

ON THE (SO-CALLED) THYMUS: IV AND THE ULTIMOBRANCHIAL BODY OF THE CAT (FELIS DOMESTICA)

FRED W. STEWART

Department of Histology and Embryology, Cornell University, Ithaca, N. Y.

FOUR PLATES

INTRODUCTION

Despite its apparent significance, the thymus IV (so-called) has received but scant attention. The presence of small aggregates of thymus tissue in close relation to the parathyreoid IV has been noted by numerous investigators during the past two decades and its occurrence, although manifestly inconstant, has been largely used in advocating a concept of 'branchiomic organs.' However, in reviewing the literature on the subject, I have been unable to discover a single investigation whose results directly afforded such evidence as would warrant the thymus IV (so-called) being placed among branchiomic structures. The statement of Verdun ('98), Groschuff ('00), Tandler ('09), Grosser ('10), and Sobotta ('14), to the effect that the anlage of the thymus IV is to be found in the diverticulum ventrale of the fourth pharyngeal pouch, rather than being evidence of the essentially metameric nature of the thymus, seems, instead, a deduction based on a general branchiomic concept. The assignment of the thymus IV to the ventral diverticulum of the fourth pouch would appear, in the present state of our knowledge, a premature one, and the need of further investigation, before making a generalization of such fundamental importance, rather imperative.

It was with this purpose in mind that the following investigation was begun. On account of the close relationship, both in origin and fate, of thymus IV and the so-called ultimobranchial body, the latter structure must needs be considered in some

detail both as to fate and probable morphology. Much discussion has centered of late about the ultimobranchial body, and in view of the recent paper of Camp ('17) no extensive literary survey is included in the present work, the reader being referred to Camp for a complete account.

HISTORICAL

We are perhaps indebted to Prenant ('94) for a clear expression of the branchiomic concept. Seeking to emphasize the metameric nature of the branchial derivatives, the latter contrived to express the relationship existing between certain structures, originating from the epithelium of the third and fourth pouches of the embryonic pharynx, by the following formula:

$$\frac{\text{troisième nodule branchiale (glande carotidienne)}}{\text{troisième fente et troisième diverticule (thymus)}} = \frac{\text{quatrième nodule branchiale (glandule thyroïdienne)}}{\text{quatrième fente et quatrième diverticule (thyroïde laterale)}}.$$

One year later, Kohn ('95) published the first of two contributions on the study of the thyroid; he, being at that time especially interested in the epithelial bodies or parathyroids, the major part of the paper concerns itself with these structures. Portion C, however, is devoted to the detailed description of "Thymusläppchen in und an der Schilddrüse (inneres und äusseres Thymusläppchen der Schilddrüse)" Kohn's conclusions may be stated in his own words as follows:

"An der Schilddrüse der Katze (und auch wahrscheinlich andere Säugethiere) ist ein neben oder unter dem äusseren Epithelkörperchen gelegenes Thymusläppchen das äussere Thymusläppchen der Schilddrüse ein regelmässiges Befund ebenso regelmässig findet man innerhalb der Schilddrüse der Katze ein neben oder unter dem inneren Epithelkörperchen gelegenes Thymusläppchen—das innere Thymusläppchen der Schilddrüse."

The frequent occurrence of lymphoid aggregates within the thyroid makes it difficult to ascertain by whom the true thymic lobules were first recognized and described. According to Kohn, they were doubtless noted by Kölliker ('79), Lupo ('88),

and by Zielinska ('94). The Lupo reference is not at my disposal; he is, however, said by Kohn to have described two thyroid components—a vesicular portion and a lympho-adenoid portion; since Lupo investigated cat thyroids and since in this form the external and internal thymic lobules are of almost constant occurrence, it seems probable that in the lympho-adenoid component of Lupo one has the thymus bodies of subsequent writers.

Zielinska ('94) describes in addition to 'Embryonale Reste' or parathyroids, small accumulations of lymphoid tissue; she calls attention to the presence of necrotic areas in the centers of some of the larger aggregates and believes to distinguish a small nematode in the heart of the necrotic area; the presumption is that Zielinska had observed thymic tissue and that the necrotic areas were really Hassall's corpuscles.

Groschuff ('96), doubtless under the influence of Kohn, made certain alterations in the formula of Prenant and expressed the third-fourth pouch homodynamy in the following manner, the change being made subsequent to the identification of the 'glande carotidienne' of Prenant with the parathyroid III and the discovery of the so-called thymus IV:

$$\frac{\text{Parathymus III (parathyroid III)}}{\text{Thymus III}} = \frac{\text{Parathymus IV (parathyroid IV)}}{\text{Thymus IV}}$$

Such is the schema as one finds it in our texts up to the present. The third pouch of mammals produces a parathyroid and the thymus III, a portion of which latter may be said to give rise to the external thymic lobule or thymus head, attached to parathyroid III in its final position in many forms under the capsule of the thyroid; the fourth pouch produces the parathyroid IV and may give rise to a thymus body bearing similar relation to the pouch and to the parathyroid IV as bears thymus III to the third pouch and to its epithelial body.

