaching close to the midline. Each of these (GII) comes into contact, but does not fuse with the corresponding inferior outgrowth (GI).

The middle basal outgrowth (T) has expanded greatly, and its tongue like process continues its growth in an anterodorsal direction. The fossae between these outgrowths are filled with vascular mesenchyme.

The middle basal outgrowth (T) is still connected to the epithelial stalk (Fig. 49). The connection of the epithelial stalk is carried anterodorsally not only by the anterodorsal growth of the middle basal outgrowth, but also by the growth of the basal portion of the pouch as a whole. The epithelial stalk is double the length of that at the previous stage.

The outgrowths of the pouch are formed from small rounded cells with centrally located nuclei, and covered externally with columnar epithelial cells (Fig. 60).

The middle basal outgrowth (T) and its tongue like process is destined to form the pars tuberalis of the gland, while the dorsolateral outgrowths (GI and GII) will contribute to the formation of the anterior lobe of the gland.

The relation of the width of the neural process to that of the pouch is in the proportion of 1:3. Comparing this with the similar proportions in previous stages (3:4, 2:3, 1:2, 2:5, and 1:3) it is clear that the transverse growth of the neural evagination up to this stage is lagging behind that of the pouch.

The plate of cartilage laid down in the ventral zone of the pituitary region, between the gland and the roof of the stomadeum, is fusiform with tapering anterior and posterior ends and maximum width in the centre. The thickness of the plate is diminished medially to form a very shallow, small fossa for the gland. In the centre of this fossa there is a capacious, nearly

circular canal, filled with loose mesenchyme tissue and through this the epithelial stalk of the pituitary passes to the roof of the stomadeum. The superior (dorsal) surface of the cartilage plate is covered with mesenchyme which passes around the epithelial stalk, through the canal to become continuous with that on the inferior (ventral) surface of the cartilage plate.

The linear dimensions of the cavity of the pouch, in this stage, are as follows:

Anteroposterior: 60μ; width: 350μ; and the dorso-ventral depth: 240μ.

STAGE VII

16½ day embryo

This stage represents Rathke's pouch as a compressed sac, connected in the midline to the roof of the stomadeum by the long epithelial stalk (Fig. 73). The cavity of the pouch is clavicular in shape (Fig. 73), horizontal in position with its long axis anteroposteriorly directed and almost parallel with the plane of the superior surface of the basal cartilage.

Fig. 81 shows that: 1) the dorsoventral axis of the confined triangular area available for the growing pituitary, though almost constant in the previous three stages, is reduced at this stage. 2) the tissue between the roof of the stomadeum and the inferior surface of the basal cartilage is increased, and 3) the ventral angle between the neural process and the wall of the forebrain vesicle is greater.

The neural process (Fig. 76) is greatly increased and all its diameters are essentially equal. It is connected to the wall of the forebrain vesicle by a very short stalk, containing within its centre the persistent proximal portion of the cavity of the neural evagination.

The relation between the width of the neural process and that of the pouch is in the proportion of 1:3.

The superior part of the original posterior wall of the pouch (Fig. 76) is in contact with the base of the neural process, while the inferior part is free and

forming the posterior boundary of the cavity of the pouch. Both of these portions are of the same uniform thickness as in $14\frac{1}{2}$ day stage (40μ), except at their junction where there is a slight thickening. The posterior wall of the pouch has multiple knob like thickenings arising from its superior portion along the lateral aspects of the base of the neural process. (Fig. 77). These small knob like outgrowths are rich in mitotic figures.

The anterior wall of the pouch consists of a small anterodorsal portion which is of similar thickness to the posterior wall of the pouch and forms the anterior boundary of the cavity of the pouch (Fig. 75), and a very markedly thickened basal portion involved in the structure of the expanding outgrowths (GI and GII).

The median basal outgrowth (T) with its tongue like process expanding anterodorsally against the forebrain, comes into close proximity with the posterior wall of the forebrain vesicle, and changes its direction, folding on itself forming a dorsal, knee like bend which contains a cavity within its centre (Fig. 74) then the process runs further anteriorly along the inferior surface of the forebrain vesicle.

The tongue like process of the basal outgrowth is considered as the tuberal process of the gland, and the dorsal knee like bend is ~~the so called~~ its dorsal horn, and its anterior portion along the inferior aspect of the forebrain vesicle is the anterior horn of the pars tuberalis.

The neural process is separated from the posterior wall of the pouch by a single layer of cells, which is in continuity with the surrounding mesenchyme at its edges (Fig. 76).

The linear dimensions of the horizontal cavity of the pouch are as follows:
Dorsoventral (original anteroposterior): 50μ;
anteroposterior (original dorsoventral): 170μ; and
the width: 420μ.

NOTE ON TOPOGRAPHICAL NOMENCLATURE

As the pouch has adopted a horizontal position, the topographical names applied to its various regions seem hardly appropriate. The developing gland has not yet adopted its final shape, but it may be convenient to apply the topographical terms used in the adult gland.

The original posterior wall of the pouch - in $16\frac{1}{2}$ day stage - consists of a superior portion in contact with the base of the neural process, and a free inferior part, and at the junction of the two portions there is a slight thickening. The superior part is destined to give the "pars intermedia", while the inferior part forms the posterior (caudal) boundary of the cavity of the pouch.

(It is noticed that the slight thickening at the junction of the two portions of the posterior wall of the pouch is seen for the first time in $13\frac{1}{2}$ day embryo)

The original anterior wall of the pouch - in $16\frac{1}{2}$ day stage - consists of a small thin anterodorsal portion and markedly thickened basal portion with the outgrowths (GI, GII and T). The thin anterodorsal portion of the original anterior wall forms the rostral boundary of the cavity of the pouch. The middle basal outgrowth (T) and its tongue like process, is separated from the rest of the original anterior wall by the intraglandular fossa which is filled with mesenchyme tissue, and is destined to form with the connected basal portion of the pouch, the pars tuberalis.

The remainder of the original anterior wall, the dorsolateral outgrowths (GI and GII), and the thickened basal portion of the pouch form the anterior lobe of the gland.

STAGE VIII

$17\frac{1}{2}$ day embryo

The pouch, at this stage (Fig. 85), is greatly
elongated (anteroposteriorly) and flattened (dorsoventrally)
and only in some embryos is it still connected in the
midline by a very long oblique epithelial stalk to the
roof of the stomadeum.   In most of the embryos examined
the epithelial stalk is interrupted along its course,
nearer to the stomadeum than to the pouch leaving both
the glandular and stomadeal connections intact.

The exact manner in which this interruption of the
epithelial stalk takes place, could not be determined, but most
probably due to appearance of vacuoles or cavities within
its structure (Fig. 213).

The cavity of the pouch, becoming semilunar (Fig.
84), is restricted to the intermediate zone of the pouch
(nearly $\frac{2}{3}$ of the width of the pouch) as the lateral walls
of the pouch are markedly thickened forming "cavity free"
lateral extensions (lateral lobes).   These lateral lobes
(lateral extensions) are formed from trabeculae and cords
of cells infiltrated with mesenchyme.

The cavity of the pouch, increasing its width and
anteroposterior length, is bounded dorsally by the pars
intermedia, ventrally by the anterior lobe, caudally by
the free inferior portion of the original posterior wall
(see above), anteriorly by the thin anterodorsal portion
of the original anterior wall (see above), and laterally

by the lateral lobes (extensions).

The outgrowths of the pouch (GI and GII) have expanded in all directions. Laterally and ventrally they send outgrowths which are considerably infiltrated by mesenchyme tissue (Fig. 83).

The middle basal outgrowth (T) has not increased in width and is situated opposite the intermediate zone of the ventral aspect of the pouch (nearly $\frac{1}{2}$ its width) from which it is separated by the intraglandular fossa filled with vascular mesenchyme tissue (Fig. 85). The tongue like process of this outgrowth (Fig. 89) extends further forward beyond the anterior end of the pouch, and the dorsal horn contains the central cavity (Fig. 85). The anterior horn passes below the inferior surface of the forebrain vesicle (Fig. 92) and its tip shows no bifurcation (Fig. 92).

The neural process (Fig. 85) is pyriform with a short narrow neck connected to the wall of the forebrain vesicle, and containing the persistent recess of the third ventricle in its intermediate third (proximal portion of the cavity of the original neural evagination).

The neck of the neural process (neurohypophysis) is longer than it is in the previous stage and is surrounded on all its aspects by what looks like bundles of nerve fibres (Fig. 86) running to the neural process. The dorsal bundle of nerve fibres being thinner than the ventral one, gives the neck of the neural process its

eccentric appearance (Fig. 84).

When these nerve tracts are followed anteriorly, the dorsal one appears to arise most probably from the paraventricular nuclei, while the ventral bundle seems to come from the supraoptic nuclei.

The width of the neural process to that of the pouch is in the proportion of 1:4 (previous stage is 1:3).

The linear dimensions of the cavity of the pouch are as follows:
Anteroposterior: 270µ; dorsoventral: 50µ; and width 480µ.

STAGE IX

18½ day embryo

The adenohypophysis (original pouch) is represented by a markedly flattened, elongated sac, with an L shaped cavity and expanded lateral lobes (Fig. 98).

The pars intermedia is noticeably elongated. The anterior end extends forwards beyond the connection with the base of the neurohypophysis and underlies the neural neck with the bundles of the nerve fibres around it (Fig. 99).

The small knob like outgrowths arising from the pars intermedia (original, superior portion of the posterior wall of the pouch) along the lateral aspects of the base of the neurohypophysis are more marked, and further outgrowths appear at this stage of the embryonic life in a more lateral position (Fig. 105).

The anterior lobe of the gland is extensively infiltrated with connective tissue. This divides the glandular tissue into loculi with an alveolar appearance (Fig. 102) which is more marked away from the midline (Fig. 104).

The outgrowths (GI and GII) of the pouch and their branches are markedly infiltrated by the connective tissue. Their original parts form the main bulk of the anterior lobe of the gland and can be easily detected (Fig. 97).

The middle basal outgrowth (T) of the pouch (pars

tuberalis) is much flattened, shows no lateral expansion corresponding to that of the pouch, and is separated from the intermediate region of the ventral aspect of the anterior lobe of the gland by the intraglandular fossa (Fig. 101). The dorsal horn of the tongue like process extends along the inferior aspect of the neural neck (see terminology), and not along its lateral aspects (Fig. 97) while the anterior horn, being flattened (Fig. 103), extends further forwards along the inferior aspect of the forebrain vesicle.

The glandular attachment of the epithelial stalk is represented by strands of cells which pass downwards and backwards from the site of junction of the middle basal outgrowth (T) and its tongue like process to the craniopharyngeal canal (Fig. 101). They pass through the canal, and the tissue between the cartilage and the roof of the stomadeum, and are connected to the latter. These strands are the remnants of the epithelial stalk of the pituitary, and they contain a number of cavities (Fig. 101) which may indicate the manner in which the connection is interrupted.

The neurohypophysis retains its pyriform appearance and dorsoventral height, while its base is much widened.

The neural stalk (neural neck + nerve bundles around it) (Fig. 99) with the recess of the third ventricle in its intermediate third, is much elongated

while its cross sectional area remains almost unchanged.

In the nerve tracts around the neural neck, some large, rounded or ovoid cells, filled with granules can be observed (Fig. 103). These cells are most probably glial cells.

The horizontal long limb of the L-shaped cavity of the pouch is four times the length of the posterior short one, and the cavity has the same measurements as in the previous stage.

STAGE X

$19\frac{1}{2}$ day embryo

There is little change in hypophysial development in this stage from the $18\frac{1}{2}$ day embryo.

The neural lobe (Fig. 106) appears slightly flatter as it is elongated anteroposteriorly with no change in its dorsoventral height.   The neural neck is also elongated.

The multiple knob like outgrowths of pars intermedia adopt an alveolar appearance (Fig. 107).

The anterior lobe of the gland (Fig. 106) is much flattened with more connective tissue infiltration.

The dorsal horn of pars tuberalis (Fig. 112) appears on the lateral aspects of the neural neck, but does not extend onto the dorsal surface.

The tongue like process and its anterior horn is greatly elongated and much flattened.   The tissue of this tongue like process shows some alveolar and tubular arrangement of its cells (Fig. 113).   At the site of junction of the middle basal outgrowth and its tongue like process, strands of cells representing the glandular attachment of the epithelial stalk of the pituitary can be observed (Fig. 108).

The relation of the width of the neurohypophysis to that of the adenohypophysis at this stage, as well as in the previous two stages, is in the proportion of; 1:4.

The remnants of the epithelial stalk of the

pituitary can be detected in the craniopharyngeal canal
and in the tissue underneath (Fig. 109) and it is
connected to the roof of the stomadeum.

The craniopharyngeal canal still persists within
the cartilage (Fig. 109) with slight reduction in its
lateral and anteroposterior diameters.

STAGE XI

$20\frac{1}{2}$ day embryo

This stage presents practically the condition of development of the pituitary of the rat at full term.

The size of the entire gland has not greatly changed.

The cavity of the pouch (residual cavity) retains its L-shaped appearance, has not suffered any reduction in its dorsoventral extent, the anterior horizontal limb is greatly elongated (giving an apparent shortening to its inferior portion) and the angle between the two portions increases.

The cavity is bounded dorsally by pars intermedia, ventrally by the anterior lobe of the gland, and caudally by the free inferior portion of the original posterior wall of the pouch.

The epithelial cells lining the cavity keep the stratified character, and no cilia can be detected.

The anterior lobe of the gland is much flattened and the alveolar arrangement of its rounded cells becomes more evident within the connective tissue stroma (Fig.116).

The pars tuberalis of the gland is also flattened, and it keeps its width opposite the intermediate region of the ventral aspect of the anterior lobe, and also the tubular arrangement of its cells.

The intraglandular fossa between the anterior lobe and the pars tuberalis is very clear; it is filled with vascular mesenchyme tissue.

The dorsal horn of the pars tuberalis extends along the lateral aspects of the neural stalk (neural neck + surrounding nerve tracts) but does not extend onto its dorsal aspect.

The anterior horn of pars tuberalis extends further forwards beyond the anterior end of the pouch, along the inferior aspect of the forebrain vesicle (Fig. 119). The anteroposterior length of the anterior horn is slightly less than the total anteroposterior length of the remainder of the gland.

The pars intermedia maintains the same thickness as the $14\frac{1}{2}$ day stage, and is in contact with the base of the neurohypophysis and its stalk. The pars intermedia is separated from the neurohypophysis by a thin connective membrane. There is slight thickening at the caudal end of pars intermedia (Fig. 117) (see above).

The multiple knob like outgrowths arising from the pars intermedia (original dorsal wall of the pouch) along the lateral aspects of the base of the neurohypophysis, appear in this stage in the midline where the neuro-hypophysis is present. (Fig. 116). In the substance of the dorsal wall (pars intermedia) they form light areas of rounded or ovoid cells arranged in an alveolar manner, while the remaining dark cells of the dorsal wall (pars intermedia) in this zone consists of wedge shaped groups of slender elongated cells with some rounded cells between them (Fig. 118). These lightly stained groups

of cells give the intermedia the appearance that it
consists of dark and light areas (Fig. 115).

To differentiate between the cells of these areas,
P.A.S. with aldehyde thionin was used; the long columnar
cells forming the dark areas appear dense blue-black
(thyrotrophs) (Paget and Eccleston, 1960) while the cells
of the light groups appear clear intense blue-green
(acidophils) (Paget and Eccleston, 1960).

The remnants of the epithelial stalk of the pituitary
can be detected in the craniopharyngeal canal and in the
tissue underneath (Fig. 122); it is connected to the
roof of the stomadeum (Fig. 120).

The craniopharyngeal canal (Fig. 121) still
persists within the cartilage, with slight reduction in
its lateral and anteroposterior diameters.

The neurohypophysis (Fig. 118) was increased
greatly in its volume, although its dorsoventral measure-
ment is the same as at the previous stage, but its base is
widely expanded.

The neural stalk (neural neck and surrounding nerve
tracts) while retaining the same diameter, has doubled
its length in comparison with the $17\frac{1}{2}$'day stage.

The areas of the nerve tracts are filled with large
ovoid or rounded cells filled with granules (Fig. 119).
These cells are most probably glial cells.

The ratio of the width of the neurohypophysis to
that of the pouch is in the proportion of; 2:5.

(previous stage is 1:4).

The linear measurements of the whole pituitary
gland at full term are; 0·35 m.m. dorsoventral;
0·5 m.m. anteroposterior; and 0·9 m.m. transverse.

STAGE XII
Neonatal animal
0 - 12 hours after birth.

It may be convenient to describe this stage in some detail and to refer in brief to the following postnatal stages up to the sexual maturity of the animal.

The pituitary gland (Fig. 123) of neonatal rat consists of two portions: 1) a dorsal, pyriform neurohypophysis with a long narrow neck connected to the wall of the diencephalon, with a very small recess of the third ventricle in the intermediate third of the proximal portion of the neck, and 2) a flattened triangular adenohypophysis with an L-shaped cavity dividing it into two unequal lobes; thin dorsal pars intermedia and thick ventral anterior lobe separated from the flattened elongated pars tuberalis by the intraglandular fossa.

The cavity of the pouch (residual cavity) is restricted to the intermediate region (nearly $\frac{2}{3}$ of its width) of the gland by the lateral, cavity-free, extensions (lateral lobes) of the gland. The cavity of the pouch keeps its L-shaped appearance and width similar to that before birth with no obliteration of any of its regions. The anterior limb of the cavity is five times the posterior (inferior) one in length, and the angle between them is increased (more obtuse)(Fig. 125).

The cells lining the cavity of the pouch form a stratified columnar epithelium.

The pars intermedia maintains the same thickness as the $14\frac{1}{2}$ day stage (40μ), and is in contact with the base of the neurohypophysis and the neural stalk. The slight thickening at the caudal end of the pars intermedia can be observed(Fig. 128).

The pars intermedia, with ordinary stains, as in the previous stage, has the appearance that it consists of dark and light areas (Fig. 127).

Application of different cytological stains (P.A.S. with aldehyde thionin, P.A.S. with aldehyde fuchsin, Mallory's trichrome, and Gomori chrome alum haematoxlin phloxine) gives similar results as previous stage (Figs. 134, 135 and 136). In sections stained with Kopsch modification of the Golgi method groups of thin spindle like cells with enlarged dorsal end are observed (Figs. 132 and 133). They extend between the two surfaces of the pars intermedia, perpendicular to these surfaces and connected to the cavity of the pouch. These groups of thin spindle like cells are most probably the dark cells of the pars intermedia.

The anterior lobe of the gland shows structure as in the previous stage, but it is further flattened.

The pars tuberalis (Fig. 130), being much flattened, is formed of two or three layers of cells which are not histologically different from the cells of the anterior lobe of the gland.

The dorsal horn of the pars tuberalis (Fig. 126)

extends on both sides along the lateral aspects of the neural stalk, and onto its dorsal surface, but there is no fusion in the midline dorsal to the stalk, i.e., no collar is formed around the neural stalk.

The anterior horn of pars tuberalis (Fig. 129) on its way to the inferior aspect of the diencephalon is greatly elongated with no bifurcation at its tip.

The pars tuberalis and its anterior horn extend as a flattened plate of cells along the intermediate region of the ventral aspect of the anterior lobe, the ventral aspect of the neural stalk, and the inferior aspect of the forebrain vesicle, within the undifferentiated mesenchyme surrounding the pituitary and separated from the anterior lobe by the intraglandular fossa and from the ventral aspect of the neural stalk by Atwell's recess, both of which are filled with a core of vascular connective tissue, and separated from the inferior aspect of the diencephalon by the membranes surrounding the forebrain.

The neurohypophysis (Fig. 136) has increased greatly in its volume, although its dorsoventral measurement is the same as the previous stage, but its base is widely expanded. The superior aspect of the neurohypophysis is nearer to the surface of the forebrain vesicle than in the previous stages, which is probably due to increase in the volume of the forebrain vesicle and its reorientation.

The neural stalk (neural neck + nerve tracts) shows the same picture that has been described before, except that it is elongated and is very slightly concave dorsally (Fig. 123).

The nerve tracts (bundles) are crowded with large ovoid or rounded cells full of granules. These cells are most probably glial cells.

The neurohypophysis is separated from the pars intermedia by a very thin connective tissue membrane which is in continuity with the undifferentiated mesenchyme tissue surrounding the whole gland, by its edges.

No remnants of the epithelial stalk of the pituitary could be detected at this stage, although the cranio-pharyngeal canal still persists with reduced antero-posterior and lateral dimensions.

The linear measurements of the whole pituitary gland at birth are as follows:

Dorsoventral height: 0·25 m.m.,   anteroposterior: 0·6 m.m, and side to side width (the greatest): 1 m.m.

The anterior horn of the pars tuberalis extends forwards beyond the anterior end of the remainder of the gland for a distance of 0·5 m.m.

POSTNATAL ANIMALS

STAGE XIII

1 week animal

The most characteristic change in the hypophysial development in this stage, is the marked increase in the volume of the gland. ($1\frac{1}{2}$ - 2 times that at birth).

The neurohypophysis doubles its volume as it grows at a faster rate than the adenohypophysis.

The neural stalk is greatly elongated and its curvature becomes more marked. (Fig. 139).

The anterior horn of pars tuberalis is very much elongated, that its anteroposterior length (extending forwards beyond the anterior end of the remainder of the gland) becomes equal to that of the remainder of the gland, i.e., the anterior horn doubles the anteroposterior length of the previous stage (at birth, 0·5 m.m., this stage, 1 m.m.).

The linear measurement of the pituitary gland at this stage are as follows:
dorsoventral height: 0·3 m.m., anteroposterior (without the anterior horn of pars tuberalis): 1 m.m., and side to side width: 1·5 m.m.

STAGE XIV

2 week animal

The gland is much elongated anteroposteriorly.

The neurohypophysis gains much in the dorsoventral measurement, while the adenohypophysis is more flattened. (Fig. 141)

The neural stalk is markedly elongated, doubling its length compared with that of the one week stage, and the curvature is more apparent (Fig. 142).

The nerve tracts contain many more large ovoid or rounded cells filled with granules, which are probably glial cells.

The anteroposterior length of the anterior horn of the pars tuberalis which has greatly increased, exceeds that of the remainder of the gland at this stage.

STAGE XV

3 week animal

The same picture as in the 2 week stage (Fig. 144).

The neural stalk doubles its length compared with that of the last stage.

The anterior horn of the pars tuberalis extends further forwards.

STAGE XVI

6 week animal

No apparent changes take place; the neural stalk and the anterior horn of the pars tuberalis keep the same length as the previous stage (Fig. 146).

It is evident through these postnatal stages that the anterior portion of the L-shaped cavity is greatly elongated, while its caudal portion becomes shorter and thinner.

M I T O T I C   A C T I V I T Y

It has been noticed that in any physiological or experimental condition which results in an increase in the total number of cells of the pituitary, mitosis must play the sole role.

Composite tables and complicated numbers may be of less significance for interpretation of the role of mitosis in the pituitary development, than the presentation of the sites of high activity in the different regions of the gland in the successive prenatal stages. An attempt has been made, as far as possible, to present these findings by diagrams, thereby avoiding lengthy description.

<u>10½ day stage</u> (Figure 147).

The cells of Rathke's pouch are in a very marked
state of activity as more than one third of the cells of
the anterior wall and less than one fourth of the cells
of the opposing posterior wall of the pouch, are in one
or other of the mitotic stages.   In general, the mitotic
figures occur in all regions of the pouch, but are most
frequently observed in the zone adjacent to the lumen of
the pouch.   The greatest number of mitoses can be seen
in the basal portion of the anterior wall of the pouch.

<u>11½ day stage</u> (Figures 148-149)

The greatest number of mitoses is found in the
ventral and dorsal portions of the pouch.   The mitotic
figures are more crowded around the cavity of the pouch
and in the basal portion of its anterior wall.

The neural evagination shows mitotic activity to a
less extent than the pouch.   The mitotic figures are
most frequently observed in the zone adjacent to the
cavity of the neural evagination.

<u>12½ day stage</u> (Figures 150-152)

Cells undergoing mitosis are to some extent less
than the previous stage in all regions of the pouch.

Mitotic figures are observed more in the anterior
wall of the pouch in particular its basal portion, in mid-
line, than in the posterior wall of the pouch.

There is also another site of high activity at the

angle between the tip of the posterior wall of the pouch and its fundus.

The cells undergoing mitotic division in the neural evagination are most frequently noticed in the zone adjacent to its cavity, its apex, and in the midline than in the lateral regions.

$13\frac{1}{2}$ day stage (Figures 153-156)

The anterior wall of the pouch shows a much higher mitotic activity than the posterior wall, in particular its basal portion which contains the greatest number of these cells.

The cells undergoing mitotic division are still crowded in the zone adjacent to the cavity of the pouch.

The cells in the midline and just lateral to it, are in a higher state of activity than those of the extreme lateral portions of the pouch.

The cells of the neural process, being in a relatively less active state than those of the pouch, are most frequently found in the apex of the process and its lateral regions.

$14\frac{1}{2}$ day stage (Figures 157-162)

The areas of the pouch in which the highest total numbers of mitoses are observed, are: 1) basal portion of the anterior wall, 2) area just dorsal to this basal region of the anterior wall, 3) apex of the pouch, in particular, in the midline, 4) at the junction of the two portions of the posterior wall of the pouch, and

5) the dorsal end of the epithelial stalk of the pouch.

More mitotic figures are observed in the lateral regions of the pouch than in the midline, except in the above mentioned zones.

The mitotic activity of the neural process is less marked than that of the pouch, and the cells undergoing mitosis are almost equally distributed through the process.

15½ day stage (Figures 163-168)

The zones of high mitotic activity in this stage are: 1) anterior wall of the pouch, 2) apex of the pouch in midline, and 3) some zones in the dorsal portion of the posterior wall of the pouch, just lateral to the midline, and at the junction of its two portions.

The neural process shows a fair distribution of the cells undergoing mitosis, although they are a little more in the midline.

16½ day stage (Figures 169-174)

The same picture of the previous stage, with more crowding in the anterodorsal portion of the original anterior wall (ventral) of the pouch, and its lateral zones.

18½ day stage (Figures 175-182)

There is a very marked decrease in the cells under-going mitosis in this stage.

More mitosis are observed around the cavity of the

pouch; along the strip of the pars intermedia, and in the anterior and lateral regions of the pouch, than the posterior and medial zones.

The pars tuberalis contains relatively very few mitoses.

The reduction is more marked in the neurohypophysis, with mitosis relatively more frequent in the midline.

$20\frac{1}{2}$ day stage (Figures 183-187)

The reduction in the number of mitosis progresses with a similar picture of distribution to that of the previous stage.

