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THE DEVELOPMENT OF THE HYPOPHYSIS CEREBRI OF THE RABBIT (LEPUS CUNICULUS L.)

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THIRTY-NINE FIGURES

CONTENTS

1. INTRODUCTION

Notwithstanding the numerous studies to which the hypophysis has been subjected, many of its deeper problems remain unsolved. Few investigators have confined themselves to the

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development of the gland in a single species. This is due, no doubt, to the alluring possibilities in broad comparative studies. As a consequence, many sweeping and unwarranted conclusions have been drawn from insufficient observations, or from observations on a few specimens in widely different vertebrate classes.

The recent recognition of a distinctive third epithelial portion of the gland lying under the membranes of the brain in the region of the tuber cinereum—the 'pars tuberalis' of Tilney ('13)—and the as yet imperfect appreciation of its interesting development, make careful ontogenetic studies highly desirable as the basis for phylogenetic comparisons.

The work which forms the basis of the present paper was undertaken in an attempt to trace the development of the hypophysis with reasonable completeness in a single mammal. To this end the rabbit (Lepus cuniculus L.) was chosen, since this animal breeds well in confined quarters, has a short gestation period, and brings forth its young in large litters. These factors combine to make possible the collection of the carefully timed embryological material so essential to chronological studies in development.

This study will treat particularly of the morphogenesis of the hypophysis from the time of its appearance until birth, giving especial attention to the ontogeny of the 'pars tuberalis' and to the development of the neural lobe; it will deal also with the differentiated histological structure of the three parts of the epithelial hypophysis at the time of birth, and finally will attempt to relate certain of the author's observations to those of other investigators.

I desire to express my sincere thanks to Professor Huber for his continued interest in this work, for his very material assistance in overcoming technical difficulties, and for the unstinting way in which he has placed the excellent facilities of the anatomical laboratories at my disposal. My wife has given valuable aid in much of the tedious work connected with the construction of the wax models.

2. REVIEW OF LITERATURE

A. Special questions concerned with the development of the hypophysis

1. Entodermal origin. An endless chain of discussion has been evoked by the question as to whether the epithelial hypophysis is derived from the entoderm or from the ectoderm, or whether it is compounded of elements derived from both of these germ layers. Since the time of Goette ('74), Balfour ('74), and Mihalkovics ('75), only a few authors have maintained that this portion of the gland is developed from entoderm alone. There have been many, however, to state that the primary ectodermal anlage is later augmented by a larger or smaller contribution from the entoderm.

Hoffman ('86) and Ostroumoff ('88) believe the hypophysis in certain reptiles to be entodermal in origin. Kupffer ('94) describes a growth from the cephalic end of the foregut to meet the dorsal wall of Rathke's pocket. This he interprets as an attempted recurrence of a primitive pre-oral mouth or 'paleostoma.' This suggestion of Kupffer's has caused many writers to attach great phylogenetic importance to the hypophysis. Furthermore, according to Kupffer, the entoderm makes important contributions to the epithelial lobe of the hypophysis.

In a previous paper (Atwell, '15) reference was made to the observations of Saint-Remy ('95), Valenti ('95 a, '95 b, and '97), Nusbaum ('96), and of Bruni ('14), according to all of whom the entoderm of the pouch-like cephalic extremity of the foregut ('Seessel's pouch') fuses with the ectodermal hypophysial anlage and possibly contributes a few cells to it.

Orrù ('00) divides the glandular portion of the hypophysis of Gongylus ocellatus into two lobes, one of which is in relation to the infundibular process, while the other lies ventral to the first. Although he cannot trace a difference histologically in these two lobes, he believes it very probable that the dorsal lobe, which lies close to the infundibular process is entodermal and that the ventral lobe is ectodermal.

A considerable portion of the controversy concerning the entodermal origin of the glandular part of the hypophysis has centered about the Ganoid, Amia calva. Dean ('96) holds that in this fish the hypophysis is ectodermal. Reighard ('00) states that the Amian hypophysis is developed entirely from ectoderm, while Prather ('00) states that it is entirely from entoderm. Gregory ('02) cannot agree with Prather and believes that this part of the hypophysis is both ectodermal and entodermal.

Reighard and Mast ('08) have presented the most conclusive observations for this form. They find that the hypophysis of Amia is ectodermal in origin. They show that Prather was in error, 1) from a lack of the early stages which show a connection of the hypophysis anlage with the mother ectoderm, and, 2) because of imperfect fixation which failed to bring out the line of separation between the hypophysis and the entoderm.

P. E. Smith ('14) has reopened the problem and comes to the conclusion that the anlage is ectodermal, but adds that "it can be said with considerable probability that the entoderm contributes to the composition of the hypophysis."

Atwell ('15) saw the epithelial connection between Seessel's and Rathke's pouches in the chick much as described by Saint Remy, Valenti and Bruni. He adds the observation that the entodermal bud which forms the connecting strand has constantly in relation to it the cephalic extremity of the notochord, both before and after the ecto-entodermal fusion has formed. The entodermal strand loses its connection with Seessel's pouch and becomes incorporated into the dorsal wall of Rathke's pouch. A relationship was noted between the anterior end of the notochord and a small entodermal bud in rabbit embyros, but it could not be shown that any entoderm fuses with the hypophysis anlage in this mammal.

It is to be noted that while the above-mentioned investigators believe that entoderm enters into the formation of the hypophysis, the majority of them freely admit that the main portion of the gland is ectodermal. The only one in recent years to claim that a considerable portion of the definitive mammalian hypophysis is derived from the entoderm is Miller ('16). This author, who studied the hypophysis of the pig (Sus scrofa) has noted that "the notochord pulls away from the pharynx carrying with it a mass of cells (entoderm)," which later becomes fused with the ectodermal anlage. This is much as described by Atwell for the chick. However, Miller further maintains that this entodermal component 'rotates anteriorly and superiorly,' becomes encapsulated by growth of the 'lateral cords,' and forms the medulla of the anterior lobe. The cells supposed to be derived from the entoderm have a different histological appearance from those derived from the ectoderm.

P. E. Smith ('16), likewise B. M. Allen ('16, '17), has removed the glandular ectodermal anlage from young larvae of the frog. In successfully operated animals, the anterior lobe was entirely lacking. Smith concludes that

> this apparently demonstrates conclusively that the entoderm has not the intrinsic power to form a hypophysis. If it enters into the formation of the gland at all, it must be considered as a tissue inclusion which becomes changed through its adaptability into glandular parenchyma, a conclusion previously drawn by the writer, Smith ('14).

2. The relation of the notochord to the hypophysis. The close proximity of the cephalic extremity of the chorda to the hypophysial anlage has been taken by many to be significant of some influence the chorda may exert on the developing gland.

Koelliker ('79) has noted in a rabbit embryo of eleven days a close relation between the anterior end of the notochord and an outgrowth from the inferior part of the dorsal wall of the hypophysis.

In the Normentafel of the rabbit's development Minot and Taylor ('05) note a "distinct connection between notochord and hypophysis" in both ten-and-one-half-day and eleven-day embryos (Nos. 11 and 12). This connection apparently had disappeared entirely by eleven and one-half days of development.

Woerdeman ('13), observing embryos of Sus scrofa corresponding in age to Nos. 71 and 78 in Keibel's Normentafel, has seen a true contact between the chorda and the dorsal wall of Rathke's pocket. He believes that he is justified in calling it a true contact because at the place of union there is no membrana propria intervening between the two structures; at this place there is a very noticeable thickening of the dorsal wall of Rathke's pocket, and the arrangement of the nuclei is very irregular.

The observations of Atwell ('15) and of Miller ('16) have been given in the previous section in treating of the entodermal origin of a portion of the hypophysis.

Baumgartner ('16) studied turtle embryos of various ages and found that the notochord is usually in direct contact with the caudal surface of Rathke's pouch. In a 4.5-mm. embryo he saw a dorsal projection from near the base of the pouch to which the end of the notochord is applied.

Parker ('17), in a study of the hypophysis region of the Marsupials, states,

> The relation of the chorda to the hypophysis is purely secondary, and my own observations lend not the slightest support to the view of Miller that the notochord makes a considerable contribution to the developing hypophysis.

She believes that the anterior end of the notochord is early in relation to the protochordal plate and that the connection often seen between the notochord and the hypophysis is effected by this plate or by a bridge connecting the premandibular somites. Of these latter traces were found in young marsupial embryos.

3. The lobes of the hypophysis. a) General. It has long been customary to consider the hypophysis as composed of two parts. One, known as the anterior lobe, is that portion derived from the ectodermal mouth invagination—and, according to certain authors, augmented by addition from the entoderm. The other, known as the posterior lobe, is that part developed from an outgrowth of the floor of the third ventricle of the brain. This usage is still common in modern text-books of anatomy and embryology. That it is entirely inadequate for the description of the gland from either an embryologic or histologic view-point will become evident from the discussion which is to follow.

Peremeschko ('67) studied the hypophysis of a number of domestic animals and of man. He notes the existence of a cleft ('Kanal') in the epithelial portion of the gland which divides it into two unequal parts—one, the 'Korkschicht,' and the other, the 'Markschicht.' The former is the main body of the epithelial lobe, while the latter is a thin lamina closely applied to the neural lobe. These two portions are also characterized by differences in histological appearance. The cells of the 'Markschicht' are poorer in protoplasm, have clearer nuclei, and are not easily changed by reagents.

Lothringer ('86) notes this intraglandular cleft and agrees with Peremeschko that it is not the separation between epithelial and brain parts. Instead, it separates the 'Epithelsaum' from the 'Epithelkörper.' The former corresponds to Peremeschko's 'Markschicht' and the latter to his 'Korkschicht.'

Herring ('08b) speaks of the epithelial investment of the neural lobe as the 'pars intermedia' obviously because of its position between the neural lobe and the remainder of the epithelial lobe, 'the anterior lobe proper.' Pars intermedia and anterior lobe proper are separated by the residual lumen of Rathke's pocket.

Stendell ('13) calls these two divisions of the anterior lobe the 'Zwischenlappen' and the 'Hauptlappen,' respectively. The residual lumen he knows as the 'Hypophysenhöhle.'

All of these writers take pains to emphasize the fact that the 'pars intermedia' is inseparably bound to the neural lobe. This is particularly evident when an attempt has been made to mechanically separate the so-called anterior and posterior lobes. Almost invariably a thin epithelial layer, the 'pars intermedia,' is found to have remained adherent to the neural lobe.

b) The anterior process. W. Müller ('71) describes for 16- and 18-cm. human, sheep, and pig embryos an anterior process of the hypophysis. His description reads: "Erstreckte sich ein schmaler, conisch sich verjüngender Fortsatz längs der vorderen Fläche des Processus infundibuli nach oben und vorn gegen das Chiasma hin."

Mihalkovics ('75) observed the formation of an anterior process during the development of the hypophysis in the rabbit. In an embryo 2 cm. in length the epithelium of the inferior part of the hypophysial sac, at the place where the stalk is attached grows forward and upward as a solid process. Continuing, Mihalkovics' own words are: "Bei Säugetieren biegt sich zuerst der untere Teil des Säckchens etwas nach vorn und aufwärts um und wächst zu einem soliden Fortsatz aus."

Kraushaar ('85) treats of the development of the hypophysis in the Rodents. His descriptions are mainly of Mus musculus. He notes an anterior process of the developing hypophysis and speaks of it in these words: "Gegen das Chiasma hin entsendet die Hypophysis einen schmalen, soliden Fortsatz."

Lothringer ('86), in describing the hypophysis of the adult dog, names that portion of the gland where 'Epithelsaum' and 'Epithelkörper' are bound together the 'Umschlagstheil.' This 'Umschlagstheil' borders the brain substance very closely. He notices that "eine schmale Fortsetzung desselben breitet sich an der Unterfläche des Tuber cinereum aus, bis wohin vermochten wir, da wir stets an vom Gehirn getrennten Organen untersuchten, nicht mit Sicherheit festzustellen." He pictures this process and labels it "Fortsatz des Epithelsaums auf den Trichter."

Haller ('97), describing the mouse, speaks of a thin part of the hypophysis which extends forward and is closely applied to the brain wall. This 'vorderer Lappen,' as he calls it, pours its secretion into the subdural space. This last statement has not been verified by subsequent observers. In '09, Haller saw a 'vorderer Fortsatz' in Erinaceus, Mustela, and Vesperugo noctula, and mentions the structure again ('10) in describing embryos of the mouse and of the roe.

Salzer ('98) figures and describes a solid anterior process which consists of glandular substance and which extends toward the optic chiasm. He also speaks of a plate-like part which lies ventral to the main body of the hypophysis. Woerdeman ('14) has interpreted this 'Platte' as the remains of the hypophysial stalk.

Grönberg ('01) studied the development of the brain and its appendages in Erinaceus europaeus. He considers the hypophysis only secondarily, but he thinks noteworthy a process which the hypophysis sends forward almost to the middle of the chiasm. Transverse sections show this process to be a broad horizontal plate. It grows forward from the place of attachment of the hypophysial stalk.

Joris ('07) saw in the meninges of the brain a mass of glandular cells which is attached at the anterior end of the hypophysis. This cell mass extends from the optic chiasm to the base of the infundibulum and divides into two diverging branches. These make an angle, open posteriorly, embracing the neck of the infundibulum. To this cell mass Joris gave the name of 'lobule de la tige.' He believed that it becomes united with the hypophysis secondarily.

Staderini ('08) describes somewhat similar relations and speaks of a 'lobus chiasmaticus' which extends forward and of a 'lobus praemammillaris' the cells of which are within the brain coverings and surround the infundibular neck.

Herring ('08a) describes and figures a lobe which he names the "tongue-like process of the pars intermedia." It extends forward and is closely applied to the brain wall. He notes that this part is more vascular than the 'pars intermedia.'

Bolk ('10) speaks of a 'lobulus bifurcatus' in primate embryos. The two arms of the lobe embrace the infundibulum near its attachment to the brain. Bolk believes that this 'lobulus bifurcatus' becomes detached to form the cell masses found embedded in the meninges.

Tilney ('13) differentiates histologically three portions of the glandular hypophysis in birds and mammal. His 'pars distalis' and 'pars infundibularis' correspond to the 'anterior lobe proper' and the 'pars intermedia' of Herring, respectively. The 'pars tuberalis' is closely applied to the tuber cinereum and extends foward toward the optic chiasm. Tilney believed that he was presenting the histological structure of a "hitherto undescribed portion of the hypophysis." Woerdeman ('14) points out that the 'lobule de la tige' of Joris, Standerini's 'lobus praemammilaris' and 'lobus chiasmaticus,' and Bolk's 'lobulus bifurcatus' are without doubt the same structure as Tilney's 'pars tuberalis.' Baumgartner ('16) expresses himself as in accord with this view of Woerdeman's. Tilney's account of the development of the 'pars tuberalis' will be referred to later.

c) The lateral lobes. Gaupp ('93) states that the hypophysis of the lizard has a three-fold anlage—a large round 'Mittelknospe' and two long 'Lateralknospen' which bud out from the mouth epithelium. These parts are separated by a venous ring. Later there appears a fourth part anterior to the 'Mittelknospe,' the 'Vordere Knospe.' The two lateral buds first unite with the gland and later separate as solid bodies. They attach themselves closely to the brain floor. It seems that they are present in the adult animal, but further observation is required to establish this point.