Verdun ('98) observed a lymphocyte infiltration and a thymic transformation in a small reticular area in close relation to the parathyroid IV in the cat and derives this reticular portion consequently from the diverticulum ventrale of the fourth pouch.

Groschuff ('00) described a thymus IV in man and on the basis of the study of calf embryos likewise assigns its anlage to the ventral portion of that pouch. Tandler ('09) found that in man the diverticulum ventrale IV regularly contained the anlage of a thymus body, basing his conclusion on certain thickenings in the epithelium of this region as observed in quite early stages, and in this statement he is followed by Grosser ('10) and Sobotta ('14). Hammar ('09) adopts a more conservative attitude and doubts the evidence for regarding the mammalian thymus a metameric structure. Similarly, Kingsbury ('14) ventures the statement that the derivation of a thymic lobule from a ventral diverticulum IV is not as yet justified.

The presence of additional branchial structures in mammals has a somewhat complicating influence on generalizations of the kind attempted by Groschuff; the place of the ultimobranial body in the schema is a point of great interest, as is likewise that of the transient fifth pouch. Discussion as to the ultimobranial body, if one regards the question as to its origin—branchial or post-branchial—as definitely determined in favor of the former, still centers about two questions: 1 its fate and, 2 its interpretation. In a discussion as to its interpretation one is naturally confronted with the problem of its place among branchiomic organs. Following the version of Tandler ('09) and homologizing the ultimobranial bodies with rudimentary fifth pouches, one may ask oneself to what extent these vestigial pouches produce those metameric structures common to the two more anterior outpocketings; the same question occurs when the theory of H. Rabl ('13) is examined, the latter seeking to homologize the ultimobranial bodies with rudimentary pouches V and VI. Getzowa ('11) has given answer—not directly, but incidentally—in what we may perhaps take as our grossest example of a branchiomic concept. She distinguishes in the thyroids of certain cretins not only a thymus IV, but likewise a parathyreoid and a thymus metamer belonging to a fifth pouch, and in addition to these a postbranchial (ultimobranial) epithelial body and postbranchial thymus metamer. No embryological study was made, and it seems to the writer

vastly questionable whether such distinction is justified by any evidence now at our disposal. The occurrence of separate thymic bodies or of separate epithelial bodies within the thyroid is doubtless subject to different interpretation, and their assignment to pouch V and to the ultimobranchial body is believed unwarranted.

In view of our lack of evidence as to the exact origin and nature of the thymus IV (so-called), it is believed desirable to avoid this terminology and to adopt the designation of Kohn. The expression 'internal thymic lobule' will henceforth be employed throughout this paper to indicate the thymus IV.

The fate of the ultimobranchial body in man has been recently investigated by Kingsbury ('14). Kingsbury was able to trace the structure, subsequent to its inclusion within the thyroid, to an inner condensation apparently marking its last phase as a distinct structure; he was unable to satisfy himself as to the exact fate of the cells involved in this inner condensation, but believed in their degeneration. Quite an opposite conclusion was presented by Badertscher ('15) in a paper (published '16) before the American Society of Anatomists. The latter showed evidence for supposing a formation of thyroid follicles from the ultimobranchial body of the pig. The paper was supplemented by demonstrations to that effect at the 1916 meetings.

MATERIAL

The occurrence of the internal thymic lobule is, as far as one may determine, in no form constant, despite the statement of Schäfer ('12). The latter's reference to Kohn should refer only to the cat—the form especially studied by Kohn. Even in the cat it is not absolutely constant. Nevertheless, the frequency of its presence in this form makes it a desirable one for study, and its selection was for this reason.

The material comprised the cat embryos of the Cornell collection, supplemented by those of the Columbia collection. In all upwards of seventy embryos were examined in stages ranging from 5.5 to 92 mm., together with older thyroids at 120, 165, 280, 295, and adult stages. Material was not available for a

histogenetic study as regards the origin of the lymphocytes and this chapter in the history of the structure is omitted rather than offering its presentation under conditions inadequate for its investigation. I desire at this point to express my appreciation to Dr. George S. Huntington for the opportunity afforded me to examine the series of cat embryos at Columbia University and for the very material assistance furnished through the gift of several larger embryos; likewise to Professor S. H. Gage for his kind permission to examine the Gage series, to Dr. H. D. Reed for four embryos, and lastly to Dr. B. F. Kingsbury for constant encouragement and advice throughout the study.