SECTION II

VOLUMETRIC GROWTH OF THE PRENATAL PITUITARY

1. Absolute growth changes.

2. Relative growth changes.

3. Relative increase in the growth of the gland and its lobes.

Construction of graphs.

The age of the embryo in days or crown-rump length in millimeters formed the abscissa of each graph, while the volume of the whole gland or its parts formed the ordinates.

I. ABSOLUTE GROWTH CHANGES

The growth in volume of the gland and its lobes when plotted against the embryonic age or length, forms in each instance a concave curve.

A. Total volume of the pituitary

The growth of the whole gland in volume during the embryonic period is represented in Table 1 and Fig. 188.

The observed volume of the whole gland is 0·1765 m. m.^{3} at birth, 0·085 m.m.^{3} at $18\frac{1}{2}$ day stage, and 0·0017 m.m.^{3} at $12\frac{1}{2}$ day stage.

The approximate increase in volume of the total gland from an embryo of $12\frac{1}{2}$ day to one at $18\frac{1}{2}$ day is 50 times, and to one at birth ($21\frac{1}{2}$ day) is 100 times, i.e. the volume of the total gland at birth is only double

that at $18\frac{1}{2}$ day stage.

Fig. 188 shows a concave curve illustrating the growth changes in the volume of the total gland during the prenatal life. It shows an approximately uniform growth in the early embryonic life, up to $17\frac{1}{2}$ day stage, and from $18\frac{1}{2}$ day stage the curve tends to be more straight representing almost equal growth in the volume of the total gland at the equal time intervals of the late embryonic life.

TABLE I

VOLUME OF THE PITUITARY AND ITS LOBES THROUGH THE PRENATAL LIFE OF RAT AND AT BIRTH. (m.m.^{3})

Age	WHOLE GLAND	ANT. L.	NEURAL L.	INTERMED.	LATERAL
day	m.m.^{3}	m.m.^{3}	m.m.^{3}	m.m.^{3}	m.m.^{3}
$12\frac{1}{2}$	0·0017	0·0014	0·0003	–	0·0002
$13\frac{1}{2}$	0·0057	0·0029	0·0008	0·0021	0·0002
$14\frac{1}{2}$	0·0122	0·0072	0·0018	0·0032	0·0004
$15\frac{1}{2}$	0·0271	0·0179	0·0035	0·0056	0·0019
$16\frac{1}{2}$	0·0358	0·0264	0·0036	0·0058	0·0049
$17\frac{1}{2}$	0·0479	0·0328	0·0058	0·0093	0·0069
$18\frac{1}{2}$	0·0850	0·0654	0·0094	0·0102	0·0278
$19\frac{1}{2}$	0·1227	0·0913	0·0169	0·0146	0·0405
$20\frac{1}{2}$	0·1489	0·1120	0·0201	0·0168	0·0452
Birth	0·1765	0·1326	0·0237	0·0190	0·0505

B. Volume of the lobes of the gland

Anterior lobe.

The growth changes in the volume of the anterior lobe of the gland during the intrauterine life, resemble the type of changes which occur in the total gland volume.

This is not surprising since the anterior lobe comprises relatively more of the gland than the other lobes.

The growth of the anterior lobe of the gland in volume during embryonic life is represented in Table I, and Fig. 188.

The observed volume of the anterior lobe of the gland at $12\frac{1}{2}$ day stage is $0\cdot0014$ m.m.^{3}, at $18\frac{1}{2}$ day stage $0\cdot0654$ m.m.^{3} and at birth is $0\cdot1326$ m.m.^{3}.

The volume of the anterior lobe of the gland at birth is approximately double that at $18\frac{1}{2}$ day stage, and the increase in the volume from an embryo of $12\frac{1}{2}$ day stage to one at $18\frac{1}{2}$ day stage is 50 times, i.e. the anterior lobe of the gland increases 100 times in volume during the prenatal life.

The growth in volume of the whole gland and the anterior lobe are similar as regards the number of times (100) that their volume is doubled through the prenatal life.

The curve (Fig. 188) representing the growth in volume of the anterior lobe of the gland, is similar to that of the whole gland, i.e. an approximately uniform growth in the early embryonic period, and at the $18\frac{1}{2}$ day stage the increase in volume becomes almost equal at the equal intervals of late embryonic life.

Intermediate lobe

The growth of the pars intermedia of the gland during prenatal life is represented in Table I, and

Fig. 190.

As the volumetric estimation of the pars intermedia is difficult at early embryonic life, it is not represented at $12\frac{1}{2}$ day stage, and in $13\frac{1}{2}$, $14\frac{1}{2}$ and $15\frac{1}{2}$ day stages is represented by the original posterior wall of the pouch.

The observed volume of the intermediate lobe is $0\cdot0093$ m.m.^{3} at $17\frac{1}{2}$ day stage, and is $0\cdot0190$ m.m.^{3} at birth.

The volume of the lobe at birth is double that at the $17\frac{1}{2}$ day stage. The intermediate lobe of the gland increases only 9 times in volume during the prenatal life.

The curve of the growth changes in the volume of the intermediate lobe (Fig. 190) during the embryonic life, resembles that of the total gland, except: 1) the number of times that their volumes are doubled through the prenatal period (total gland: 100, pars intermedia: 9) and 2) the critical time at which the curve tends to be more straight (total gland: $18\frac{1}{2}$ day, pars intermedia: $17\frac{1}{2}$ day).

Neural lobe

The growth of the neural lobe of the gland in volume during the prenatal life is shown in Table I, and Fig. 190.

The observed volume of this part of the gland at an embryo of $12\frac{1}{2}$ day is $0\cdot0003$ m.m.^{3}, of $16\frac{1}{2}$ day is $0\cdot0036$ m.m.^{3}, of $18\frac{1}{2}$ day is $0\cdot0094$ m.m.^{3}, while at $19\frac{1}{2}$ day is

0·0169 m.m.^{3}, and finally at birth is 0·0237 m.m.^{3}.

The neural lobe appears later in embryonic life, and increases in the early prenatal period at a slower rate in comparison with that of the total gland or its anterior lobe. The volume of the total gland or its anterior lobe at birth is double that at the $18\frac{1}{2}$ day stage, but the volume of the neural lobe at birth is approximately three times that at the $18\frac{1}{2}$ day stage.

The curve (Fig. 190) representing the growth changes in the volume of the neural lobe of the gland during the embryonic period resembles that of the total gland, except: 1) the number of times that their volumes are doubled through the prenatal life (total: 100, neural,79), 2) the critical interval of embryonic life at which the curve tends to be less concave (total: $18\frac{1}{2}$ day, neural: $19\frac{1}{2}$ day).

Lateral lobes (extensions)

These are the cavity-free lateral extensions of the anterior lobe of the gland. The lateral walls of the original pouch keep thin up to $17\frac{1}{2}$ day stage, then they are greatly thickened, restricting the cavity of the pouch into the intermediate region of the gland.

The changes in growth of the volume of the lateral lobes of the gland in embryonic life is represented in Table I, and Fig. 189.

The observed volume of these lobes at the $12\frac{1}{2}$ day stage is 0·0002 m.m.^{3}, at the $17\frac{1}{2}$ day is 0·0069 m.m.^{3},

at the $18\frac{1}{2}$ day is 0·0278 m.m.^{3}, and finally at birth is
0·0505 m.m.^{3}.

The approximate increase in the volume of the
lateral lobes of the gland from an embryo of $12\frac{1}{2}$ day to
one at $18\frac{1}{2}$ day is 140 times, and to one at birth is 250
times.

The lateral lobes, although increase in the early
prenatal period at a slower rate in comparison with
the anterior lobe of the gland, but the number of times
that their volume is doubled exceed greatly that of the
anterior lobe (250).

Fig. 189 shows the growth changes in the volume
of the lateral lobes in prenatal life.

2. RELATIVE GROWTH CHANGES

The relation between the volume of each lobe of the
gland to the volume of the total gland in the different
stages is shown in Table II, and Fig. 191.

It is observed at the $16\frac{1}{2}$ day stage that the
anterior lobe comprises 73·8% of the total gland volume,
and the remainder of the volume is 16·2% pars intermedia,
and 10% pars nervosa.

In early prenatal life the anterior lobe comprises
relatively less of the gland than it does later, while the
intermedia, on the contrary, comprises more in the early
intrauterine life, and the nervosa makes the smallest part
of the gland.

The relative volume of each lobe of the gland is changed in the course of development; in the $18\frac{1}{2}$ day stage the anterior lobe forms 76·8%, while the pars intermedia (11·9%) and the pars nervosa (11·3%) are almost equal, then the relative volume of the nervosa exceeds that of the intermedia up to birth.

TABLE II

RELATIVE VOLUME OF THE LOBES OF THE PITUITARY TO TOTAL
GLAND THROUGH THE PRENATAL LIFE OF RAT

Age	Ant.Lobe.	Neural.L.	P.Intermedia	Lateral L.
day	per cent	per cent	per cent	per cent
$12\frac{1}{2}$	–	17·7	–	1·1
$13\frac{1}{2}$	50·9	14·0	35·1	3·2
$14\frac{1}{2}$	59·0	14·8	26·2	3·1
$15\frac{1}{2}$	66·1	13·1	20·8	7·0
$16\frac{1}{2}$	73·8	10·0	16·2	13·4
$17\frac{1}{2}$	73·1	12·1	14·8	14·3
$18\frac{1}{2}$	76·8	11·3	11·9	32·7
$19\frac{1}{2}$	74·5	13·7	11·9	33·0
$20\frac{1}{2}$	75·2	13·5	11·3	30·3
Birth	75·8	13·4	10·8	28·6

The relative volume of each lobe of the gland is changed in the course of development; in the $18\frac{1}{2}$ day stage the anterior lobe forms 76·8%, while the pars intermedia (11·9%) and the pars nervosa (11·3%) are almost equal, then the relative volume of the nervosa exceeds that of the intermedia up to birth.

It can be observed from Table II that the relative volume of each lobe to the total volume of the gland

appears to change very slightly from the $19\frac{1}{2}$ day stage, i.e. the rate of increase in the volume of each of the lobes is almost the same.

The calculated relative volume of the lobes of the pituitary gland of the rat, at late prenatal life ($19\frac{1}{2}$ and $20\frac{1}{2}$ day stages) and birth, is as follows: anterior lobe: 75·5%; intermediate lobe: 11%; and the neural lobe: 13·5%, of the total volume of the gland.

3. RELATIVE INCREASE IN THE GROWTH OF THE PITUITARY AND ITS LOBES

The volumes of the gland and also of each of its lobes are considered as being equivalent to 100% at birth.

The relative increase in prenatal life is given in Table III, and Fig. 192.

It can be observed that the volume of the total gland and of each of its lobes forms at $20\frac{1}{2}$ day stage approximately 85% of that at birth, and at the $19\frac{1}{2}$ day stage each comprises about 70%. This relation may show as mentioned before; 1) the growth of the total gland volume and each of its lobes is almost the same at the equal time intervals of the late embryonic life, i.e. 15% per day (birth <u>100</u>%; $20\frac{1}{2}$ day, <u>85</u>%; and $19\frac{1}{2}$ day <u>70</u>%), and 2) the rate of increase in the volume of the gland and each of its lobes is the same, e.g. at the $19\frac{1}{2}$ day stage the gland and each of its lobes f_orms 70% of the

volume at birth, and at the 20½ day stage all form the same relation, i.e. 85% of their volumes at birth.

The volume of the total gland in the 18½ day stage is approximately half of that at birth, the anterior lobe keeps the same relation, while the intermedia reaches it (50% of the volume at birth) earlier (17½ day stage) and the nervosa later.

TABLE III

VOLUME OF THE PITUITARY AND ITS LOBES CALCULATED
IN PERCENTAGES OF THEIR VOLUMES AT BIRTH

AGE	WHOLE GLAND	ANT.L.	NEURAL L.	INTERMED- IATE L.	LATERAL L.
Day	%	%	%	%	%
12½	1·0	1·0	1·3	–	0·4
13½	3·2	2·2	3·3	11·0	0·4
14½	6·9	5·4	7·6	16·8	0·8
15½	15·4	13·5	14·8	29·0	3·8
16½	20·3	19·9	15·2	30·5	9·7
17½	27·1	24·6	24·5	48·5	13·7
18½	48·2	49·3	39·7	53·7	55·0
19½	69·5	68·9	71·3	76·8	80·0
20½	84·4	84·4	84·8	88·5	89·5
Birth	100	100	100	100	100

The lateral lobes at 17½ day stage form only 13·7% of their volume at birth, but their growth is greatly increased at the 18½ day stage as they form 55% of their volume at birth.

SECTION III

RELATION OF THE CEPHALIC END OF THE NOTOCHORD TO THE DEVELOPING PITUITARY GLAND

$10\frac{1}{2}$ day stage

The notochord, consisting of faintly stained ovoid cells (Fig. 193) is separated from the entoderm, except where it is connected to the anterior portion of the foregut where it makes a very slight evagination (Fig.194). The anterior end of the notochord beyond this connection (Fig. 193), is directed anteriorly and dorsally to come into close contact with the posterior wall of Rathke's pouch (Fig. 193), but no actual point of fusion can be demonstrated (Fig. 193).

$11\frac{1}{2}$ day stage

The notochord follows the configuration of the entoderm as far forwards as the tip of the foregut. Here it dips down to come in contact with the entoderm through a mass of cells (Fig. 196) similar to those of the notochord itself, while its anterior end beyond this connection (Fig. 195) runs towards the posterior wall of the stomadeal evagination (Rathke's pouch).

$12\frac{1}{2}$ day stage

The very slight evagination at the tip of the foregut is marked (Fig. 198), and the notochord is connected to its tip by a cord of cells, similar to those of the notochord itself, and is considered as its "descending

limb", while that running further anteriorly and dorsally, beyond this connection, to Rathke's pouch is the "anterior or ascending limb or branch" of the cephalic end of the notochord (Fig. 198).

$13\frac{1}{2}$ day stage

The ascending and descending branches of the cephalic end of the notochord are more evident (Fig. 200).

No detachment of the notochord from the entoderm can be detected. On the contrary, the connection of the descending branch to the epithelial evagination is more marked, and becomes very clear (Fig. 200).

$14\frac{1}{2}$ day stage

The notochord runs anteriorly on the dorsal surface of the caudal part of the prochondral mesenchyme condensation (Fig. 201), which takes place in the ventral zone of the area of the undifferentiated mesenchyme surrounding the pituitary, and a short distance posterior to its bifurcation it dips into the condensation near the dorsal surface (Fig. 203). After a short course it emerges on to the superior surface of the condensation to reach its bifurcation. From here the ascending branch of the cephalic end of the notochord runs a very short, horizontal course after which it is anteriorly and dorsally directed to the posterior wall of the pouch (Fig. 205) where sometimes it is responsible for an indentation of its posterior wall (Fig. 204), but no actual fusion ever takes place. The descending branch

of the cephalic end of the notochord is incorporated into the prochondral mesenchyme condensation, but it can be detected (Fig. 205) to its epithelial connection.

The epithelial evagination becomes less marked though it is present, and in some embryos it becomes a mere thickening in the epithelium, connected to the descending branch of the notochord (Fig. 204).

The surrounding mesenchyme makes a definite membrane around the cells of the notochord which become clearly outlined.

$15\frac{1}{2}$ day stage

The cartilage is laid down in this stage.

The notochord caudal to its bifurcation has the same course described in relation to the prochondral mesenchyme condensation. The ascending branch of the cephalic end of the notochord has the same course described in the $14\frac{1}{2}$ day stage, while the descending branch takes a different course; a) either it is incorporated into the cartilage (Fig. 206) as described in the prochondral condensation, running ventrally to the epithelial evagination which becomes a mere thickening in the epithelium connected to the strand of the cells of the descending limb which is more apparent underneath the cartilage plate, b) or the cartilage forms a canal through which the descending branch of the notochord passes ventrally (Fig. 207) to its connection to the epithelium, in a similar manner to the canal of the

epithelial stalk of the pituitary.

16½ day stage

At this stage, the portion of the notochord caudal
to its bifurcation follows the same course mentioned
before.

The descending branch, also, has the course
described in the 15½ day stage, but the ascending branch
which is formed from horizontal and anterodorsally
directed parts, either loses the latter part, or it still
runs to the posterior wall of the pouch to come in close
contact (Fig. 210), but is actually separated from it by
the mesenchyme envelope of the notochord (Fig. 211).

17½ day stage

The notochord at this stage follows the course
observed in the previous stage.   The descending branch
of the cephalic end of the notochord has its special
canal through the cartilage plate (Fig. 215).   The
horizontal portion of the ascending branch runs a short
course on the dorsal surface of a piece of cartilage
lying between the canals of the notochord and of the
epithelial stalk of the pituitary (craniopharyngeal canal)
(Fig. 216).   It then bends ventrally in the cranio-
pharyngeal canal and comes into very close proximity to
the remnants of the epithelial stalk in the canal but no
actual contact is demonstrated (Fig. 213).

Fig. 215 shows the bifurcation of the cephalic end
of the notochord, the presence of a specific canal for

its descending limb in the cartilage plate, and the intimate relation of the notochord to the gland and its epithelial stalk.

The notochord, up to this stage, is a well defined, elongated rounded structure, with a small rounded ball like termination.

$18\frac{1}{2}$ day stage

The descending limb of the notochord is no longer clear. The anterodorsal portion of its anterior branch has disappeared leaving only its horizontal portion lying on the dorsal surface of the sphenoid cartilage, just caudal to the pituitary (Fig. 217).

The caudal portion of the notochord has its previous course.

$19\frac{1}{2}$ and $20\frac{1}{2}$ day stages

The remnants of the cephalic end of the notochord are found on the dorsal surface of the cartilage, just caudal to the pituitary gland (Figs. 218-219).

It has disappeared from the occipital region except for the small portion embedded in the basioccipital cartilage.

At Birth

No remnants of the notochord, whatever, can be detected.

SECTION IV

MENINGEAL RELATIONS OF THE DEVELOPING GLAND

The pituitary body, stomadeal and neural
components, lies in a mass of essentially unorganised,
loose mesenchyme tissue which occupies the space between
the fore and hindbrain vesicles and the roof of the
stomadeum.

At the $14\frac{1}{2}$ day stage, this cranial blastema or
primary mesenchyme condensation begins to differentiate.
The ventral zone is occupied by the prochondral
mesenchyme condensation of the sphenoid, which surrounds
the epithelial stalk of the pituitary.   Indistinct
marginal condensations of mesenchyme cells have formed
close to the opposed surfaces of the brain vesicles.
These marginal condensations have not yet separated from
the rest of the undifferentiated mesenchyme in which the
developing gland is found.

At the $15\frac{1}{2}$ day stage, the posterior marginal
condensation, close to the surface of the hindbrain
vesicle, separates from the rest of the undifferentiated
mesenchyme.   The latter (the mass of the
undifferentiated mesenchyme around the pituitary gland),
appears to be in relation to the forebrain vesicle alone.

Fig. 220 shows the appearance of a dorsally pointed
cavity (indicated by arrow 2 in the figure) in the
undifferentiated mesenchyme related to the forebrain
vesicle (black), separating the marginal condensation

close to the posterior wall of the forebrain vesicle, in the zone dorsal to the neural process, from the rest of the undifferentiated mesenchyme, giving the latter the appearance of a triangular mass connected by its apex (arrow 1) to the marginal condensation of the forebrain vesicle.

Ventral to the neural process, at this stage - $16\frac{1}{2}$ day - the marginal condensation on the posterior wall of the forebrain vesicle is not separated from the undifferentiated mesenchyme, but sends a process from its posterior aspect which passes posteriorly below the gland towards the cartilage, forming the base of the triangular area available to the pituitary.

At this stage, $16\frac{1}{2}$ day, the marginal condensations around the opposed surfaces of the fore and hindbrain vesicles, have not yet differentiated into membranes.

The $17\frac{1}{2}$ day stage is characterised by the formation of a narrow elongated neck connecting the neural process to the forebrain vesicle, surrounded by nerve tracts, and the marginal condensation around the posterior aspect of the forebrain vesicle separates from the rest of the triangular mass of the undifferentiated mesenchyme in the region ventral to the neck of the neural process. By this separation, the layer of condensed mesenchyme on the posterior aspect of the forebrain vesicle is connected to the undifferentiated mass of mesenchyme surrounding the pituitary only in two sites: 1) at the apex of the undifferentiated triangular mass, and 2) around the

connection of the neural stalk to the posterior wall of the forebrain vesicle.

The pituitary gland as a whole with the entire length of its neural stalk, is surrounded by the undifferentiated mesenchyme, bounded by the condensed mesenchyme at the margins of the triangular mass, which sends processes towards the basal cartilage bounding the pituitary area.

The dorsal surface of the cartilage, at this stage, has no definite perichondrium.

Later, there is separation of the meninges on the surfaces of the brain vesicles. This separation takes place close to the brain surface and is limited by the marginal condensations on the surfaces of the brain vesicles, and does not extend further towards the pituitary than the site of the connection of the neural stalk to the forebrain.

The marginal condensation around the brain vesicles, is in the position of and has the structure of the dura and can be identified as such at this stage.

The triangular mass of the undifferentiated mesenchyme around the pituitary, is connected at its apex to the dura mater of the forebrain.

At the $18\frac{1}{2}$ day stage, the mesenchyme condensation around the gland forms the perichondrium of the dorsal surface of the cartilage, completing the formation of the boundaries of the pituitary region (Fig. 223).

No differentiation takes place in the mesenchyme

around the pituitary gland, and the three membranes which develop around the brain are not formed.   Thus pia-archnoid, and subdural and subarchnoid spaces, do not differentiate, at any time, during the development of the pituitary, and the membranes and the spaces do not extend towards the gland beyond the junction of the neural stalk of the neurohypophysis with the forebrain, and the apex of the triangular mass of the undifferentiated mesenchyme with the dura mater.

The undifferentiated mesenchyme between the gland and the perichondrium forms the surrounding capsule of the pituitary (Fig. 224).

There are some aspects concerned with the meningeal relations of the pituitary.

1. At the $14\frac{1}{2}$ day stage, the middle basal outgrowth (T) of the anterior wall of the pouch with its tongue like process, leaves a fossa between it and the anterior aspect of the gland (Fig. 221) filled with mesenchyme tissue through which pass blood vessels, so this core of mesenchyme and the blood vessels through it, could not be looked on as pial derivatives, and also the later vascular connective tissue infiltration of the glandular tissue.

2. At the $15\frac{1}{2}$ day stage, a single layer of cells, which separates the pouch from the neural process can be detected.   It is in continuity with the undifferentiated mesenchyme surrounding the pituitary at its periphery.

3. At the $16\frac{1}{2}$ day stage, the tuberal process of the
pituitary gland lies ultimately in the surrounding
undifferentiated mesenchyme of the gland. The same
condition is present when differentiation of the brain
membranes appear at the $17\frac{1}{2}$ day stage, the tuberal
process is bounded to the undifferentiated mesenchyme of
the pituitary and has no covering of the membranes of the
brain (Fig. 222). In the $18\frac{1}{2}$ day stage, this tuberal
process extends forwards, anterior to the gland, carrying
with it an envelope of the undifferentiated mesenchyme
tissue, which later blends with the adjacent dura of the
brain.

Thus, the undifferentiated mesenchyme tissue forms
a capsule for the entire circumference of the body of the
gland covering the outer surfaces of the adeno and neuro-
hypophysis and extending between them.

Subsequently, instead of the formation of the
typical meninges in this region, the mesenchyme around
the pituitary gives rise to an external lamina of
condensed mesoderm with an inner zone of loose
connective tissue.

The pituitary region may be considered as one of
the regions into which the differentiation of special
meningeal layers does not extend.

SECTION V

DEVELOPMENT OF THE VASCULAR SUPPLY OF THE PITUITARY

The pituitary comes to lie at an early period of prenatal life in a field of undifferentiated mesenchyme through which are scattered several groups of blood cells, and later at the $13\frac{1}{2}$ day stage, these islets form capillary blood vessels applied to the periphery of the pituitary.

Fig. 225 is a representation of the vascular pattern of the pituitary at the $14\frac{1}{2}$ day stage.

At this stage, the tongue like process of the middle basal outgrowth (T) of the original anterior wall of the pouch grows anterodorsally leaving the intra-glandular fossa filled with mesenchyme between it and the anterior aspect of the pouch.

The internal carotid artery, on each side, attains its position in the undifferentiated mesenchyme lateral to the pituitary by passing between the tympanic bulla posteriorly and the prochondral condensation of the basisphenoid anteriorly.

During its course through this undifferentiated mesenchyme the internal carotid gives two small branches; one anterior to the epithelial stalk of the pituitary, and one posterior to it. The two branches run dorsally and medially towards the pouch. The former can be designated as the anterior (superior) hypophysial artery, and the latter, the posterior (inferior) hypophysial artery.

The posterior (inferior) artery runs dorsally close to the posterior aspect of the pouch to the level of the neural process then it runs medially and gives a tiny branch between the pouch and the neural process, continuing its course along the posterior aspect of the neural process. At the posterosuperior angle of the process, it pierces it and breaks into several branches which supply more than its caudal half.

This artery supplies areas of the pouch posterior to the connection of the epithelial stalk of the pituitary with Rathke's pouch.

The anterior (superior) artery runs anteriorly and dorsally to the junction of the neural process with the forebrain vesicle where it ends by dividing into several branches: 1) runs medially and dorsally onto the lateral aspect of the neural process (free from the connection with the pouch), passing onto its dorsal aspect, enters and supplies the proximal portion of the neural process, 2) runs posteroventrally between the pouch and the neural process, and 3) runs to the intraglandular fossa and is larger than the other two, and has been designated by Xuereb et al., (1954), as "Artery to trabecula".

This vascular pattern is not modified in the two successive stages; the $15\frac{1}{2}$ and the $16\frac{1}{2}$ day stages, except that the "artery to trabecula" gives off two off-shoots near its origin from the anterior (superior) hypophysial artery. These two branches take a similar course to that of the "artery to trabecula" and terminate

in the mesenchyme tissue between the outgrowths (GI and GII) of the pouch.

At the $17\frac{1}{2}$ day stage (Fig. 226), the same vascular pattern persists.   At that time the pituitary gland is surrounded by undifferentiated mesenchyme, and no vessel of pial origin finds its way to the gland.

At this stage, the posterior (inferior) hypophysial artery supplies the caudal portion of the anterior lobe (ventral wall of the pouch), gives a branch between the pouch and the neurohypophysis, and runs along the posterior aspect of the neurohypophysis to the postero-superior angle where it terminates in the neurohypophysis and supplies more than its caudal half.