Chiarugi ('94) notes two epithelial strands in Cavia cobaya located at the place where the hypophysis is constricted off from the epithelium of the mouth. He believes that these are homologous to the 'Lateralknospen' of Gaupp.

Weber ('98) saw, in Chiroptera, a tripartite hypophysis fundament. He does not hold, as does Gaupp, that these three parts are separate at the beginning. Rather, a single anlage early differentiates into two 'bourrelets lateraux' and a 'crete mediane.'

Rossi ('96) describes a median part and two lateral parts for the hypophysis of the chick.

Nusbaum ('98) (referred to by Woerdeman, '14) states that the hypophysis develops from two sources, namely, from an unpaired out-pouching of mouth epithelium and from a pair of epithelial thickenings derived from the primitive gut.

Economo ('99) speaks of two 'Seitensprossen' to be seen during the development of the hypophysis in doves and chicks. In dove embryos the buds, or sprouts, appear between the fourth and seventh days. They are said to be arranged on each side of the infundibular process. During a part of their development they possess lumina which communicate with the hypophysis cavity. He notes a similarity to Gaupp's observations on the Reptiles.

Standerini ('03) traces the developing hypophysis in reptiles. The anlage is simple, but later the gland consists of a median part and two lateral parts.

Bolk ('10) describes an hypophysial anlage of three divisions in young embryos of Macacus cynomolgus.

Tilney ('11) observed in Aspidonectes two accessory pouches which arise from the main oral evagination. He believed that the importance of these and similar accessory pouches has been exaggerated, "since it is a common tendency in many forms for the anlage of the gland to present multiple diverticula."

Bruni ('13) noted that in the Sauropsida Rathke's pouch is early differentiated into a single 'lobo medio' and two 'lobi laterali.' In mammals the lateral lobes appear much later.

d) The relation of the lateral lobes to the 'pars tuberalis.' Gisi ('07), in a dissertation treating of the brain of Hatteria punctata, speaks of a thin anterior process of the hypophysis which is termed the 'pars terminalis.' Of this part it is stated: "Wahrscheinlich ist diese Pars terminalis der Hypophyse das Endproduct der seiten Knospen an den früheren Embryonalstadien."

Herring ('08 a) speaks only briefly concerning the development of his "tongue-like process of the pars intermedia." He says:

> The anterior lobe also grows forward and laterally. The neck of the sac retains a tubular character for some time, and becomes somewhat convoluted. One of these convolutions (fig. 5, *k*) applies itself to the under surface of the brain and gives rise to the tongue-shaped process which extends forwards from the anterior lobe towards the optic chiasma.

To Tilney ('13) must be given the credit for first clearly showing that the 'pars tuberalis' has its origin from two lateral buds. Tilney has traced the development of the 'pars tuberalis' in the cat and in the chick. It

> arises as a relatively late structure. It has its origin in two secondary diverticula or sprouts from the body of the pituitary sac. These sprouts, the tuberal processes, ultimately fuse with each other across the median line, displace the body of the pituitary sac ventrad and thus secondarily assume their juxta-neural position.

Tilney emphasizes both the histological and developmental separateness of 'pars tuberalis' from 'pars infundibularis' (Herring's 'pars intermedia').

In his interesting study of the comparative development of the hypophysis, Woerdeman ('14) has seen the 'lobuli laterali' in several mammals and traces their development into the 'lobulus bifurcatus' of Bolk. This lobule divides into cell masses which lie in the meninges of the brain and which, in some cases, lose connection with the main body of the hypophysis. Woerdeman also has traced the early history of the lateral lobes. They arise from two enlargements of the thickened epithelial plate which lies anterior to Rathke's pocket and which later becomes incorporated into the hypophysial anlage.

Miller ('16), in his study of the hypophysis of Sus scrofa, speaks only briefly of the 'lateral cords.' According to his description, these cords 'grow round and encapsulate' that mass of cells supposedly derived from the entoderm. They eventually form the cortical layer of the anterior lobe.

Baumgartner ('16) has described the development of the lateral lobes of the reptilian hypophysis. He sees the lateral buds early separated from Rathke's pouch by furrows which begin on the cranial side. He states:

> In the later development of the lateral buds in turtles, the tips grow forward and form a thin layer closely applied to the floor of the brain (the part termed by Tilney 'pars tuberalis') and to a thin cortical zone around the middle of the anterior lobe.

In alligators, the lateral buds give rise

> to the pars tuberalis and two bands encircling the anterior lobe; in lizards, they appear to persist as isolated masses or to disappear, while in snakes, they completely disappear.

Baumgartner believes that the cortical zone or bands described by him for turtles and alligators have been overlooked in other vertebrates, since Miller ('16) is the only observer who has described a similar structure (Sus scrofa).

Parker ('17) finds that the development of the 'pars tuberalis' in the Marsupials begins at an early stage.

> The portion of Rathke's pouch lying posterior to the duct becomes subdivided into two lobes, which are respectively distal and proximal in relation to the hypophysial duct, and are separated from each other by a horizontal constriction. While the distal lobe thickens and forms the glandular tissue of the pars buccalis (probably meaning Tilney's 'pars distalis') as well as the pars infundibularis, the proximal lobe remains thin walled.

It is drawn out laterally and curves up to reach the brain wall on each side. Later the two sides fuse to surround the infundibulum.

4. The structure of the intermediate part. Besides the glandular cells and the small amount of connective tissue accompanying the few blood-vessels, a number of observers have noted in the pars intermedia certain distinctive cells which have been variously interpreted as nerve cells, sensory cells, or supporting cells.

Lothringer ('86) describes scattered marginal cells in addition to the cylindrical secreting cells. They may either reach the surface or be bent back upon themselves.

Pirone ('05) sees in the intermediate portion of the hypophysis, cylindrical cells which present the structure characteristic to the supporting cells of sensory epithelium. He used Cajal's method and states that he is able to confirm the findings of Gentes and Gemelli.

Gemelli ('05, '06) makes mention of nerve fibers entering the pars intermedia from the neural lobe and also of 'glio-epitheliari' cells in this part. He considers that the posterior lobe of the hypophysis is sensory in nature.

Retzius ('94) describes and figures structures in the pars intermedia which he has called neuroglia cells. They are shown by the Golgi method. One type consists of long, fine spindle-shaped cells which extend through the entire thickness of the pars intermedia. Others are peculiar, branched forms which touch only one surface of the epithelium or neither. The nuclei for the most part lie near the surface bordering the cleft. The end of the spindle-shaped cells towards the neural lobe often widens out into a three-cornered foot.

Herring ('08) finds long, thin nucleated cells in the pars intermedia of the kitten's hypophysis. These cells, which are brought out by use of Cajal's silver method, are numerous and take a vertical course through the epithelium. They appear to be of ectodermal origin and to act as supporting cells. Similar cells may be found in the adult, but are better seen in the young animal (p. 139).

Trautmann ('09), in studying the hypophysis of the cat, has seen 'fadenartige' cells which extend through the entire width of the intermediate part. These are well brought out by the Golgi method. Another type of cell also was seen which Trautman describes in these words:

> Im Epithelsaum der Katze konnte ich ferner durch die Golgische Methode zwischen den obengenannten fadenartigen, Zellgebilden verästelte Gebilde darstellen, die verschiedenartig zu den ersten verlaufen, mannigfaltige Gestalten aufweisen und weder Basis noch Peripherie erreichen.

Cajal ('11) figures bi-polar cells in the intermediate lobe of the mouse. These are made visible by the use of Golgi's method. He has also seen nerve fibers which extend from neural lobe to intermediate part. For these reasons, he considers that the superior (posterior) lobe of the hypophysis has a sensory nature. On this point Cajal says:

> Deux fait semblent indiquer que le lobe superieur de l'hypophyse doit etre un organe sensorial; c'est, d'une part, la richesse Tu plexus axile inclus dans le lobe nerveux et l'epithelium adjacent; c'est, d'autre part, l'existence de nombreuses cellules bipolaires epitheliales particulieres, signalees par Retzius et nous dans l'epithelium de la gland.

Miller ('16) remarks that the 'spindle-shaped supporting cells' constitute one of the interesting structures in the intermediate lobe of the hypophysis of the pig.

Vanderburgh ('17) sees in the pars intermedia of the guinea-pig's hypophysis, supporting cells which extend from the cleft towards the pars nervosa. The branched variety appear as "little black triangles which are molded to fit the interspace between the cells." The unbranched were "much elongated and usually more transparent." The stains used by Vandenburgh did not produce satisfactory evidence as to the nature of these cells.

Stendell ('14) gives a summary of the observations concerned with these special cells of the pars intermedia. He says that true ectodermal supporting cells having the nature of the ependyma of the central nervous system have been definitely observed only in the hypophysis of mammals, more specifically in the Carnivora and in a few Rodents. They are best seen in the cat and dog and are most readily demonstrated by silver impregnation methods.

He considers that without doubt these elements are true supporting cells. More remarkable and quite foreign to the nature of the pars intermedia are the glia cells which have been described. They have not often been called neuroglia cells, but are described as 'branched structures' which are brought out by the Golgi methods (Trautmann and others). Of the probable origin of these cells Stendell says:

> Da jedoch die ependymären Stützzellen als von Hirnlappen her eingewanderte Elemente anzusehen sind, ist auch für die gliösen, die ja mit jenen genetisch ein System ausmachen, die Erklärung gegeben. Sie sind entweder mit jene zusammen eingedrungen oder direct innerhalb des Zwischenlappens von der Oberfläche in profunde Lagen verdrängte Ependymzellen.

5. *The development of the neural lobe.* Recent studies on the morphogenesis of the hypophysis have been confined almost entirely to the epithelial portion of the gland. As a consequence, the literature treating of the development of the neural lobe is very scanty.

Müller ('71) believed that in mammals the specific neural tissue of the lobe is much reduced in amount during the latter half of fetal life and that connective tissue is substituted. Müller calls the fully developed infundibular process a "connective-tissue appendage of the brain."

Mihalkovics ('75), treating of the development of the neural lobe of the rabbit's hypophysis, states that its earliest appearance is due to the pressure of the hypophysial pouch against the wall of the forebrain, and not to a relation with the anterior extremity of the notochord. A protrusion of the brain wall results above the apex of the epithelial pouch and may be termed the 'primitive Trichter.' It represents not only the later 'Trichter fortsatz,' but also that portion of the ventricular floor which is to become the tuber cinereum.

Grönberg ('01) states that from the beginning the processus infundibuli is a hollow sac which can be compared in shape to the finger of a glove. In his stage 'D' the lumen begins to disappear at the caudal extremity of the lobe. Further description is omitted, but he makes reference to his figures 33 to 36 for details as to the disappearance of the cavity of the lobe.

Herring ('08 a) saw great importance in the early and close union between the buccal and cerebral portions of the hypophysis. Like Salzer, he could find no connective tissue between the infundibular process and the hypophysial sac in early stages. He believes that this close connection has some morphological significance, perhaps bespeaking the bucconeural duct observed by Andriezen in Ammocoetes, Amphioxus, and Balanoglossus. He denies that the neural lobe degenerates into a connective-tissue appendage. He finds that the connective tissue is small in amount. Treatment with Cajal and Golgi methods shows the structures formerly described as connective-tissue cells to be ependymal and neurogliar elements.

Stendell ('14) traces the form and position of the neural lobe from the lowest fishes to the Mammals. In the fishes, the neural portion can be considered as little more than a modified region of the floor of the third ventricle. In the Elasmobranchs and the Ganoids, the neural part sends numerous hollow processes into the substances of the intermediate lobe. In the Teleosts, the processes are solid and branched. Stendell considers that first in the Amphibia does one find a true neural lobe, that is, an unbranched, solid thickening of the ventricular floor to which the epithelial part attaches itself and develops (p. 27). This he considers the usual arrangement of parts in all the higher vertebrates.

B. Development of the hypophysis in the rabbit. So far as I have been able to discover, no author has confined himself to describing the development of the hypophysis in the rabbit alone. Several investigators have included, however, a consideration of this animal in their comparative studies.

Mention has already been made of a connection between notochord and dorsal wall of the hypophysis which was observed in an eleven-day rabbit embryo by Koelliker. Likewise it has been noted that peculiar 'neuroglia-like' cells were seen by Retzius in the pars intermedia of a rabbit eight days after birth.

Müller ('71) used embryos of the pig, the sheep, and the rabbit in his study of the development of the hypophysis. He gives a common description for all embryos of the same length. For example, his description of a 16-mm. stage may be applied equally well to any one of these three forms.

The rabbit was the mammalian type chosen by Mihalkovics ('75) in his study of the hypophysis. His descriptions begin with an embryo 5 mm. in length. The oral membrane is still intact. The first appearance of the hypophysis is the 'Hypophysenwinkel' a shallow infolding of the oral ectoderm just anterior to the oral plate. In a 6-mm. embryo, the oral membrane has just ruptured. Both upper and lower stumps are still to be seen. In this stage the earliest appearance of the primitive infundibulum is to be noted. A 12-mm. embryo shows a definitely formed 'Hypophysentasche' which communicates with the oral cavity by a much-constricted opening. The 'Trichterfortsatz' is small and conical. A 16-mm. embryo presents a longer 'Trichterfortsatz' and the hypophysial pocket has been further constricted off from the mouth epithelium, so that the connecting 'Hypophysengang' contains only a minute lumen. The further cutting-off of the hypophysial pouch, the formation of the anterior process and of the 'Drüsenschläuche' are traced by a description of 2-, 3-, and 4-cm. embryos.

Although not studying the development of the hypophysis, Lothringer ('86), Rogowitsch ('89), and Stieda ('90) made important early observations on the anatomy and histology of the gland in the rabbit.

Minot and Taylor ('05) give definite but necessarily brief statements concerning the development of the hypophysis in their "Normal Plates of the Development of the Rabbit." The hypophysis of the rabbit is first visible in their embryo No. 9, nine and one-half days of development, as a "very small evagination of ectoderm on the dorsal side of the mouth just in front of the oral plate," which has begun to rupture. In an embryo of ten days no essential difference is to be noted. At ten and one-half days the diverticulum of the hypophysis is "well marked, rather four-sided in cross-section, and closely approximated to the wall of the forebrain." During the next day the pouch becomes longer and more closely applied to the brain wall. In embryo No. 14 (twelve days) the anlage of the infundibulum is "present as a very small evagination of the floor of the forebrain. The upper end of the hypophysis is slightly expanded laterally, slightly concave toward the forebrain, and is joined to the infundibulum." During the next day and a half the infundibular evagination becomes more distinct and the mouth of the hypophysial pouch more constricted. At fourteen days the hypophysis is no longer open to the mouth, but is connected with the oral ectoderm by a solid epithelial cord. In embryo No. 19 (fifteen days) the infundibulum is a little longer than in preceding stages and overlies the hypophysis (epithelial portion) more. The hypophysis is bent concave toward the forebrain. By sixteen days there can be seen a beginning of the cords of the hypophysis which first appear as solid outgrowths. These cords are larger and more vascular in a seventeen-day embryo. At eighteen days the connecting cord between hypophysis and oral ectoderm is broken through just above the ectoderm. The Normentafel studies do not extend beyond twenty days of development. At this stage some embryos still show a small connecting strand between hypophysis and oral ectoderm. The infundibulum is open to the third ventricle. The hypophysis is much bent and contains a cavity. Two lateral upward prolongations of the hypophysis are to be seen on either side of the infundibulum. The cords of the hypophysis appear as a vascularized outgrowth of the anterior wall, irregular in shape, solid except for the contained vessels. The pituitary fossa is well marked at this time.