Five reconstructions were made of the caudal pharyngeal complex (the term used by Kingsbury ('14) to designate fourth pouch and ultimobranchial body) previous to its involvement in the thyroid, and three subsequent to this period. The latter three are not shown, since it is not believed that they contribute points of further value to this study.

DESCRIPTION OF STAGES

In the earliest of the embryos (5.5 mm.) of which a reconstruction (figs. 1 and 2) of the pharyngeal region was made, conditions resemble closely those shown by Coulter ('09) in his reconstruction of the pharyngeal pouches of the cat embryo of 5 mm. in connection with a study of the fifth aortic arch. Four pouches are differentiated. The third pouches, whose brief description is introduced for the sake of comparison, exhibit well-marked ventral diverticula directed towards the thyroid; the latter is present as a hollow downpocketing from the floor of the pharynx, not as yet stalked; one should doubtless describe them as directed toward the bifurcation of the truncus aorticus, the position of the vessels seeming the main factor in determining their morphology. The aortic arches were, however, not reconstructed. Ectoderm and entoderm are in contact along a line, which, due to the curvature of the region, is almost a horizontal one. Dorsad of the ectodermal contact there are present blunt, rather poorly developed dorsal extensions of the entodermal pouch—

the so-called dorsal diverticula. Development of the fourth pharyngeal pouch has proceeded farther on the right side than on the left, there being as yet no ectodermal-entodermal contact on the left side. On the right, ectoderm and entoderm are in contact along a line nearly parallel to and approximately half as extensive as the third pouch contact; likewise on the right side one finds a well-marked ventral diverticulum IV, similarly directed towards the bifurcation of the truncus aorticus; on the left side the ventral diverticulum is evident as a very slight downpocketing, of considerably less prominence than its fellow. Dorsal diverticula are not present as regions of prominence.

Caudal to the fourth pouch (figs. 1 and 2) one finds a further outpocketing towards the ectoderm; this likewise is more marked on the right side. It is distinctly towards the ectoderm, although I have been unable to detect an ectodermal contact. There seems no reason for failing to recognize in this last evagination the remnant of a fifth pharyngeal pouch. This more caudal outpocketing opens into the pharynx with the fourth pouch, there being no evidence of an internal demarcation between the two regions. No ventral or dorsal diverticula of this rudimentary fifth pouch are present. Posterior to the fifth pouch on the left side the entoderm narrows rather abruptly; on the right, however, there is a seeming tendency, as evidenced by the gradual constriction, for somewhat more of the entoderm to become involved. It is this fifth pouch together with the suggested involvement of a more caudal region of the pharynx, which the writer recognizes as the so-called ultimobranchial body. Its subsequent history may be followed in succeeding stages.

In a reconstruction (fig. 3) of the caudal pharyngeal region in an embryo of 7 mm., the following facts may be noted: with the beginning formation of the constriction, subsequently the ductus pharyngobranchialis IV, the individuality, if one may employ the term, of the ultimobranchial body becomes less and less apparent, and the evagination which in earlier stages was clearly towards the ectoderm and was recognizable as a fifth pouch is now present as a caudally directed outpocketing of the

fourth pouch. A slight ridge on the lateral aspect of this caudally directed portion may perhaps be taken as representative of the farthest point reached during development towards a fifth ectodermal-entodermal contact; this is however, uncertain. In none of the several embryos of about this stage have I been able to observe a fifth contact, although the condition is closely approximated in all of them; a fifth branchial cleft may be safely said never to exist in the cat. At least among the constituents of the ultimobranchial body are those cells which would have been involved in a fifth ectodermal contact, had such existed; whether or not more material is involved is a point for subsequent discussion.

The fourth pouch possesses a prominent diverticulum ventrale, directed as in the preceding embryo of 5.5 mm., towards the bifurcation of the aorta; there is yet distinguishable no thickening or marked proliferation in the entodermal cells of the diverticulum ventrale, which might serve to identify it as a possible thymus anlage. The dorsal diverticulum is small and poorly defined; one has no evidence of modification to mark the beginnings of a parathyreoid IV. In this embryo there is no fourth pouch ectodermal contact; such was, it will be remembered, present at 5.5 mm. and was likewise observed in embryos of 7.5, 8, and 8.5 mm. The line of previous contact is, however, clearly recognized in the reconstruction; considerable variation is doubtless to be found in the time of severing the ectodermal connection and apparently its effect on the form assumed by the complex in later stages is quite marked. Conditions in the third pouch resemble those previously described and do not merit further attention.