The anterior hypophysial artery, on each side, runs anteriorly and dorsally to the ventral aspect of the neural stalk where it ends by dividing into several branches.
(The site of termination of the anterior hypophysial artery has been called "Atwell's recess" (Campbell, 1966); the anterior region of the intraglandular core of mesenchyme is limited dorsally by the neural stalk, and ventrally by the pars tuberalis).

1.   The "artery to the trabecula" with its two offshoots (Fig. 227), runs ventrally and caudally to enter the substance of the anterior lobe of the gland, supplying more than its rostral half and anastomosing with the similar branches of the posterior hypophysial artery.

2.   The anterior hypophysial artery also gives a twig which runs between the pouch and the neurohypophysis to meet its fellow from the posterior artery.

3.   The neural stalk artery which arises from the anterior hypophysial artery at its end, runs along the neural stalk, supplies it and the rostral portion of the neurohypophysis, and anastomoses with the branches of the posterior hypophysial artery.

4.   A small twig from the anterior hypophysial artery at its end runs forwards along the dorsal aspect of the tuberal process.   This artery, similar to the others, lies within the undifferentiated mesenchyme around the pituitary, and no vascular connection exists between the pituitary arterial pattern and that of the hypothalmus.

The vascular supply of the pituitary in postnatal life.

The vascular pattern observed at birth (0-12 hours after birth)(Fig. 228) is almost similar to that at puberty (6 weeks after birth).

Arterial pattern.

Two main arteries, anterior (superior) and posterior (inferior), arise from the intracavernous portion of the internal carotid artery (Fig. 231) on each side.   As the internal carotid artery is ventral and lateral to the gland, the anterior and posterior arteries run medially and dorsally towards the pituitary gland.

The anterior hypophysial artery

It runs a very short course from its origin,
medially and dorsally to reach Atwell's recess (see above),
where it divides into its branches:

a)   The "artery to the trabecula" (Fig. 234), runs
posteriorly and ventrally in the connective tissue core
into the intraglandular fossa, between the pars tuberalis
and the anterior lobe proper of the gland.   It gives off
two branches near its origin from the anterior hypophysial
artery, at the anterior end of the gland, which run
posteriorly in the substance of the anterior lobe.   The
"artery to the trabecula" with its two branches, supplies
most of the anterior lobe except its caudal portion which
is supplied by the posterior hypophysial artery (Fig.232),
whose branches anastomose with those of the "artery to
the trabecula".

b)   The artery to the pars tuberalis (Fig. 236), runs
anteriorly along the dorsal aspect of the pars tuberalis
to its tip, within its envelope of the undifferentiated
mesenchyme.   It supplies the tuberal lobe, but not the
hypothalamus, and forms a fine network within the lobe.

c)   The artery to the neural stalk and the rostral
portion of the neurohypophysis (Fig. 230) runs dorsally
along the lateral aspect of the neural stalk, then
dorsally and posteriorly to enter the substance of the
neurohypophysis, where it terminates into branches
forming a very fine network in the stalk and the neuro-

hypophysis.   These rami anastomose with those of the
posterior hypophysial artery which supplies the main
portion of the neural lobe.

d)   The interlobar artery (Fig. 237), runs posteriorly
from its origin to the space between the stomadeal and
neural portions of the gland to anastomose with its
fellow from the posterior hypophysial artery.   This
artery supplies the neurohypophysis and anastomoses with
its network.

The posterior hypophysial artery

It is of a considerable size, and runs medially and
dorsally towards the gland.

It divides, usually, at the beginning of its course
into two branches; a very slender one going to supply
the caudal portion of the anterior lobe of the gland, and
a main one running dorsally along the posterior aspect of
the gland to the posterosuperior angle of the neuro-
hypophysis (Fig. 232), where it terminates in its
substance, supplying its main caudal portion.   Its
branches anastomose with those of the anterior hypophysial
artery forming a very fine network in the neurohypophysis.

During its course along the posterior aspect of the
gland, the posterior hypophysial artery sends a branch
between the pouch and the neurohypophysis, to meet its
fellow from the anterior hypophysial artery.   This
artery gives its twigs dorsally to the neurohypophysis,
anastomosing with its fine network.

Sometimes, the posterior hypophysial artery divides at its origin, and arises as two branches which have the typical course described above.

The vascular network of the neurohypophysis (Fig. 238) is similar to that of the tuberal lobe and neural stalk, but is finer and more rich than that of the anterior lobe of the pituitary (Fig. 233).

Capsular arteries

Those are small, slender twigs which arise from the internal carotid artery and the posterior communicating artery and run through the undifferentiated mesenchyme around the gland and along its condensed margins. The largest of these capsular twigs arises from the posterior communicating artery, and runs along the posterior aspect of the mesenchyme, dorsally to the apex of the triangular mass of the undifferentiated mesenchyme in which the gland is located.

The venous drainage (at birth, and postnatal)

The main portion of the neurohypophysis is drained via the posterior hypophysial vein, which runs ventrally along the lateral aspect of the posterior hypophysial artery to the cavernous sinus, while the anterior hypophysial vein situated in Atwell's recess drains the neural stalk and the rostral portion of the neural lobe, and also receives blood from the anterior lobe via a vein on the ventral aspect of the anterior lobe of the gland. The anterior hypophysial vein runs from Atwell's

recess ventrally, along the lateral aspect of the anterior hypophysial artery to the cavernous sinus.

A number of venous tributaries of considerable size, can be observed (Figs. 235 and 236), running parallel to each other along the sides of the pars tuberalis from the hypothalamus. These unite to form a vessel which runs posteriorly, along the ventrolateral aspect of the pars tuberalis, to the anterior pole of the anterior lobe of the gland, where it becomes difficult to trace it further. It is therefore not known whether it drains through the tissue of the lobe or to its venous drainage.

These venous tributaries form, most probably, the only vascular link between the hypothalamus (median eminence) and the pituitary gland (anterior lobe through the pars tuberalis).

The blood supply of the neural lobe and neural stalk, as well as that of the anterior lobe of the gland, all running through undifferentiated mesenchyme, are neither of dural nor of pial origin.

ORIGIN OF RATHKE'S POUCH

It is not surprising that the developmental inter-
pretation of the pituitary has had a checkered career.

In 1838, Rathke describes the ectodermal stomodeal
pouch which is now almost universally associated with the
origin of the pituitary, but twenty-three years later
(1861), he completely reverses his opinion and decides
that the stomodeal evagination first described by him
plays no part in the development of the gland. Muller
(1871) however, revives Rathke's original view: that
the anlage of the pituitary is double; the glandular
portion arising from the ectoderm of the stomadeum, and
the neural portion arising from the infundibular process
of the diencephalon.

Since that time, there has been continuous
discussion as to whether the adenohypophysis is derived
from ectoderm, or entoderm, or whether it is composed of
elements derived from both of these germ layers.

By far the larger group of investigators uphold
Rathke's original concept. This concept is subjected to
experimental verification by Smith (1916) and Allen (1916,
1917) who state that they removed the glandular ectodermal
anlage from young larvae of the frog. In successively
operated animals the anterior lobe is entirely lacking.
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his fine work on the development of the hypophysis in the rabbit and man, confirms Smith's (1916) observations. Parker (1917) however, in her exhaustive study on the development of the pituitary in Marsúpialiα, reopens the problem. She notices that portions of the buccopharyngeal membrane and of the entodermal wall of Seessel's pouch come to be incorporated in the hypophysis. The contribution of the dorsal portion of the buccopharyngeal membrane to the formation of Rathke's pouch is first mentioned by Herring (1908) as he observes that the posterior wall of the hypophysial pouch forms the anterior layer of the upper stump of the buccopharyngeal membrane. Herring (1908) concludes, without providing any evidence, that this portion of the buccopharyngeal membrane has disappeared, and there is no evidence of any entodermic contribution to the pituitary gland. Parker's (1917) view is quite different as she states that it is perfectly clear that the portion of the buccopharyngeal membrane which marks the point of junction of ectoderm and entoderm comes to be situated within the tissues of the hypophysis which accordingly cannot be regarded as exclusively of ectodermal origin.

Brahms (1932) in the cat, states that it is possible from the mode of development that some of the material of the dorsocaudal end of the epithelial stalk of the pituitary may contain entoderm from the anterior end of the foregut, but he further adds without evidence,

that this part of the structure is almost always reabsorbed without at any time contributing any material to the hypophysis proper, and that the hypophysis is, therefore, an altogether ectodermal structure.

Miller (1916) introduces another view by claiming that in the pig a considerable portion of the definitive hypophysis is derived from the entoderm as the notochord pulls away from the pharynx carrying with it a mass of entodermal cells which later becomes fused with the ectodermal anlage forming the anterior lobe of the gland. This view is questioned by the work of Nelson (1933) on the development of the gland in the same animal (pig). Nelson (1933) finds that the contacts between the posterior wall of the pouch and the cephalic end of the notochord are insignificant and not constant, and concludes that any contact between the chorda and the pouch is an accidental relation of parts.

In man, Tilney (1936) states that the human pituitary has a twofold ectodermic origin, but whether the entoderm contributes to the actual formation of the organ remains an open question. He adds that it seems safest to maintain that the entoderm does participate in the formation of the gland in some vertebrates, and later investigations may prove that it plays a role in many other animals and even possibly in man.

Recently, Falin (1961) and Levina (1965) conclude that the human hypophysis is exclusively of ectodermal origin.

In the rat, Schwind (1928) states that the
buccopharyngeal membrane is ruptured in most of the eight
somite embryos (ten days three hours), but remnants can
be observed on either side of the midline which indicate
its former position.   These remnants persist until the
thirteen somite stage (eleven days six hours) and are
important in marking the ectodermal-entodermal boundary.
The ectoderm anterior to the buccopharyngeal membrane
which is in contact with the infundibular surface of the
neural plate in the midline will form the epithelium of
Rathke's pouch.   Schwind (1928) concludes that the
hypophysis of the albino rat is ectodermal in origin.

The first stage, in the present study, at which the
hypophysial anlage can be detected is the $10\frac{1}{2}$ day stage,
at which no remnants of the buccopharyngeal membrane are
observed.   The anterior extremity of the notochord is in
close contact with the posterior wall of the pouch, but no
actual fusion ever takes place.   Therefore, it cannot
contribute to the formation of the pouch.   Since the
cephalic extremity of the notochord is connected to the
dorsal end of the buccopharyngeal membrane, which marks
the boundary between the surface ectoderm and the
entoderm of the foregut, it can be stated that the
pituitary gland of the rat is of ectodermal origin.

MECHANICS OF DEVELOPMENT

One of the most important characteristics of the developing pituitary is the close union maintained between the stomadeal and the neural portions from the earliest stages. This neuro-ectodermal connection is variably interpreted, by different authors.

Mihalkovics (1875) in his complete account of the early development of the pituitary, suggests that the wall of the pouch presses upon the adherent base of the forebrain vesicle, giving rise at its upper extremity to a fold in the wall of the brain which becomes the neural lobe. Herring (1908) expands this view and states that no doubt this contact is contributing to the formation of the pouch and the neural lobe, but is probably of morphological significance as well, and betokens the existence of an ancestral vertebrate of a communication between stomadeal cavity and neural canal.

Adelmann (1922) introduces a different view, as he believes that the formation of the hypophysial pouch at first does not involve an active ingrowth of material, but that its formation is brought about entirely through the sharpness of the head bend which results in the pinching off of an area of ectoderm anterior to the buccopharyngeal membrane.

Kingsbury and Adelmann (1924) explain this concept as the increase in the sharpness of the embryonic head bend, together with the lateral growth of the mesenchyme,

separating the ectoderm of the stomadeal roof and the
neural ectoderm, except in the region of the hypophysial
pouch.   This difference in the degree of the separation
of the neuroectodermal contact results in pulling out
of the hypophysial pouch.   They conclude that in the
early stages at least, hypophysial development is "not an
active proliferation" on the part of Rathke's pouch, but
is dependent upon the development of the head as a whole.

This view, "hypophysial development is not an active
proliferation on the part of the pouch", is widely
accepted by almost all the investigations (Brahms, 1932;
Nelson, 1933; and Gilbert, 1934, 1935) on the
development of the pituitary, of the Cornell University.

So Brahms (1932) tries to prove this view by
stating that Rathke's pouch is formed ventrally by the
ectoderm of the hypophysial area and dorsally by the
ectoderm of the upper part of the buccopharyngeal membrane
which remains as a stump after rupture.   He adds that
the neuroectoderal contact in the hypophysial area is
fast and firm and it resists separation that the forces
attendant upon the increase in distance (sharpness of the
head bend, and the growth of mesoderm) might effect.
This results in drawing out of the regions, and
apparently the oral ectoderm responds more readily to the
applied stresses than does the neural ectoderm.   He
considers the fact that the epithelial stalk of the
pituitary is at first tubular, as an indication of the

stretching of the hypophysial region in the formation of the hypophysial sac. (The formation of the epithelial stalk of the pituitary is a late stage of the development of the pouch).

Gilbert (1934, 1935) states without any precise evidence, that the "hypophysis does not develop as a result of the presence of predetermined potencies for hypophysial development in the tissues involved, but rather that it is determined by the normal configuration of materials (persistent adherence of surface ectoderm to the neural tube), and growth processes (marked expansion of the neural tube and the general development of mesenchyme between the ventral head ectoderm and the floor of the forebrain) in the prochordal region of the head".

On the other side of the problem, stands the most acceptable view that Rathke's pouch is an "active" evagination of the roof of the stomadeum. So, Parker (1917) emphasises that the development of the hypophysial pouch is due to rapid growth of the differentiated epithelium of the hypophysial region and not to any mechanical power exercised by the chorda or any other structure.

Tilney (1936) describes the process of formation of the pouch in the human embryo; the roof of the stomadeum shows a definite thickening which is pronounced enough to merit special designation and this be called the "pituitary mouth plate". The cells in this region are

arranged in three or four layers, while the cells more lateral to them in the roof of the mouth form an epithelium of only two layers. This pituitary plate not only becomes thicker but shows a distinct arching which at first involves the entire plate symmetrically; later the arching becomes more pronounced near the midline, and the stomadeal pouch has become the median pituitary pouch.

Similar observation is recorded in the rat by Phillips and Schmidt (1959) who state that examination of the 11 day rat embryo reveals that Rathke's pouch was starting to form, indicated by a thickening of the stomadeal epithelium and its later evagination towards the floor of the diencephalon.

Schwind (1928) believes that the dominant factor in the early development of the hypophysis of the rat is the growth and folding over of the forebrain vesicle which crowds the "rapidly growing" hypophysial ectoderm into the mesoderm below the rostral flexure of the neural tube, accompanied by the forward shift of mesenchyme to form the territory of the maxillary process.

At the $10\frac{1}{2}$ day stage of the present study, the anterior wall of the pouch is in close contact with the posteroventral wall of the forebrain vesicle and no mesenchyme intervenes between the two structures.

If the adherence between the surface ectoderm (ectodermal pituitary plate) and the floor of the neural tube is intimate and firm, and the formation of cephalic

flexure of the adherent neural tube played the most
active part in pinching off the pouch without any active
participation on the part of the pouch; the formation
of the hypophysial sac will become impossible unless the
buccopharyngeal membrane, or the entoderm will form the
posterior wall of the pouch.

The view held by Brahms (1932) and Gilbert (1934,
1935) admits the entoderm to contribute to the
formation of the pouch.

The statement of Gilbert (1934, 1935) that "the
hypophysis does not develop as a result of the presence
of predetermined potencies for the hypophysial
development in the tissue involved", is very doubtful,
and equally the view held by Adelmann (1922) and Kingsbury
and Adelmann (1924) that "in the early stages, at least,
hypophysial development is not an active proliferation on
the part of Rathke's pouch" requires re-evaluation, as
evidence of mitotic activity of the pouch, in particular
in the early stages, is clear and definite.

1.   The number of the mitotic figures found in the
pouch at the very early stage ($10\frac{1}{2}$ day stage) are very
numerous.   More than one third of the total number of
the cells of the anterior wall of the pouch, and less than
one fourth of those of the posterior wall, are in one or
other of the mitotic stages at the same time.   Falin
(1961) states that at 4-5 week stage the epithelial cells
of Rathke's pouch of the human pituitary are dividing
intensely and often show mitotic figures.   The presence

of this intense mitotic activity of the cells of the
pouch is so self evident, that Kingsbury himself states
later (Kingsbury and Roemer, 1940), that mitosis in the
pars buccalis is, in early stages, relatively abundant.

2.   The fact that the pouch is formed due to the
presence of this intense mitotic activity of the
differentiated epithelium of the hypophysial region, is
recorded by many authors among them are; Parker, 1917;
Schwind, 1928, Tilney, 1936; and Phillips and Schmidt,
1959.

3.   The cells of the stomdeal pouch are much more
active than the cells of the stomadeal epithelium near
the site of the pouch.   Tilney (1936) observes this
fact and he adds that the cells in the pituitary region
are arranged in three or four layers, while the cells
more lateral to them in the roof of the stomdeum form an
epithelium of only two layers.

        The mitotic activity shown by the cells of the
pouch is much higher in comparison to that of the
surrounding mesenchyme.

4.   The basal portion of the anterior wall of the pouch
is formed of two layers of very active cells.   This most
active region of the pouch is apparently the first part
to grow and differentiate.   This differential growth of
the pouch may be considered as an indication of its
activity, because if it was passively pinched off without

any activity on the part of the pouch, the cells of the
pouch, at least in the very early stages, would show a
uniform rate of activity and growth, but actually the
tissue has to grow and proliferate, at least, to meet
this pull.

5. At the $10\frac{1}{2}$ day stage, the initial area of contact
forms the anterior wall of the pouch, but at the $11\frac{1}{2}$ day
stage this initial area of contact is incorporated in
the fundus of the wedge shaped pouch which is in contact
with the neural evagination. Intense mitotic activity
in the cells of the basal portion of the anterior wall of
the pouch to meet the incorporation of the anterior wall
in the fundus of the pouch, is very clear and self
evident.

The evidence offered by Brahms (1932) and Gilbert
(1935) to indicate that the formation of the hypophysial
pouch is brought about entirely through the sharpness of
the head bend, is the case of cyclopia in which there is
early separation of the neuro-ectodermal contact brought
about by abnormal cephalisation and rotation and
resulting in the absence of the hypophysis. Interpret-
ation of an abnormality to normal developmental
processes is never a valid evidence.

The development of the cephalic end of the notochord
and its relation to the developing gland will be
mentioned later; in this connection, however, it may be
stated that the presence of the notochord as described in

this study, gives an impression that it acts as a barrier to the backward growth of the sac, and takes no part in the formation of the pouch.

It can be stated from the present study, at least in the rat, that the development of Rathke's pouch is not a completely passive process, and the pouch is, at least partly, an active evagination of the roof of the stomadeum.

Although the American school of the Cornell University claims a similar inactive process in the development of the neural lobe of the pituitary, no investigation, except Gilbert (1935), gives evidence for this conclusion.

Brahms (1932) believes that the neuroectodermal contact is the earliest morphological indication of the presence of the anlagen of the pituitary. He states that the stomadeal evagination is an expression of the mechanics of growth, but the neural evagination is an intrinsic one. Later, he applies, however, the mechanics of growth to the neural evagination as he states that it is probable that the dorsally growing processes of pars distalis and pars intermedia, which extend along the floor of the forebrain on either side of the neck of the neural evagination, play a part in mechanically drawing out the evagination.

Gilbert (1934) finds that the pars neuralis in the cat cannot develop as an active evagination from the

infundibular region of the floor of the forebrain, since practically no mitosis occur in this region of the brain during the period of the hypophysial development.   In 1935, through her attempt to analyse the growth rates and shiftings occurring in surrounding regions of the brain and head, Gilbert suggests that the formation of the pars neuralis is the result of two developmental factors, namely: the presence, in the floor of the brain, of inactive tissue which is firmly adherent to the apex of the pouch, and the pressure exerted on this inactive region by the adjacent rapidly growing regions.   She states that mitoses are relatively numerous in the optic and the premammillary regions at all stages and scarce in the infundibular, postoptic, and postinfundibular regions, and the last three regions comprise the inactive region of the diencephalic floor, which is subjected to the growth pressures of the optic and premammillary regions. To explain the mechanics underlying her view, Gilbert states that the contours of the diencephalic floor are such that, the rostral part of the inactive region is subjected to a cephalocaudally directed pressure, while its caudal region is subjected to a caudo-ventrally directed pressure, and the result of these combined growth pressures is the rotation of the inactive infundibular region of the brain floor and the adjacent wall of Rathke's pouch from a dorsoventral to a cephalocaudal plane.   She adds that the rotation of a small segment of

the brain floor produces a small depression or outpocketing in the brain floor which becomes the pars neuralis of the hypophysis. To support her statement Gilbert puts her results in Table I, the lower part of which, including the rat, is quoted, hereafter.

Gilbert depends mainly, in her analysis, on the figures mentioned in this Table.

TABLE I (AFTER GILBERT, 1935)

Data concerning the distribution of mitoses in the diencephalic floor

SIZE m.m.	OPTIC	PREMAMM- ILLARY	INFUNDI- BULAR	POSTOPTIC
RAT				
3	25	9	8	4
5	36	3	1	0
6	31	2	3	7
7	28	2	0	8
CALF				
6	7	8	11	6
9	14	15	13	15
11	68	7	13	21
12	71	9	8	33
PIG				
6	9	10	16	9
9	4	18	6	3
11	13	12	7	5
14	8	24	9	4

Great doubt can be shed upon these results.

1. Gilbert (1935) mentions neither the method followed in counting the mitoses (per section, per area, per volume, per gland; every section, sections at regular

intervals, etc.), nor the number of specimens, nor the variation in counts in any animal. These criticisms are equally applicable to all the previous methods used to count mitoses as they are not standardised. (See material and methods).

2.   To show the table in such way is greatly misleading, as in that particular study only the very early stages concerned with the beginning of the development of the neural lobe must be considered.   The first stage, in the case of the rat, in the table is 3 m.m. stage, which corresponds to the $12\frac{1}{2}$ day stage of the present study, while the neural evagination is already well developed at the previous $11\frac{1}{2}$ day stage.

3.   It is quite clear from Gilbert's table that the infundibular region is not an "inactive" region as the figures representing the number of mitoses in it are comparable to those of the other regions (these figures are underlined in the table) specially in the first early stages.   In 3 m.m. rat embryo the number of mitoses in the infundibular region is represented by (8) which is clearly very similar to the number (9) of mitoses in the so called "active" premammillary region.   In the 6 m.m. calf and pig embryos the number of mitoses in the infundibular regions exceeds that of the premammillary and optic regions.

4.   Evidence of activity of the developing infundibular

region of the forebrain vesicle, has been recorded by many authors. (Parker, 1917; Atwell, 1918; Oldham, 1941; and Phillips and Schmidt, 1959).

Phillips and Schmidt (1959) observe a thickening in the wall of the diencephalon, which is in close contact with the apex of the developing pouch, establishing the site of the future infundibulum on the 11th prenatal day in the rat.

At the $10\frac{1}{2}$ day stage, of the present study, the zone of the posteroventral wall of the forebrain vesicle in close contact with the apex of the developing pouch, is rich in mitotic figures. Later, at the $11\frac{1}{2}$ day stage, the neural evagination, resting on the central area of the fundus of the developing pouch, shows frequent mitotic figures, but to less extent than the pouch, with a result that its growth is lagging behind that of the pouch to a late stage ($18\frac{1}{2}$ day) of prenatal life.

5.   The view held by Gilbert concerning the growth pressures, cannot be supported as it is not in accord with the common theory of the mechanics of evagination (Lewis, 1947).

6.   Gilbert describes a rotation of the inactive infundibular region of the brain floor and the adjacent wall of Rathke's pouch from a dorsoventral to a cephalocaudal plane, and such rotation does not exist (will be discussed later) though some reorientation takes

place in the later stages of prenatal life after consolidation of the neural evagination and full development of the neural lobe.

Some investigators claim that the activity of the developing neural evagination may be induced by; 1) the presence of the cephalic end of the notochord which may act mechanically in drawing it out (Muller, 1868, and Dursy, 1869), 2) the pressure exerted by the developing pouch upon the base of the forebrain vesicle giving rise at its upper extremity to a fold in the wall of the brain which becomes the infundibulum (Mihalkovics, 1875).

There is no evidence that the notochord plays any role in the development of the neural evagination, as its cephalic end is in contact with the basal part of the posterior wall of the pouch, not its tip. In keeping with this Parker (1917) states that the notochord exercises no traction whatever either on the pouch or on the infundibulum. She bases this on the absence of any actual contact between the notochord and the pituitary.

The presence of the pouch opposite the wall of the forebrain vesicle, may act to initiate the activity of the infundibular region of the wall of the forebrain vesicle. This statement may be supported by the following points:
1. The appearance of the pouch always precedes that of the neural evagination.
2. The presence of a number of mitoses in the

infundibular region of the forebrain vesicle just
opposite the tip of the developing pouch.

3. The experimental observations of Smith (1920) showing
absence or subnormal neural lobe in case of absence of the
stomadeal evagination, and of Giroud and Roux (1959)
showing absence or duplication of the infundibulum in
every case of absence or duplication of the pouch
respectively.

It can be stated from the present study, at least
in the rat, that the development of the neural
evagination is not a completely passive process, and the
evagination develops as an active outpouching of the
floor of the forebrain vesicle, just as Rathke's pouch
is, at least partly, an active evagination of the roof
of the stomadeum.

FACTORS AFFECTING SHAPE OF GLAND

Rathke's pouch at the $10\frac{1}{2}$ day stage, is a finger
like evagination in the midline, of the roof of the
stomadeum. The stomadeal evagination has an
asymmetrical appearance with the anterior wall in close
contact to the posteroventral wall of the forebrain
vesicle. No mesenchyme intervenes between the two
structures, but it is present elsewhere around the
periphery of the pouch. At the $11\frac{1}{2}$ day stage the pouch
becomes a wide, wedge shaped diverticulum, having a

centrally depressed fundus with surrounding raised edges.
A finger like evagination of the posteroventral wall of
the forebrain vesicle, representing the primordium of the
neural lobe, projects in a posteroventral direction, and
its ventral aspect is in close proximity to the indented
central portion of the fundus of the pouch, with no
mesenchyme tissue intervening between the two structures,
but this tissue fills the very narrow interval between
the pouch and the forebrain vesicle except along the
midline.

The separation of the pouch and the forebrain
vesicle, is most probably, due firstly, to the growth in
the volume of the two structures, and secondly to the
invasive growth of the surrounding mesenchyme, indicated
by the presence of the mesenchyme-free area along the
midline.
The change in shape of the pouch may be brought about by:
1. marked increase in the dorsoventral axis of the pouch
indicated by the presence of a great number of mitotic
figures in the tip and basal portions of the pouch,
with 2. the posteroventral growth of the developing
neural evagination, contacting the pouch in the midline
and indenting it, evidenced by the fact that the regions
of the pouch lateral to the site of the neural evagination
keep their original finger like shape and project
dorsally around the depressed central area of the fundus
of the pouch.