3. MATERIAL AND METHODS

The rabbit embryos used in this study were obtained from the rabbit colony of the Department of Anatomy of the University of Michigan. The majority of them were obtained during the course of the study and accurate records have been kept of their ages.

Females which have already born young were selected and the date of birth of the previous litter obtained if recent. It is known that a female will generally submit to coition shortly after parturition, but such a procedure is undesirable, since the suckling of young probably lengthens the gestation period (compare King

'13, on the albino rat). It is possible to wean the young rabbits at the end of one month, and the mother will then usually submit to coition within one or two days. Record was made of the time of insemination (Long and Mark, '11), and all ages referred to in this study are counted from the time of insemination to the time the embryos were obtained.

When a certain stage of development was desired the mother was sacrificed and the uterus was quickly removed and placed in normal salt solution, from which the freed embryos were transferred to the fixing fluid. In the case of all the younger embryos the amnion was carefully removed under the binocular microscope and the umbilical cord was tied to retain as much blood as possible in the vessels of the embryo.

For fixation Zenker's, Carnoy's and Bouin's fluids were employed. After sectioning and staining had been begun, it was found that Zenker's solution did not produce entirely satisfactory results in conjunction with the stains employed, so for the most of the work Carnoy's or Bouin's fluid was used. Decalcification was found necessary beginning with the eighteen-day embryos, and was accomplished by the use of a decalcifying fluid, made up after a somewhat empirical formula devised by Professor Huber and used successfully in his laboratory for several years. The formula is:

HNO_3	100 cc.
NaCl	20 grams
H_2O	600 cc.
Absolute alcohol	1400 cc.

It has the advantage of maintaining the tissues in a fairly high grade of alcohol during the process of decalcification. This is especially to be desired in the treatment of material which has been preserved in Carnoy's fluid. The tissues were cleared in xylol and embedded in 58° paraffin.

In the case of some of the younger stages series were cut on the rotary microtome, but most of the embryos were sectioned with the sliding microtome, by means of Huber's water-on-the-knife method. Not any series was cut at a thickness greater than 5 microns and several complete series were prepared at 3 microns.

The most useful staining combination was found to be iron-alum hematoxylin and Congo red. The latter solution was prepared as suggested by Huber ('15). For stages up to and including the twentieth day, series were prepared in sagittal, frontal, and transverse planes; later stages were prepared in the sagittal plane only.

To better show the form of the developing gland and to avoid errors in the interpretation of sections, the Born method of wax-plate reconstructions was freely used. A model of the hypophysis was prepared for each day of its development from earliest appearance up to and including the twentieth day. From this time until birth every second day is represented by a model. Additional reconstructions from other ten-, eleven-, twelve-, and thirteen-day embryos, together with an enlargement of the neural lobe and pars intermedia of one of the sixteen-day embryos raises the total number of models constructed to twenty-six. The magnification chosen was comparatively great—× 400 for the younger stages, including the sixteen-day embryo; × 200 for the seventeen- to twenty-two-day stages, inclusively; while for the four oldest stages it was found necessary to reduce the magnification to 100 diameters. The plan has been to reconstruct the neighboring brain wall, the oral (or nasal) epithelium, and a part of the cartilage of the hypophysial fossa, when that is present. This has been adhered to in all of the younger stages. The brain wall has been removed from the models of the nineteen- and twenty-eight-day embryos to present a dorsal view of the gland.

Use has also been made of the His method of projective reconstruction, and by this graphic means ventral views of the neural lobe have been obtained from transverse sections for certain stages.

4. THE DEVELOPMENT OF THE HYPOPHYSIS OF THE RABBIT BY DAYS

10-day stage. The hypophysis is well indicated in embryo A, which possesses sixteen pairs of primitive segments and has a seventeenth partly formed. A wax-plate reconstruction of this embryo, which includes the anterior part of the notochord, the epithelium of the anterior end of the foregut, the epithelium of the mouth invagination, and the adjacent brain wall, is shown in figure 1. The hypophysis anlage is present as a shallow pouch much wider from side to side than from front to back. The oral plate is intact. The cephalic extremity of the notochord bends around the foregut and terminates at the dorsal wall of the hypophysis fundament. A contact between notochord and hypophysis cannot be observed in this embryo.

Figure 2 presents a sagittal section of a timed ten-day embryo (27D). It is slightly older than the preceding, but the oral membrane is still unbroken. A comparatively large evagination of the brain wall is seen dorsal to Rathke's pocket. This corresponds to the 'primitive Trichter' of Mihalkovics. In this embryo the extremity of the notochord is in close contact with the wall of hypophysis anlage.

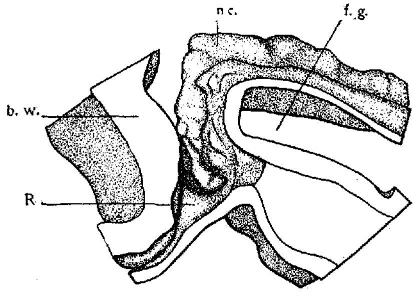
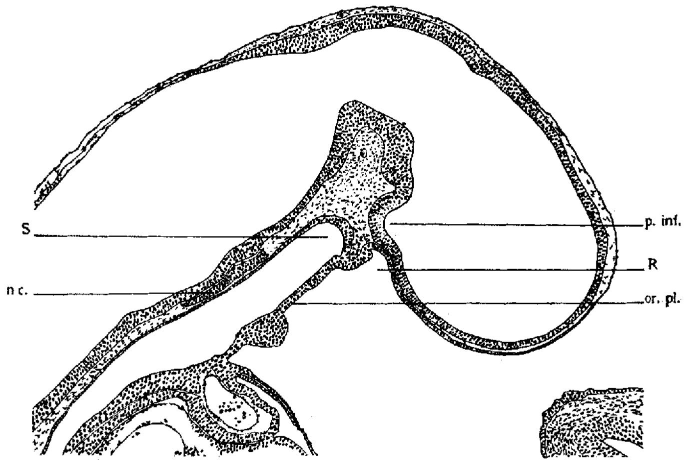


Fig. 1. Model of hypophysis region of a sixteen-somite rabbit (embryo A). × 100. The anterior end of the notochord and portions of the epithelium of the foregut, oral pit, and brain wall are shown. Viewed from the left side. *nc.*, notochord; *f.g.*, foregut; *R*, Rathka's pouch, and *b.w.*, brain wall.

Another ten-day embryo (27A) shows the oral membrane in the process of rupture. A sagittal section of this embryo is given in figure 3. A noteworthy feature is the presence of a thickened epithelium, continuous with the hypophysial wall, which extends nasalward from Rathke's pocket for some distance. Its rather abrupt termination is marked by x (fig. 3).

A wax-plate reconstruction prepared from this embryo shows that the hypophysial pouch has deepened, and on each side, at its nasal border, has developed a ridge-like protuberance. As seen



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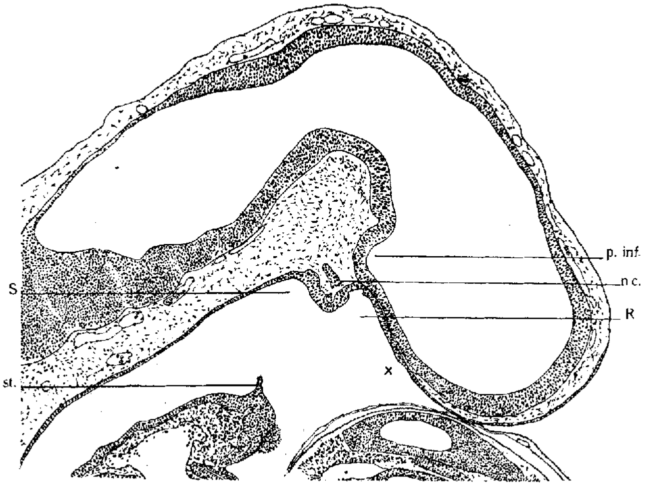

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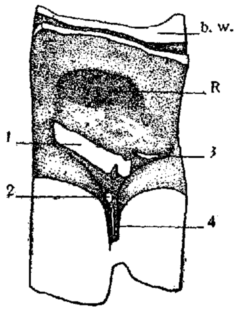
Fig. 2 Sagittal section of head end of a ten-day rabbit embryo (27D) showing oral membrane intact. × 50. Nasal end at right. *p. inf.*, primitive infundibulum; *R*, Rathke's pouch; *or. pl.*, oral plate; *S*. Seessel's pouch; *nc.*, notochord.

Fig. 3 Sagittal section of head end of ten-day rabbit embryo (27A) showing oral membrane ruptured. × 50. Nasal end at right. *st.*, stump of oral plate; other abbreviations as in figure 2.

from the inside, each ridge is indicated by a shallow groove. It appears as if these ridges were developing from the thickened epithelium which lies in front of the early hypophysial pouch.

The rupture of the oral membrane is not complete, as is shown by the presence of two openings through which the foregut communicates with the exterior. The end of the notochord is drawn out to a point and is in contact with a prominent bud extending from the dorsal wall of Rathke's pocket.



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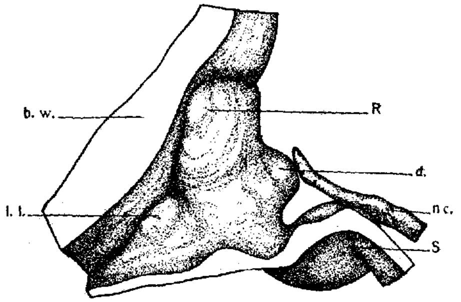

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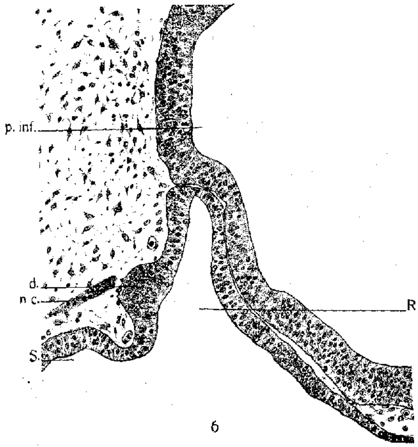
Fig. 4 Model of hypophysis region of rabbit embryo B (about ten days), viewed from the oral surface. × 100. *R*, Rathke's pouch; *b.w.*, brain wall; 1, *2, 3, 4*, perforations in the oral plate.

Fig. 5 Model of hypophysis region of eleven-day embryo (25A) viewed from the left side. × 100. *l.l.*, lateral lobe; *d.* diverticulum from Rathke's pouch toward which the notochord is directed. Other abbreviations as in figures 1 and 2.

Another embryo (Series B) also shows the breaking of the oral membrane. In figure 4 one views a reconstruction of this embryo from the oral side. The membrane has broken through in four places, thus furnishing four separate communications between the foregut and the oral invagination.

11-day stage. By the end of the eleventh day of development the hypophysial pouch has deepened considerably and has expanded laterally near its apex. A constriction near the middle of the pouch serves to separate the apical portion from the more inferior portion bearing the ridge-like protuberances (l. l. fig. 5). These latter have become more prominent due to their partial constriction from the oral epithelium. These prominent elevations I interpret as the homologues of the lateral lobes of lower forms. Later stages of development of the rabbit will show how these early lateral lobes give rise to the pars tuberalis of complete development. A transverse section through the region of the lateral lobes is shown in figure 7. The lobes are constricted from the thickened epithelium just nasal to the early hypophysial pouch.



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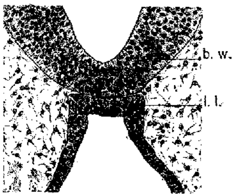

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Fig. 6 Sagittal section, hypophysis region of eleven-day rabbit embryo (25A). × 100. Nasal end at right. *p. inf.*, primitive infundibulum; *R*, Rathke's pouch; *S*, Seessel's pouch; *nc.*, notochord; *d*, diverticulum of Rathke's pouch to which the notochord is directed.

Fig. 7 Transverse section just nasal to Rathke's pouch, from rabbit embryo C, about eleven days. × 100. *l.l.*, lateral lobe in process of being constricted off; *b.w.*, brain wall.

In embryo 25A (figs. 5 and 6) the notochord ends close to a large thickened evagination of the dorsal wall of the hypophysis from which it is separated by a very narrow space. The condition presented by this embryo corresponds very closely to that of the eleven-day rabbit embryo described by Koelliker ('79).

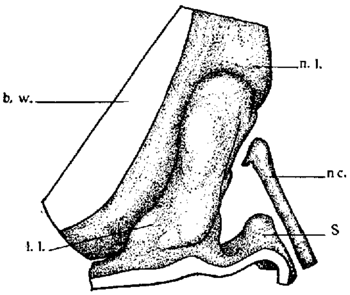
In embryo C, which is only slightly more advanced, the notochord divides into two parts near its cephalic termination. One branch ends at the apex of Seessel's pouch, while the other is directed dorsally, forming almost a right angle with the first part.

The primitive infundibulum is present as a large, shallow evagination of the brain wall.

12-day stage. The first evidence of the definitive neural lobe, or infundibular process, appears in the twelve-day stages. Embryo 24A (figs. 8 and 9) shows the infundibulum as a small part of the early primitive infundibulum pushing against the apex of Rathke's pocket. The latter is more expanded laterally and is noticeably constricted off from the oral epithelium. The lateral lobes are well marked. The notochord bends sharply some distance above the apex of Seessel's pouch and directs a pointed extremity toward a small bud of epithelium near the middle of the dorsal wall of Rathke's pocket. There is here a considerable distance between the notochord and the epithelial bud. Another embryo, very slightly older (embryo D) does not show a contact between notochord and hypophysis. Instead the chorda terminates in close relation to a small epithelial bud just anterior to the apex of Seessel's pouch. Figure 10 shows in a dorsal view how the neural lobe is indenting the hypophysial pouch and pushing its apex backward. The portion of Rathke's pocket in contact with the neural lobe is the earliest appearance of what is later to form the pars intermedia of the fully developed gland.

Up to the twelfth day the anterior wall of the hypophysis lies close to the brain without the intervention of connective tissue. At this time, however, mesenchymal cells wander in and the two are gradually separated up to the neck of the neural lobe. The latter lies close upon the future pars intermedia for about two days longer.