In the reconstruction of the caudal pharyngeal region in an 8.5-mm. embryo (fig. 4), the complex is found to present more the appearance of a rounded vesicle. The diverticulum ventrale IV is present as before, but is of greatly diminished prominence. In a basal view of the complex, the diverticulum ventrale IV may be said to constitute the cephalic vertex of a triangle, the lateral angle consisting of the portion along the line of former ectodermal contact and the posteromesial portion

the region to be designated as ultimobranchial. The beginning downgrowth of the complex is evidenced by the increased curvature of the caudal pharyngeal region and by a lengthening of the ductus pharyngobranchialis IV; there is also a tendency for the region of the ultimo to become more ventral in position and to occupy a larger portion of the base of the complex; this, coupled with the reduction of the diverticulum ventrale IV, causes the latter to appear as an outpocketing from a complex consisting of pouch IV proper and the ultimobranchial body, thus reversing former conditions. A point perhaps worthy of note at this time is the more exact morphology of the ductus pharyngobranchialis IV. Recognizing the existence of a fifth pouch which later in its development appears as an evagination from a fourth pouch, one should perhaps designate their common opening into the pharynx as ductus pharyngobranchialis IV + V. The interpretation of further pouch-forming value in the more caudal pharyngeal region intrudes itself in this definition; the recognition of the relation of the ductus to the fifth pouch is, however, clear. It is likewise desirable to call attention at this time to the relatively great distance to which the placodal attachments become drawn into the ganglion of the tenth nerve. The remnants of these placodal attachments may be found in some cases as vesicular structures within the mass of ganglion cells at considerably later stages; their cells are in a state of rapid proliferation, and there seems no doubt but that the ganglion receives a component from these placodes.

In a 9.5-mm. embryo relations are similar to those just described, with the following exceptions; on the dorsolateral aspect of the complex one finds an outpocketing of considerable size; this represents the region of the last attachment to the vesicula cervicalis and has in the downgrowth of the complex become somewhat drawn out previous to its separation from the ectoderm; its presence or absence must be regarded as a function of those two determining factors, the downward growth of the complex and the duration of the ectodermal contact; the caudal and ventral portions of the complex as well as perhaps the caudal portion of the above-mentioned outpocketing may be designated

as ultimobranchial in origin. At this stage the parathyreoid IV is present as a well-marked hollow projection on the cephalo-dorsal aspect of the complex. The latter may then be said to consist of four definable regions—distinguishable approximately, but not with definite regional boundaries; an anterior portion consisting of pouch IV proper, parathyreoid IV, diverticulum ventrale IV, the last passing gradually into the posteroventral portion—the region of the ultimobranchial body.

In a 13-mm. embryo (fig. 6) a diverticulum ventrale IV can no longer be distinguished as a separate prominence; the region of the parathyreoid IV, while not so prominent in relation to other portions of the complex as in the embryo just described, has grown enormously in proportion and now constitutes the major portion of the cephalic region of the complex; the parathyreoid is at this time a solid mass of cells. The caudal and lateral portions of the complex are thickened with a partial occlusion of the lumen, the cavity persisting in the more medial region—that more directly continuous with the ductus pharyngobranchialis. The ductus is narrowed, but does not show evidence of great extension due to the 'descent' of the complex. A feature to be noted in this embryo is the presence of a quite distinct cavity of the ultimobranchial body (fig. 7). The latter cavity is separate from that of the remainder of the complex in a small region only, situated at the base of the ductus and in the figure giving the appearance of a separate ductus pharyngobranchialis V.

A narrow cord-like mass of cells extending from the lateral aspect of the complex marks the position of the former connection with the ectoderm; it possesses a central core of quite densely packed cells; the cells on the periphery show a tendency to loosen and to shade off into the surrounding mesenchyme. The latter is condensing somewhat around the complex and a delimitation of boundaries is difficult; for this reason the cord of cells as shown in the reconstruction may be somewhat exaggerated; its exaggeration does not, however, alter its value as a point of orientation. Using this ductus branchialis IV as a landmark together with the parathyreoid IV, one would place the inferior

and posterior portions of the complex with the ultimobranchial body.