It may be stated that the portion of the anterior

wall of the pouch in close contact with the forebrain vesicle, at the $10\frac{1}{2}$ day stage, forms the central portion of the fundus which is in contact with the neural evagination i.e. the initial area of contact. The cells of the anterior wall of the pouch are more active than those of the posterior wall, in particular the basal portion of the anterior wall which is formed of two layers of very active cells, at the $10\frac{1}{2}$ day stage, while at the $11\frac{1}{2}$ day stage the activity of this portion is greatly increased to meet the incorporation of the "initial area of contact" of the anterior wall into the fundus of the pouch.   Schwind (1928) in the rat, attributes the change in the shape of the pouch to purely mechanical factors as he states that the optic chiasma and the pontine flexure of the hindbrain prevent any growth in an anterior or posterior direction, and the infundibular process is pressed against the top of the pouch, so that the top of the pouch bulges into its own lumen.

At the $13\frac{1}{2}$ day stage, Rathke's pouch is an ovoid, elongated, incompletely closed sac, connected in the mid-line to the roof of the stomadeum.   The pouch is no longer flattened, but its fundus still exists, most probably incorporated into the posterior wall of the pouch. Facts justifying the latter statement are mentioned on page 68.   The neural evagination is a solid mass of cells and its cavity is restricted to the most proximal portion of the evagination.   The distal half of the neural process is related to and in contact with the dorsal

portion of the posterior wall of the pouch (previous fundus and the initial area of contact of the anterior wall of the pouch). This dorsal portion of the posterior wall of the pouch, extending from the dorsal end of the pouch to a very slight projection on the posterior aspect of the pouch, represents the primordium of the "pars intermedia" of the gland.

It can be noticed that all the primordia of the various lobes of the adult gland are represented at this early stage; as the basal portion of the anterior wall of the pouch, in its intermediate region, can be divided into three equal zones; two prominent dorsolateral knob like projections, and an intermediate basal ridge like growth connected to the epithelial stalk of the pituitary. The two dorsolateral outgrowths will contribute to the formation of the anterior lobe proper, while the middle basal one will be traced in the formation of the pars tuberalis of the gland.

At the $14\frac{1}{2}$ day stage, the pouch is represented by a closed, oblique, kidney shaped sac, connected in the midline to the roof of the stomadeum by the solid epithelial pituitary stalk, and directed anterodorsally with its dorsal end occupying the interval between the neural process and the wall of the forebrain vesicle.

Change in the shape of the gland is effected by intrinsic and extrinsic factors. The intrinsic factors are: 1) the rapid growth of the basal portion of the

anterior wall of the pouch shifting the inferior part of the pouch anterior, and 2) the marked increase in the size of the neural lobe invaginating the dorsal portion of the original posterior wall of the pouch which is in contact with it. This is demonstrated by the marked difference between the concave shape of the wall of the pouch in contact with the neural lobe and the convex shape of the regions of the pouch lateral to this contact.

The extrinsic factors affecting the shape of the gland are based on a fact that the growth of the pouch is confined to the triangular area bounded by the roof of the stomadeum on one side, and the angle between the neural lobe and the forebrain vesicle on the other (Schwind, 1928, and Brahms, 1932). Change in the dorso-ventral diameter of this confined triangular space, probably, plays the most significant part in the change of shape and direction of the developing pouch.

At the present study the dorsoventral diameter of this confined space is found to be almost unchaged throughout the three successive ($13\frac{1}{2}$, $14\frac{1}{2}$ and $15\frac{1}{2}$ day) stages, and is, moreover, reduced at the $16\frac{1}{2}$ day stage.

The change in the dorsoventral diameter of this confined area is most probably due to the following factors:

1. The loose mesenchyme tissue around the epithelial stalk of the pituitary at the $13\frac{1}{2}$ day stage, is changed into prochondral mesenchyme condensation at the $14\frac{1}{2}$ day

stage occupying the ventral zone of the confined triangular area.

At the $15\frac{1}{2}$ day stage, thick cartilage is laid down in this ventral zone, and at the $16\frac{1}{2}$ day stage, the tissue between the inferior aspect of the basal cartilage and the roof of the stomadeum is increased.

2. At the $15\frac{1}{2}$ day stage, the neural lobe lies at right angles to the wall of the forebrain vesicle, while at the $16\frac{1}{2}$ day stage, the anterior angle is greatly increased suggesting either an opening out of the cephalic flexure (forward movement of the forebrain vesicle) or a dorsal movement on the part of the neural lobe. The latter appears improbable as it would result in the increase of the dorsoventral diameter which is actually reduced. The reduction in this diameter is so great that it cannot be attributed to the increase in the volume of the tissue between the cartilage and the roof of the stomadeum alone. The opening out of the cephalic flexure plays a very important role in reducing the available space for the growing pouch in the dorsoventral direction, while it increases the anteroposterior diameter of this confined area for the growth of the pouch in this direction in the following stages.

These factors hinder the growth of the pouch in a dorsoventral direction and compress the pouch in particular its dorsal portion. Their role can be evidenced by:

a. Dorsal shift of the pouch as evidenced by the

elongation of the connected epithelial stalk. b. Change of the direction of the developing pouch; at $13\frac{1}{2}$ day stage, the long dorsoventral axis of the pouch is almost parallel to the vertical axis of the confined space; it becomes oblique at the $14\frac{1}{2}$ and $15\frac{1}{2}$ day stages with the dorsal end of the pouch in the angle between the neural lobe and the forebrain vesicle, while the ventral extremity of the anterior wall of the pouch is separating from the wall of the forebrain vesicle, and at the $16\frac{1}{2}$ day stage it becomes anteroposteriorly directed and almost parallel with the plane of the superior surface of the basal cartilage. c. The main growth of the pouch occurs in its width.

Many investigators claim, without details, a superior and anterior rotation of the pouch (Nelson, 1933, in the pig: DeBeer, 1926, in higher vertebrates: Atwell, 1918, in the rabbit: and Rae, 1930, in the guinea pig). Brahms (1932) states that although there is an apparent tendency towards such a rotation in the cat, it fails to take place, and he believes the cause of this failure is the persistence of the epithelial stalk of the pituitary which serves to hold down the pars distalis, and the anteroposterior elongation of the head which tends to stretch the gland in a direction that is opposite to that which the rotation path would follow.

In the rat, Schwind (1928) states that as the pars distalis develops and the sphenoid cartilage increases in thickness, considerable pressure is brought to bear upon

the pars nervosa and it; rotates towards the midbrain,
with the pars intermedia and the lumen.

The pouch, in particular the dorsal portion, is
compressed and not rotated. This statement is supported
by the following evidences.

1.   The "whole" residual cavity of the pouch does not
change its direction, i.e. it does not rotate. Thus the
original posteroventral part of the cavity does not change
either its shape, direction, or extent even in the post-
natal life.

2.   The "whole" original posterior wall of the pouch does
not change its direction. This is demonstrated by the
relative position of the slight thickening found on the
posterior aspect of the pouch marking the boundary of
the future pars intermedia. At the $14\frac{1}{2}$ day stage, this
slight thickening is opposite the junction of the two
portions of the sigmoid cavity, and at the $16\frac{1}{2}$ day stage,
is opposite the posterosuperior angle of the residual
lumen, a position which it keeps even in the postnatal
animals.

SOME GENERAL FEATURES OF THE DEVELOPMENT OF THE
PITUITARY
EPITHELIAL STALK – PHARYNGEAL HYPOPHYSIS –
CRANIOPHARYNGEAL CANAL

Rathke's pouch is widely open to the stomadeum at the beginning of its growth. At the $12\frac{1}{2}$ day stage, constriction of this opening can be detected and in the following stage the direct communication between the cavity of the pouch and the stomadeum is a mere slit like orifice within a narrow stalk of cells, connecting the basal portion of the pouch to the roof of the stomadeum in the midline. This connection is called the "epithelial pituitary stalk".

At the $14\frac{1}{2}$ day stage, the epithelial stalk is a solid cord of cells, expanded dorsally where it is continuous with the middle basal outgrowth (T) of the anterior wall of the pouch, while it tapers ventrally to meet at right angles the cuboidal epithelium of the roof of the stomadeum, and is surrounded throughout its course by the prochondral mesenchyme condensation.

The anteroposterior reduction of the dimension of the orifice and the formation of the epithelial stalk is, most probably, not due to a factor in the structure of the pouch itself, as there is no undue thickening of the basal portions of the anterior and posterior walls of the pouch. The surrounding mesenchyme is in a state of activity, indicated by presence of a number of mitotic figures within it. The only direction in which there is

not a barrier for the growth of this mesenchyme is
laterally, as the presence of the growing hind and fore-
brain vesicles might hinder its expansion, thus it may
affect the anteroposterior diameter of the pouch.   No
mesoderm grows in the course of the pouch at this stage,
and the dorsoventral axis of the pouch may not be affected
by the presence of the growth of the mesenchyme, probably
because the main growth of the pouch is in this direction,
and secondly because of the presence of the neural lobe
with no mesenchyme between it and the fundus of the pouch.
Herring (1908) states that the narrowing of the neck of
the pouch and its closure are due to the growth of the
connective tissue around it.   This view is supported by
Brahms (1932) and Schwind (1928).   Schwind (1928) states,
in the rat, that in all probability the condensation of
the mesenchyme to form the procartilage is the main
factor in the final closure of the pouch.   He adds that
this view is supported by a study of similar stages of
chick and pig.   He concludes that in these forms, as well
as in the rat, the condensation of the mesenchyme and the
formation of procartilage go on concomitantly with the
closure of the pouch and the formation of the epithelial
stalk.

At the $15\frac{1}{2}$ day stage, the epithelial stalk is still
connected to the anterodorsally growing middle basal out-
growth (T) of the anterior wall of the pouch.   This
connection is carried anterodorsally, not only by the
rapid growth of the middle basal outgrowth of the anterior

wall, but also by the growth of the basal portion of the pouch as a whole.   This basal growth of the pouch and its anterior wall, carrying with it the dorsal connection of the epithelial stalk anterodorsally while its ventral end is still at right angles with the roof of the stomadeum, gives an erroneous interpretation of a migration of the epithelial stalk.   Frazer (1916) mentions that the stalk is implanted in the roof of the stomadeum, surrounded by paraxial mesoderm, and this part is gradually dislocated forward and elongated, resulting in a long epithelial strand drawn out from the post-sphenoid region in a forward direction so far that its point of implantation becomes situated on the ventral part of the roof between the nasal openings.

Brahms (1932) notes a nasal migration which he believes to be brought about by the degeneration and resorption of the bone of the ventral wall of the cranio-pheryngeal canal and the formation of new bone on the dorsal wall.   The view of Atwell (1918) may be correct, in part, as he believes that the apparent migration of the epithelial stalk from the ventral side to the nasal end of the anterior lobe is due to the bending of the gland to form the intraglandular fossa, to the approximation of the tuberal lobe to the brain wall, and in later stages to a rapid growth of the glandular anterior lobe.

The epithelial stalk at the $15\frac{1}{2}$ day stage, is double the length of that at the previous stage.   The

increase in length of the epithelial stalk appears to be both active, for mitotic divisions in its substance and in the adjacent, very active, expanding middle basal out-growth of the anterior wall of the pouch, and passive as is indicated by the lateral attenuation of the stalk. A similar view is expressed by Boyd (1956).

Rathke's pouch at the $17\frac{1}{2}$ day stage is still connected in the midline, in some embryos, to the roof of the stomadeum by a very long oblique epithelial stalk. In most of the embryos examined, the epithelial stalk is interrupted along its course, nearer to the stomadeum than to the pouch, leaving both the glandular and stomadeal connections intact.

The time at which the epithelial stalk is interrupted is subject to some variation. Attention has been called by Gronberg (1901) and Atwell (1918) to a similar variation in the development of the pituitary of Erinaceus europacus and rabbit respectively.

There is some indefiniteness in the exact position at which the break in the epithelial stalk occurs. Tilney (1936) and Boyd (1956) assume that the continuity of the epithelial stalk appears to be lost at a point mid-way between the stomadeal roof and the main mass of the developing gland, while Atwell (1918) and Schwind (1928) state that the stalk is detached from the stomadeal epithelium.

The exact manner in which this interruption of the epithelial stalk takes place, could not be precisely

determined, but most probably due to appearance of
vacuoles or cavities within its structure.   Such
cavities are observed by Tilney (1936) but are
differently interpreted.   Schwind (1928) claims that the
epithelial stalk is detached from the stomadeal
epithelium due to the increase in the thickness of the
sphenoid cartilage, and he adds that at time of break,
the epithelium and the lower portion of the stalk show
many degenerating cells.   The present study is unable to
confirm any of Schwind's observations.

The glandular attachment of the epithelial stalk,
at later stages, is represented by strands of cells
which pass downwards and backwards from the site of the
junction of the middle basal outgrowth (T) and its
tongue like process, to the craniopharyngeal canal.   They
pass through the canal, and the tissue between the basal
cartilage and the roof of the stomadeum, and are
connected to the latter.   These strands represent the
remnants of the epithelial stalk of the pituitary and
they contain a number of cavities which may indicate the
manner in which the connection is interrupted.

At full term, the remnants of the epithelial stalk
can still be detected in the craniopharyngeal canal and
in the tissue underneath, and are connected to the roof
of the stomadeum, but at birth these remnants no longer
exist, although the craniopharyngeal canal persists with
reduced anteroposterior and lateral dimensions, even
after birth.

A similar picture is described by Kingsbury and Roemer (1940) in the dog, where the stalk tends to persist at its upper and lower ends producing the "parahypophysis" and "pharyngeal hypophysis" respectively.

Boyd (1956) in his exhaustive study on the pharyngeal hypophysis note that this term is generally applied to the stomadeal connection of the epithelial stalk which has structural features as the adenohypophysis and grows during prenatal life. He states that the pharyngeal hypophysis is constantly present in man, that it usually possesses a rich vascularisation, and that its cells can differentiate as do those of the adenohypophysis. Boyd is unable to find the structure in late embryos and foetuses of other mammals available including the rat. Schwind (1928) states that he is unable to find the structure in any of the rat series examined, but Atwell (1918) finds epithelial remains between the sphenoid and the epithelium of the stomadeum, and also can identify the place of attachment of the stalk to the gland in all the stages up to and including full term embryos.

The "craniopharyngeal canal" is a term originated by Landzert (1868) as he finds a complete canal present in 10% of newborn children examined by him. Greig (1924) finds the canal in 40% of anthropoid apes, and states that it is present in rabbits, cats, and other animals with considerable frequency. Brahms (1932) confirms these findings in the cat, but Atwell (1918) in the rabbit, states that the sphenoid bone may become

solid as early as the 18th day or may contain a foramen as late as the 24th intrauterine day.

In the rat, at the $13\frac{1}{2}$ day stage, the hollow epithelial stalk is surrounded by loose mesenchyme tissue, but at the $14\frac{1}{2}$ day stage, the solid stalk is surrounded by the prochondral mesenchyme condensation in which cartilage is laid down at the $15\frac{1}{2}$ day stage.

The plate of cartilage laid down around the epithelial stalk in the ventral zone of the pituitary region between the gland and the roof of the stomadeum, is fusiform with tapering anterior and posterior ends, and maximum width in the centre. The thickness of the plate diminishes medially to form a very shallow small fossa for the gland. In the centre of the fossa there is a capacious, nearly circular canal, filled with loose mesenchyme tissue and through this the epithelial stalk of the pituitary passes to the roof of the stomadeum.

At birth, the craniopharyngeal canal which passes through the basisphenoid, still persists with reduced anteroposterior and lateral dimensions.

Tilney (1936) however, offers serious objections to the term "craniopharyngeal duct". "In the first place there is no such structure, and secondly, if such structure did exist, it would deserve some other designation than craniopharyngeal which assertively implies that the pituitary has a pharyngeal origin. The evidence at present is strongly in favour of pituitary derivation not from the pharynx but from the roof of the

stomadeum". The term "craniopharyngeal" is applied to the adult where the end of the craniopharyngeal canal, when it persists, runs to the adult pharynx, though it is only developed from the stomadeum.

RESIDUAL CAVITY

After the epithelial stalk of the pituitary has become a solid structure, the remains of the original cavity of Rathké's pouch is known as the residual lumen of the gland.

The residual cavity conforming to the shape of the pouch, is fusiform in shape with a ventrodorsally directed long axis at the $13\frac{1}{2}$ day stage, but at the $14\frac{1}{2}$ day stage it becomes sigmoid in appearance and consists of two portions; an anterodorsal portion roofed by the future pars intermedia, and a free posteroventral portion which keeps its shape, direction, and anteroposterior extent throughout the developmental period of the gland.

At the $16\frac{1}{2}$ day stage, the cavity of the pouch is, generally, clavicular in shape, and horizontal in position with its long axis anteroposteriorly directed and almost parallel with the plane of the superior surface of the basal cartilage.

The cavity of the pouch from the beginning is bounded laterally by thin lateral walls, which at the $17\frac{1}{2}$ day stage are markedly thickened forming cavity-free lateral extensions of the pouch which restrict the

semilunar cavity to the intermediate region of the pouch.

At the $18\frac{1}{2}$ day stage, the cavity of the pouch is L-shaped in sagittal section with an elongated, horizontal, anterior limb (the original anterodorsal portion of the sigmoid cavity: Fig. 55 and Fig. 98) and a short, posterior one (the original posteroventral portion of the sigmoid cavity of the $14\frac{1}{2}$ day stage). The anterior limb of the cavity is nearly four times the length of the unchanged posterior portion.

At full term, the cavity of the pouch retains its L-shaped appearance, has not suffered any reduction in its dorsoventral extent, and its anterior arm is greatly elongated and the angle between its two limbs is increased. The epithelial cells lining the cavity keep the stratified character, and neither branches of the cavity into the substance of the gland, nor ciliated cells bordering the cavity, can be detected.

The L-shaped appearance of the residual cavity is described by many authors (Atwell, 1918; in the rabbit, and Schwind, 1928, in the rat), but Atwell (1918) observes an additional limb in the substance of the anterior lobe which disappears later. The latter observation is recorded by Herring (1908) in the cat as he states that, sometimes, the cleft is more complicated and branches of it may run into the substance of the anterior lobe.

Brander (1936) observes that the cubical cells lining the residual cavity are sometimes ciliated, but

Schwind (1928) states that no ciliated epithelium is detected bordering the lumen.

Atwell (1939) claims that the residual cavity has become so much subdivided that only small portions are to be seen, and later it is entirely lacking. In man, Atwell (1926) observes that the rostral part of the lumen disappears first leaving a portion of the cavity at the apex which is more or less prominent and serves to separate the pars anterior from the pars intermedia, but Brander (1936) states that the residual lumen does not disappear but persists, in man, though it may be inconspicuous. Brander adds that the lining of the cleft is composed from the original cubical epithelium, but these lining cells may undergo transformation into basophil cells.

In the rat, Schwind (1928) states that in some series the lumen is restricted to the posterior portion of the gland, but in others, even at twenty days, there is no obliteration of the lumen.

In the present study, at birth and up to the 6 week stage (sexual maturity) the residual cavity of the pouch keeps a similar width and shape to that before birth, with no obliteration of any of its regions. The anterior limb of the cavity is greatly elongated anteroposteriorly and the angle between the two portions of the residual cavity is increasing, giving the posterior limb of the cavity an apparent shortening.

LOBES OF THE PITUITARY

1. PARS TUBERALIS

Pars tuberalis is the name given by Tilney (1913) to a portion of the hypophysis lying in close relation with the tuber cinereum of the forebrain vesicle.

Some investigators have previously identified several of the essential features of the formation of the pars tuberalis. These observations, in the main, have afforded an inadequate basis for a full and complete description of this glandular structure. The organ-genetic process, in most cases, has either been over-looked altogether or not pursued in sufficient detail. In other instances the interpretation of the adult condition has offered only a partial evaluation of the facts.

In the region where Rathke's pouch narrows to form the epithelial stalk which connects the pouch to the roof of the stomadeum, there arise outgrowths which may take the form either of a single median sprout, or two lateral outgrowths, or a median and two lateral out-growths.

Tilney (1913) has traced the development of the pars tuberalis in the cat and in the chick, and finds that the pars tuberalis has its origin in two sprouts from the body of the pituitary sac. These sprouts or lateral processes ultimately fuse with each other across the median line, displace the body of the pituitary sac

ventrally and thus secondarily assume their juxta-neural position.

No investigation before Tilney (1913) claims the presence of a structure similar to pars tuberalis arising from the lateral lobes of the hypophysis.

Muller (1871) describes for 16 and 18 cm. human, sheep, and pig embryos, an anterior process which passes on the ventral aspect of the neural stalk on its way towards the optic chiasma. A similar anterior process running forwards and upwards from the inferior part of the hypophysial sac, is observed by Mihalkovics (1875) in a 2 cm. rabbit embryo, at the side of attachment of the epithelial stalk. The same structure is described by Kraushaar (1885) in rodents, Lothringer (1886) in the dog, Haller (1897) in the mouse, Salzar (1898) in the pig and the rabbit, Gronberg (1901) in Erinaceus europaeus, Joris (1907) in mammals, Staderini (1908) in reptiles, and Bolk (1910) in primates (Macacus cynomolgus).

Herring (1908) in the cat (subject of Tilney's study) describes and figures a lobe extending from the body of the gland forwards, and closely applied to the brain wall, which he designates "the tongue like process of the pars intermedia", but speaking about its development, Herring (1908) states that the neck of the sac retains its tubular character for some time and becomes somewhat convoluted, and one of these convolutions is applied to the undersurface of the brain and gives rise to the tongue shaped process which extends

forwards from the anterior lobe towards the optic
chiasma.

The view that the pars tuberalis has its origin
from two lateral outgrowths, proposed by Tilney (1913)
has left a very confusing literature on the subject.

Some investigators claim that these lateral
processes eventually form the cortical layer of the
anterior lobe (Miller, 1916, in pig), others take an
intermediate position, claiming that these lateral
processes form the pars tuberalis and share in the
formation of the anterior lobe, (Baumgartener, 1916, in
reptiles; Atwell, 1918, in rabbit; and Tilney, 1936,
in man). A third group of investigators, although
observing the median elevation or ridge at the thickened
proximal portion of the epithelial stalk or at its
junction with the anterior wall of the pouch, still
adopts Tilney's view (Atwell, 1918, in the rabbit; 1926,
in man; Brahms, 1932, in the cat; Schwind, 1928, in
the rat; and Nelson, 1933, in the pig). Nelson (1933)
in the pig, observes a thickening of the anterior wall of
Rathke's pouch near the angle between sac and epithelial
stalk, and he believes that it represents the first
appearance of the lateral lobes which are destined to
form the pars tuberalis. A similar position is taken by
Atwell (1926) who observes, in man, a ridge in the mid-
line bearing at its nasal end an elevation he termed "the
anterior chamber", but adhering to Tilney's view, he
states that the lateral lobes are at the "Ventral Marrgin"

of the pouch close to the attachment of the stalk.

In the rat, at the $13\frac{1}{2}$ day stage of this study, the basal portion of the anterior wall of the pouch, in its intermediate region (nearly half its width) can be divided into three equal zones; two prominent, dorso-lateral knob like projections, and an intermediate basal, ridge like growth connected to the epithelial stalk of the gland.   The latter growth projects mainly into the lumen of the pouch.   This middle, basal, ridge like outgrowth is greatly enlarged and expanded in all directions at the $14\frac{1}{2}$ day stage.   It is in contact with the medial aspects of each of the dorsolateral knob like outgrowths, and continues anterodorsally, anterior to them, in a form of tongue like process which reaches the upper limit of the projections.   The tongue-like process of the middle basal outgrowth (T) leaves a fossa-like interval between it and the anterior aspect of the pouch, which is filled with vascular mesenchyme.

At the $15\frac{1}{2}$ day stage, the middle basal outgrowth (T) has expanded greatly, and its tongue like process continues its growth in anterodorsal direction.   The middle basal outgrowth is still connected to the epithelial stalk, and this connection is carried antero-dorsally as a result of this and of the basal portion of the pouch as a whole.

Schwind (1928) in the rat, states that at the $13\frac{1}{2}$ day stage, the lateral lobes which give the pars tuberalis, are marked swellings above the opening of the pouch, and

connected across the midline by a low ridge." He presents a figure (18) as "a microphotograph of a sagittal section of a $13\frac{1}{2}$ day rat embryo showing the 'temporary cortex' of the anterior lobe", but he considers the same structure in the text as origin of the pars tuberalis. This figure corresponds to figure (17) of the present study which illustrates a parasagittal section of the $13\frac{1}{2}$ day stage showing the dorsolateral knob-like projection which ultimately contributes to the formation of the anterior lobe of the gland.

Schwind (1928) does not mention how this cortex is formed and merely states that the cells of the "inner" portions of the anterior wall of the pouch become rounded while the "outer" cells retain their columnar shape. He adds "that the temporary cortex of the nasal end of the anterior lobe is formed in this way as described by Miller (1916) for the pig and by Atwell (1918) for the rabbit", and he believes that the temporary cortex is continued to the sides over the lateral lobes.

At the $16\frac{1}{2}$ day stage, of the present study, the median basal outgrowth (T) with its tongue like process, coming in close proximity with the posterior wall of the forebrain vesicle, changes its direction folding on it-self to form a dorsally directed, knee like bend with a central cavity within it, and then the process runs further forward along the inferior surface of the fore-brain vesicle.

The tongue like process of the middle basal out-

growth is considered as the "tuberal process" of the gland, the dorsally directed knee like bend is the so called "dorsal or caudal horn" of the pars tuberalis, and the anterior portion running along the inferior aspect of the forebrain vesicle is the "anterior or nasal horn" of the pars tuberalis. The middle basal outgrowth (T) and its tongue like process, are separated from the rest of the original anterior wall of the pouch by the intra-glandular fossa which is filled with vascular mesenchyme tissue; these structures with the connected portion of the pouch are destined to form the pars tuberalis of the adult gland. At the $17\frac{1}{2}$ day stage, the pars tuberalis has not increased in lateral width and is situated opposite the intermediate zone of the ventral aspect of the pouch from which it is clearly separated by the intra-glandular fossa. Its tongue-like process, the "tuberal process", extends further forward beyond the anterior end of the rest of the gland, and the "anterior horn" of the pars tuberalis passes below the inferior surface of the forebrain vesicle. At the $18\frac{1}{2}$ day stage, the pars tuberalis is much flattened dorsoventrally, and the "dorsal horn" of the lobe extends along the inferior aspect of the neural stalk, and not along its lateral aspects which it reaches at the following stage ($19\frac{1}{2}$ day).