13-day stage. The constriction of Rathke's pouch from the oral ectoderm has proceeded so far by the end of the thirteenth day that the lumen connecting the cavity of the pouch with the mouth cavity is very narrow. This is shown by the sections and models of embryos 6A, 6B and 6C. Figure 11 shows a sagittal section of the hypophysis region from embryo 6B. The neural lobe has increased in length and forms an acute angle with the brain wall on the nasal side of its attachment. Into this angle the apex of Rathke's pouch is tightly wedged. The cavity of the neural lobe has become very irregular and its wall shows a number



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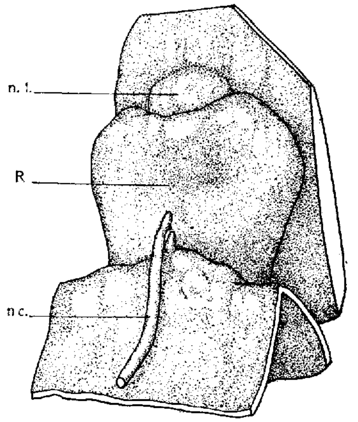

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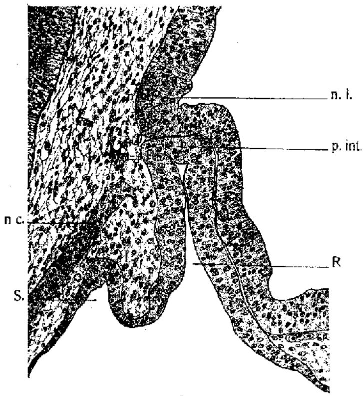

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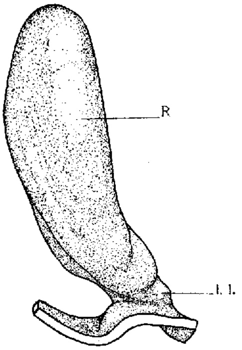

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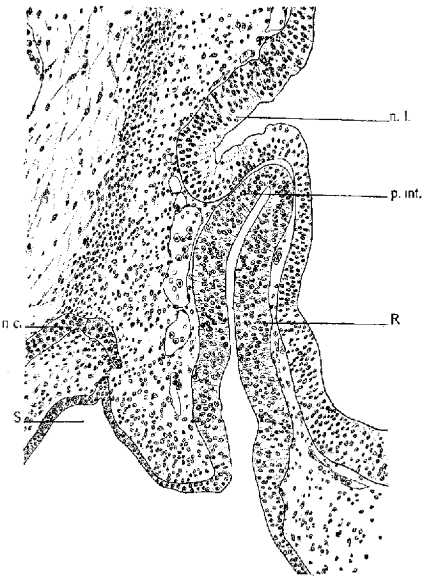

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Fig. 8 Model of hypophysis region, twelve-day rabbit embryo, viewed from left side. × 100. *b.w.*, brain wall; *n.l.*, neural lobe; *n.c.*, notochord; *S*, Seessel's pouch; *l.l.*, lateral lobe.

of angular foldings. This is the beginning of a very complicated series of reduplications and compressions by which the lumen of the lobe is obliterated. In rabbit 6B the anterior termination of the notochord is near a small epithelial bud projecting from the tip of Seessel's pouch (fig. 11). In 6A the notochord sends a strand of cells toward a small epithelial bud which projects from the dorsal wall of Rathke's pocket near its constriction from the oral epithelium.

The cavity of the epithelial pouch of the hypophysis is constricted slightly near its middle (fig. 11). The entire pouch has assumed a curved shape with the concavity toward the brain floor.

The lateral lobes, on account of the constriction of the hypophysial sac from the mouth, have been drawn together and form a transverse ridge across the nasal end of the hypophysis near its attachment to the oral epithelium. The rounded termination of this ridge on each side is the tip of the lateral lobe (l.l., fig. 12).

14-day stage. In the fourteen-day embryos the attachment of the hypophysis to the oral epithelium has been reduced to a solid stalk. The original cavity of Rathke's pouch is present throughout the length of the gland, but does not extend into the stalk. The gland has assumed a more concave form and a considerable amount of connective tissue is present between the hypophysis and the brain wall (fig. 13).

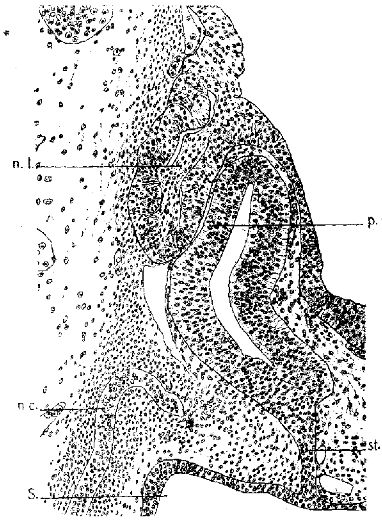
The lateral lobes have begun to grow laterally forming definite, bud-like projections (l.l., fig. 14). Each bud lies close to the main body of the hypophysis, but is clearly separated from it by a deep groove. These buds will be traced into the formation of the pars tuberalis.

Fig. 9 Sagittal section of hypophysis region, twelve-day embryo (24A); nasal end at right. × 100. *R*, Rathke's pouch; *p.int.*, pars intermedia; *n.l.*, neural lobe; *nc.*, notochord; *S*, Seessel's pouch.

Fig. 10 Model of hypophysis region of rabbit embryo D, about twelve days, viewed dorsally and somewhat from the right. × 100. *n.l.*, neural lobe; *R*, Rathke's pouch; *nc.*, notochord.

Fig. 11 Sagittal section of hypophysis region, thirteen-day embryo (6B), nasal end at right. × 100. *R*, Rathke's pouch; *n.l.*, neural lobe; *p. int.*, pars intermedia; *nc.*, notochord; *S*, Seessel's pouch.

Fig. 12 Model of epithelial portion of hypophysis from thirteen-day embryo (6A) viewed from the right. × 100. *R*, Rathke's pouch; *l.l.*, lateral lobe.



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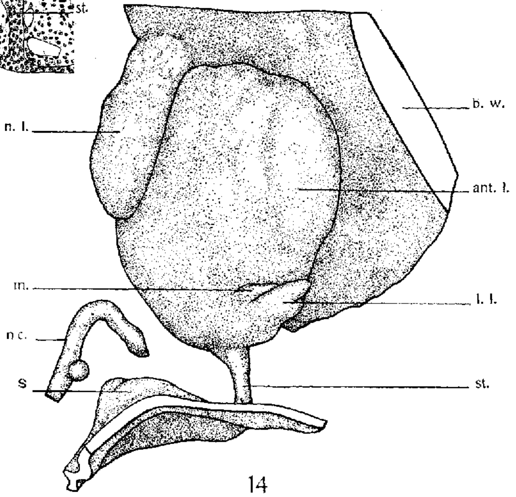

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Fig. 13 Sagittal section of hypophysis region, fourteen-day embryo (10A). × 100. Nasal end at right. *n.l.*, neural lobe; *p. int.*, pars intermedia; *nc.*, notochord; *S*, Seessel's pouch; *st.*, stalk.

Fig. 14 Model of hypophysis region, fourteen-day embryo (10A). × 100. Viewed from the right and somewhat dorsally. *ant. l.*, anterior lobe; *b.w.*, brain wall; *n.l.*, neural lobe; *l.l.*, lateral lobe; *st.*, stalk; *S*, Seessel's pouch; *nc.*, notochord; *m.*, constricted portion perhaps equivalent to Woerdeman's 'dorsaler Mittelraum.'

Just dorsal to each bud is another, smaller outgrowth, *m,* fig. 14. It seems to me not improbable that this eminence can be compared to the dorsal part of the 'Mittelraum' of Woerdeman ('14). A median eminence of the transverse ridge connecting the two lateral buds may correspond to the 'Vorraum' of Woerdeman. This, at least, is the interpretation Woerdeman has placed on Salzer's ('98) model from a 1.9-cm. pig embryo. I cannot agree with Woerdeman that this single median eminence forms the anterior extension of the pars tuberalis, as will be explained more fully further on.

The neural lobe is irregular in outline and its lumen has become very tortuous and labyrinth-like. As a result of the corrugations and compressions of its wall, folds of the wall and detached cells are to be found in the cavity of the lobe and constitute an important factor in its obliteration. Neural lobe and pars intermedia have become separated by a small amount of connective tissue. The notochord terminates just anterior to the apex of Seessel's pouch.

15-day stage. No new structures are visible in the fifteen-day stages, but the gland shows a gradual development in all its parts. The stalk is longer and of smaller diameter. It tapers gradually from the gland to its attachment with the oral epithelium. The neural lobe is proportionately larger and more convoluted and its lumen has become more intricately divided. Besides the cells which are to be found in the cavity of the neural lobe, other cells may be seen which have wandered outward through the basement membrane and are forming a cortex around the outside of the lobe. The connective tissue separating if from the intermediate part is somewhat increased in amount. One of the embryos shows some interesting connections (*cont.,* fig. 15) between neural and intermediate parts. They are similar to the contacts to be described for the sixteen-day and older embryos and will be treated more fully with those stages.

The lateral lobes (l.l., figs. 16 and 17) are larger than in the previous stage. They are solid, never having shown a lumen. Because of the continued 'cupping' of the hypophysis, these lobes have been drawn closer to the brain wall and are directed somewhat towards it as well as laterally. The median eminence on the transverse ridge connecting the two lateral lobes, seen in the fourteen-day stage, is here present. The extremity of the notochord is in relation with a pointed bud of epithelium from Seessel's pouch (figs. 15 and 16).

16-day stage. At sixteen days the lateral lobes have enlarged and lie close to the brain wall. On each side the lobes are sharply constricted from the remainder of the gland. In the midline they are not well separated from each other. The mass formed by the two lobes will form the pars tuberalis of Tilney. Already it has begun to be vascularized, and in this respect is in advance of the remainder of the gland. This is shown in the model (fig. 18) by its roughened surfaces. Precartilage indicates the future sphenoid bone with a shallow fossa to contain the gland. The hypophysial stalk is attached to the gland just nasal to the con-

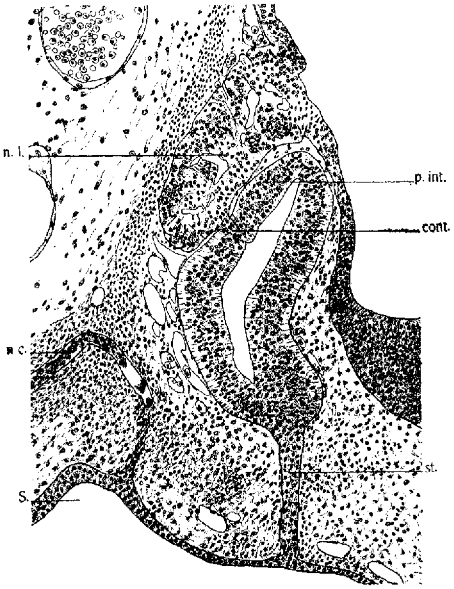
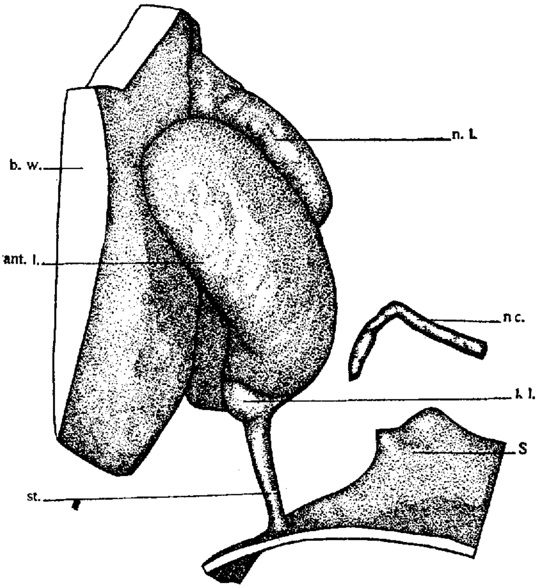


Fig. 15 Sagittal section of hypophysis region, fifteen-day embryo (7A). × 100. Nasal end at right. *cont.*, definite contact between neural lobe and pars intermedia; other abbreviations as previously.



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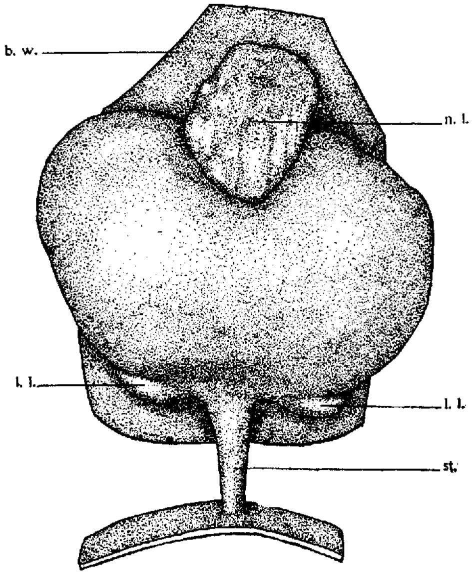

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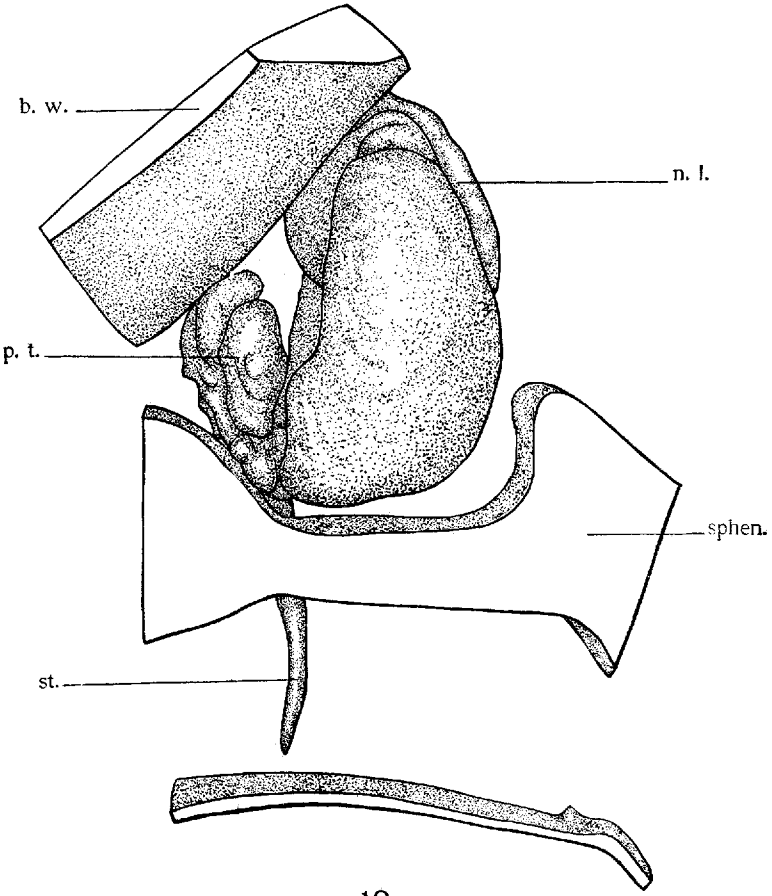
Fig. 16 Model of hypophysis region, fifteen-day embryo, viewed from left side. × 100. Abbreviations as in figure 14.

Fig. 17 Same model as shown in figure 16, here viewed dorsally and caudally, with Seessel's pouch removed. × 100. Abbreviations as in figure 14.



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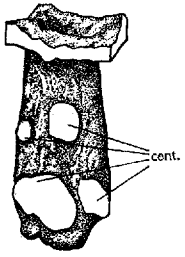

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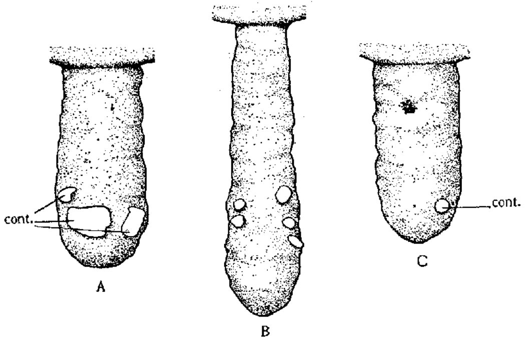

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striction which separates off the lateral lobes. It extends through an opening in the sphenoid and ends near the oral epithelium, from which it is entirely separated (embryo 8A). This is not true for all of the sixteen-day stages. Some of them show the stalk still firmly attached to the epithelium. The notochord ends in the caudal portion of the hypophysial fossa.