The time varies at which the connection with the pharynx is broken. The earliest embryo where a break was noted was one of 10.5 mm. and the latest in which a pharyngeal connection could still be made out was one of 14 mm. The complex is, at the time of the rupture of the pharyngeal duct, nearly at the level of the lateral extensions of the thyroid, and hence this break is quite speedily followed by its contact with and subsequent inclusion within the median thyroid. The extent of the inclusion is a matter of great variation. In an embryo of about 16 mm. the lower tip of the complex is barely in contact with the thyroid cords; three regions may now be recognized: the parathyroid IV, a region containing a large cavity, to be identified as approximately the cavity of the fourth pouch proper, and lastly a large ventral mass of cells constituting the ultimobranchial body; the latter contains traces of a nearly obliterated cavity. The cells of the walls of the region designated as pouch IV proper seem loosened and are connected by fine protoplasmic strands; they are indistinguishable from those cells which comprise the thymus III anlage. It is perhaps not quite safe to speak of the cavity of pouch IV proper, since it is quite certain that portions of the wall in this region contain ultimobranchial tissue. A better term would be main cavity of the complex, since no especial significance is contained in this designation. The ultimobranchial body, including the region of the absorbed diverticulum ventrale IV, may be said to comprise by far the largest portion of the complex. Inclusion within the thyroid may apparently occur to varying extent, ranging from mere contact to a deep imbedding of the complex within the gland. The extent to which the inclusion occurs seems purely an expression of the differential growth of the two structures. When deeply imbedded, the complex lies at the inner termination of the so-called vasculostromal hilus (hile vasculo-conjonctif, Prenant). The existence of this so-called hilus seems purely a function of the growth relations between complex and thyroid.

Up to the present time the relations and regions have been comparatively well defined; however, subsequently to the union of the caudal pharyngeal complex with the thyreoid, difficulties are vastly increased. Two complications are introduced at this point, the first being the more or less intimate fusion of thyreoid and ultimo, the second being the various rotations and growth transformations occurring at this time. It may be safely said at present that there is not now nor is there ever after its first involvement in the complex as a whole, a definite, distinct diverticulum ventrale IV. Its fate cannot be determined apart from that of the ultimobranchial body.

The best index to the transformations and growth shiftings which occur in the complex at about this time may be found in following the position and direction of the cavity designated as the main cavity of the complex. This is possible so long as the latter persists in discernible form. As may be ascertained, the normal, unaltered direction of the cavity would be in approximately a sagittal plane; this condition obtains in certain of the embryos examined. In others one has evidence of varying degrees of rotation, serving to modify the general position which the complex occupies as regards the thyreoid, without, however, at the same time causing any marked change in the relation of the parts of the complex to one another. Apparently the more typical change is a rotation of the complex about a vertical axis, the rotation serving to place the plane of the main cavity of the complex in a frontal position (fig. 9) and to bring the parathyreoid IV into a relatively more medial position; the situation of the cavity, whatever it be, is sufficient to indicate approximately the region of the former diverticulum ventrale IV. Soon, however, increase in the thickness of its walls brings about an obliteration of the cavity, and the parathyreoid IV alone is left for orientation. The latter, inasmuch as all regions of the complex are growing and overstepping their former extents, is not of great value as a landmark.

A typical stage at about the time of the obliteration of the cavity may be described (Cat 163-3; estimated length 18 mm.) as follows: the complex occupies a position on the medial aspect

of the thyroid; the upper and medial portions of the complex itself consist largely of parathyreoid IV; this upper portion lies free from the median thyroid, considerable mesenchyme intervening between the two structures. Passing downward one finds this condition succeeded by a region of markedly loosened cells, lateral in position to the parathyreoid IV and consequently more deeply imbedded in the thyroid; these loosened cells are connected by fine protoplasmic strands and constitute a reticulum; mesial to the reticular area, between it and the surrounding thyroid cords one has a zone of compression. The cells in the compressed area are of two sorts, crowded reticular cells and mesenchymal cells; they can be distinguished only at points where abundant mesenchyme may be traced easily from the region between complex and thyroid to the extrathyreoid mesenchyme. It is the formation of this reticular area which gives one the first picture in the histogenesis of the internal thymic lobule of the thyroid. No evidence can be found for assigning this reticular area to any definite portion of the caudal pharyngeal complex, such as, for example, a diverticulum ventrale IV. Explanation for the compressed zone is doubtless to be found in the oppositional growth of the two tissues and is in itself somewhat suggestive. The complex passes subsequently into a more condensed mass of cells; its central portion shows a tendency to become loosened; on the periphery the cells of the thyroid blend most intimately with the condensed mass. As was indicated, all trace of cavity is obliterated.

From this time on extension of the reticular area seems the main transformation; it may not be said, however, that increased reticulation is a fast rule in the histogenesis, for complete reticulation of the complex at an earlier stage may be found succeeded by minimum reticulation at a later one. In other words, the reticulating process, while probably to be considered an advance in the histogenesis, whether retrograde or not, proceeds at greatly different rates. It is nearly complete at 25 mm., likewise 37, 44, and 47 mm., stages to be afterwards described; it is on the other hand quite minimal in a 52-mm. stage.