The tissue of the tongue like process "the tuberal process" shows some alveolar and tubular arrangement of its cells. At the site of the junction of this process with the middle basal outgrowth (T), strands of cells

representing the glandular attachment of the epithelial stalk of the pituitary can be observed. The pars tuberalis shows no bifurcation at any stage of its development.

Schwind (1928) states that at the 15 day 20 hours stage (corresponds to the $16\frac{1}{2}$ day stage of the present study), that the lateral lobes grow forward and have their expanded ends pressed against the floor of the diencephalon. He observes that the temporary cortex has disappeared except in few places, but makes no mention of the mechanism. At the $17\frac{1}{2}$ day stage, he states that the distal expanded ends of the pars tuberalis are connected to each other and to the pars distalis by a flattened shelf of cells, while he omits the description, origin, and development of this shelf.

His figures 9 and 10 represent portions of mid-sagittal reconstructions of 15 days 20 hours, and 17 day rat embryos respectively. These figures show the pars tuberalis in the midline, though he states that fusion of the two portions of the pars tuberalis takes place at the 20 day stage. These figures also show the epithelial stalk of the pituitary (which is a midline structure) connected to the pars tuberalis.

Schwind (1928) describes the formation of the anterior and dorsal horns of the pars tuberalis at the 19 day stage, but it actually takes place at the $16\frac{1}{2}$ day stage (similar to 15 days 20 hours stage of Schwind), and at the 20 day stage (full term) he finally records that

the pars tuberalis has grown forward, and is "now" a plate or tongue like process.

In the present study, the pars tuberalis is much flattened at full term, but it keeps its width opposite the intermediate region of the ventral aspect of the anterior lobe, and also retains the alveolar and tubular arrangement of its cells. The dorsal horn of the pars tuberalis extends along the lateral aspects of the neural stalk but not onto its dorsal aspect, and its anterior horn (of the pars tuberalis) extends further forward along the inferior aspect of the forebrain vesicle. The vascular mesenchyme in the intraglandular fossa is very clear, separating the anterior and tuberal lobes.

At birth, the pars tuberalis is much flattened and formed of two or three layers of cells which are not histologically different from the cells of the anterior lobe of the gland. The dorsal horn of the pars tuberalis extends onto the dorsal aspect of the neural stalk, but there is no fusion in the midline dorsal to the neural stalk, i.e. no collar is formed around the neural stalk. The anterior horn of the pars tuberalis is so greatly elongated that its anteroposterior length becomes only slightly less than the total anteroposterior length of the remainder of the gland.

The same picture, with continuous elongation of the anterior horn of the pars tuberalis up to the 3 week animal, is observed in the postnatal animals up to sexual maturity.

Tilney (1913) observes a tubular arrangement of the cells of the pars tuberalis of the adult gland, but Schwind (1928) does not describe such an arrangement in the prenatal gland. Tilney (1913) also describes a collar of the pars tuberalis tissue around the neural stalk in the adult rat which is not observed either here or by Schwind (1928) in embryonic life.

The pars tuberalis, the tuberal process, the anterior and dorsal horns of the pars tuberalis, extend as a flattened plate of cells along the intermediate region of the ventral aspect of the anterior lobe, the ventral aspect of the neural stalk, and the inferior aspect of the forebrain vesicle, within the undifferentiated mesenchyme surrounding the pituitary. They are separated from the anterior lobe by the intra-glandular fossa, from the ventral aspect of the neural stalk by Atwell's recess, (both of which are filled with a core of vascular mesenchyme), and from the inferior aspect of the diencephalon by the membranes surrounding the brain.

2. ANTERIOR LOBE

The anterior wall of Rathke's pouch gives rise to the main body of the anterior lobe of the gland. Processes which convert the uniform wall of Rathke's pouch into the glandular anterior lobe of the typical adult gland, are variably described by different authors.

Some investigations claim that the pars distalis consists of a medullary core and a cortical zone formed by the distal portions of the lateral lobes (Baumgartener, 1916, in reptiles; Atwell, 1918, in the rabbit; and Tilney, 1936, in man), but most of the authors state that the anterior lobe is formed by proliferation of the cells of the basal part of the anterior wall of the pouch just above its neck (Herring, 1908, and Brahms, 1932, in the cat; Parker, 1917, in marsupialia; Schwind, 1928, in the rat; Nelson, 1933, in the pig; and Brander, 1936, in man).

Parker (1917) in Phescolaretes, states that the rapid multiplication of the cells of the walls of Rathke's pouch results in the outgrowth of numerous processes from the outer surfaces of the walls, and they become larger and arise in number, so the pars distalis consists of a mass of tubules and cell cords separated from one another by connective tissue. Brander (1936) in man, states that the pars anterior develops by extensions of Rathke's pouch turning upwards and towards the centre of the organ in such a way that the anterior lobe consists of lobules which do not completely fuse, so that in the adult it is possible to recognise certain planes which represent the developmental periphery of the organ.

In the present study, at the $13\frac{1}{2}$ day stage, the basal portion of the anterior wall of the pouch, in its intermediate region (nearly half of its width), can be

divided into three equal zones; two prominent, dorso-
lateral, knob like projections (GI, Fig. 33), and an
intermediate basal ridge like growth (T) connected to the
epithelial pituitary stalk.

At the $14\frac{1}{2}$ day stage the two dorsolateral out-
growths (GI, Fig. 34) expand greatly in all directions,
and are separated by a narrow median space which is an
extension of the interval between them and the pars
tuberalis, and like it, is filled with vascular
mesenchyme tissue.

At the $15\frac{1}{2}$ day stage, dorsal to these outgrowths
(GI), there are similar separate outgrowths (GII, Fig.72)
reaching close to the midline. Each of these dorsal
outgrowths (GII) comes into contact, but does not fuse
with the corresponding inferior outgrowth (GI). These
outgrowths of the pouch are formed of small rounded cells
with centrally located nuclei, and covered externally
with columnar epithelial cells. These outgrowths expand
and the anterior wall of the pouch, at the $16\frac{1}{2}$ day stage
consists of a small, thin anterodorsal portion which forms
the anterior boundary of the pouch cavity, and a very
markedly thickened basal portion involved in the
structure of these outgrowths. Parker (1917) in
Marsupialia, observes the production of a similar pair of
large dorsolateral outgrowths from the wall of the pouch
which contribute to the formation of the pars distalis.
Atwell (1918) in the rabbit, records that dorsal to each

lateral bud there is another outgrowth, in the 14 day stage, but he states that its fate is unknown.

At the $17\frac{1}{2}$ day stage, the outgrowths (GI and GII) of the anterior wall of the pouch, send outgrowths laterally and ventrally, which are considerably infiltrated by mesenchyme tissue. Also, at this stage, the lateral walls of the pouch are markedly thickened forming cavity-free lateral extensions of the anterior lobe which consist of trabeculae and cords of cells infiltrated with mesenchyme tissue. At the $18\frac{1}{2}$ day stage, the outgrowths (GI and GII) are markedly infiltrated by the connective tissue. Their original parts form the main bulk of the anterior lobe of the gland and can be easily detected.

Later, the anterior lobe of the gland is flattened dorsoventrally with further connective tissue infiltration. The alveolar arrangement of its rounded cells becomes more evident within the connective tissue stroma. Schwind (1928) in the rat, observes that the pars distalis is formed by the growth of the cells of the anterior wall of the pouch, and he states that they begin to break up into epithelioid cords and masses at the 15 day stage.

3. PARS INTERMEDIA

Pars intermedia is the term applied by Herring
(1908) to the epithelial investment of the neural lobe and
defined by Atwell (1926, 1939) as that portion of the wall
of Rathke's pouch which early comes in contact with the
neural lobe, remains relatively thin and epithelium-like,
faces the residual lumen by which it is separated from
the anterior lobe, and does not become strongly
vascularised.

This portion of the pituitary gland receives little
attention because of the old concept that its
development shows no point of special interest till
Wislocki (1929) claims that the pars intermedia is
completely lacking in the porpoise, and this observation
is confirmed and extended by Valso (1934) in whales;
Geiling (1935) in fin-back and sperm whales; Wislocki
(1938a) and Oldham (1941) in armadillo; Oldham, McCleery,
and Geiling (1938) in manatee; and Delwader, Tarr, and
Geiling (1934), Rahn (1938, 1939), and Rahn and Painter
(1941) in birds.

In the rat, at the $11\frac{1}{2}$ day stage, the finger like
stomadeal evagination is changed into a wedge shaped
diverticulum having a centrally depressed fundus with
surrounding raised edges. The ventral aspect of the
neural evagination is in close contact with the indented
central portion of the fundus of the pouch (the initial
area of neuroectodermal contact) and no mesenchyme

intervenes between the two structures. At the $13\frac{1}{2}$ day stage, the fundus of the pouch which is in contact with the neural lobe is seen to be incorporated into the posterior wall of the pouch forming its dorsal portion. It extends from the dorsal end of the pouch to a slight projection on the posterior aspect of the pouch, and it forms the primordium of the pars intermedia.   Later, that portion of the dorsal wall of the pouch is invaginated by the great increase of the size of the connected neural lobe. At the $14\frac{1}{2}$ day stage, the posterior wall of the pouch consists of two portions; the superior part in contact with the neural lobe, and the inferior free part.   Both of these portions are of uniform thickness, except at their junction, where there is slight projection on the posterior aspect of the pouch. The cells of this projection are rich in mitotic figures.

At the $15\frac{1}{2}$ day stage, the neural lobe is separated from the pouch by a single layer of mesenchymal cells which is in continuity with the surrounding undifferentiated mesenchyme tissue at the periphery.

Multiple knob like thickenings, rich in mitotic figures, arise at the $16\frac{1}{2}$ day stage, from the dorsal portion of the original posterior wall of the pouch, along the lateral aspects of the base of the neural lobe.

At the $18\frac{1}{2}$ day stage, the pars intermedia is markedly elongated anteroposteriorly, so its anterior end extends forward beyond the connection with the base of

the neural lobe and underlies the neural stalk. The small knob like outgrowths arising from the dorsal wall of the pouch along the lateral aspects of the base of the neural lobe are more marked, and further similar out-growths appear at this stage of development from the dorsal wall of the pouch in a more lateral position to the area of contact between the base of the neural lobe and the intermedia. These outgrowths appear to adopt an alveolar arrangement in the next stage.

At full term, the pars intermedia maintains the same thickness as in the $14\frac{1}{2}$ day stage, and is in contact with the base of the neural lobe and its stalk. It is separated from the neurohypophysis by a thin connective tissue membrane, and there is slight thickening at the caudal end of the pars intermedia (original slight projection along the posterior aspect of the pouch seen at the $13\frac{1}{2}$ day stage and the following stages). The multiple knob like outgrowths arising from the dorsal wall of the pouch along the lateral aspects of the base of the neural lobe, appear at full term, in the midline in contact with the neurohypophysis. In the substance of the pars intermedia they form light areas of rounded or ovoid cells arranged in an alveolar manner, while the remaining dark cells of the pars intermedia consist of wedge shaped groups of slender elongated cells with some rounded cells between them. The lightly stained groups of cells give the intermedia the appearance that it consists of dark and light areas.

Using P.A.S. with aldehyde thionin, the long

columnar cells forming the dark areas appear dense blue black (thyrotrophs) while the cells of the light groups appear clear intense blue green (acidophils).

In sections stained with Kopsch modification of the Golgi method, groups of thin spindle like cells with enlarged dorsal ends are observed. They extend between the two surfaces of the pars intermedia, perpendicular to these surfaces, and are connected to the cavity of the pouch. These groups of thin spindle like cells are most probably the dark cells of the pars intermedia.

The cytological differentiation (P.A.S. with aldehyde thionin and with aldehyde fuchsin, chrome alum haematoxlin phloxine) of these cells and their connection with the cavity of the gland, indicate that most of them are actively secreting.

The thin spindle like cells of the pars intermedia, most readily demonstrated by silver impregnation methods, are described by many investigators (Lothringer, 1886; Pirone, 1905; Gemelli, 1905; Trautmann, 1909; Stendell, 1914; Herring, 1908; Miller, 1916; Vanderberg, 1917; Retzius, 1894; and Atwell, 1918), and almost all of them attribute a supporting function to these cells.

The alveolar arrangement of the lightly stained cells of the pars intermedia, is also observed by a number of investigators; " smaller or larger islands of relatively large clear cells occur next to the neural lobe" (Kingsbury and Roemer, 1940, in the dog), "the

tubules of the pars intermedia when distended with colloid present an alveolar appearance in sections" (Brander, 1936, in man), "coarse and dense acini characterise the pars intermedia" (Tilney, 1936, in man). Herring (1908a) states that there is increased activity of the cells of the pars intermedia after thyroidectomy and probably an increase in the number of these cells in animals which live for some time after the operations.

The light and dark areas of the intermedia, have been studied by Zeigler (1963) in a light and electron microscope examination of the pars intermedia of the rat. Zeigler states that the dark and light areas shown by light microscopy in the P.A.S. stained pars intermedia, is confirmed by the electron microscope. The dark cells are specially endowed with a well developed Golgi apparatus and numerous free ribosomes, and he considers that they are evidence of secretory activity in the pars intermedia. Zeigler concludes that the intermedia is similar to the pancreas and the anterior lobe of the pituitary, where the epithelial cells act as chemoreceptors.

It is well known that numerous outgrowths in form of vesicles or epithelial nests, arise dorsally from the pars intermedia (Frazer, 1916; DeBeer, 1926; Herring, 1908; Schwind, 1928; Tilney, 1936; Brander, 1936; Bauer, and Haugh, 1960; and Falin, 1961). Some investigators claim that these epithelial cells actually invade the tissue of the pars nervosa (DeBeer, 1926;

Herring, 1908; Falin, 1961; and Bauer, and Haugh, 1960),
others state that: "they are at the lateral borders of
the pars nervosa" (Schwind, 1928), "are deeply situated
and often separated from the nervous substance by a
single layer of flattened cells" (Herring, 1908), or
"they extend eventually a very considerable distance
along the lateral aspects of the neural lobe and remain
within the mesenchyme showing no sign of penetrating or
invading the nervous tissue but instead they are enveloped
by it" (Brander, 1936).

Atwell (1918) in the rabbit, claims that these
extensions are outgrowths of the neural lobe into the
pars intermedia, although he states that it is difficult
to be certain of their exact origin. He then states
that these extensions disappear at the 20 day stage, and
two knob like processes extend from the pars intermedia,
at the 22 day stage, to the caudal extremity of the neural
lobe, and at the 30 day stage, outgrowths from the pars
intermedia may be seen entering the pars nervosa. The
contacts seen by Atwell in 16-20 day stages, which he
considers have not been described by any other observer,
are interpreted in the present study, as the multiple
knob like projections arising from the dorsal portion of
the original posterior wall of the pouch.

4. NEURAL LOBE

The appearance of a neural evagination lined by
tall ependymal cells as a primordium of the neurohypophysis
is a well known fact.

At the 11½ day stage, a finger like evagination of
the posterior wall of the forebrain vesicle, projects in
a posteroventral direction and its ventral aspect is in
close contact with the indented central portion of the
fundus of the pouch (initial area of contact) with no
mesenchyme tissue intervening between them.   The neural
evagination has a more or less symmetrical appearance, and
lies at right angles to the forebrain vesicle to which it
is connected.   There is a direct communication between
the cavity of the neural evagination and the cavity of
the forebrain vesicle through a small circular orifice
at the base of the evagination.   The evagination being
thick walled, its cavity occupies only the intermediate
third of its whole thickness.   The walls of the
evagination are uniformly thick and their cells are
arranged in two or more layers of elongated cells with
basal or centrally located nuclei.   These cells are of
the same type (ependymal) as those of the neighbouring
walls of the forebrain vesicle.

The distal part of the neural evagination becomes a
solid mass of cells at the 13½ day stage, and its cavity
is restricted to the most proximal portion of the
evagination.   The distal half of the neural lobe is

related and connected to the dorsal portion of the posterior wall of the pouch, while its proximal portion which is connected to the forebrain vesicle is free and surrounded with mesenchyme.

Various authors describe different methods by which the cavity of the neural evagination disappears.   In the rat, this process is most probably achieved by: 1) The uniform increase in the thickness of the walls of the evagination, evidenced by the persistence of the wide proximal portion and disappearance of the narrow caudal portion of the cavity.   The persistent portion of the cavity is much less than the original cavity of the neural evagination at the $12\frac{1}{2}$ day stage.   (A similar observation is recorded by Mihalkovics, 1875, in the rabbit, and Gronberg, 1901, in Erinaceus europaeus), and 2) The increase of the surrounding mesenchyme which invests the neural evagination and infiltrates its tissue dividing it into lobules.   Atwell (1918) describes the disappearance of the cavity of the neural evagination in the rabbit by a series of complex foldings and compressions which result in partial obliteration of the cavity, while Mihalkovics (1875) in the rabbit also, states that the cavity of the neural evagination is obliterated by growth of its walls and makes no mention to the foldings noticed by Atwell.

The neural lobe has a distinct lobular pattern out-lined by septa of the vascular mesenchyme.   The cells of the lobules are irregularly arranged, essentially ovoid in shape, and small in size.

Bodian (1951) has called attention to the lobular pattern of the neurohypophysis as he states that the neurohypophysis of the opossum is divided into well organised lobules by connective tissue septa, and that the lobules are particularly well developed at the periphery of the neurohypophysis but centrally are distorted.   He adds that the lobulation of the neuro-hypophysis is not unique to the opossum, as similar pattern is noted in the mole, pig, and certain primates. Duncan (1955, 1956) and Payne (1959) have observed the lobular pattern in the nervosa of birds.   Roth and Luse (1964) confirm Bodian's findings in the neurohypophysis of the opossum, as they study, by electron microscopy, the fine structure of the lobules (Bodian, 1951, states that each lobule is divided into three regions, a hilar, a palisade, and a septal zone).

Schwind (1928) in the rat, states that the cells of the pars nervosa arrange themselves in cords which are invested by an infiltration of connective tissue and capillaries from the adjacent mesenchyme.

At the $14\frac{1}{2}$ day stage, the neural lobe increases greatly in size and invaginates the dorsal portion of the posterior wall of the pouch which is in contact with it. At the $15\frac{1}{2}$ day stage, it becomes conical in shape with a dorsal rounded apex and a base separated from the pouch by a single layer of mesenchyme cells which is in continuity with the surrounding undifferentiated mesenchyme at its periphery.   The neural lobe lies at right angles

to the wall of the forebrain vesicle and appears as though sitting on the dorsum of the pouch. At the $16\frac{1}{2}$ day stage, the anterior (ventral) angle between the neural lobe and the wall of the forebrain vesicle is increased, and the lobe is connected to the wall of the forebrain by a very short neck containing within its centre the persistent proximal portion of the cavity of the neural evagination. The neural lobe, up to and including this stage, consists mainly of tall ependymal cells which line the cavity of the evagination. They are modified into small ovoid cells when closure of the evagination takes place, and are partly separated by connective tissue elements.

At the $17\frac{1}{2}$ day stage, the neural lobe is pyriform in shape, and its neck is longer than it is in the previous stage. The surface of the neural neck is composed on all its aspects by what appears to be a layer of nerve fibers running to the neural lobe. On the dorsal surface the nerve fiber layer is thinner than on the ventral surface and this gives the neck of the neural lobe its eccentric appearance. If the nerve tracts are followed to the brain the dorsal fibers appear to arise, most probably, from the paraventricular nuclei, while the ventral fibers seem to come, most probably, from the supraoptic nuclei.

The source of these hypothalamic hypophysial tracts from these nuclei is now universally recognised, in

particular after the experimental observations of
O'Connor (1947) which indicate atrophy of the supraoptic
and paraventricular nuclei after interruption of the
pituitary stalk. O'Connor (1947) concludes that the
axons of the cells of these nuclei enter the neural
stalk and reach the neural lobe.

At the later stages of embryonic life, and birth,
the neural lobe retains its pyriform appearance and dorso-
ventral height, but its base is much widened. The neural
stalk is much elongated, while its cross sectional area is
almost unchanged. In the nerve tracts round the neural
neck, some large, rounded or ovoid cells filled with
granules can be observed, and these are most probably
glial cells.

The superior aspect of the neural lobe is nearer to
the surface of the forebrain vesicle than before birth,
which is probably due to increase in the volume of the
forebrain vesicle and its reorientation (see page 155);
that it is not due to pressure from below, as stated by
Schwind (1928), is evident by the unchanged dorsoventral
height of the neural lobe and the marked flattening of
the adenohypophysis.

By one week after birth, the neural lobe has
doubled its volume at birth; the neural stalk is greatly
elongated and its curvature is more marked. The length
of the neural stalk is doubled by the second postnatal
week, and the height of the neural lobe is considerably
increased. The nerve tracts, at birth and in early

postnatal life, are crowded with large, ovoid or rounded cells, full of granules; some of these cells show mitotic figures. These cells are probably glial cells among the nerve axons going to the neural lobe.

The angle formed by the attachment of the neural lobe to the brain wall undergoes an interesting series of changes (see above). Attention has been called by Atwell (1918) in the rabbit, and Schwind (1928) in the rat, to similar changes.

The components of the neurohypophysis in the rat, at birth and in early postnatal life are:

the original tall ependyma cells lining the cavity of the original neural evagination (small ovoid cells; ? pituicytes),

the original connective tissue elements (fibro-blasts, fibrocytes, and fibers) from the process of development and in the walls of the blood vessels,

large rounded or ovoid cells among the nerve axons (glial cells), nerve fibers, and blood vessels with their capillaries.

No epithelial cells from the intermedia of the gland can be observed in the neural lobe, and neither nerve cells, nor Herring bodies are visible in the developing neurohypophysis.

Green and Maxwell (1959) in a comparative study on the pituitary in vertebrates conclude that the primitive neurohypophysial cells are exclusively ependymal and that they are secondarily invaded by nervous and

connective tissue elements as modified gliofibroblasts.

Almost all investigations on the neurohypophysis record the same view (Green and Maxwell, 1959) in connection with the contents of the neural lobe, but only a few authors claim the presence of nerve cells (Berkley, 1894; Oldham, 1941; and Holmes, 1959). Holmes (1959) in the ferret, states that occasional nerve cells are found throughout the central region of the lobe, and in the junctional region where the neural stalk becomes continuous with the main neural lobe these cells are aggregated to form a distinct nucleus.

Other investigators, however, emphasise the absence of nerve cells in the neural lobe (Herring, 1908a; Koelliker, 1879; Wislocki and Geiling, 1936; and Vasquez-Lopez, 1953).

Although, some authors claim the presence of a considerable amount of connective tissue within the neural lobe (Muller, 1871; Bucy, 1930; and Kerr, 1943), the presence of fibroblasts in the neurohypophysis is confirmed by Roth and Luse (1964) and Lederis (1965) by electron microscopy.

Vasquez-Lopez (1942) in the horse and (1953) in the rabbit, confirms the presence of glial cells in the neuro-hypophysis, and he states that the neuroglia lies in the same areas as the nerve tracts, and no specific type of neuroglia is peculiar to the neurohypophysis.

Pituicytes, this is a term first used by Bucy (1930) to describe the main cellular elements found in the

bovine neurohypophysis. Bucy mentions that the
pituicytes vary greatly in size and shape, the nuclei are
small "round, oval, or elongated", the finely granular
cytoplasm has no constant shape, the processes may be
long or short, and the cells may be unipolar, bipolar, or
sometimes multipolar. Bucy makes no mention of the
origin of the pituicytes of the adult neurohypophysis,
but the universally recognised concept is that they
develop from the original ependymal cells lining the
cavity of the neural evagination (Oldham, 1941;
Griffiths, 1940; and Falin, 1961).

Invasion of the neural lobe by epithelial cells
from the intermedia has been recorded by many
investigators (Herring, 1908; DeBeer, 1926; Bauer and
Haugh, 1960; and Falin, 1961), while some observers
have not noted such migrations (Wislocki and Geiling,
1936; Vasquez-Lopez, 1953; and Green and Maxwell,
1959).

Green and Maxwell (1959) state that the old
observation of the so called cellular infiltration of
the neural lobe needs re-evaluation.

As regards the function of the neural lobe there
are three conflicting theories:
1. The posterior lobe of the mammalian pituitary is a
"brain gland" not by virtue of tissue of brain origin,
but by the growth into it of epithelial cells of ectodermic
origin from the intermediate lobe. (Herring, 1908a;

DeBeer, 1926; and Bauer and Haugh, 1960).

Some views can be offered against this concept:

a. The present study cannot give support to this view as no cellular migrations from the intermedia of the gland to the neural lobe can be detected at any stage during the development of the gland up to sexual maturity.

b. No cellular infiltration from the intermediate lobe into the neurohypophysis is observed in many publications (Vasquez-Lopez, 1953; and Green and Maxwell, 1959).

c. Lack of the pars intermedia of the pituitary of some vertebrates and the complete separation of the neural and epithelial portions of the gland from the first, shed doubts on this theory. (Wislocki and Geiling, 1936; and Oldham, 1941).

d. The cells of the neural lobe are cytologically and developmentally separate from those of the pars intermedia and pars tuberalis, and an admixture of pars intermedia and pars neuralis is due simply to physical interdigitation of two diverse cell types in a relationship which has no functional significance (Gersh, 1939).

e. Cytological evidence suggests that the pars intermedia stands in one category with the anterior lobe and not the neural one. (Brander, 1936; Zeigler, 1963; and the present study, see "development of the functional activity").

2. The neural lobe of the pituitary gland serves as an

"organ for storage and release" of hormones elaborated
by the neurons of the supraoptic and paraventricular
nuclei of the hypothalamus, and carried down the axons
of the hypothalamohypophysial tract into it.   (All the
secretory granules and vesicles are contained within the
cell membranes of the axons and none appears in the
interstitial spaces between axons).   (Bargmann and
Scharrer, 1951; Hild, 1951; Palay, 1953, 1955; Vasquez-
Lopez, 1953; Scharrer and Scharrer, 1954; Bodian, 1951;
Roth and Luse, 1964; and Lederis, 1965).