One of the most interesting observations made in the sixteen-day embryos is the intimate relation between neural lobe and intermediate part. This condition was found constantly present in all the specimens of this age which have been examined. In addition, it has been observed in some of the fifteen-, seventeen-, eighteen-, and twenty-day embryos. This intimacy consists of a number of definite contacts between neural and intermediate portions. The areas in contact are definitely circumscribed and at these places the basement membranes of the two parts are lacking. One of these contacts is shown in transverse section in figure 21A. It is not easy to determine whether the contact is due to the active growth of one part into the other, or merely to the passive fusion of the two parts. There is some evidence, however, that the contacts are due to the active penetration of outgrowths from the neural lobe into the intermediate part. As evidence in favor of this view the following facts may be pointed out: a) at most of the contacts a cone-shaped structure, having its base on the neural lobe, can be traced into the pars intermedia; b) the basement membranes of the two parts can be traced on each side of this cone for some distance into the pars intermedia, giving the appearance of having been pushed in; c) often the staining of the cone indicates a similarity in structure to that of the neural lobe, although this is not always conclusive.

Fig. 18 Model of hypophysis region, sixteen-day embryo, viewed from left side. × 100. *sphen.*, portion of cartilage of sphenoid; *p.t.*, pars tuberalis; other abbreviations as previously.

Fig. 19 Model of neural lobe of hypophysis from sixteen-day embryo, viewed from surface which was in apposition to the pars intermedia. × 100. *cont.*, cut surfaces of contacts between neural lobe and intermediate part.

Fig. 20 Neural lobe of hypophysis from three embryos viewed as in figure 19. × 100. These figures were obtained by the His method of graphic reconstruction from transverse sections. A and C from sixteen-day embryos, 8D and 8E, respectively; B, from eighteen-day embryo, 12B. *cont.*, contact areas.

These contacts vary in number from one to five. To show their relative sizes and position, the neural lobe and pars intermedia of embryo 8A were reconstructed in wax at a magnification of five hundred diameters. The two were then separated by cutting the contacts. The model of the neural lobe is shown in figure 19 viewed from the surface which was in apposition to the pars intermedia. Four distinct areas of contact may be seen. They are arranged in two pairs, one of which is near the caudal or free end of the lobe, while the other lies near its middle. They are unequal in size and the caudal pair is the larger. Similar views of the neural lobe in other sixteen-day embryos have been obtained by the His method of graphic reconstruction. One, showing three contacts (from embryo 8D), is shown in figure 20A. Another showing one contact (embryo 8E) is given in figure 20C. In general the contacts are near the caudal end of the neural lobe. This is always true when only a single contact is present.

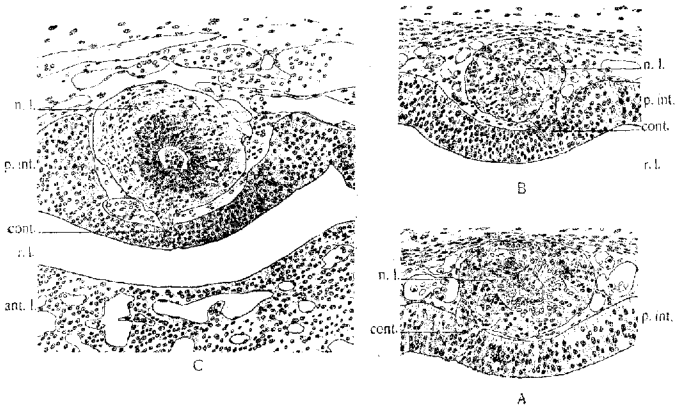


Fig. 21 Transverse sections showing contacts between neural lobe and pars intermedia. × 100. *A*, from sixteen-day embryo (8D); *B* from eighteen-day embryo (12B); *C*, from twenty-day embryo (13B). *n.l.*, neural lobe; *p. int.*, pars intermedia; *cont.*, contact; *r.l.*, residual lumen; *ant.l.*, anterior lobe.

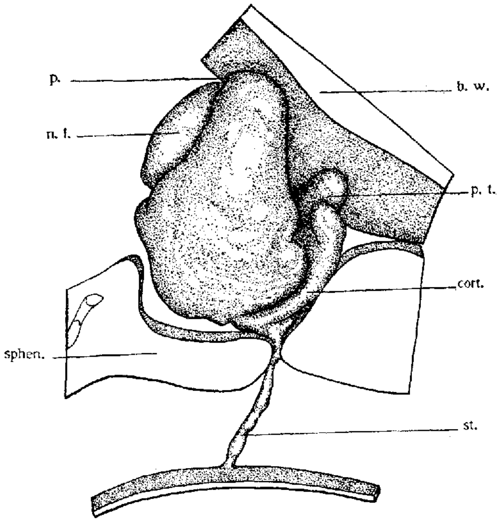
A further observation should be recorded here. On the surface of the intermediate part facing the residual lumen of the hypophysis is found a slight indentation to correspond to the center of each contact (fig. 21).

17-day stage. In the model of embryo 28A (fig. 22) the pars tuberalis is seen to have a larger surface in contact with the brain wall than in the previous stage. The lateral lobes which compose it are coming to lie between the anterior lobe proper and the brain wall. The two lateral lobes are now well separated in the midline. That portion of the lateral lobe between the brain wall and the hypophysial stalk is deeply constricted off from the remainder of the gland and forms a cortex for the nasal end of the anterior lobe proper (*cort.*, fig. 22). In this embryo the stalk is attached to the oral epithelium. Embryo 28A shows one of the contacts mentioned in the previous stage as seen connecting neural and intermediate parts. Near its apex the hypophysis is sending up two processes (*p.*, fig. 22) to surround more closely the neck of the neural lobe. A study of sections shows that the residual lumen extends into these processes.

The foldings of the neural lobe have resulted in the formation of two layers in its wall. The innermost consists of cells radially arranged about the central lumen, which is partially filled by cells irregularly disposed. An outer, or cortical, layer consists of cells very irregularly placed. Many remnants of the original basement membrane are to be seen between these two layers (compare fig. 21B, eighteen days). The neural lobe now makes an angle of about ninety degrees with the brain wall at its attachment.

18-day stage. In this stage the pars tuberalis is more extensively applied to the brain wall and processes have begun to extend both nasally and caudally. The lobes have become more closely compressed between the anterior lobe proper and the brain. Between the brain wall and the hypophysis a cup, or fossa, is formed. This is the 'oberne Dell' of Mihalkovics. It contains connective tissue rich in blood-vessels, many of which may be traced into the anterior lobe. The cortex at the nasal end of the anterior lobe is here well marked (*cort.*, fig. 23).

The neural lobe is directed caudally (fig. 23) making now an acute angle on the caudal side of its attachment. The lobe has elongated and is constricted at its neck. The processes from the apex of the hypophysis have extended farther backward around



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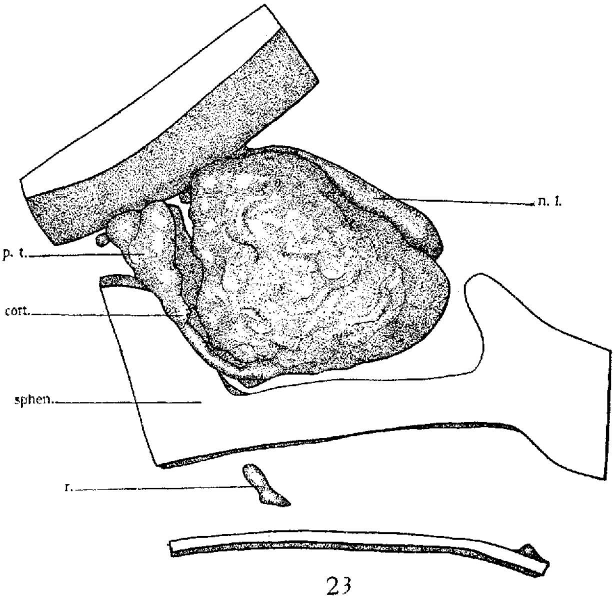

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Fig. 22 Model of hypophysis region, seventeen-day embryo (28A), viewed from right side. × 50. *b.w.*, brain wall; *n.l.*, neural lobe; *p.t.*, pars tuberalis; *cort.*, cortical plate; *sphen.*, portion of sphenoid; *st.*, stalk; *p.*, process surrounding neck of neural lobe.

Fig. 23 Model of hypophysis region, eighteen-day embryo, viewed from left side. × 50. *r.*, remains of stalk below sphenoid, or 'pharyngeal hypophysis.' Other abbreviations as in figure 22.

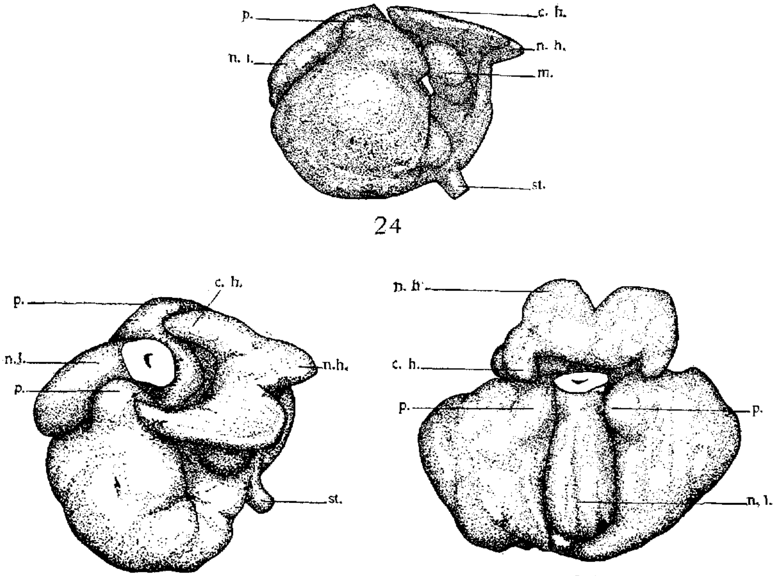
its neck. Certain embryos show contacts between neural and intermediate parts and others do not. Figure 21, *B*, a transverse section from embryo 12B, shows a cone-shaped process of the neural lobe entering the intermediate part. A graphic reconstruction of the neural lobe of this embryo (*b.*, fig. 20) shows that in all there are five contact areas. This is the greatest number counted in any embryo. Small strands of connective tissue are to be observed penetrating into the epithelium of the pars intermedia.

The stalk in embryo 12A is represented by a small knot attached to the gland and by an entirely isolated mass of epithelial cells, situated ventral to the sphenoid cartilage (*r.*, fig. 23). Such an epithelial mass forms a 'pharyngeal hypophysis.' The possession of a pharyngeal hypophysis is perhaps the normal condition for certain stages of development.

19-day stage. By the end of the nineteenth day a most interesting stage of development has been attained by the lateral lobes. They now have a considerable area flattened out against the brain wall. They are united in the midline and each is sending out a pair of blunt nasal horns (*n.h.*) and a pair of sharper, longer caudal horns (*c.h.*), as shown in figures 24, 25, and 26. The two nasally directed horns extend toward the optic chiasm, lying close to the brain wall. The caudal horns likewise lie close to the brain wall and are extending back to surround the neck of the neural lobe. This part which lies close to the brain wall is the pars tuberalis. It is rapidly assuming its final position. Ventral to the pars tuberalis on each side is a comparatively large solid process (*m.*, fig. 24). The processes growing up to surround the neck of the neural lobe are prominent (*p.p.*, figs 24, 25, and 26)

The stalk (which has been cut short in the model) extends through the sphenoid cartilage and is attached to the nasal epithelium. The attachment of the stalk to the gland is nearer the nasal end than formerly.

20-day stage. At twenty days (figs. 27 and 28) the pars tuberalis has extended farther caudally and its caudal horns are insinuating themselves between the brain wall and the anterior lobe proper (*c.h.*, fig. 27). The entire surface of the epithelial portion of the gland is much roughened by the presence of blood-vessels. The anterior lobe and the pars tuberalis are well vascularized at this time. The pars intermedia is non-vascular. As shown in figure 27, the stalk extends through the sphenoid cartilage and ends near the nasal epithelium, but shows no connection with it.



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Figs. 24, 25, and 26 Model of hypophysis from nineteen-day embryo. × 50. Brain wall, sphenoid cartilage and nasal epithelium not reconstructed. Figure 24, from right side; figure 25, dorsally and from right side; figure 26, dorsally. *c.h.* and *n.h.*, caudal and nasal horns, of pars tuberalis; *m.*, secondary eminence (dorsal part of 'Mittelraum?'); other abbreviations as in figure 22.

A sagittal section of embryo 13A is shown in figure 28. The fossa, *f*, caused by the bending of the hypophysis and the growth of the lateral lobes toward the brain, is somewhat smaller than previously, having become reduced by the rapid growth of the anterior lobe. A transverse section (embryo 13B, fig. 21C) shows very clearly one of the outgrowths of the neural lobe extending into the pars intermedia. This is the latest stage in which such neuro-epithelial contacts were observed.

22-day stage. The general relations of the fully developed gland have been nearly attained at this time. The nasal horns of the pars tuberalis have extended to the optic chiasm. The horn of the left side in embryo 20A has outstripped its fellow in development and the two meet well to the right of the midline. This is not the general rule, as is shown by other stages. Usually the two sides are symmetrical. The caudal horns have entirely displaced the remainder of the hypophysis from contact with the floor of the third ventricle. They have encircled the neck of the neural lobe and lie close together, but are not yet united (fig. 29). The processes from the body of the hypophysis (*p.p.*, fig. 29) have extended well around the neck of the neural lobe. It is to be noted that they have the caudal horns of the pars tuberalis between themselves and the brain wall. Two knob-like processes (*e.e.*, fig. 29) extend from the pars intermedia to the caudal extremity of the neural lobe and are fused with it. They have the structure of the pars intermedia.

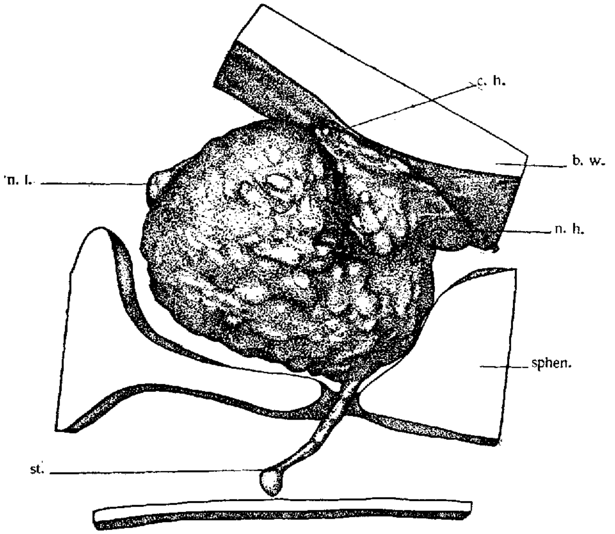


Fig. 27 Model of hypophysis region from twenty-day embryo viewed from right side. × 50. *n.h.*, nasal horn, *c.h.*, caudal horn, of pars tuberalis; other abbreviations as in figure 22.

The pars tuberalis lies in the pia mater of the brain. It has begun to show a tubular or alveolar structure and is histologically different from both the pars intermedia and the anterior lobe proper. The third ventricle sends lateral extensions to correspond with the area of contact of the pars tuberalis.