Considerable advances mark conditions found in a 25-mm. embryo (Cat No. 8, Professor Gage's collection). The complex occupies a mesial position as before with regard to the median thyroid lobes; of its constituents one has medially the parathyroid IV, which in structure closely resembles its adult condition; fused laterally with it is the ultimobranchial body. Union of ultimobranchial body and thyroid is very intimate; one has the appearance of a loose mass of cells bordered on and fused peripherally with growing thyroid cords. There can be detected no cord formation in the ultimobranchial body, and at least in this embryo there is no doubt but that the surrounding cords belong to the median thyroid. As one traces the complex, the ultimobranchial body increases in size and one has a clearly perceptible strand of mesenchyme between it and the thyroid. The cells of the complex medial to the parathyroid IV in the region where one would place according to data previously obtained, the approximate position of the main cavity of the complex are distinctly syncytial and resemble in all ascertainable detail the syncytial thymus III anlage. The remaining cells are not so clearly syncytial and what protoplasmic processes are present are coarser; there is a tendency toward the appearance of spaces.

No change worthy of note occurs up to the larger 30-mm. stages. In two embryos of 37-mm. each, interesting conditions exist. In the first (fig. 10) the parathyroid IV composes the upper and medial portions of the complex; the remainder is completely reticulated; the meshes of the reticulum are wider in the central part than toward the periphery and a small cyst is present, bounded by reticular cells which send slender strands into its lumen. The particular feature of the stage is found in the fact that the complex is almost entirely outside of the median thyroid, cords of the latter extending only around its basal portion. Degenerated epithelial nuclei are present; they are darkly staining and somewhat resemble in their appearance the future lymphocytes; a cytological study as regards degenerating epithelial cells and lymphocytes or transforming epithelial cells and lymphoid cells is impossible without special fixation and

staining. In the second of the 37-mm. embryos a similar appearance is presented; the complex is likewise nearly completely extrathyreoid in position; cords of thyreoid cells, at times almost isolated from the median thyreoid mass, surround the basal portion, but at no point is there a clean break in the continuity between that thyreoid tissue applied closely to the ultimobranchial body and the main body of thyreoid.

At 40-mm. the complex is posteromesial as regards the thyreoid, being, however, almost wholly imbedded. Parathyreoid IV is free in the mesenchyme; the ultimobranchial body is reticular and is fused with the thyreoid save for a small area on its medial surface. Points of compression are noted (fig. 11) and a small cyst is present; several regions of poor staining capacity probably indicate the beginnings of a more general cyst formation.

In a 47-mm. embryo conditions are such as demand considerable study. Both of the parathyreoids (III and IV) lie well above the thyreoid and are adjacent to each other. The ultimobranchial body¹ is a relatively huge structure greatly elongated. It possesses a wide-meshed reticular core (fig. 12); the remaining cells are rather closely packed. On the extreme periphery of the body one encounters here and there isolated cords of cells, a few cells in extent, which resemble in their appearance and staining characteristics the cells of the median thyreoid. No connection is traceable between these cords and the thyreoid proper. One finds likewise small remnants of thyreoid cords, similarly isolated, bordering on the surface of the parathyreoid IV. In view of the evidence presented by previous writers for a thyreoid formation in the ultimobranchial body, the question naturally arises as to whether or not these isolated thyreoid cords are to be regarded as structures formed from the ultimobranchial body. I am inclined to believe that they are not. As evidence that these cords are formed from ultimobranchial tissue one has only the factor of their position. No transitions between these cords and either the denser or the reticular portion of the ultimo-

¹ The term 'ultimobranchial body' is used to designate portions of the caudal pharyngeal complex other than parathyreoid IV, although material not strictly 'ultimobranchial' in origin is included in this appellation.

branchial body can be found. My own interpretation would be that one had had, subsequent to a former more intimate relation to the thyroid, such growth transformation as to separate the two structures, leaving a narrow portion of thyroid tissue applied to the surface of the complex; the presence of cords likewise applied to the surface of the parathyreoid IV seems to strengthen this interpretation, as does also the long drawn-out shape of the complex itself. The size of the ultimobranchial body is probably largely a function of its growth condition; an extrathyreoid ultimo develops under far less restriction than does a tissue closely surrounded by growing thyroid. In considering the position of the reticular area, it will be remembered that its location was central as regards the complex. It would be difficult to assign it to a diverticulum ventrale IV by virtue of its present situation. Anticipating a subsequent lymphoid invasion of this reticular area, the logical assignment for those investigators who adhere to a metameric derivation of the thymus, would be to ascribe it to a diverticulum ventrale IV. This is by no means shown to be the case; a portion of the ultimobranchial region is surely involved in the reticular area.