3.   The neural lobe of the mammalian pituitary is a
"true endocrine gland" as its parenchymatous glandular
cells can produce and secrete hormones.   Rennels and
Drager (1955) in the rat, state that the recent emphasis
on the hypothalamic source of neurosecretory material
which relegates the neural lobe of the pituitary to the
role of a passive reservoir has resulted in the concept,
which they believe erroneous, that the pituicytes serve no
part in the normal secretory process, and they add that
there is ample experimental evidence that the pituicytes
are essential to the normal secretory and release
mechanism whereby the posterior lobe hormones are dis-
charged into the circulation.   Some evidence, in support
of a secretory activity on the part of the intrinsic
elements of the neural lobe, is recorded:

a.   presence of secretory osmophilic granules in the
pituicytes (Gersh, 1939), b.   appearance of Gomori

substance (secretory material) in the neural lobe before
it can be detected in the hypothalamus, (Green and Van
Breeman, 1955), c. appearance of material resembling
secretory substance in degenerating tissue cultures of
neural lobe even when the cultures are grown from
transplants of new growth apparently free of Gomori
substance (Green and Van Breeman, 1955).

From this evidence, some investigators conclude
that the cells of the hypothalamus do not appear to be
the only source of the secretory substances, as the
cells of the neural lobe may perform acts of secretion
(Wethington, 1958; Payne, 1959; Falin, 1961; Green and
Maxwell, 1959; and Green and Van Breeman, 1955).

This problem is likely to remain unsolved till
proof is supplied from the destruction of the pituicytes
(not the nerve fibers) of the neural lobe excluding
their role (if any) in the mechanism of release and
secretion of the hormones of the posterior lobe.

MITOTIC ACTIVITY OF THE FOETAL PITUITARY

In recent years much emphasis has been placed on the statement that mitosis occurs only rarely in the normal adult pituitary and that it is not common even in younger animals.   It can be said that mitosis should take place to account for growth of the gland, as well as to compensate for the cells lost, therefore failure to observe mitosis may mean that they were not looked for in the right way, rather than they do not occur at all.

A review of the literature on the pituitary of the rat, strongly suggests that in any physiological or experimental condition which results in increase in the total number of cells, mitosis must play the sole role.

Presentation of the distribution of mitotic figures and the sites of high mitotic activity in the different regions of the gland in the successive prenatal stages, reveals that the epithelial cells of Rathke's pouch are dividing intensively and very frequently show mitotic figures in the early stages of the prenatal life, up to and including the $16\frac{1}{2}$ day stage, after which there is a relative reduction in the number of the mitotic figures all over the pouch, and this relative reduction progresses steadily till birth.

The neural lobe shows mitotic activity, but to a lesser extent than the epithelial pouch, so that its growth lags behind that of the pouch in early intrautrine life.

Falin (1961) reports that in 4-5 week human fœtus, the epithelial cells of Rathke's pouch are dividing rapidly and often show mitotic figures. Pomerat (1941) also finds considerable mitotic activity in immature and young mature rats; and at birth the number of mitosis is $99 \cdot 3/\text{m.m.}^2$ or 14/section (Pomerat, 1941; Table I). Dawson (1942) has calculated about 39,000 mitoses in the anterior pituitary of immature monkey, (57/section).

The cells of the pouch at the $10\frac{1}{2}$ day stage, of the present study, are in a very marked state of activity. In general, the mitotic figures occur in all regions of the pouch, but are most frequently observed in the zone adjacent to the lumen of the pouch. The greatest number of mitoses can be seen in the basal portion of the anterior wall of the pouch. This great mitotic activity and the differential degree in its extent, in different regions of the pouch, can be considered as an indication that the pouch, in part, is an active evagination of the roof of the stomadeum, just as the presence of frequent mitotic divisions in the cells of the forebrain vesicle just opposite the tip of the developing pouch, is an indication, in part, of the active process underlies the development of the neural evagination.

The mitotic figures are more crowded in the basal portion of the anterior wall of the pouch at the $11\frac{1}{2}$ day stage, to meet the incorporation of 'the initial area of contact' of the anterior wall in the fundus of the pouch.

At the $12\frac{1}{2}$ day stage, there is another site of high

mitotic activity at the angle between the dorsal end of
the posterior wall of the pouch and the posterior end of
its fundus. This site is most probably the slight
projection along the posterior aspect of the pouch, just
adjacent to the caudal end of the neural lobe, observed
at the $13\frac{1}{2}$ day stage. The cells of this slight
projection are rich in mitotic figures, and later, form
the enlarged caudal extremity of the pars intermedia.

At this stage, the cells undergoing mitotic division
in the neural evagination are most frequently noticed in
the zone adjacent to its cavity, its apex, and in the mid-
line more than in the lateral regions. This state,
probably, accounts for 1) the increase in thickness of
the walls of the evagination resulting in the obliteration
of its cavity, and 2) its growth, which are observed in
the $13\frac{1}{2}$ day stage.

At the $13\frac{1}{2}$ day stage, the anterior wall of the pouch
shows a much higher mitotic activity than the posterior
wall, in particular its basal portion which contains the
greatest number of these cells. The cells in the midline
and just lateral to it are in a higher state of activity
than those of the extreme lateral portions of the pouch.
At this stage, the basal portion of the anterior wall of
the pouch is greatly increased, giving rise to the three
outgrowths of the anterior wall of the pouch, namely the
two dorsolateral knob like outgrowths (GI) and the median
basal one (T).

The mitotic activity of the neural lobe is more at
its apex and lateral regions, and possibly underlies the
great increase in its size observed in the next stage
($14\frac{1}{2}$ day stage).

At the $14\frac{1}{2}$ day stage, the areas of the pouch in
which the most frequent number of mitoses are observed
are: 1) Basal portion of the anterior wall (accounts for
the growth of the outgrowths of the anterior wall (GI and
T), 2) Area dorsal to this basal region of the anterior
wall (accounts for the appearance of the two dorsal out-
growths (GII) of the anterior wall at the $15\frac{1}{2}$ day stage),
3) Apex of the pouch specially in the midline (accounts
for the increase of the dorsoventral dimension of the
pouch increasing the region in contact with the base of
the neural lobe demonstrated by the reduction of the
contact - free ventral aspect of the neural lobe), 4) A
zone along the posterior wall just adjacent to the area
of this wall connected to the neural lobe (see above),
and 5) At the dorsal extremity of the epithelial stalk
of the pouch (accounts for its dorsoventral elongation).

At the $15\frac{1}{2}$ day stage, the sites of high mitotic
activity, in addition to the apical region of the pouch in
the midline, are some zones along the dorsal portion of
the original posterior wall of the pouch just lateral to
the midline.   These are interpreted as the cells forming
the multiple small knob like projections observed along
the lateral aspects of the base of the neural lobe at the
$16\frac{1}{2}$ day stage (Figures 57, 58 and 65).   That these out-

growths arise from the cells of the dorsal portion of the
original posterior wall of the pouch is a piece of
evidence against Atwell's view that the neuroepithelial
contacts observed at the 16-20 day stages of the rabbit
are processes from the neural lobe, not the pouch.

At the $16\frac{1}{2}$ day stage, the great number of mitoses
is in the lateral regions of the pouch more than its
medial portion accounting for the appearance of the
cavity - free lateral extensions of the anterior lobe of
the gland at the next stage ($17\frac{1}{2}$ day stage).

At the $18\frac{1}{2}$ day stage, there is a great number of
mitoses along the strip of the dorsal wall of the
cavity of the pouch (pars intermedia) which may account
for the anteroposterior elongation of the pars intermedia
so it underlies both the neural lobe and neural stalk.

It can be stated that consideration of the role
played by mitosis during the study of growth in the pre-
natal life, may give a clear view of the processes of
the development of the pituitary.

FUNCTIONAL ACTIVITY OF THE FOETAL PITUITARY

The appearance of chromophillic granules in the pituitary before birth could be regarded as morphological evidence of functional activity in the foetal gland. There is good evidence indicating the appearance of these granules in the early stages of the intrauterine life of different animals: 1) In the chick; Rahn (1938, 1939) on the 10th day, Martindale (1941) on the 11th, Studitskii (1946) on the 9th, Tixier-Vidal (1956) on the 7th, and Phillips (1962) on the 5th day of incubation. 2) In the pig; Nelson (1933) in 70-100 m.m. crown rump length, and Moore (1950) in 50-170 m.m. foetal stage. 3) In man; Moore (1950) in the third or fourth month, Brewer (1957) in 19th week and Falin (1961) and Levina (1965) in 8-9th week. 4) in the rat; Phillips and Schmidt (1959) in the 14th day stage.

Application of differential cytological methods (Gomori chrome alum haematoxlin phloxine, P.A.S. with aldehyde thionin, and P.A.S. with aldehyde fuchsin) to foetal pituitary tissue of the rat at the $14\frac{1}{2}$ day stage, all reveal the presence of faintly stained, finely distributed granules in the cells of the pouch, specially those arranged close to the cavity of the pouch, and those forming the outgrowths of the pouch.

These cytological methods and also Kopsch modification of Golgi method, were applied to the pituitary of the rat at late prenatal life and at birth

to study, in particular, the cells of the pars intermedia of the pituitary for the following reasons:

1. There is an exhaustive cytological study on the anterior lobe but not the pars intermedia, of the gland.

2. To determine whether this portion of the gland may function during embryonic life, and to try to shed light on the nature of this function.

3. To determine the role played by the thin spindle like cells in the pars intermedia.

4. To verify the suggestion of both Brander (1936) and Zeigler (1963) that the pars intermedia, as regard function, stands in the same category with the anterior lobe.

The cells of the dark groups of the pars intermedia suggest thyrotrophic type, while the cells of the light groups appear to be of acidophilic nature.

The thin spindle like cells of the dark groups are readily demonstrated in Kopsch modification of the Golgi method.

It is suggested that these morphological criteria indicate that the pars intermedia of the rat in late pre-natal life and at birth, may have the ability to secrete thyrotrophic and growth hormones. Similar observations are recorded on the cytology of the anterior lobe of the pituitary (Severinghaus, 1933; Knigge, 1957, 1958; Barnes, 1962).

That the acidophils are the source of the growth

hormone can be deduced from the work of Knigge (1958),
Meneghelli and Scapinelli (1960, 1961, 1962), and Leznoff
et al. (1960). Some investigators prove that the foetal
pituitary has the ability to secrete growth hormone
(Smith and Dortzbach, 1929, in the pig, and Meneghelli
and Scapinelli, 1962, in sheep).

It seems certain that the anterior lobe hormone,
thyrotrophin, must be present in the foetal circulation,
for in its absence:

a. thyroid activity could not take place (Rumph and
Smith, 1926),

b. there would be retarded development of thyroid
follicles (Raynaud, and Frilley, 1948; and Jost, 1953),

c. there would be a reduced ability of foetal thyroid
to concentrate I^{131} (Jost, Morel and Marois, 1952),

d. and the thyroid would be subnormal (Brewer, 1957).

Neither maternal hypophysectomy nor maternal
thyroidectomy modifies the growth of the foetal thyroid,
and neither maternal thyrotrophin nor foetal thyrotrophin
would seem to cross the placental barrier to any extent
which is physiologically significant (Hwang and Wells,
1959).

It is the general consensus that near the end of
gestation or incubation, the embryonic pituitary and
thyroid glands of warm blooded animals are capable of
synthesising and releasing their respective hormones into
the blood.

Phillips and Schmidt (1959) have shown that the rat pituitary is capable of synthesising "thyrotrophin" early in its development (14th day) and that its release into the body occurs about the 18th or 19th day.

Evidence in favour of the thyrotrophic function attributed to the pars intermedia, is as follows:

a. Herring (1908) states that there is increased activity of the cells of the pars intermedia after thyroidectomy, and probably increase in their number in animals which live for some time after the operation.

b. McNary (1959) records that few metallophilic cells when stained with ammoniacal silver, and occasional spindle shaped cells can be identified extending in the pars intermedia of the rat. McNary states that following thyroidectomy there is an increase in the size and metallophilia of these cells.

c. Maurer and Lewis (1922) demonstrate the presence of active secreting products (thyrotrophin) and of characteristic granules in the pars intermedia of the 175 m.m. pig foetus.

In this connection the foetal pituitary gland can also secrete: adrenocorticotrophin (Coetzee and Wells, 1957; Kitchell and Wells, 1952; Milkovic and Milkovic, 1962, 1963; and Wells, 1947), gonadotrophin (Smith and Dortzbach, 1929), and oxytocic substance (posterior lobe), (Gersh, 1939; McCord, 1915; Bell and Robson, 1927; and Snyder, 1928).

It is suggested that the pars intermedia of the rat

pituitary, in late prenatal life and at birth, similar
to the anterior lobe, may have the ability to secrete
the pituitary factors for growth, and thyroid
stimulation.

VOLUMETRIC GROWTH OF PRENATAL PITUITARY

I. ABSOLUTE GROWTH CHANGES

The growth in volume of the total gland (without the residual cavity) and its lobes when plotted against the embryonic age or length, forms in each instance a concave curve.

The observed volume of the whole gland is 0·1765 m.m.^{3} at birth, and the approximate increase in its volume from an embryo of $12\frac{1}{2}$ days to one of $18\frac{1}{2}$ days is 50 times and to one at birth is 100 times.

There is nearly uniform growth in early embryonic life up to the $17\frac{1}{2}$ day stage, after which there is almost equal growth in the volume of the total gland through each equal time interval of the late embryonic life.

The growth changes in the volume of the anterior lobe of the gland during intrauterine life, are similar to the type of changes which occur in the total gland volume, as the anterior lobe comprises relatively more of the gland than the other lobes. The observed volume of the anterior lobe at birth is 0·1326 m.m.^{3}. The growth in volume of the anterior lobe and of the whole gland are, also, similar as regards the increase in their volume (100 times) through prenatal life.

The observed volume of the intermediate lobe at birth is 0·0190 m.m.^{3}, and the approximate increase in its volume from an embryo of $13\frac{1}{2}$ days to one at birth is only 9 times.

The neural lobe appears later in embryonic life, and increases in early prenatal life at a slower rate in comparison to the total gland or its anterior lobe. Its observed volume at birth is 0·0237 m.m.^{3}, and the approximate increase in its volume from an embryo of $12\frac{1}{2}$ days to one at birth is 79 times.

The cavity-free lateral extensions of the anterior lobe remain thin up to the $17\frac{1}{2}$ day stage, then they are greatly thickened restricting the cavity of the pouch into the intermediate region of the gland. Their observed volume at birth is 0·0505 m.m.^{3}, and the approximate increase in their volume from an embryo of $12\frac{1}{2}$ days to one at birth is 250 times.

II. RELATIVE GROWTH CHANGES

The relation between the volume of each lobe of the gland to the volume of the total gland in the different prenatal stages and at birth, has been observed.

In early prenatal life the anterior lobe comprises relatively less of the total gland than it does later, while the intermedia, on the contrary, comprises more, and the nervosa makes the smallest part of the gland. The volume of each lobe of the gland as a proportion of the whole, however, is changed in the course of development, although this change takes place almost entirely before the $19\frac{1}{2}$ day stage, and thereafter the

rate of increase in the volume of each of the lobes is almost the same.

The calculated relative volumes of the lobes of the pituitary of the rat in late foetal life ($19\frac{1}{2}$ and $20\frac{1}{2}$ day stages) and at birth are as follows:

Anterior lobe (including pars tuberalis) is 75·5%; Intermediate lobe 11% and Neural lobe is 13·5% of the total volume of the gland.

The pars tuberalis is included within the anterior lobe.

In a number of vertebrates the pars tuberalis is equal or nearly equal in size to the pars intermedia (Atwell, and Woodworth, 1926).

TABLE

AUTHOR	ANIMAL	ANT. LOBE.	INTER- MEDIA.	NERVOSA
Covell (1926)	man; adult	78%	2%	20%
	full term	78%	2%	20%
Rasmussen (1924)	man; adult (capsule 8%)	72%	2%	18%
Rasmussen (1947)	man; at birth male	79·2%	2·1%	18·7%
	female	79·8%	1·9%	18·2%
	average life	75·7%	2·7%	21·6%
	(without the stalk and the capsule of the gland)			
Rasmussen (1921)	wood chuck	46%	2·5%	51·5%
Jackson (1917)	albino rat (epithelial parts)	92%	8%	
Bjorkman (1915)	rabbit	70%	13%	17%
Present study	rat; full term and birth	75·5%	11%	13·5%

The above table shows a comparison of the relative volumes of the lobes of the prenatal rat's pituitary with volumetric determination on man and animals.

From this it is evident that the adult relationships of the lobes of the gland are established at about the time of birth or even in late foetal life.

III.   RELATIVE INCREASE IN THE GROWTH OF THE PITUITARY AND ITS LOBES

The volumes of the gland and of each of its lobes are considered as being equivalent to 100% at birth and the relative increase in prenatal life has been observed.

There is a common observation that the volume of the total gland and of each of its lobes, at the $20\frac{1}{2}$ day stage, forms approximately 85% of that at birth, and at the $19\frac{1}{2}$ day stage, each comprises nearly 70% of its volume at birth.   This relation may indicate:

1. That the rate of increase in volume of the gland and of each of its lobes in the late foetus is the same, i.e. all increase by the same 15% as each comprises 70% of the birth volume at the $19\frac{1}{2}$ day stage, 85% at the $20\frac{1}{2}$ day stage, and 100% at birth.

2. That the growth of the total gland volume and of each of its lobes shows almost equal increase through each equal time interval of the late embryonic life, i.e. 15% increase per day in relation to the volume at birth.

DEVELOPMENT OF THE NOTOCHORD IN THE HEAD AND ITS
RELATION TO THE PITUITARY

At the $10\frac{1}{2}$ day stage, the notochord consists of faintly stained, encapsulated, ovoid cells. It is only connected to the entoderm at one point on the anterior portion of the foregut where there is a very slight evagination of the epithelium. The anterior end of the notochord beyond this connection is directed anteriorly and dorsally to come in close contact with the basal portion of the posterior wall of Rathke's pouch, but no actual point of fusion can be demonstrated.

The notochord, at the $11\frac{1}{2}$ day stage, following the configuration of the entoderm as far forwards as the tip of the foregut, dips down to come into contact with the entoderm through a mass of cells similar to those of the notochord itself, while its anterior end beyond this connection runs towards the posterior wall of Rathke's pouch. The very slight evagination at the tip of the foregut, representing remains of Seessel's pouch, becomes marked at the $12\frac{1}{2}$ day stage, and the notochord is connected to its tip by the cord of cells seen in the previous stage. This may be called the "descending branch" of the notochord, while the portion of the notochord running further anteriorly and dorsally beyond this connection to Rathke's pouch, is its "anterior or ascending branch". These branches of the cephalic end of the notochord become more evident at the $13\frac{1}{2}$ day

stage, and the connection of the descending branch to the epithelial evagination is more marked and very clear.

At the $14\frac{1}{2}$ day stage, condensation of the prochondral mesenchyme is observed in the ventral zone of the area of the undifferentiated mesenchyme surrounding the pituitary. The notochord runs anteriorly on the dorsal (superior) surface of the caudal part of this condensation, a short distance posterior to its bifurcation, the notochord dips into the condensation running for a short course near the superior surface of the condensation. The notochord emerges from the condensation after this short course and runs forward on its dorsal surface to the site of bifurcation. The ascending branch of the notochord runs a very short horizontal course after which it is anteriorly and dorsally directed to the posterior wall of Rathke's pouch where sometimes it is responsible for an indentation of the basal portion of the posterior wall, but no actual fusion has been seen.

The descending branch of the notochord is incorporated into the prochondral condensation, but it can be traced to the epithelial evagination which in some embryos becomes a mere thickening in the epithelium.

The surrounding mesenchyme makes a definite membrane around the cells of the notochord which become clearly outlined.

The presence of a distinct evagination or thickening

of the pharyngeal epithelium, just caudal to Rathke's pouch, which is connected to the notochord by its tip, is recorded by many investigators in the rat (Huber, 1912; Schwind, 1928; and Phillips and Schmidt, 1959), and the other animals (Kupffer, 1893; William, 1908; Grunwald, 1910; and Oldham, 1941). This evagination, or thickening of the lining epithelium is regarded by those investigators as the remains of Seessel's pouch

At the 15½ day stage, cartilage is laid down in the prochondral condensation. The notochord caudal to its bifurcation, as well as its ascending branch run the same course as described in the previous stage; but the descending branch has a variable course; either it is incorporated into the cartilage, or the cartilage forms a canal through which the descending branch passes ventrally to its connection with the epithelial evagination which becomes a mere thickening in the epithelium. This canal is similar and caudal to the craniopharyngeal canal through which the epithelial stalk of the pituitary passes to its stomadeal connection.

At the 16½ day stage, the ascending branch of the notochord consists of horizontal and anterodorsally directed parts. The latter part is either lost or it passes to a point close to the posterior wall of Rathke's pouch, from which it is separated by the mesenchyme envelope of the notochord.

The bifurcation of the cephalic end of the notochord, the presence of a special canal for its descending limb

in the cartilage plate, and the intimate relation of the notochord to the gland and its epithelial stalk, are very clearly evident at the 17½ day stage.

Later, only the horizontal portion of the ascending branch of the notochord can be detected on the dorsal surface of the sphenoid cartilage just caudal to the pituitary. The notochord also disappears from the occipital region except for a small portion embedded into the basioccipital cartilage.

At birth, no remnants of the notochord can be detected.

Bifurcation of the cephalic end of the notochord into ascending and descending branches, is mentioned by many investigators (Saint Remy, 1896; Kupffer, 1893; Grunwald, 1910; Keibel, 1889; Huber, 1912, in pig; 1917, in man; Atwell, 1915; and Oldham, 1941). Saint Remy (1896) states that in all Amniotes the anterior end of the notochord is bent down to maintain its insertion in the epithelium, and one can distinguish an ascending part, the termination of the principal part of the notochord, and a descending part attached to the entoderm. He adds that the descending branch, the summit of the angle, and a part of the ascending branch disappear later in the development.

Some investigators, on the other hand, claim that the cord of cells which connects the notochord to Seessel's pouch, is to be regarded as prechordal mesoderm plate which disappears as the sphenoid cartilage

develops (Aasar, 1931; and Schwind, 1928).

The present study in the rat can confirm the observation of Saint Remy (1896) of the presence of a descending branch of the notochord, as:

1. The group of cells connecting the notochord to the remains of Seessel's pouch is quite similar to those of the notochord itself.

2. At the $13\frac{1}{2}$ day stage and later, the notochord and its branches are very clear, and can be easily detected, in particular after the formation of the mesenchyme envelope around its cells.

3. The descending branch does not disappear as the sphenoid cartilage develops; on the contrary, it has its specific, transient canal through the cartilage (Fig.215).

As regards the relation of the cephalic end of the notochord to the developing Rathke's pouch, many investigators mention no actual contact between the notochord and the pouch (Herring, 1908; Parker, 1917; Atwell, 1918; Aasar, 1931; Schwind, 1928; and Nelson, 1933); some observers, on the other hand, claim the presence of a true contact between the notochord and the posterior wall of Rathke's pouch (Koelliker, 1879; Miller, 1916; Atwell, 1915; Woerdemann, 1913; Minot and Taylor, 1905; and Adelmann, 1922) although the last mentioned two authors state that this connection disappears later.

Woerdemann (1913) believes that he is justified in

describing a true contact because at the place of union there is no proper membrane intervening between the two structures, at this place there is a very noticeable thickening of the posterior wall of Rathke's pouch, and the arrangement of the nuclei is very irregular.

The present study in the rat is unable to confirm any of these observations. On the contrary; 1) A definite mesenchyme membrane envelopes the cells of the notochord, and 2) The posterior wall of Rathke's pouch is of uniform thickness.

Huber (1912) states that the head notochord has a characteristic course in each form of animal, e.g. in rabbit embryo, along the ventral surface of the basi-occipital cartilage; in pig, through the middle of the cartilage; and in rat, along the dorsal surface of the basioccipital cartilage. Schwind (1928) in the rat, mentions that the notochord lies embedded in the superior surface of the sphenoid cartilage, and ends at the posterior wall of what will later be the sella turcica.

The role played by the cephalic end of the noto-chord in the development of the pituitary gland, is variably interpreted by different authors.

Giroud and Roux (1959) from their experimental work record that in the rat (3 cases; due to riboflavin deficiency, niacin reduction, and vitamin A excess) as in birds, cases of duplication of the anterior end of the

notochord are accompanied by duplication of the pouch as well as the infundibulum. They conclude that these findings are in favour of an inductive action of the chordal system on the development of the adenohypophysis, either direct or indirect through the infundibulum which is found always simultaneously doubled. Mihalkovics (1875), Herring (1908) and Parker (1917), however, state that the notochord does not play any role in the formation of the pituitary as it is never in actual contact with it.

In the present study there is no evidence that the notochord plays any role in the development of the neural evagination, as its cephalic end is in contact with the basal part of the posterior wall of the pouch, not its tip. It may be stated that the presence of the notochord as described in this study (no actual contact between it and the pouch), gives an impression that it acts as a barrier to the backward growth of the sac, and takes no part in the formation of the pouch.

NERVOUS SUPPLY OF THE PITUITARY GLAND

The connection of the hypophysis with the
hypothalamus can no longer be questioned.   It is
generally agreed that the supraoptic and the
paraventricular nuclei are the source of the hypothalamo-
hypophysial tracts which converge in the tuber cinereum
on the neural stalk through which they enter the neural
lobe, where they form an exceedingly complicated plexus
of non myelinated nerve fibers which ramify to all parts
of the lobe (Hair, 1938); Rasmussen, 1938; Truscott,
1944; and Payne, 1959).

The nerve supply of the epithelial portion of the
pituitary, on the contrary, has been demonstrated, in
negligible amount, in a very limited number of animals,
and the source, nature, and manner of termination of
such nerve fibers, is subject to considerable debate.

Some investigators claim that the pars anterior
receives unmyelinated nerve fibers from the carotid
plexus accompanying its arterial channels, and these
fibers are vasomotor sympathetic (Berkely, 1894;   Tello,
1912; and Dandy, 1913), secretory (Pines, 1925; and
Croll, 1928), or parasympathetic via the greater
petrosal nerves (Hair, 1938; and Zacharias, 1942).

Harris (1960) in his exhaustive review on the neural
control of the pituitary concludes that experimental
evidence disproves the concept of sympathetic and
parasympathetic innervation of the pars distalis.

Some observers record that the innervation of the anterior lobe of the pituitary is derived from the hypothalamo-hypophysial tract (Brooks and Gersh, 1938, 1941; Rasmussen, 1938; Truscott, 1944; Dawson, 1953; Vasquez-Lopez, 1948; and Zeigler, 1963).

Most of the observations indicate that the nerve terminals in the epithelial part of the pituitary are of the knob like variety (Hair, 1938; and Vasquez-Lopez, 1948), but some claim the presence of a pericellular network of nerve fibers (Brooks and Gersh, 1941).

Almost all the investigators indicate that the innervation of the epithelial part of the gland is very scanty and almost negligible, except Truscott (1944) who claims copious innervation of the anterior lobe of the pituitary of the rat.