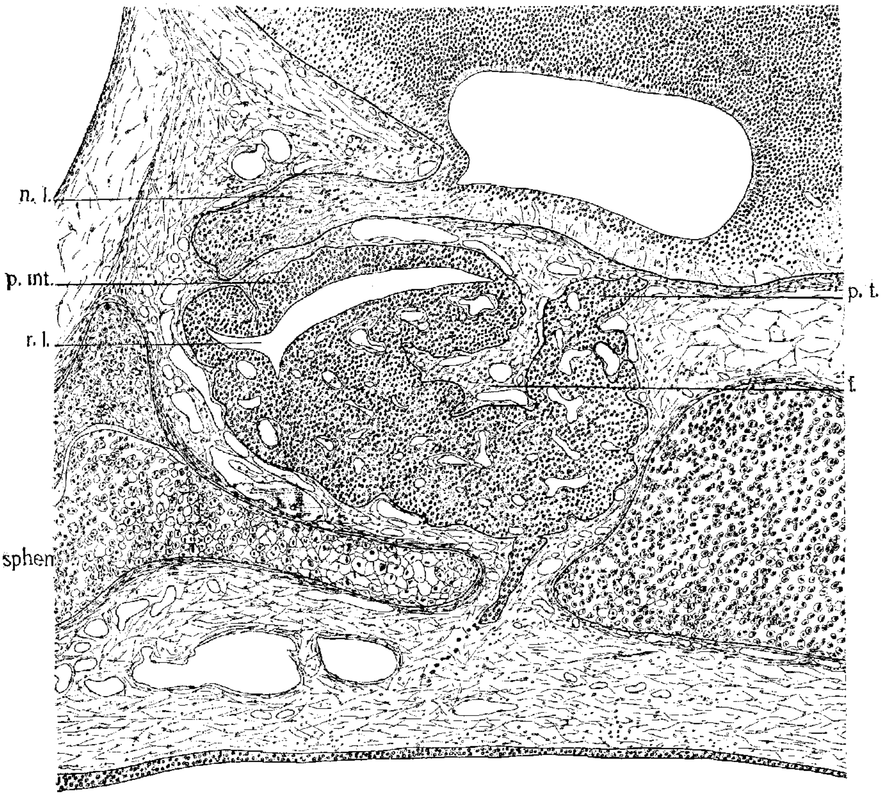
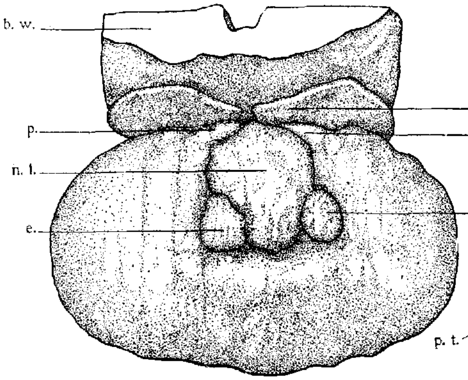


Fig. 28 Sagittal section of hypophysis region from twenty-day embryo (13A). × 75. Nasal end at right. *n.l.*, neural lobe; *p. int.*, pars intermedia; *r.l.*, residual lumen; *sphen.*, cartilage of sphenoid; *p.t.*, pars tuberalis; *f.*, fossa containing connective tissue.

The fossa or 'oberne Dell' has become greatly reduced and the connective tissue it contains has been compressed. This tissue serves to separate distinctly the pars tuberalis from the pars intermedia.

The stalk in embryo 20A extends through the sphenoid, but is not attached to the nasal epithelium.

24-day stage. As shown in figure 30, the most notable change exhibited by the gland at this stage is its increase in cephalocaudal diameter. Up to this time the transverse diameter has been as great or greater than the anteroposterior. The change is due mainly to rapid growth of the tissue of the anterior lobe proper Another result of the rapid growth has been a pressing of the neural lobe toward the brain wall so that the angle formed caudal to its attachment is very acute. The attachment of the hypophysial stalk is relatively much nearer the nasal extremity of the gland than formerly.



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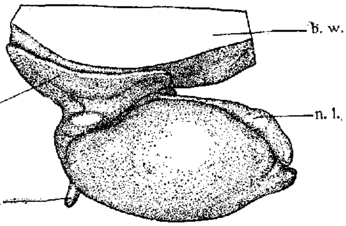

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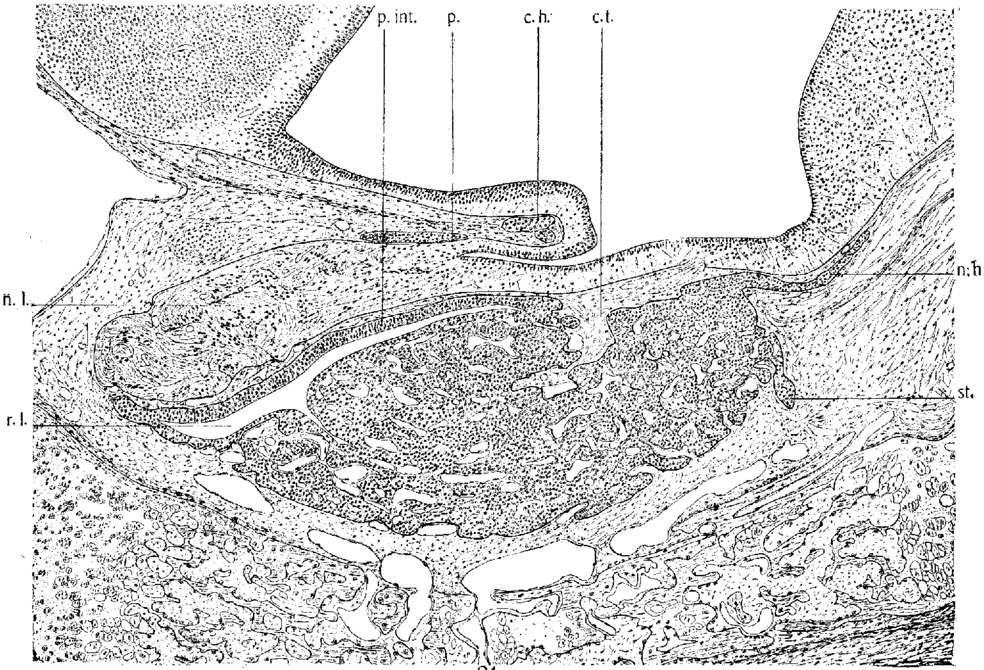
Fig. 29 Model of hypophysis and brain wall from twenty-two-day embryo, viewed dorsocaudally. *c.h.*, caudal horn of pars tuberalis; *b.w.*, brain wall; *p.p.*, processes growing around neck of neural lobe; *n.l.*, neural lobe; *e.e.*, knob-like processes having structure of pars intermedia.

Fig. 30 Model of hypophysis and brain wall from a twenty-four-day embryo, viewed from left side. × 25. *b.w.*, brain wall; *n.l.*, neural lobe; *p.t.*, pars tuberalis; *st.*, stalk.

26-day stage. The advances in development shown at this time are a general increase in the size of the gland, especially of the glandular anterior lobe, a closer compression of the neural lobe and the brain wall, and the further apparent migration nasalward



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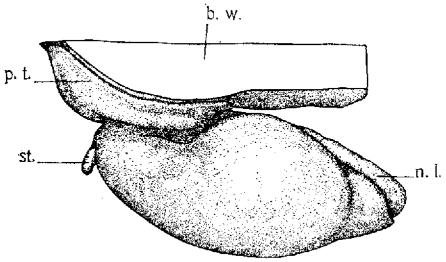

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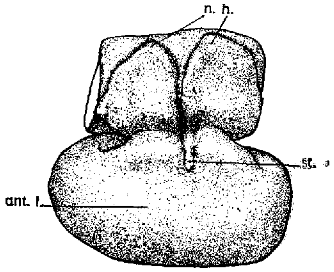

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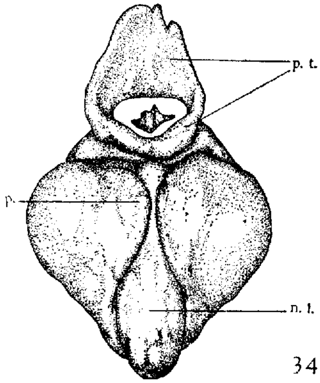

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of the attachment of the hypophysial stalk. A sagittal section from embryo 22A is shown in figure 31. A wax-plate reconstruction made from this embryo is viewed from the left side in figure 32 and from the nasal end in figure 33. Figure 31 is from a section which is not exactly central. This makes it possible to view structures which are not at this time present in the midline. For example, nasal and caudal horns of the pars tuberalis are cut, and likewise one of the processes (*p.*) which grow up to nearly surround the neck of the neural lobe. The residual lumen can be traced into these processes and the part lying next to the neural lobe presents the structure of the pars intermedia. It is not out of place to emphasize again the distinctness of the caudal horns of the pars tuberalis and these processes of the pars intermedia. It is evident that Herring ('08) has not distinguished between the two, as he labels them (in the cat) the "extension of the pars intermedia round neck of gland."

A nasal view of the gland (fig. 33) shows the two nasal horns of the pars tuberalis as broad plates with blunt, rounded terminations. They have grown close together in the midline but have not fused. Likewise the caudal horns are close together but unfused.

28-day stage. By this time the caudal horns of the pars tuberalis have fused with each other across the midline, and completely surround the neck of the neural lobe. The nasal horns

Fig. 31 Sagittal section of hypophysis region from twenty-six-day embryo (22A). × 50. Nasal end at right. Section is not exactly median so that the process, *p.*, which with its fellow tends to surround the neck of the neural lobe, is shown. *n.l.*, neural lobe; *r.l.*, residual lumen; *p. int.*, pars intermedia; *c.h.*, caudal horn, and *n.h.*, nasal horn of pars tuberalis; *c.t.*, connective tissue in the fossa; *st.*, attachment of stalk.

Fig. 32 Model of hypophysis and adjacent brain wall from a twenty-six-day embryo, viewed from left side. × 25. *b.w.*, brain wall; *n.l.*, neural lobe; *p.t.*, pars tuberalis; *st.*, stalk.

Fig. 33 Same model shown in figure 32, viewed from nasal end. × 25. *n.h.*, nasal horns of pars tuberalis; *ant.l.*, anterior lobe; *st.*, stalk.

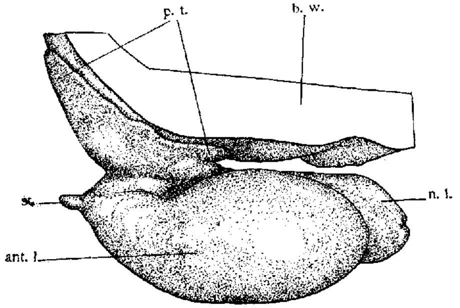
Fig. 34 Model of hypophysis from twenty-eight-day embryo. × 25. Brain wall has been removed so as to present a dorsal view of the gland. The two nasal horns and the two caudal horns of pars tuberalis have fused. *p.t.*, pars tuberalis; *p.*, process growing up to surround neck of neural lobe; *n.l.*, neural lobe.

Fig. 35 Sagittal section of hypophysis region from thirty-day-embryo (at term). × 50. Nasal end at right. *n.l.*, neural lobe; *p. int.*, pars intermedia; *r.l.*, residual lumen; *d.m.*, dura mater; *p.*, process growing up around neck of neural lobe; *p.t.*, pars tuberalis; *c.t.*, connective tissue of fossa; *st.*, stalk.

also have fused, but not so completely. The processes of the pars intermedia have grown up so as almost to surround the neural lobe, not only at its neck, but also for a considerable distance towards its free extremity. This is well shown by a model from which the brain wall has been removed, thereby presenting a dorsal view of the gland (fig. 34). Pars tuberalis and pars intermedia are distinctly separated by the connective tissue which has been imprisoned in the fossa. The neural lobe shows irregular lumina. It has been pushed dorsally to lie almost parallel with the floor of the third ventricle. The stalk is attached at the nasal end of the gland.

30-day stage. This stage presents practically the condition of development of the hypophysis of the rabbit at birth. In fact, before the embryos could be removed from the anaesthetized mother at least one was found to have entered the birth canal. The entire gland has increased in size, but especially the anterior lobe. The neural lobe is relatively more constricted at its neck, while the caudal extremity is enlarged and knob-like. The pars intermedia lies in contact with a larger proportion of the surface of the neural lobe, by reason of the processes (*p.*, fig. 35) which it sends around the infundibular neck. Outgrowths from the pars intermedia may be seen entering the neural lobe. One of these is plainly shown in figure 35. The pars tuberalis now completely surrounds the infundibulum and extends nasally to the optic chiasm. The dura mater caudal to the infundibulum separates the process of the pars intermedia from the pars tuberalis, while nasal and ventral to the infundibulum the connective tissue (*c.t.*, fig. 35) imprisoned in the fossa serves a similar purpose. The pars tuberalis lies in the pia mater of the brain floor the arachnoid spaces being located between it and the dura mater. The two nasal horns show a line of fusion in the model of embryo 17A.

The three epithelial parts of the gland, anterior lobe or pars anterior, pars intermedia, and pars tuberalis, are histologically distinct at this time. A somewhat schematized midsagittal section of a wax-plate reconstruction from a thirty-day embryo is shown in figure 37. Cut surfaces are distinguished as follows: brain wall and neural lobe, lined; pars anterior, fine stipple; pars intermedia, solid black, and pars tuberalis, coarse stipple. Enlarged drawings for histologic detail were made from the three regions squared (A, B, and C, fig. 37). These are reproduced in A, B, and C, respectively, of figure 38.



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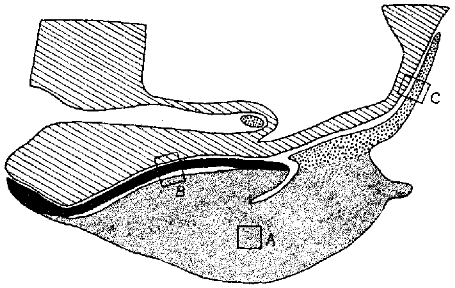

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Fig. 36 Model of hypophysis and adjacent brain wall from thirty-day embryo, viewed from left side. × 25. *b.w.*, brain wall; *p.t.*, pars tuberalis; *st.*, stalk; *ant.l.*, anterior lobe; *n.l.*, neural lobe.

Fig. 37 Diagrammatic midsagittal section of model shown in figure 36. × 25. Nasal end at right. Brain wall and neural lobe, lined; pars intermedia, solid black; pars tuberalis, coarse stipple; anterior lobe proper, fine stipple. A, B, and C indicate the regions enlarged and shown in A, B, and C, respectively, of figure 38.

The pars anterior (A, fig. 38) is made up of an irregular network of cell-cords between which lie large, irregular shaped blood-vessels. A small amount of connective tissue intervenes between the wall of the blood-space and the glandular parenchyma.

The pars intermedia (B, fig. 38) is a relatively thin epithelial strip, very poorly vascularized, which lies close to the neural lobe, or infundibular process. A thin layer of connective tissue containing blood-vessels is to be seen between the two. Strands of connective tissue penetrate from this layer into the pars intermedia. Besides the epithelial cells of the part, spindle-shaped cells which stain darkly with the iron hematoxylin are to be seen, extending mainly in a direction perpendicular to the epithelial surface. A few show evidences of branching. On account of the thinness of the sections employed (5μ) not many can be traced from one surface to the other. These are doubtless the supporting cells observed by Retzius, Cajal, Trautmann, Herring and others.