Complete reticulation and great reduction characterize the stages examined between 50 and 60 mm. It is evident, however, that at no time can one safely predict what one may expect. The reduction is well shown in two embryos of 50 mm., two at 55 mm., one at 57 mm. and one at 60 mm. On the other hand, in two 52-mm. embryos reduction and reticulation are minimal. In the first of the 52-mm. embryos conditions may be briefly described as follows: the complex is situated on the medial aspect of the thyroid; the upper portion is free in the mesenchyme; in the next succeeding sections fusion with the thyroid appears, on first examination, complete; careful study serves, however, to reveal boundary distinctions in all but a few strands. The upper portion of the ultimobranchial body is composed of densely packed cells and a gradual transition may be observed to a loose-meshed reticulum (fig. 13). In the caudal portion of the reticular area one finds the often-encountered reticular lined cyst; one notes a typical gradual loss of staining capacity

as one approaches the border of the cyst and a fraying out of cell processes into its lumen. The cyst contains cell fragments and the bordering reticular cells possess characteristically granular nuclei. The complex is so shaped and the sectioning plane so oriented that in the figure two distinct denser cell masses are evident; these are, however, continuous in succeeding sections. In the second of the 52-mm. embryos the ultimobranchial body is also divisible into a denser and a reticular area; both are somewhat reduced. Evidences of compression are noted in the reticulum adjacent to the median thyreoid and thyreoid cords seem to be invading the reticulum. This introduces another factor in the reduction of the ultimobranchial body, the first being found in the cyst formation. These two processes—cyst formation, surrounding pressure and closure together with the ingrowing of thyreoid cords—are largely responsible for the extent and the persistence of the ultimobranchial tissue and probably constitute circumstances determining whether one is or is not to have the subsequent development of an internal thymic lobule of the thyreoid.

Embryos of 71- and 75-mm. show no new features. Embryos of 74 and 77 mm., however, show lymphocyte infiltration. This process is farther advanced in these stages than it is in a 79-mm. embryo; the latter may therefore be described first. The ultimobranchial body (fig. 14) is entirely reticular; large numbers of lymphocytes are to be found in the peripheral portions of the network, the latter seeming a region of rapid proliferation. This peripheral densely infiltrated portion is not identical with the future cortex; the division into cortex and medulla, such as one finds in the thymus III, is of quite late occurrence. It is to be noted that the stage just described is the first one where marked numbers of lymphocytes are found in the meshes of the reticulum. Small round cells have been noted in earlier stages, but it has never been possible to differentiate between degenerated epithelial nuclei and lymphocytes. Infiltration is throughout the entire peripheral area of the reticulum. In 74- and 77-mm. stages the lymphocytes are principally found in the region of the reticulum just adjacent to the

parathyreoid IV. In the 74-mm. embryo the central area of the reticulum is largely cystic.

Conditions at 82 mm. resemble those found at 79 mm. The lymphocyte infiltration is most marked on the posterolateral (thyreoid) aspect of the complex; two small cysts are present. At 83 mm. the internal thymic lobule is very large (fig. 15). More than the original reticulum is involved in this case, there being a dense lymphocyte infiltration of the adjacent embryonic connective tissue. There are two possible interpretations: first, that the surrounding connective tissue is a source of the invading lymphocytes at this time or, secondly, that one is dealing with an overflow from the central mass. The second is the more probable; the lymphocytes occupying the reticular area are greatly crowded; the boundaries between the outside connective tissue which contains lymphocytes and that which does not is at many points very abrupt and one gets the impression of the pushing out of lymphocytes from the central mass; a peculiar feature in the internal thymic lobule of this embryo is the fact that although there is evidence of great crowding of lymphocytes in what is apparently a limited space, a cyst lined by reticular cells is present, on the very border of which the infiltration is minimal. A similar dense packing of lymphocytes is noted in the internal thymic lobule of the opposite side; this likewise terminates in a cyst; degenerating reticular cells are to be observed around the dense mass of lymphocytes and around the border of the cyst.

The most noticeable feature in embryos of 90 and 92 mm. is an increase in the size of certain cells of the reticulum; this increase is accompanied by an increased homogeneity of the cytoplasm and a nuclear enlargement. The increased quantity of cytoplasm is followed by its colloid degeneration; previous to or accompanying the cytoplasmic colloid degeneration, during the period of cell enlargement, surrounding reticular cells are pressed into concentric arrangement about the central cell or cells. These changes mark steps in the development of Hassall's corpuscles. This description agrees fully with the account of the process as given by Bell ('05). The corpuscles formed in

this manner would correspond to the ordinary type of concentric corpuscle of Bell. There is noticeable some slight lymphocyte proliferation in the surrounding thyroid tissue. This is more marked in the thyroid of a 120-mm. embryo. A parathyreoid cyst is present at 120 mm., and there is a notable increase in the size of Hassall's corpuscles (fig. 16).