Herring (1908) using Cajal and Golgi methods of silver impregnation finds no nerve fibers in the pars anterior of the cat, and Brooks and Gersh (1938, 1941) using the silver pyridine impregnation method reveal an extremely scanty supply of nerve fibers in the anterior lobe of the rat pituitary.

Green's studies on the gland of seventy six species of animals failed to demonstrate nerve fibers in the pars distalis (Harris, 1962).

Truscott's observations are highly questionable as he does not demonstrate the course of a single fiber, but mentions "it is almost impossible to demonstrate them by photomicrographs without sacrificing the definition of

the surrounding field, so the nerve fibers are followed only by small segments". It is very doubtful if his figures (10 and 11) actually demonstrate nerves and it is more probable that the structures detected are connective tissue fibers.

Green (1951) states that "contrary to the observations of Truscott, no nerve fibers are found in the pars distalis of the rat pituitary".

The present study using Rasmussen pyridine silver method, Kopsch modification of Golgi method, and Peters' protein-silver mixtures, shows no nerve fibers in the epithelial part of the pituitary gland of the rat in late foetal life and early postnatal stages, when some pituitary functions are already established. (see functional activity).

Most recent techniques as phase contrast microscopy and electron microscopy, which clearly differentiate between recticular fibers and nerve fibers, also fail to reveal any innervation of the gland cells in the pars distalis. Green (1951) states that phase contrast microscopy provides circumstantial evidence against copious innervation of the adenohypophysis in the rabbit and in man. Harris (1960) states that "Palay, and Farquhar and Rinehart have failed to find any nerve fibers in the pars distalis of the pituitary by the use of the electron microscope".

DEVELOPMENT OF THE MENINGEAL RELATIONS OF
THE PITUITARY

Embryological study of the membranes around the pituitary has received very little attention, and the interpretation of adult condition has offered only a partial evaluation of the facts. Great uncertainty exists regarding the arrangement of the meninges around the pituitary, and opinions vary widely in regard to the degree to which the leptomeninges extend around the epithelial and neural portions of the gland.

Sterzi (1902) has put forward the theory of meningeal differentiation around the brain and the spinal cord. The meninges arise from a vascular membrane "the primitive meninx" closely investing the brain and cord. This membrane splits subsequently into two membranes; the outermost of which becomes the fibrous dura, while the inner becomes the primitive pia mater. The latter is extremely vascular, becomes greatly thickened and separates further into two layers of which the inner becomes the definitive pia, while the outer becomes the archnoid. The two layers are connected by a multitude of fine trabeculae, the open meshes of which become the subarchnoid space.

Hughson (1924) in the first study of the membranes around the pituitary, states that the buccal derivative of the pituitary is separated from the stomadeum and embedded in mesenchyme between brain and sphenoid before

separate meninges have developed. He concludes that all three meningeal layers when they ultimately differentiate into distinctive membranes, are destined to enclose and surround the entire pituitary, when completely differentiated.

In the rat, the pituitary, stomadeal and neural components, lies in a mass of essentially unorganised, loose mesenchyme tissue which occupies the space between the fore and hindbrain vesicles and the roof of the stomadeum. At the $14\frac{1}{2}$ day stage, indistinct condensations of mesenchyme cells have formed close to the opposed surfaces of the hind and forebrain vesicles. The posterior marginal condensation closely investing the surface of the hindbrain vesicle separates, at the $15\frac{1}{2}$ day stage, from the rest of the undifferentiated mesenchyme in which the developing gland is found, and the latter appears to be in relation with the forebrain vesicle alone.

In this undifferentiated mesenchyme, at the $16\frac{1}{2}$ day stage, a dorsally directed cavity can be detected. This cavity separates the marginal condensation closely investing the caudal aspect of the forebrain vesicle - in the zone dorsal to the neural neck - from the rest of the undifferentiated mesenchyme, giving the latter an appearance of a triangular mass connected by its apex to the marginal condensation closely investing the fore- brain vesicle. Later, the marginal condensation close to the forebrain vesicle also separates from the

triangular mass of the undifferentiated mesenchyme in the region ventral to the neural stalk. By this separation, the marginal layer of condensed mesenchyme closely investing the caudal aspect of the forebrain vesicle becomes connected to the undifferentiated mass surrounding the pituitary only in two sites: 1. At the apex of the triangular undifferentiated mass, and 2. Around the connection of the neural stalk to the posterior wall of the forebrain vesicle.

The pituitary gland as a whole, with the entire length of the neural stalk, is surrounded by the undifferentiated mesenchyme, bounded by condensed mesenchyme at the margins of the triangular mass, which sends mesenchyme processes towards the basal cartilage.

Later, there is differentiation of the meninges closely investing the opposed surfaces of the hind and forebrain vesicles, which takes place close to the brain surfaces and is limited externally by the distinct marginal condensation on the surfaces of the brain. This differentiation does not extend further towards the pituitary than the site of the connection of the neural stalk to the forebrain.

The marginal condensation around the brain vesicles, is in position (Sterzi, 1902; Harvey and Burr, 1926; and Sensenig, 1951), and has the structure of the dura mater and can be identified as such at this stage. So, the triangular mass of the undifferentiated mesenchyme around the pituitary is connected 1) at its

apex and 2) around the connection of the neural to the forebrain vesicle, to the dura mater of the forebrain vesicle.

At the $18\frac{1}{2}$ day stage, the undifferentiated mesenchyme condensation forms the perichondrium on the dorsal surface of the basal cartilage, completing the formation of the boundaries of the pituitary region.

There is no differentiation of the mesenchyme around the pituitary gland into the three membranes which develop around the brain. Pia-archnoid, and subdural and subarchnoid spaces, do not differentiate, at any time, during the development of the gland, and the membranes and the spaces do not extend towards the pituitary beyond the junction of the neural stalk with the forebrain, and the apex of the triangular mass of the undifferentiated mesenchyme with the dura mater.

The undifferentiated mesenchyme surrounding the gland, forms a capsule for the entire circumference of the pituitary, covering the outer surfaces of the adeno and neurohypophysis and extending between them.

There is a considerable disagreement on the nature of the membranes of the pituitary in previous investigations, and even the statements of the same observer are not consistent.

Wislocki (1937a) in a developmental study of the meningeal relations of the pituitary in man and monkey, states that "there is no evidence of delamination of

leptomeninges around the body of the gland"; then he states again that "the undifferentiated mesenchyme forms the pia mater" (which is a part of the leptomeninges), and in a third place he states that "the dura developing around the body of the pituitary fuses with the surface of the anterior and neural lobes and hence prevents permanently the development of the pia archnoid or of a subdural space around the body of the pituitary". In another part of the same publication, Wislocki says that "the pial hypophysial mesenchyme situated between the pituitary and the brain gives rise to the stroma of the epithelial pituitary", and finally he states that "the subarchnoid space when completely differentiated forms a cistern which encloses the neural stalk (whole) in the form of a collar". Wislocki (1937) states that the neural lobe in the embryo is surrounded by a delicate condensation of pia mater. Later, the neural lobe pushes its way into the developing sella turcica, and its distal pole becomes covered with the dural mesenchyme of the sella and whatever pia may have existed previously vanishes. Wislocki, however, concludes that the dura forms a capsule for the entire circumference of the body of the pituitary, involving the outer surfaces of the pars distalis and intermedia, and the distal pole of the neural lobe.

Parker (1917) mentions that the dura mater forms a connective tissue capsule for the whole pituitary, and the pia mater constitutes a very thin layer covering the

brain and passing continuously over the surface of the neural lobe lying between it and the pars intermedia. The pia mater also completely invests the pars tuberalis.

In the rat, there are some points related to the development of the undifferentiated mesenchyme surrounding the pituitary:

1.   At the $14\frac{1}{2}$ day stage, the middle basal outgrowth (T) of the anterior wall of the pouch, leaves a fossa like interval between it and the anterior aspect of the pouch. This is filled with undifferentiated mesenchyme through which pass blood vessels.   Since no differentiation into membranes takes place in this mesenchyme, this core of mesenchyme and its blood vessels, as well as the latter vascular mesenchyme infiltration of the glandular tissue, are considered of undifferentiated nature, i.e. neither pial nor dural.

2.   At the $15\frac{1}{2}$ day stage, a single layer of cells separates the pouch from the neural lobe, and is in continuity with the undifferentiated mesenchyme surrounding the pituitary at its periphery.

This membrane is variously interpreted; Wislocki (1937) as pia mater; Oldham (1941) as dura; Wislocki and Geiling (1936) dura and pia archnoid; Wislocki (1938) dura and subdural space; Parker (1917) pia mater; and Atwell (1918) as connective tissue containing blood vessels.

3.   Parker (1917) states that the pia mater completely invests the pars tuberalis, while Boyd (1960) states that the fibrous capsule which is closely applied to the surface of the gland extends anteriorly to enclose the pars tuberalis.

In the present study, at the $16\frac{1}{2}$ day stage, the tuberal process of the pituitary lies in the surrounding undifferentiated mesenchyme of the gland.   At the $18\frac{1}{2}$ day stage, this tuberal process extends forward, anterior to the remainder of the gland, carrying with it an envelope of the undifferentiated mesenchyme tissue, which later blends with the adjacent dura of the brain.

The pituitary region may be considered as one of the regions into which the differentiation of special meningeal layers does not extend.

The mesenchyme around the pituitary, instead of forming the typical meninges in this region, gives rise to an external lamina of condensed mesoderm with an inner zone of loose connective tissue.

DEVELOPMENT OF THE VASCULAR SUPPLY OF THE
PITUITARY GLAND

The pituitary comes to lie at an early period of prenatal life in a field of undifferentiated mesenchyme through which are scattered several groups of blood islands, and at the $13\frac{1}{2}$ day stage, these islets form capillary blood vessels applied to the periphery of the pituitary.

At the $14\frac{1}{2}$ day stage, the tongue like process of the middle basal outgrowth (T) of the original anterior wall of the pouch (prospective pars tuberalis) grows anterodorsally leaving an intraglandular fossa filled with mesenchyme tissue between it and the anterior aspect of the pouch.

The internal carotid artery, on each side, attains its position in the undifferentiated mesenchyme lateral to the pituitary by passing between the tympanic bulla posteriorly and the prochondral condensation of the basisphenoid anteriorly. During its course through this undifferentiated mesenchyme the internal carotid, on each side, gives two small branches; one anterior to the epithelial stalk of the pituitary and one posterior to it. The two branches run dorsally and medially towards the pouch. The former is designated as the anterior (rostral, or superior) hypophysial artery and the latter the posterior (caudal or inferior) hypophysial artery.

The posterior hypophysial artery, on each side,

runs dorsally, close to the posterior aspect of the pouch, up to the level of the neural lobe, then it runs medially, gives a very tiny branch between the pouch and the neural lobe, and continues its course along the posterior aspect of the neural lobe. At the posterosuperior angle of the neural lobe, the artery enters the neural lobe and breaks into several branches which supply more than its caudal half. The posterior hypophysial artery supplies areas of the pouch posterior to the connection of the epithelial stalk of the pituitary with Rathke's pouch.

The anterior hypophysial artery runs anteriorly and dorsally to the junction of the neural lobe with the forebrain vesicle, where it ends by dividing into several branches; 1) runs medially and dorsally onto the lateral aspect of the proximal portion of the neural lobe, passing onto its dorsal aspect. It enters and supplies the proximal portion of the neural lobe; 2) runs ventrally between the pouch and the neural lobe, and 3) runs to the intraglandular fossa and is larger than the other two, it has been designated by Xuereb et al (1954) as "artery to the trabecula". The latter vessel, at successive stages ($15\frac{1}{2}$ and $16\frac{1}{2}$ day stages) gives off two offshoots near its origin from the anterior hypophysial artery. These branches, two on each side, take a similar course to that of the parent artery (artery to trabecula) and run anteroposteriorly in the mesenchyme between the outgrowths of the original

anterior wall of the pouch.

At the $17\frac{1}{2}$ day stage, after the long axis of the pouch has become anteroposteriorly directed, the same vascular pattern persists. The pituitary gland is surrounded with undifferentiated mesenchyme and no vessel either of pial or of dural origin finds its way to the gland.

At this stage, the posterior hypophysial artery supplies the caudal portion of the anterior lobe, gives a branch between the pouch and the neural lobe, and runs along the posterior aspect of the neural lobe to its posterosuperior angle where it terminates in the neural lobe and supplies more than its caudal half.

The anterior hypophysial artery, on each side, runs anterodorsally along the ventral aspect of the neural stalk to Atwell's recess where it gives the following branches. 1) "Artery to the trabecula", that runs with its two offshoots, anteroposteriorly to enter the substance of the anterior lobe of the gland, supplying more than its anterior half and anastomosing with branches of the posterior hypophysial artery. 2) Interlobar artery, that runs between the pouch and the neural lobe to meet its fellow from the posterior artery. 3) Neural stalk artery, that runs along the neural stalk, supplies it and the anterior portion of the neural lobe and anastomoses with branches of the posterior hypophysial artery. 4) Pars tuberalis artery, that runs forward along the dorsal aspect of the tuberal process. This is

similar to the other branches of the anterior hypophysial artery in a) that it lies within the undifferentiated mesenchyme around the pituitary and b) gives no branches to the tuber cinereum.

The vascular pattern of the pituitary at birth is similar to that at puberty; two main arteries; anterior and posterior hypophysial on each side from the intra-cavernous portion of the internal carotid artery.

The anterior hypophysial artery, reaching Atwell's recess, divides into its branches. Campbell (1966) states that in the rat and rabbit, there seems little doubt that the vessels that overlie Atwell's recess are those that penetrate the adenohypophysis in all directions bringing its main blood supply.

1. Artery to the trabecula, runs from its origin from the anterior hypophysial artery, anteroposteriorly in the connective tissue core into the intraglandular fossa between the pars tuberalis and the anterior lobe proper of the gland. The presence of a similar artery is recorded in many investigations but with variable inter-pretations. Herring (1908a) in the cat, is the first to record this vessel as he states that the blood vessels of the anterior lobe, which arise from the internal carotid artery, are extremely numerous and wide, running more or less parallel to one another in an anteroposterior direction. Fuchs (1924) in man, states that these branches of the anterior (superior) hypophysial artery

enter the anterior lobe embedded in the conspicuous
strands of connective tissue on either side of the midline
and Popa and Fielding (1930, 1930a, 1933) mention that,
in man, a branch of the internal carotid takes a special
course before opening into sinusoids and it gives
branches to the neural lobe before it enters the anterior
lobe.   Xuereb, Prichard, and Daniel (1954) observe that
in man, each superior hypophysial artery distributes
branches to the hypophysial stalk and gives off a
substantial branch, the artery to the trabecula, which
courses through the pars distalis.   The same observation
is recorded by Landsmeer (1951) in the rat.   Xuereb et
al. (1954) state, however, that no branches of either the
superior (anterior) or the inferior (posterior)
hypophysial arteries supply the epithelial tissue of the
pars distalis.   Stanfield (1960) in man, on the other
hand, states that a variable number of small arteries
supply the anterior lobe DIRECTLY with ARTERIAL blood;
the largest and most constant of these is the artery to
the fibrous core.   'Espinasse (1934) studying the
development of the vascular supply of the human pituitary
states that an artery can be clearly seen leaving the
internal carotid, and within the connective tissue core
it enlarges to form the sinusoids which ramify and
anastomose in all directions, bringing the blood into
the most intimate contact with the glandular portions of
the pituitary.

2.   The artery to the pars tuberalis, runs forward along the dorsal aspect of the pars tuberalis to its tip, within its envelope of the undifferentiated mesenchyme. It supplies the tuberal lobe, but not the hypothalamus, and forms a fine vascular network within the lobe. The existence of such a branch supplying the tuberal lobe is recorded by many investigators: Basir, 1932, in dog; Brander, 1936, in man; 'Espinasse, 1934, in man; Green and Harris, 1947, in rat; Green, 1948, in rabbit and rat; and Cummings and Habel, 1965, in sheep. Green (1948) states that the superior (anterior) hypophysial arteries form two groups; and anterior and posterior. The anterior group penetrates the pars tuberalis in the angle between the hypophysial (neural) stalk and the optic chiasma. They have a fairly well defined elastic lamina as well as smooth muscle walls, and some branching of the arteries into arterioles in the pars tuberalis can be observed. 'Espinasse (1934) in his developmental study of the vascular supply of the human pituitary, states that as the pars tuberalis pushes forwards, an artery is seen actually in process of being involved in the upgrowing glandular tissue.

3.   The artery to the neural stalk runs dorsally along the lateral aspects of the neural stalk, then onto its dorsum to enter its substance, where it terminates in branches forming a very fine network in the stalk and proximal part of the neural lobe. These rami anastomose with those of the posterior hypophysial artery which

supply the main portion of the neural lobe.   Similar
observations are recorded by Nikolskaia, 1929, in man;
Basir, 1932, in dog; Wislocki, 1937b, 1938, in cat and
monkey; Green, 1948, in rat and rabbit; Xuereb,
Prichard, and Daniel, 1954, in man; Daniel and Prichard,
1956, 1957, in rat and sheep; Stanfield, 1960, in man;
and Cummings and Habel, 1965, in sheep.

4.   The interlobar artery runs posteriorly between the
stomadeal and neural portions of the gland to anastomose
with its fellow from the posterior hypophysial artery.
This branch supplies the neural lobe and contributes to
its network.   Brander, 1936, and Stanfield, 1960, in man,
describe a similar interlobar artery from the anterior
(superior) hypophysial artery.

Some investigators mention the presence of the
anterior (superior) hypophysial artery as a branch from
the internal carotid with at least three of the above
mentioned branches.   Brander (1936) describes, in man,
an artery springing from the internal carotid artery
which divides into three branches. 1) One passes
upwards in the groove between the pouch and the neural
lobe (interlobar). 2) One, the largest, penetrates the
capsule of the pituitary and thus supplies branches to
all parts of the organ (artery to the trabecula). 3) The
third passes forwards in the dura (artery to pars
tuberalis).   Wislocki (1937b) states that in the cat the
superior (anterior) hypophysial artery sends separate

branches to the stalk, the anterior lobe, and the neural lobe.

The posterior hypophysial artery is of considerable size and runs medially and dorsally towards the gland. It divides, usually, at the beginning of its course into two branches; a very slender one going to supply the caudal portion of the anterior lobe, and a main branch running dorsally along the posterior aspect of the gland to the posterosuperior angle of the neural lobe, where it terminates in its substance supplying the major part of its caudal portion. During its course along the posterior aspect of the gland, it sends a branch to run between the pouch and the neural lobe, and to meet its fellow of the anterior artery. This artery gives its rami dorsally to the neural lobe, anastomosing with its fine network.

The branches of the posterior hypophysial artery anastomose with those of the anterior hypophysial artery forming a very fine network in the neurohypophysis.

The vascular network of the neurohypophysis is similar to that of the pars tuberalis and neural stalk, but is finer and more rich than that of the anterior lobe of the gland. Although Stevens (1937) states that the anterior lobe of the cat hypophysis is more richly supplied than the neural lobe, Brown (1924) records that the pars nervosa of the rat is richly supplied with vessels, and its capillaries are more numerous, forming a

close network in contrast to the coarse network of the anterior lobe.

Almost all the investigators claim the same source of the blood supply of the neural lobe from the posterior hypophysial branch of the internal carotid (Herring, 1908; Mudd, 1918; Fuchs, 1924; Nikolskaia, 1929; Brown, 1924; Dandy and Goettsch, 1910-1911; Basir, 1932; Stevens, 1937; Wislocki, 1937a; Landsmeer, 1951; Xuereb, Prichard and Daniel, 1954; Jewell, 1956; Daniel and Prichard, 1956, 1957; Glydon, 1957; Holmes and Zuckerman, 1959; Barrington, 1963; and Cummings and Habel, 1965).

Fuchs (1924) states that minute twigs of the posterior (inferior) hypophysial arteries pierce the capsule of the anterior lobe supplying the latter with some collateral blood, and Landsmeer (1951) states that in the rat, the caudal (posterior) hypophysial artery mainly contributing to the neural lobe, regularly gives off a branch to the anterior lobe. Daniel and Prichard (1956), on the other hand, state that in the rat the posterior hypophysial artery supplies only the neural lobe, and does not give any branch to the anterior lobe as Landsmeer (1951) has stated.

However, the existence of such a vascular supply to the caudal portion of the anterior lobe from the posterior hypophysial artery is obvious for the following reasons:

1.   The above mentioned observations of Fuchs (1924) and
Landsmeer (1951) indicating the presence of arterial
branches from the posterior hypophysial running to that
portion of the anterior lobe.

2.   The observations recorded in this study of a branch,
on each side, from the posterior hypophysial artery
running to the caudal portion of the anterior lobe.

3.   The experimental results of Daniel and Prichard
(1956), Barrnett and Greep (1951), and Holmes and
Zuckerman (1959) which indicate an absence of necrosis of
the caudal part of the anterior lobe either after
application of cautery to or section of the neural stalk,
while the anterior portion of the lobe is affected,
demonstrating that this caudal portion of the anterior
lobe has a different source of blood supply than the
rest of the lobe.

4.   The observation recorded by Cummings and Habel
(1965), that Indian ink injection via the carotid, in the
sheep, fills the vessels of the stalk and the rostral
part of the anterior lobe but in some cases fails to
reach the more caudal region of the anterior lobe
(the posterior hypophysial artery in sheep arises from
the carotid rete and not from the carotid artery).

5.   Green and Harris (1947) record in the rat that the
anterior part of the pars distalis usually contains more
injected material than its caudal extremity.   They
interpret this as an indication of the direction of
blood flow in an anterior to posteroinferior direction.

6. Morphologically, the caudal portion of the anterior lobe supplied by the posterior hypophysial artery, is the original basal portion of the pouch posterior to the epithelial stalk, which contributes to the formation of the pars tuberalis and anterior lobe, and is supplied by the posterior hypophysial artery at the $14\frac{1}{2}$ day stage, and retains its blood supply from this vessel in the later stages.

In connection with the ARTERIAL blood pattern of the anterior lobe of the pituitary, the following debated problems could be considered. 1) The presence of direct arterial blood supply to the anterior lobe. 2) The presence of anastomoses between the anterior and posterior hypophysial systems. 3) The presence of ARTERIAL connection with the hypothalamus either through the neural stalk or the pars tuberalis. 4) The direction of flow of blood to the anterior lobe.

DIRECT ARTERIAL BLOOD SUPPLY

Almost all the investigations, before Wislocki (1937a) modified the original view of the pituitary portal circulation of Popa and Fielding (1930, 1933), record that the arterial blood supply of the anterior lobe of the pituitary comes through the anterior (superior) hypophysial arteries arising mainly from the internal carotid on both sides. (Herring, 1908; Dandy

and Geottsch, 1910-1911; Parker, 1917; Fuchs, 1924;
Nikolskaia, 1929; Basir, 1932; Popa and Fielding, 1930;
and Brander, 1936). After the introduction of Wislocki's
(1937a) view, there are two views concerning the arterial
blood supply of the anterior lobe.

1. The anterior lobe of the pituitary appears completely
devoid of arterial blood supply and is served only by
portal blood. Green and Maxwell (1959) in a comparative
study of the innervation and blood supply of the pituitary
state that no vertebrate has been found in which the blood
supply to the anterior lobe and pars tuberalis does not
first come into relationship with the neurohypophysis.
Xuereb, Prichard and Daniel (1954) state that no branches
either of the anterior or posterior hypophysial arteries
supply the epithelial tissue of the pars distalis in
human pituitary. Daniel and Prichard (1956) in the
rat, and (1957) in the sheep, draw the conclusion that
the anterior lobe of the pituitary has no arterial blood
supply. Similar observations are recorded by Goldman
and Sapirstein (1962) who study the nature of the blood
supply of the rat pituitary by radioactive microsheres,
and by Cummings and Habel (1965) who study the vascular
supply of the bovine pituitary; no direct arterial
supply to the pars distalis is described.

2. The anterior lobe of the pituitary receives its
blood supply from the internal carotid along two different
routes; a negligible direct one, and a significant portal
one. (Wislocki, 1937, in cat and monkey; McConell, 1953,

and Stanfield, 1960, in man; Jewell, 1956, in sheep; and Landsmeer, 1951, in rat).

Some investigators define the branches of the anterior hypophysial artery (artery to the trabecula and its branches) through the substance of the anterior lobe, but they interpret them as portal vessels (Green and Harris, 1947, in the rat; Glydon, 1957, in the rat), while others state that they eventually supply the lower stem of the neural stalk (Xuereb, et al., 1954), but Landsmeer (1951) in the rat observes a large Artery "losing itself" among the large anterior lobe sinuses, and he interpretes it as the posterior hypophysial artery on its way to the neural lobe.

A direct arterial blood supply of the anterior lobe of the pituitary is present as the following evidence can support. 1) Anatomical observations of the presence of branches from the internal carotid artery running to the anterior lobe in fixed and cleared preparations. 2) The presence of anastomoses in the caudal portion of the anterior lobe between the branches of the generally accepted posterior hypophysial artery and those of the anterior hypophysial artery. 3) Green and Harris (1947) define clearly the presence of the artery to the pars tuberalis of the rat pituitary, and Landsmeer (1951) describes the artery going to the neural stalk of the rat, and the artery to the trabecula going to the anterior lobe is very clearly connected to those well defined arteries. 4) 'Espinasse (1934) in his detailed

study of the development of the vascular supply of the
human pituitary, states that an artery can be clearly
seen leaving the internal carotid, and within the core of
connective tissue, the artery enlarges to form the
sinusoids of the anterior lobe.   He concludes that these
vessels are a part of the arterial supply which has been
secondarily involved and enclosed by the growing gland.
5) The experimental evidence, stated before, the results
of which are compatible with the presence of a direct
arterial supply to the anterior lobe.   Daniel and
Prichard (1956), have applied a cautery to the neural
stalk of the rat pituitary to interrupt the portal
circulation, at different levels.   In every case there
are many regions of the anterior lobe (rostral poles,
lateral and dorsal borders, caudal area, a narrow rim
along the ventral surface) which survive the operation,
although they interpret the cause of the frequent
survival of the major part of the lobe, as "the inter-
mittent venous reflux into the sinusoids", "sufficient
diffusion of oxygen from the highly vascular dura mater
which overlies it", or to "minute connection with
capsular vessels which they have not seen".   None of
these suggestions seems adequate and none has been
demonstrated.