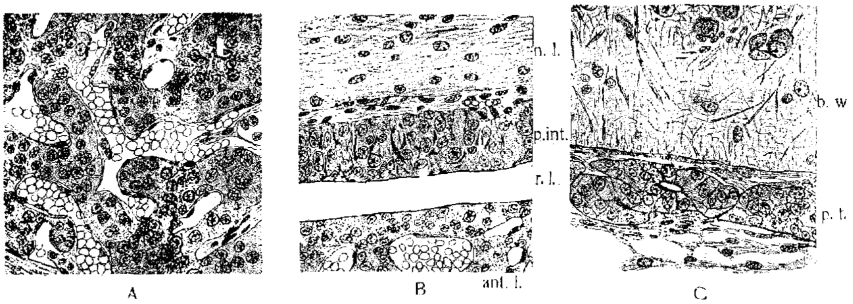

Fig. 38 Detail drawings of the regions indicated by A, B, and C of figure 37. × 250. A, anterior lobe proper; B, pars intermedia; C, pars tuberalis. *n.l.*, neural lobe; *p. int.*, pars intermedia; *r.l.*, residual lumen; *ant.l.*, anterior lobe; *b.w.*, brain wall; *p.t.*, pars tuberalis.

The pars tuberalis is a thin layer lying in the pia mater. It exhibits a distinct tubular or alveolar structure. The lumen of the tubule is small. The wall of the tubule, when this is cut squarely, is seen to be made up of a single layer of cells which are cubical or low columnar. Figure 39 presents another view of the pars tuberalis and shows the fairly large and numerous blood-vessels, many of which can be seen between the glandular lamina and the brain floor.

5. DISCUSSION OF OBSERVATIONS

A. The relation of the entoderm and the notochord to the hypophysis

I can find no evidence for asserting that the entoderm contributes to the formation of the hypophysis of the rabbit. Although the anterior extremity of the notochord is sometimes attached to the dorsal wall of Rathke's pocket in young embryos, it has not been possible to observe that it brings a bud of entoderm from the wall of the foregut to become fused with the hypophysis, after the manner described for the pig (Miller, '16).

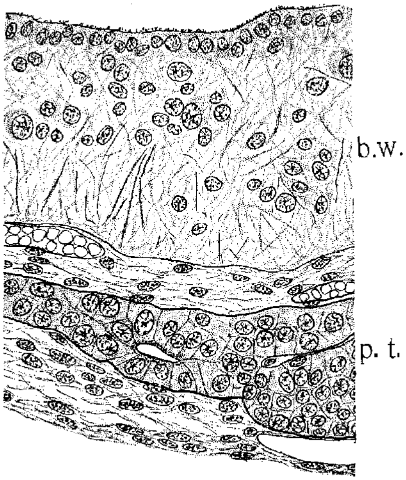

Fig. 39 Another detail drawing of the pars tuberalis. × 400. *b.w.*, brain wall; *p.t.*, pars tuberalis. Several bloodvessels are shown in the pia mater.

Miller states that the notochord pulls away from the pharynx, carrying with it a mass of entodermal cells which come to lie in relation with Rathke's pouch. It seems to me not unlikely that what he has seen is comparable to what has been described for bird embryos (Atwell, '15). It is also probable that his 'mass of entodermal cells' is the same as the cell cord observed by Nusbaum ('96) in dog embryos, although Nusbaum does not speak of a relation of the notochord to these cells.

But to assert, as Miller does, that the medulla of the anterior lobe—a very considerable portion of the gland—is developed from the entodermal cell mass seems to me unwarranted. Certainly, the fact that the medulla of the anterior lobe has a different histological structure from that of the cortex is not sufficient proof that the two are derived from different germ layers. To be convincing, it would be necessary to trace the development of the medullary part from the entodermal mass, maintaining the identity of the latter during the various stages.

Since the publication of a previous study (Atwell, '15), a number of other ten-, eleven-, and twelve-day embryos have been prepared, and their study has revealed some new instances of connection between the notochord and Rathke's pocket. It is to be emphasized, however, that this connection is not constant. Its adventitious nature argues that it is the slowly disappearing remains of some ancient structure. Further work is needed to elucidate this point, and for the present it must be considered highly problematical. The recent suggestion made by Parker ('17) that the connection between notochord and hypophysis may be nothing more than the remnant of the canal uniting the premandibular head cavities is worthy of consideration. It is of interest to note that a somewhat similar idea was expressed by Mrs. Gage ('06).

Since Kupffer's suggestion in 1894 that a fusion of the foregut with Rathke's pocket may be taken as indicative of an earlier communication between their cavities—the pre-oral mouth—not a few observers have attached great morphological significance to the hypophysis. Miller ('16) does not maintain that the entodermal mass observed by him to fuse with Rathke's pouch is the relic of a pre-oral mouth. Rather, he attaches such a significance to a perforation in the superior free stump of the oral membrane, This, again, seems to me questionable. If it can be demonstrated that the oral membrane frequently ruptures in a number of places, as is definitely shown by two reconstructions from the rabbit, then perforations in its fragments cannot be considered particularly significant, especially since my observations do not indicate that there is any regularity in their arrangement.

B. Some general features of the development of the hypophysis

1. The hypophysial stalk. Rathke's pouch is widely open to the mouth invagination at the beginning of its growth. At the twelfth day constriction of the opening has begun. By the end of the thirteenth day, a short stalk has been formed (figs. 11 and 12) which contains a narrow lumen, joining the cavity of the pouch with that of the mouth. At fourteen days, the stalk is solid and is much decreased in diameter (figs. 13 and 14). At fifteen days (fig. 16) it has lengthened and tapers from the gland to the epithelium.

The time at which the stalk becomes separated from the oral, or nasal, epithelium is subject to great variation. Thus, it has been seen that the stalk is separated from the oral ectoderm in one sixteen-day embryo (8A, fig. 18), while it is still attached as late as nineteen days (embryo 11B). The stalk may have lost its connection with the gland, and the sphenoid have become solid as early as the eighteenth day (embryo 12A, fig. 23), or the connection may persist, and the sphenoid contain a foramen, as late as the twenty-fourth day (embryo 23A). Attention has been called by Grönberg ('01) to a similar variation in the development of the hypophysis of Erinaceus europaeus.

It is a rule that the stalk separates from the epithelium earlier than from the gland. This is amply shown by a consideration of the several stages just mentioned. Epithelial remains are common between the sphenoid and the epithelium of the nasopharynx. Their persistence gives rise to a structure of irregular shape, which has been termed the pharyngeal hypophysis (*r.*, fig. 23).

The place of attachment of the stalk to the gland may be identified in all the stages up to and including the thirty-day embryo (fig. 35). In the latter of these stages, it shows itself as a short knob of glandular tissue having the structure of the anterior lobe proper. Mention has already been made of the apparent migration of the attachment of the stalk from the ventral side to the nasal end of the anterior lobe. This is due to the bending of the gland to form the fossa, to the approximation of the lateral lobes to the brain wall in the formation of the pars tuberalis, and, in the later stages, to a rapid growth of the glandular anterior lobe proper. The identification of this point is of use in tracing the fate of the temporary cortex which is formed at the nasal end of the gland during the development of the lateral lobes, and mention will be made of it in that connection.

2. The residual lumen. After the hypophysial stalk has become a solid structure, at fourteen days of development, the remains of the original cavity of Rathke's pocket is known as the residual lumen, or epithelial cleft. It serves to separate the pars intermedia from the anterior lobe proper. Its true significance was first recognized by Peremeschko ('67) and later by Lothringer ('86).

As shown by figure 13, the residual lumen at first extends from end to end of the gland and conforms to its general shape. Very soon, however, as the nasal end of the gland bends closer to the brain wall, the lumen does not extend to this extremity. As the bending continues and the neural lobe presses more against the dorsal wall of the epithelial portion, the lumen becomes L-shaped, in a sagittal section with one limb extending ventrally into the anterior lobe. As the neural lobe continues to increase in length, an additional limb of the lumen is formed, and thus the L-shape is converted into a Y- or T-shape. This process is shown at its initial stage in a nineteen-day embryo and at a later one in a twenty-day embryo (fig. 28). The limb of the Y which extends forward into the anterior lobe becomes obliterated. Approximation of its walls is seen in a twenty-six day embryo. The residual lumen may also be traced laterally in relation with the processes of the pars intermedia which surround the neck of the neural lobe.

C. The pars tuberalis and its development

Pars tuberalis is the name given by Tilney ('13) to a portion of the hypophysis lying in close relation with the tuber cinereum of the diencephalic floor. Doubtless, Bolk ('10) and Woerdeman ('14) refer to the same structure when they speak of the 'lobulus bifurcatus.'

For the rabbit it has been possible to trace the anlagen of the pars tuberalis from an earlier stage than that given by Tilney ('13) for the chick and the cat or by Miller ('16) for the pig. On this point my observations are essentially in accord with those of Woerdeman ('14) for the rat. From the thickened epithelial plate which early lies in front of Rathke's pocket (fig. 3) two thickened ridges are soon developed. These ridge-like protuberances or lateral lobes may be seen in sections of rabbit embryos taken during the tenth day of development. They are well shown in eleven- and twelve-day embryos (figs. 5 and 8). As the hypophysial pouch is constricted from the mouth cavity the lateral lobes form the lateral knob-like extremities of a transverse ridge or thickening lying at the nasal end of the hypophysis (fig. 12). At fourteen days (fig. 14) the lateral lobes have begun to grow out laterally and present rather sharper extremities than formerly. This, I take it, is the stage at which the lateral lobes were first recognized by Tilney and by Miller. From the observations here recorded I would reverse the chronology given by Tilney for the appearance of the pars tuberalis and the pars intermedia. Tilney states that the anlagen of the pars tuberalis appear relatively late, while I find that they may be recognized in the rabbit at ten days of development, and that a definite pars intermedia is not present until the definitive neural lobe is formed (twelfth day). At fifteen days the lobes are somewhat larger (figs. 16 and 17) and by sixteen days they form a large mass, deeply constricted off from the remainder of the gland, and having its tip in contact with the brain wall (fig. 18). Reconstructions of the seventeen- and eighteen-day stages (figs. 22 and 23) show the development of a cortical layer or plate overlying the nasal end of the anterior lobe. It has been formed from that part of the lateral lobes which lies between the stalk and the tips touching the brain wall. Baumgartner ('16) has traced the development of cortical zones and bands from the lateral lobes, which persist in the adult of certain reptiles. He suggests that these have been overlooked in mammals, since Miller ('16) is the only observer to record the formation of a cortex from the lateral cords (for the pig).

In the case of the rabbit, a cortex is not formed from the lateral lobes for the entire anterior lobe, and the cortical plate at the nasal end of the gland, as seen in the seventeen- and eighteen-day models, does not persist long in this position. This is conclusively shown by the shifting of the attachment of the stalk. When the cortex is present, it lies between the stalk and the root of the forming pars tuberalis. In the later stages of development the attachment of the stalk is at the extreme nasal end of the anterior lobe and comes very close to the attachment of the pars tuberalis. A layer extending between the two would cover only a very inconsiderable portion of the gland.

Salzer ('93) describes an epithelial 'Platte' to be seen at the anterior end of a reconstruction of the hypophysis from a 19-cm. pig embryo. Woerdeman ('14) believes that Salzer's epithelial plate is nothing else than a remains of the hypophysial stalk, but this would seem impossible, since Salzer states that the 'Platte' is about one-third as wide as the entire gland when viewed from in front. It is not unlikely that this 'Platte' is the same structure as the cortical layer, or plate, here described for seventeen- and eighteen-day rabbit embryos.

At eighteen days the lateral lobes have just begun to flatten out on the suface of the brain and thus to form the definite pars tuberalis. One day later a considerable portion lies on the brain wall. Each half of the pars tuberalis possesses a blunt nasal horn and a longer, sharper caudal horn (figs. 25 and 26). These latter constitute the 'cornua' of Bolk's 'lobulus bifurcatus,' and the strong central fusion of the two halves corresponds to his 'corpus lobuli bifurcati.' It would seem to me that the term 'lobulus bifurcatus' is applicable only to a passing stage of development of the pars tuberalis, such, perhaps, as here shown in figures 25 and 26. As we have seen, the pars tuberalis is not forked when development has been completed, but entirely surrounds the neck of the neural lobe, the two prongs of the fork (caudal horns) having fused at their extremities. Such a terminology must, of course, disregard the presence of a pair of nasal horns, and neither Bolk nor Woerdeman mentions having distinguished these.

Later development consists mainly of a spreading out of the pars tuberalis on the surface of the brain. The caudal horns extend backward and surround the neck of the neural lobe. The two horns have met in the midline by the end of the twenty-eighth day. The two nasal horns extend forward to the optic chiasm. Their fusion with each other is accomplished almost to completion during the last three days of intra-uterine development.

At birth the pars tuberalis lies in the pia mater of the floor of the brain except for a strong connection which unites it with the anterior lobe proper, this passing through the dura mater. The structure of this part is different from either that of the pars intermedia or that of the anterior lobe. It is well vascularized, and is thus in strong contrast to the pars intermedia. However, its vessels are not so prominent as those of the anterior lobe. But the most striking feature noticed in the pars tuberalis is the tubular arrangement of its cells. In general, the tubules seem to run nasocaudally. The tubular structure of the part may be observed as early as the twenty-second day.

The connective tissue imprisoned in the fossa (*c.t.*, figs. 28, 31, and 35) is of the greatest importance, since it serves to demark sharply the pars tuberalis from the pars intermedia. Thus it is clearly shown that the 'Fortsatz' (anterior part of the pars tuberalis) of Lothringer is not properly to be spoken of as the 'Fortsatz des Epithelsaums.' The same objection must be made to Herring's use of the term 'tongue-like process of the pars intermedia,' as Tilney ('13) has pointed out.

Haller's statement ('97), that a thin layer of the hypophysis lying close to the brain—doubtless the pars tuberalis—pours its secretion into the subdural space, has not received confirmation from other observers. If it shall be shown that the pars tuberalis possesses a secretory function different from that of the other two parts of the gland, then the manner of absorption of its product will be of interest.

From the richness of its blood-supply, it is generally believed that the secretion of the anterior lobe enters the vascular system directly. On histological grounds, Herring ('08 b) believed that the pars intermedia sends its secretion into the neural lobe, and that this secretion makes its way into the cerebrospinal fluid. Confirmation of this theory has been obtained by Cushing and Goetsch ('10) from the injection of concentrated cerebrospinal fluid which produced the characteristic reactions called out by extracts of the posterior lobe.

Structurally, there are three possibilities for the absorption of a secretion from the pars tuberalis. One is that the secretion is given off into the cerebrospinal fluid in the subdural, or rather the subarachnoid, space. The isolated position of the part—separated as it is by the dura mater from the remainder of the gland—and its tubular structure lend some plausibility to this view. Another possibility is that the secretion is taken through the brain floor and enters the cerebrospinal fluid in the third ventricle. In support of this view, the lateral extensions of the third ventricle corresponding to the size and shape of the pars tuberalis may be recalled. The third possibility is that the secretion is absorbed directly into the blood-vessels, and their relative abundance would be in favor of such a view.