PRESENCE OF ANASTOMOSES BETWEEN ANTERIOR AND POSTERIOR
HYPOPHYSIAL SYSTEMS

Wislocki (1937a) in a developmental study of the

human pituitary states that the vascular pial mesenchyme
conveys a plexus of capillaries, venules and arterioles
(anterior hypophysial) to the hypophysial paranchyma, and
as the surface of the distal part of the neural lobe
becomes attached to the developing dura within the sella
turcica, the blood supply of the neural lobe is dural in
origin, and hence is essentially independent of the blood
supply of the pial origin reaching the neural stalk and
the buccal components of the pituitary. This view is
held by Green and Harris (1947) in the rat; McConell.
(1953) and Barrington (1963) in man; but morphological
and experimental evidence argues against this view, and
confirms the presence of a very rich anastomosis between
the anterior and posterior hypophysial systems. Fuchs
(1924) is the first to indicate the presence of the
anastomoses between the twigs of the anterior and posterior
hypophysial arteries. Later, Xuereb et al. (1954) record
that interarterial anastomoses are a characteristic
feature of the vascular arrangements of the human
pituitary, while Stanfield (1960) states that anastomoses
between anterior (superior) and posterior (inferior)
hypophysial artery systems occur in the fibrovascular
region in front of and lateral to the neural stalk,
Cummings and Habel (1965) observe branches from the
anterior (rostral) hypophysial artery joining branches
from the posterior (caudal) hypophysial artery within the
substance of the lower stem of the neural stalk of the
bovine pituitary. On the experimental side; Jewell
(1956) concludes that the blood reaching the neural lobe

via the posterior hypophysial artery, may readily flow
into the anterior lobe, and the blood passes via
anastomoses joining the vessels of the anterior part of
the neural lobe with vessels of the adjacent parts of the
pars distalis and pars tuberalis; these anastomoses
appear to form an additional vascular route other than
that afforded by the portal vessels whereby the neuro
and adenohypophysis are linked.   Holmes and Zuckerman
(1959) also record that vascular connections between the
neural process and the pars distalis are found in all
the animals examined.

VASCULAR CONNECTION BETWEEN THE PITUITARY AND THE HYPOTHALAMUS

Harris (1962) puts the view that the mammalian
system consists of small arterial twigs from the internal
carotid and posterior communicating arteries, which supply
a plexus lying between the pars tuberalis and the median
eminence.   Capillaries or sinusoids of varying shape and
size, often in the form of loops, arise from this plexus,
and penetrate into the nervous tissue of the median
eminence to form the primary plexus of the portal vessels,
and then drain by the large trunks of the portal vessels
which run down the pituitary stalk into the sinusoids of
the pars distalis.

Wislocki (1937b and 1938) states that in monkey
and cat the existence of large portal veins is unlikely

as the anastomoses between the vessels of the hypothalamus
and the neural stalk appear to be relatively small and
quite local in character, and the interior of the neural
stalk is relatively avascular in this zone.   In his
developmental study of the vascular supply of the human
pituitary, Wislocki (1937b and 1938) again states that
vascular connection between the gland and the hypothalamus
is almost exclusively of capillary dimension and of no
great importance, and he emphasises that the neural
stalk, in its interior, is relatively avascular as
compared with the extensive ingrowth of vessels into the
rest of the brain.   Wislocki (1937) concludes that study
of the adult and foetal material gives no evidence of the
presence of important vascular connections between the
neural stalk of the pituitary and the hypothalamus.
Landsmeer (1951) in the rat records a similar observation,
and Cummings and Habel (1965) find that the vascular
connection between the neural stalk of the bovine
pituitary and the hypothalamus is very slight.

Experimental data also argue against the presence
of a significant vascular connection between the
hypothalamus and the pituitary gland through the neural
stalk, as Mahoney and Sheehan (1936) find that obstruction
of the neural stalk of the monkey does not interfere with
the nourishment of the pituitary or with the discharge of
the pituitary hormones into the general circulation, and
Holmes and Zuckerman (1959) find that no effect seems to
occur in any part of the pars distalis when the neural

stalk is divided close to the median eminence.

The vascular connection between the hypothalamus and the pituitary through the pars tuberalis is questioned. Niemineva (1950) in an embryological study states that about the middle of the foetal period, the capillary tufts which penetrate into the region of the median eminence from the pars tuberalis are not demonstrable, and he concludes that if the hypothalamus regulates the function of the pars distalis by the neurovascular channels, this regulation cannot begin before the end of the foetal period. (see development of the functional activity of the pituitary). In the rat Landsmeer (1951) states that it is clear that the flow through the median eminence may be diminished without interfering with the blood supply of the anterior lobe, and it seems possible that the anterior lobe may be filled up without any contribution from the area of the median eminence. He concludes that no vascular connections of any importance have been discovered between the pituitary and the hypothalamus.

Although no vascular connection can be detected between the hypothalamus and the neural stalk, and no arterial connection between the pars tuberalis and the median eminence, nevertheless in the present study, a number of venous tributaries of considerable size can be detected running parallel to each other along the sides of the pars tuberalis from the hypothalamus. These unite to form a vessel which runs posteriorly to the anterior

pole of the anterior lobe of the gland where it becomes difficult to trace it further. It is therefore not known whether it drains through the tissue of the lobe or to its venous drainage. Landsmeer (1951) draws attention to those "true venous extensions in the median eminence" which are drained by the tuberal lobe, and he states that their significance remains obscure.

The pituitary complex thus seems to be an area with its own vascular organisation, and its different parts are united in an organ which in view of its vascular system can be looked upon as a whole, and is connected to the hypothalamus through a considerable venous connection between the tuberal and the median eminence, running towards the anterior lobe of the gland.

DIRECTION OF FLOW OF BLOOD TO ANTERIOR LOBE

Almost all the investigators record that all parts or lobes of the pituitary drain via hypophysial veins to the cavernous sinuses, but Popa and Fielding (1930) describe vessels running along the neural stalk which collect blood from both lobes of the pituitary and distribute it to the hypothalamus. Since that time, the view of the direction of the blood flow has been considered to be the chief argument. Wislocki (1937) finding no vascular connection between the neural stalk and the hypothalamus, in foetal and adult material, interprets these vessels as running from the neural stalk,

not the hypothalamus, to the anterior lobe through the pars tuberalis, and the direction of flow through them is in the direction of the anterior lobe. Wislocki (1937a) does not give evidence for the change in the direction of flow in the fixed material, but Green and Harris (1949) observe the direction of the flow of the blood through these vessels of the living rat, and state that these vessels are true portal vessels carrying the blood towards the anterior lobe of the gland.

The observation of the direction of the flow of the blood towards the pituitary is never an indication of the presence of portal veins; 1) It is clear from the present study, and similar observations, that the artery going to the anterior lobe runs from its origin from the anterior hypophysial artery at the angle between the neural stalk, and the forebrain vesicle, and the direction of the blood through these arteries is the same as that observed by Green and Harris (1949). 2) The present study observes the presence of a vein on each side of the tuberal lobe receiving tributaries from the median eminence and carrying the blood towards the anterior lobe of the gland, and the direction of blood through these venous channels is similar to that observed by Green and Harris (1949).

HYPOTHALAMO-HYPOPHYSIAL PORTAL SYSTEM

The hypothalamo-hypophysial portal system is a much debated anatomical entity. Popa and Fielding (1930, 1933) are the first to describe vessels running along the neural stalk, and placed between two sets of distribution i.e. the sinusoids of the pars distalis and the capillaries of the neural lobe on the one hand, and the secondary net in the hypothalamus on the other. These vessels are said to collect blood from both lobes of the pituitary and distribute it to the hypothalamus. Being doubtful of the nature of these vessels, Popa and Fielding (1930) state that they refer to them as veins because they carry the blood away from the blood vessels in the pituitary. This view is opposed by three groups of investigators. 1) That claims a change of the direction of flow of blood through these vessels. 2) That claims an absence of vascular connections between the neural stalk and the hypothalamus. 3) That studies the nature of these vessels.

The first group of investigators (Green and Harris, 1947, 1949; Green, 1948; Harris, 1960, 1962) observing the direction of the flow of the blood towards the anterior lobe in the living animal (rat), state that the mammalian system consists of small arterial twigs from the internal carotid artery and posterior communicating artery which supply a plexus lying between the pars tuberalis and the median eminence. Capillaries or sinusoids of varying shape and size often in the form of

loops from this plexus, penetrate into the nervous tissue of the median eminence to form the primary plexus of the portal vessels and then drain by the large trunks of the portal vessels which run down the neural stalk into the sinusoids of the pars distalis. Harris (1962) puts the view that the hypophysial portal vessels are anatomically so disposed that they form the basis of a connecting link between the central nervous system and pars distalis.

The second group of investigators, the largest, (Wislocki, 1937a; McConell, 1953; Wislocki and Geiling, 1936; Daniel and Prichard, 1956, 1957; Xuereb, Prichard and Daniel, 1954a; Stanfield, 1960, and Cummings and Habel, 1965), observing no vascular connection between the neural stalk and the median eminence, and being convinced that experimental interruption of the neural stalk close to the median eminence has no effect on the anterior lobe, claims that the first set of capillaries is present in the neural stalk itself (and sometimes neural lobe) and not in the hypothalamus, and the portal vessels run along the neural stalk (through the pars tuberalis, Wislocki, 1937a) to the anterior lobe where they enter the sinusoids. Wislocki (1937) states that in the monkey there is a rich plexiform layer of capillaries lying in the part of the pars tuberalis covering the neural stalk, and that that plexus is coextensive with the pars tuberalis, but does not extend onto or into the surrounding tuber cinereum adjoining the attachment of the stalk to the base of the brain.

Wislocki (1937) concludes that the study of the adult and foetal material gives no evidence of the presence of important venous connections between the stalk and the hypothalamus.

The nature of the portal vessels is not clearly defined by the above two groups of investigators. In the adult monkey Wislocki (1937) states that small vessels, APPARENTLY venules, arise from this plexus (between stalk and pars tuberalis) and are interpreted as portal veins, while in the developmental study he (Wislocki, 1937) states that he cannot ascertain directly from the foetal stages at his disposal how the portal venules arise.

The third group of investigators ('Espinasse, 1934) studying the nature of the portal vessels during development of the pituitary, concludes that the hypothalamo-hypophysial portal vessels are a part of the ARTERIAL supply, which has been secondarily involved and enclosed by the growing gland, and as the neural stalk lengthens during development, the vessels assume their distinctive form.

The present study is in accord with the first view as regards the direction of the flow of the blood towards the anterior lobe (see above; direction of flow ...), with the second view as regards the absence of the vascular connection between the neural stalk and the median eminence (see above; vascular connection with the hypothalamus...), and with the third view as regards

the arterial nature of the vessels which are a part of
the arterial supply of the gland (see above; arterial
supply of the anterior lobe).

The analogy of the hepatic portal vein does not
help to make the presence of the pituitary portal system
clear, since, firstly there is a pre-existing vein
appropriated by the developing liver and continuing after-
wards as a vein. Secondly, the liver has its own
arterial blood supply and is not entirely dependent on
the portal vessels as is suggested (Xuereb, et al. 1954;
Daniel and Prichard, 1956, 1957; Green and Maxwell, 1959;
Goldman and Sapirstein, 1962; Cummings and Habel, 1965;
and others) in the case of the anterior lobe of the
pituitary.

Developmental evidence argues against the presence
of hypothalamic control of the pituitary functions
through the hypothalamohypophysial portal system; the
capillary tufts essential to the portal system which
penetrate from the sinusoids of the pars tuberalis into
the region of the median eminence and the neural stalk
are not demonstrable in man except towards the end of the
foetal life (Niemineva, 1950) and in the rat at the fifth
day after birth (Glydon, 1957 and Campbell, 1966), but
there is an early involvement of the hypophysis in the
hormonal function at least from the third month of human
embryonic life (Falin, 1961) and of the rat a long time
before birth (Phillips and Schmidt, 1959). Recently,
Bearn (1967) on an experimental basis, states that,

although the hypophysial portal system is already established in the rabbit foetus, "the functional development of the rabbit foetal pituitary (in respect of liver glycogen deposition), is not dependent on the foetal hypothalamus".

The foetal hypophysial activities (thyrotropic, adrenocorticotropic, ..) are independent of hormones from the maternal hypophysis or from the placenta (Hwang and Wells, 1959).

It can be stated, at least in the rat, that the vascular supply of the pituitary is an independent entity, connected to the hypothalamus via venous tributaries running, through the tuberal lobe, to the anterior lobe of the gland, which may act as a "connecting link" between the central nervous system and the anterior lobe of the gland (when it becomes certain that they drain through the tissue of the anterior lobe), in a similar way to the portal link described by Harris (1962).

1. The pituitary gland of the albino rat is of ectodermal origin.

2. Rathke's pouch appears, at the 10½ day stage, partly as an active evagination of the roof of the stomadeum, initiated by the presence of the neuroectodermal contact (between neural tube and surface ectoderm), and brought about by active proliferation of the stomadeal cells. The pouch, most probably, is limited posteriorly by the presence of the developing cephalic end of the notochord, and is dependent in its further morphogenesis on the growth of the head region.

S U M M A R Y

The development of the neural lobe is not a

and

completely passive process and the neural evagination

C O N C L U S I O N S

develops, at the 11½ day stage, as an active outpouching of the floor of the forebrain vesicle.

1. Analysis of the mechanics underlying morphogenesis, rotation, and change of the direction of the long axis of the gland, shows that the pouch does not undergo any rotation, but it is compressed as its growth in the dorsoventral direction is hindered by the following factors: a. Intrinsic; 1) The rapid growth of the basal portion of the anterior wall of the pouch, and 2) The marked increase in the size of the neural lobe invaginating the dorsal portion of the original posterior wall of the pouch, which is in contact with it. b. Extrinsic; The reduction of the dorsoventral diameter

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b. Extrinsic; The reduction of the dorsoventral diameter

of the confined triangular area available for the growth
of the pouch (bounded by the roof of the stomadeum on one
side, and the angle between the neural lobe and the
forebrain vesicle on the other), and this is brought
about by; 1) Laying down of thick cartilage in the
ventral zone of the confined area. 2) An increase in the
volume of the tissue between the basal cartilage and the
roof of the stomadeum, and 3) The opening out of the
cephalic flexure (forward reorientation of the forebrain
vesicle).

4. The epithelial pituitary stalk connecting the basal
portion of the pouch to the roof of the stomadeum, in
the midline, becomes solid at the $14\frac{1}{2}$ day stage due to
the growth of the surrounding mesenchyme. This
connection is interrupted, usually, at the $17\frac{1}{2}$ day stage,
nearer to the stomadeum than to the gland, by the
appearance of cavities or vacuoles within its substance.
Its remnants are found in the craniopharyngeal canal,
the tissues between the roof of the stomadeum and the
basal cartilage, and are connected to the roof of the
stomadeum. The stomdeal connection represents the
pharyngeal hypophysis. At birth, neither the remnants
of the epithelial stalk nor the pharyngeal hypophysis
can be detected in the rat. The anterodorsal growth of
both the basal portion of the pouch and the prospective
pars tuberalis connected to the expanded dorsal end of
the epithelial stalk, carries this connection antero-

dorsally with no migration on the part of the epithelial stalk.

5. The craniopharyngeal canal in the basisphenoid cartilage (bone), through which the epithelial stalk of the pituitary (or its remnants) passes, persists after birth with reduced anteroposterior and lateral dimensions.

6. After the epithelial stalk of the pituitary becomes a solid structure, the original cavity of Rathke's pouch known as the residual cavity, conforms to the shape of the gland.   In late prenatal life, due to the extensive growth of the lateral walls of the pouch, the residual cavity becomes restricted in the intermediate region of the gland.   The cavity has an L shape in sagittal sections.   At birth the cavity keeps its shape and width similar to that before birth with no obliteration of any of its regions.   The epithelial cells lining the cavity keep the stratified character and no cilia can be detected.

7. The pars tuberalis appears at the $13\frac{1}{2}$ day stage as a slight ridge like outgrowth of the basal portion of the anterior wall of the pouch, in the midline and not as two lateral processes.   This outgrowth is connected to the epithelial stalk of the pituitary.   It grows anterodorsally forming a tongue like process which leaves an intraglandular fossa filled with vascular mesenchyme,

between it and the anterior aspect of the pouch. At the 16½ day stage, the pars tuberalis, coming in close proximity with the posteroventral wall of the forebrain vesicle, changes its direction by folding on itself and forming a dorsally directed knee like bend, it then grows further forward along the inferior surface of the forebrain. The anterior portion beyond this bend is the "anterior horn" of the pars tuberalis which is elongated along the inferior aspect of the forebrain but shows no bifurcation at any stage of development. The dorsal bend, applied to the ventral aspect of the neural stalk, gives the "dorsal horns" on the lateral aspects of the stalk at the 19½ day stage. These extend onto the dorsum of the stalk by birth, but have not fused in the midline on the dorsal aspect by the onset of sexual maturity in the animal, i.e. no collar is formed around the neural stalk. The pars tuberalis is formed of small rounded cells which show an alveolar or tubular arrangement, and is enclosed in its own part of the envelope of the undifferentiated mesenchyme which surrounds the whole gland, and not in the membranes of the forebrain.

8. The anterior wall of Rathke's pouch gives rise to the main body of the anterior lobe. At the 13½ day stage, two dorsolateral outgrowths of the basal portion of this wall, one on each side of the midline are observed, and other similar two dorsal outgrowths appear at the 15½

day stage. All these outgrowths, formed of small round cells, grow extensively and involve the whole anterior wall of the pouch. They are later infiltrated by the surrounding vascular mesenchyme forming the connective tissue stroma between the glandular cells of the lobe which show an alveolar arrangement. The original parts of these outgrowths which form the main bulk of the anterior lobe of the gland, can be easily detected. In the late prenatal stages the anterior lobe is greatly flattened dorsoventrally.

9. The pars intermedia can be defined very early as the area of the fundus of the pouch (initial area of neuro-ectodermal contact) in contact with the developing neural evagination, and is later, at the $13\frac{1}{2}$ day stage, incorporated in the original posterior wall of the pouch forming its dorsal portion. It retains the same thick-ness as at the $14\frac{1}{2}$ day stage even after birth. At the $16\frac{1}{2}$ day stage, multiple knob like outgrowths arise from the posterior aspect of the original posterior wall of the pouch along the lateral aspects of the base of the neural lobe. These cells are rich in mitotic figures, later attain an alveolar appearance, and develop in the midline in contact with the neural lobe. In the substance of the pars intermedia they form light areas of rounded or ovoid cells arranged in an alveolar manner, while the remaining dark cells of the pars intermedia consist of clumps of slender elongated cells with some rounded cells between them. These lightly stained

groups of cells give the intermedia the appearance that
it consists of dark and light areas.

10.   The neural lobe appears at the $11\frac{1}{2}$ day stage, as a
hollow evagination with a central cavity lined by tall
ependymal cells similar to the neighbouring cells of the
forebrain vesicle.   At the $13\frac{1}{2}$ day stage, it becomes a
solid mass of small rounded or ovoid cells divided into
lobules by connective tissue septa from the surrounding
mesenchyme, and its lumen becomes restricted to the
proximal portion.   The neural lobe (neural process)
develops a short neck at the $16\frac{1}{2}$ day stage, which
becomes elongated, and its surface is composed on all
its aspects of what appears to be a layer of nerve fibers
running to the neural lobe.   On the dorsal surface the
nerve fiber layer is thinner than on the ventral surface
and this gives the neck of the neural lobe its eccentric
appearance.   If the nerve tracts are followed to the
brain, the dorsal fibers appear to arise, most probably,
from the paraventricular nuclei, while the ventral fibers
seem to come, most probably, from the supraoptic nuclei.
These nerve tracts are filled with glial cells which show
some mitotic figures.

The components of the neural lobe of the rat
pituitary, at birth and in early postnatal life, are;
the original tall ependymal cells lining the cavity of
the neural evagination (modified, small ovoid cells,
"pituicytes"), original connective tissue elements from

the process of development and in the walls of the blood vessels (fibroblasts, fibrocytes, and fibers), glial cells among the nerve axons, nerve fibers, and blood vessels with their capillaries. No epithelial cells from the intermedia can be observed, and neither nerve cells, nor Herring bodies are visible in the developing neural lobe. The angle between the neural lobe and the forebrain undergoes a series of changes which are recorded and their significance in the morphogenesis of the pituitary is discussed. The theories concerning the function of the neural lobe are recollected, and further investigations are required to solve this problem.

At first the neural lobe is in contact with the pars intermedia, but at the $15\frac{1}{2}$ day stage a layer of the surrounding undifferentiated mesenchyme has grown between them.

11. The epithelial cells of Rathke's pouch divide rapidly, and very frequently show mitotic figures in the early stages of prenatal life up to and including the $16\frac{1}{2}$ day stage, after which the gland shows a relative reduction in the number of the mitotic figures which progresses steadily till birth. The neural lobe shows mitotic activity to a lesser extent than the pouch. The role played by mitosis in the morphogenesis of the gland has been considered.

12. Application of differential cytological methods indicates the presence of faintly stained, finely

distributed granules in the cells of the pouch, specially those arranged close to the cavity of the pouch and those forming the outgrowths of the pouch of the pituitary of $14\frac{1}{2}$ day stage.   In late prenatal life, and at birth, the cells of the dark groups of the pars intermedia suggest thyrotrophic type, while the cells of the light groups appear to be acidophils.

It is suggested that the pars intermedia of the rat in late prenatal life and at birth, may have the ability (as has the anterior lobe) to secrete thyrotrophic and growth hormones.

13.   The total volume of the pituitary gland at birth is $0 \cdot 1765$ m.m.^{3}.   The calculated relative volumes of the lobes of the pituitary gland of the rat in late prenatal life and at birth are as follows: The anterior lobe (including the pars tuberalis), $75 \cdot 5\%$;   the intermediate lobe, 11%;   and the neural lobe is $13 \cdot 5\%$ of the total volume of the gland.

14.   The cephalic end of the notochord is bifurcated into ascending and descending branches.   The descending branch runs ventrally to a slight evagination of the roof of the stomadeum caudal to Rathke's pouch.   This represents the remains of Seessel's pouch which later becomes a mere thickening of the epithelium, and when the basal cartilage is laid down, the descending branch of the notochord passes through it, sometimes in a special

canal similar but caudal to the craniopharyngeal canal
through which the epithelial stalk of the pituitary
passes.   The ascending branch is formed of horizontal
and anterodorsally directed portions.   The latter comes
close to the posterior wall of the pouch, sometimes
indenting it, but no actual fusion can be demonstrated;
and later the mesenchymal envelope around the cells of
the notochord becomes more clear and evident.   The
anterodorsal portion disappears earlier than the
horizontal one.   Caudal to its bifurcation, the notochord
rests on the dorsum of the caudal part of the basal
cartilage, and is embedded for a short course in its
substance, near its superior aspect.   At birth no
remnants of the notochord can be detected.   The notochord
plays no part in the development of the pituitary and
never acquires actual contact with it, though it may
passively act as a barrier to the backward growth of the
pouch.

15. Application of various silver impregnation methods
does not reveal the presence of nerve fibers within the
epithelial components of the rat pituitary either in pre-
natal life or at birth.

16. Embryological study of the membranes around the
pituitary shows that its neural and epithelial components
are located in a triangular mass of undifferentiated
mesenchyme, bounded by condensed mesenchymal margins and
the perichondrium of the cranial base, and connected to

the dura mater surrounding the posterior aspect of the forebrain vesicles at two sites: 1) the apex of the triangular mass, and 2) around the connection of the neural stalk to the forebrain vesicle. No differentiation takes place in the loose mesenchyme around the pituitary gland, and the three membranes which develop around the brain are not formed. Thus, the pia-archnoid, and subdural and subarchnoid spaces do not differentiate at any time during the development of the pituitary, and the membranes and spaces do not extend towards the gland beyond, the junction of the neural stalk with the forebrain vesicle, and the apex of the triangular mass of the undifferentiated mesenchyme with the dura mater. The undifferentiated mesenchyme forms a capsule for the entire circumference of the body of the gland covering the outer surfaces of the adeno and neurohypophysis and extending between them. The mesenchyme around the gland gives rise to an external lamina of condensed mesoderm with an inner zone of loose connective tissue. The core of tissue in the intra-glandular fossa is of undifferentiated mesenchyme, and the blood vessels in it cannot be looked upon as pial derivatives for this reason and because it lies external to the dura mater. Also the later vascular connective tissue infiltration of the glandular tissue cannot be considered as part of the pia mater for the same reasons. The tuberal process of the pituitary gland lies in the surrounding undifferentiated mesenchyme and when it

extends forwards anterior to the remainder of the gland, it carries with it its own envelope of the undifferentiated mesenchyme, which later blends with the adjacent dura of the brain.

17.   The intercavernous portion of the internal carotid artery gives, on each side, two main branches to supply the pituitary; the anterior (superior) and the posterior (inferior) hypophysial arteries. The posterior artery supplies the main caudal portion of the neural lobe, the most caudal region of the anterior lobe, and sends an interlobar branch between the caudal portions of the neuro and adenohypophysis. The anterior artery, in Atwell's recess, gives branches to; 1) the neural stalk supplying it and the rostral portion of the neural lobe, 2) along the dorsal aspect of the pars tuberalis, supplying it, but not the tuber cinereum, 3) an inter-lobar branch between the rostral portions of the adeno and neurohypophysis, and 4) a large "artery to the trabecula" branch which runs anteroposteriorly to supply, with its two offshoots, the main rostral portion of the anterior lobe of the gland.

The branches of the anterior and posterior systems anastomose freely, giving the gland the sense of a vascular unit.

The interlobar branches contribute to the neural lobe vascular network. The vascular network of the neural process is similar to that of the stalk and pars

tuberalis, but more rich and fine than the coarse one of the anterior lobe. The pars intermedia is nearly avascular. Small slender capsular arteries which arise from the internal carotid and posterior communicating arteries are detected and traced within the capsule of the gland. The blood is drained from the gland via posterior and anterior veins which follow the course of the corresponding arteries to the cavernous sinuses.

A number of venous tributaries of considerable size, running parallel to each other along the sides of the pars tuberalis from the hypothalamus, unite to form a vessel which runs posteriorly along the ventrolateral aspect of the pars tuberalis to the anterior pole of the anterior lobe, where it becomes difficult to trace it further. The vascular supply of the pituitary is an independent entity, connected to the hypothalamus (only) via venous tributaries running through the tuberal lobe, to the anterior lobe of the gland, which may act as a connecting link between the central nervous system and the anterior lobe of the gland.

18. The direction of flow of the blood within the "artery to the trabecula" and its branches which supply the sinusoids of the anterior lobe, and also within the venous channel collecting blood from the tributaries of the median eminence along the sides of the pars tuberalis, is towards the anterior lobe, i.e. from anterior to caudoventral destination, similar to that direction observed by Green and Harris (1949) in the living rat.

19.   No hypothalamo-hypophysial portal system
(described by Green and Harris, 1947) has been seen, in
the rat, and the nature of the portal circulation is
discussed.

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