D. The development of the neural lobe

So far as I have been able to ascertain, the foldings and compressions by which the cavity of the neural lobe is divided up and by which a cortex is formed, have not been described by any previous observer. The cavity of the neural lobe, which is a continuation of the third ventricle of the brain, remains open in only one family of mammals, the Felidae (Tilney '15). Herring ('08 a) has chosen the domestic cat for the subject of his studies on the development of the hypophysis, because the cavity is open in adult animals. In all other mammals, so far as is known, the neural lobe becomes a solid structure, containing only a shallow, funnel-like depression at its neck, the infundibulum proper.

According to Grönberg ('01), obliteration of the cavity of the processus infundibuli in Erinaceus europaeus begins at the caudal extremity of the lobe and proceeds toward the neck. He does not mention any foldings of the infundibular wall. Mihalkovics ('75), for the rabbit, has noted that the central cells are radially arranged, while the outer cells are smaller and irregularly disposed. He states merely that the cavity of the lobe is obliterated by a growth of the infundibular walls.

Almost from its earliest appearance, the walls of the neural lobe of the rabbit's hypophysis show a number of foldings (figs. 11 and 13). These rapidly become more complicated, and during the fourteenth day, cells from the wall have entered the lumen of the lobe so that its cavity is partially obliterated and very irregular in shape. Sometimes septa, or partitions, are formed which divide the communication with the third ventricle into two or more openings. This is seen in models of fifteen- and seventeen-day embryos.

Around the outside of the lobe, a cortical zone is formed by much the same process as that by which cells obliterate its cavity. Apparently the basement membrane is broken through to permit masses of cells to escape to the exterior of the lobe. At any rate, the cell masses often do not seem to be definitely surrounded by a membrane and portions of the original basement membrane are to be seen between the medulla and the cortical zone. As shown by figure 21, the medullary layer has its cells radially arranged, while the cells of the cortical zone are very irregularly disposed. The cortical layer becomes fibrillar in structure in later stages, and the cell bodies become more widely separated. This is well shown in a twenty-day embryo (fig. 21, C).

Müller ('71) and Mihalkovics ('75) have maintained that the infundibular process, or neural lobe, becomes converted into a "connective-tissue appendage of the brain" through the gradual replacement of its nervous elements by connective-tissue cells. Herring ('08 a), by employing the methods of Golgi and Cajal, has shown that the neural lobe does not become a connective-tissue appendage, but that it is composed of a somewhat modified ependymal and neurogliar tissue. I have not made use of these special stains for nervous tissue, but, by carefully following the development of the neural lobe, I am not able to find that any considerable amount of connective tissue becomes incorporated into it. The blood-vessels are very few in the lobe prior to the twentieth day of development. Even after this time, they are never very numerous, and the connective tissue accompanying them is small in amount.

The angle formed by the attachment of the neural lobe to the brain wall undergoes an interesting series of changes. At thirteen days (fig. 11) the lobe makes an acute angle with the brain wall in the nasal side of its attachment. It is into this angle that the apex of Rathke's pocket is seen to be fitted. By seventeen days (fig. 22), the angle formed by the neural lobe and the brain wall is approximately ninety degrees. After this time, the angle is acute on the caudal side of the attachment of the lobe. The acuteness of the angle gradually increases, until at thirty days the neural lobe lies almost parallel to the floor of the third ventricle (fig. 35).

E. The neuro-epithelial contacts and their significance

Contacts between the neural lobe and the intermediate part, such as are here recorded for certain fifteen- and sixteen-day and older embryos, have not been described by any other observer. It is true that Herring ('08 b) based his theory, that the secretion of the pars intermedia is absorbed through the brain, on the fact that the neural lobe is apparently invaded by cell masses and secretion globules from the intermediate part. But this is quite different from what I have observed in the sixteen-day and related stages of the rabbit's development. Reasons have already been enumerated why these contacts appear to me to be due to an active growth of processes of the neural lobe into the intermediate part. Attention has been called to the presence of a small depression, corresponding to the center of each contact which may be seen on that surface of the pars intermedia which faces the residual lumen. It has been noted that the contacts vary in numbers from one to five, and that they were found constantly present in all of the sixteen-day embryos examined and in certain fifteen-seventeen-, eighteen-, and twenty-day embryos.

With these facts in mind, a survey may be made of the explanations which are to be found for the possible significance of these contacts or ingrowths.

1. Herring ('08 a) has seen, in a single cat embryo near term, an opening uniting the cavity of the neural lobe with the residual lumen. He interprets this as a recurrence of some ancestral bucconeural communication. It might be argued that the contacts observed for the rabbit are an attempt to form such a communication, notwithstanding the fact that no lumen is to be found in them. If there were constantly only one of these contacts to be seen, this hypothesis might demand serious attention, but since they vary in number, and may be as many as five, it seems to me very improbable that this is the correct explanation.

2. Another possibility is that these contacts are an imperfect, temporary recurrence of the condition normal for the fishes, in which forms numerous processes from the brain floor enter the pars intermedia. Such structures are pictured by Stendell ('14) in his figures 19 to 24, pages 20 to 26. If this interpretation be correct, similar structures should sometimes be found in the vertebrates between the mammals and the fishes, and one would expect them to become larger and more constant as the vertebrate scale is descended.

3. The most likely possibility, it seems to me, of the significance of these contacts is that they are a means for supplying the ependymal and neurogliar supporting tissue to the pars intermedia. That such tissue is really to be found in the intermediate part is indicated by the observations of Pirone, Gemelli, Retzius, Herring, Trautmann, Cajal, and others. They have been described by Retzius for the rabbit, eight days after birth. Stendell believes that these tissue elements have wandered in from the neural lobe, but he quotes no observations to substantiate such a view. The other possibility is, of course, that the spindle-shaped elements which have been noted are peripheral supporting cells developed *in situ* in the epithelium of the pars intermedia after a manner similar to the supporting cells of the olfactory epithelium. This view would receive some support from the close relation of the hypophysis to the olfactory organ in the Monorrhina. However, the fact that the pars intermedia of the hypophysis in the highest order of vertebrates shows cells which may

be termed neurogliar and others which may be called ependymal (Stendell) gives the transfer theory considerable significance, although for the present it must remain an hypothesis merely.

F. Terminology and phylogeny of the lobes of the hypophysis

The terminology, still to be found in text-books of anatomy and embryology, which speaks of that portion of the hypophysis derived from the brain as the 'posterior lobe' and that derived from the oral invagination as the 'anterior lobe,' must be considered entirely inadequate. Physiologists recognize two very different internal secretions as being produced by the hypophysis. One is obtained from the 'posterior lobe' and causes a marked rise of blood-pressure, increased secretion of urine and of milk, a general contraction of involuntary muscle, especially of the uterus, etc. The other is obtained from the 'anterior lobe' and does not markedly influence blood-pressure on introduction into the circulation, but is thought to influence body growth, particularly of the bones. It is held that the secretion attributed to the 'posterior lobe' is in reality not formed by the nervous portion of the hypophysis, but by its epithelial covering, the 'pars intermedia.' 'Posterior lobe' to the physiologist means neural portion together with the epithelial layer which is closely adherent to it. Or, more succinctly stated, 'posterior lobe' means neural lobe plus pars intermedia, and 'anterior lobe,' as understood by the physiologist until recently, means buccal portion minus pars intermedia.

The recently recognized pars tuberalis must be considered a distinct portion of the gland, both embryologically and histologically, as urged by the present study and by the investigations of Tilney, Baumgartner, and Parker. 'Anterior lobe,' then, should mean buccal portion minus pars intermedia and pars tuberalis. Thus any adequate consideration of the lobes of the mammalian hypophysis must recognize four parts—the neural lobe, and three divisions of the epithelial lobe. These three parts are pars anterior propria, pars intermedia and pars tuberalis.

It is well known that in the Elasmobranchs there is to be found a pair of hypophysial lobes which lie inferior to the main body of the gland, and are known as the 'inferior sacs' or 'inferior lobes.' Baumgartner ('15) has studied the development of the hypophysis in Squalus acanthias and figures several wax reconstructions of the embryonic organ. He speaks of the epithelial part of the hypophysis in Squalus as consisting of four lobes: an 'anterior lobe,' a 'superior lobe,' and a pair of 'inferior lobes.' In another study Baumgartner ('16) has treated very fully the development of the hypophysis in the Reptiles. He speaks of Rathke's pouch, two lateral buds, and an anterior bud.

Woerdeman ('14) feels justified in homologizing the lateral lobes of mammals with similar structures in the Reptiles and also with the inferior lobes or ventral sacs, of the Selachians. The 'lobulus bifurcatus' of mammals in reality represents a much-reduced complex of Selachian 'Vorraum,' 'Mittelraum,' and 'lobuli laterali.' Woerdeman believes that "wahrscheinlich der Lobulus bifurcatus ein rudimentäres Organ darstellt, und dass der vordere Teil der Hypophysen anlage sich sehr wenig entwickelt bei den meisten, ja fast völlig unentwickelt bleibt bei anderen Säugetieren."

If we accept the homologies drawn by Woerdeman, we may briefly summarize the history of the lateral lobes as follows: In the Elasmobranchs the hypophysis possesses a pair of lobes which lie ventral to the main body of the hypophysis and thus are a considerable distance removed from the brain wall. These inferior lobes or ventral sacs remain separate from one another, but are connected by ducts to the cavity of the body of the hypophysis. In the higher vertebrates, two homologous lobes (lobuli laterali) do not retain a position ventral to the main body of the gland, but grow toward the brain. They may be said to insinuate themselves between the main body of the gland and the diencephalic floor. They fuse with each other and form a lobe which extends forward to the optic chiasm and posteriorly to embrace the infundibular stalk. Thus a new 'juxta-neural' (Tilney) portion of the gland is formed. The anterior portion of this lobe has been called 'Fortsatz des Epithelsaums' (Lothringer); 'vordere Lappen,' 'vordere Fortsatz' (Haller); 'lobus chiasmaticus' (Staderini); 'pars terminalis' (Gisi), and 'tongue-like process of the pars intermedia' (Herring). The posterior part of the lobe Staderini has called the 'lobus praemammilaris.' Ontogeny shows that anterior and posterior portions are a unity, so they may be named as one lobe. Joris has called the lobe the 'lobule de la tige,' Bolk terms it the 'lobulus bifurcatus,' and Tilney names it the 'pars tuberalis.'

From their very similar development and fate it would seem that the lateral lobes of the Mammals may safely be considered homologous to the lateral lobes of the Reptiles.

It is to be noted that no adequate description exists concerning the development of lateral lobes in either the Teleosts or the Amphibia. For this reason, it must be somewhat precarious at the present time to homologize the lateral lobes of embryos of the Amniota with the ventral sacs of the Elasmobranchs.

I cannot agree with Woerdeman when he homologizes the anterior part of the mammalian 'lobulus bifurcatus' (pars tuberalis) with the median unpaired 'Vorraum' of the reptilian and selachian hypophysis (compare his fig. 30, G and H). According to my observations on the rabbit, the anterior portion of the pars tuberalis has a paired origin, being formed by the fusion of the blunt nasal horns of the lateral lobes. If a homologue of the 'Vorraum' be present during the development of the hypophysis of the rabbit, it is best recognized at the fourteenth and fifteenth days. After this time it must be very much reduced, even more so than stated by Woerdeman.

6. SUMMARY AND CONCLUSIONS

1. The hypophysis evagination is plainly visible in a rabbit embryo having sixteen primitive segments. In age this corresponds to the earlier part of the tenth day after insemination. The definite neural lobe first appears during the twelfth day.

2. The cephalic extremity of the notochord is directed toward a bud-like outgrowth of the dorsal wall of Rathke's pouch in certain ten-, eleven-, and twelve-day embryos, but this relation is not constant. No evidence can be found for stating that the entoderm contributes to the formation of the hypophysis of the rabbit.

3. The stalk connecting the hypophysis with the oral epithelium becomes solid during the fourteenth day. It loses its connection with the epithelium at a variable time—as early as the sixteenth-day or as late as the twenty-fourth. The place of attachment of the stalk to the gland is indicated even until the time of birth; it shows an apparent migration to the nasal end of the anterior lobe proper.

4. The residual lumen of Rathke's pouch at first extends from end to end of the epithelial portion; later it does not reach to the nasal extremity. The bending of the gland gives the lumen an L-shape in sagittal sections, with one limb extending into the anterior lobe proper. The L-shape is changed into a T- or Y-shape by the addition of another limb which is in relation with the portion of the pars intermedia extending around the caudal end of the neural lobe. The limb extending into the anterior lobe becomes obliterated. The remainder of the lumen is present at birth and separates the intermediate part from the anterior lobe proper.

5. From the thickened epithelium just nasal to the early Rathke's pocket two ridge-like elevations are developed. These have been called the lateral lobes. As the hypophysial evagination is constricted from the oral cavity the lateral lobes constitute the lateral terminations of a transverse ridge lying at the nasal end of the gland. At fourteen days the lobes have begun to grow out laterally, and are more sharply constricted from the body of the hypophysis.

The lateral lobes are the anlagen of the pars tuberalis and of a temporary cortical plate at the nasal extremity of the gland. They begin to be in relation with the brain wall at sixteen days and by nineteen days a considerable portion lies spread out under the floor of the third ventricle. There are present at this stage two blunt nasal horns extending toward the optic chiasm and two sharper caudal horns extending backward to surround the neck of the neural lobe. The caudal horns have completely surrounded the infundibulum and have met in the midline by the end of the twenty-eighth day. The nasal horns fuse with each other during the last two or three days of development.

Since the pars intermedia is not definitely present until the definitive neural lobe has begun to form (twelfth day), the anlagen of the pars tuberalis precede it in appearance by two days (in the rabbit). This reverses the chronology of their appearance as given by Tilney ('13).

The pars tuberalis comes to lie in the pia mater of the diencephalic floor. In the rabbit it maintains its connection with the parent gland, at least as late as the time of birth, by a strong stalk which penetrates the dura mater of the diphragma sellae. It shows distinctly a tubular structure with the tubules extending for the most part in a nasocaudal direction.

The pars tuberalis constitutes a portion embryologically and histologically different from the remainder of the gland. It is sharply demarked from the pars intermedia, even until the time of birth, by the dura mater and by connective tissue which has become imprisoned in the fossa. Thus Lothringer's name, 'Fortsatz des Epithelsaums' and Herring's term, 'tongue-like process of the pars intermedia,' as used to designate the anterior portion of the pars tuberalis, are not descriptive of the development of the part. The same objection may be urged in reference to Herring's confusion of the caudal part of the pars tuberalis with the "extension of pars intermedia round neck of gland."

6. The neural lobe undergoes a series of complex foldings and compressions which results in the dividing up and partial obliteration of the cavity of the lobe and in the formation of a medullary layer and a cortical layer.

7. Definite contacts between the neural lobe and the intermediate part are to be seen in sixteen-day and related stages of development. Reasons are given for the belief that these contacts are due to the growth of processes from the neural lobe into the intermediate part. The suggestion is offered that the contacts may constitute a mechanism for supplying the ependymal and neurogliar elements which have been observed in the intermediate part by Retzius, Cajal, Trautmann, Herring, and others.

8. From a similarity in development and fate the lateral lobes of the Mammals and of the Reptiles may be considered homologous. It is somewhat precarious, for the present, to homologize

the lateral lobes of the Reptiles and Mammals with the inferior lobes of the Elasmobranchs.

In the rabbit the anterior part of the pars tuberalis cannot be homologized with the 'Vorraum' of the lower vertebrates, since it is seen to be developed from the paired blunt nasal horns of the lateral lobes.

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