In a kitten of twenty-six days absence of the internal thymic lobule is noted for the first and only time during the entire study. The parathyreoid IV is deeply imbedded in the thyroid and is unusually small. Medially to it one finds a narrow tubular cyst (fig. 17), bordered by large cells, with uniformly staining cytoplasm and nuclei of varying degree of staining capacity; similar cells occupy portions of the cavity of the cyst, and one finds occasional fine protoplasmic strands passing between them; it seems probable that, in this cyst, one has the remains of the ultimobranchial body. It is impossible to identify the cyst with the remains of the cavity of the caudal pharyngeal complex, and it is doubtless to be considered a new formation. The obliteration of the cavity in all of the embryos examined is a matter of early occurrence and the subsequent appearance of cystic cavities is to be regarded as a purely secondary factor.

In a kitten of age three months, ten days, the internal thymic lobule is a relatively enormous structure; it is traceable through 128 sections of 10 micra thickness. Connective tissue separates it from the thyroid in its upper portions, but otherwise fusion with the latter predominates. Lymphocytes are present in the thyroid on the anterior, posterior, and lateral aspects of the internal thymic lobule; certain thyroid follicles surrounded by lymphocytes seem to be undergoing a degeneration; small aggregates of thyroid cells together with strands of connective tissue belonging to degenerated follicles are to be found within the internal thymic lobule; some of these contain colloid, doubtless true thyroid colloid and at first sight resemble Hassall's corpuscles. I have been unable to trace any relationship between these structures and the true corpuscles of Hassall. In addition to the internal thymic lobule one finds three other lymphoid aggregates within the thyroid or in its immediate

vicinity; one of these is the so-called thymus head (external thymic lobule of Kohn) and the others are isolated bits of lymphatic tissue, no connection being traceable between these and either the internal or the external thymic lobule.

Division of the internal thymic lobule into a cortex and medulla is not observed until adult stages and may be absent. Hassall's corpuscles may be present in the adult medulla in large numbers. As has been indicated, they are of epithelial origin and are derived through the enlargement and subsequent degeneration of reticular cells; in their formation considerable areas of the reticulum of the medulla may become involved; reticular cell processes may be greatly thickened to the extent of producing the appearance of fenestration; small Hassall's corpuscles are frequent in these areas.

Of the types of cyst recognized by Verdun ('98), the following, of caudal pharyngeal complex origin, were distinguished:

a. Frequent degeneration cysts of the type lined by reticular cells, encountered in stages ranging from 25 to 92 mm.

b. Persistence cysts of the type found in the embryo of 165 mm., described above.

c. Cysts of parathyreoid origin; the identification of these last with persisting portions of the cavity of the fourth pharyngeal pouch is unsafe; they seem to be of purely parathyreoid origin.

d. Cysts due to the corpuscles of Hassall.

The often encountered and described ciliated epithelium in cysts of branchial origin I have never observed in the cat.

DISCUSSION

It would seem unnecessary to enter into a detailed discussion of homologies in endeavoring to interpret the morphology of the ultimobranchial bodies. These have been adequately discussed by Kingsbury ('14) and Camp ('17). In view of the difference in interpretation expressed by these two recent investigators, it may perhaps be well to briefly review the considerations involved. In speaking of an homology, it seems desirable to adhere to the stricter sense of the term and to designate as homologous only

those structures which belong fundamentally to the same source—structures, which although their subsequent development may be marked by the greatest variation, are phylogenetically the same structure. This is a point directly emphasized by Kingsbury and perhaps misinterpreted by Camp.

The ultimobranchial body of mammals has been homologized with pouches as far back as the sixth (H. Rabl ('13) in the guinea-pig), but, as Kingsbury very aptly remarks, this fails to meet the requirements of homology when one considers elasmobranchs where one has six functional pouches, and caudad of these an ultimobranchial (postbranchial, suprapericardial) body, which Camp has recently homologized with the ventral portion of a rudimentary seventh pouch in *Acanthias*. Even though the ultimobranchial body of the cat develops essentially as a fifth pouch and may on that basis be homologized with a fifth pouch in amphibia, it could on no conceivable basis be homologized with a structure developing posterior to a fifth pouch. The same reasoning obtains for the attempted homology of the ultimobranchial bodies of amphibia with those of elasmobranchs; a structure which in amphibia develops as a sixth pouch may be homologized with all or with some part of a sixth pouch in elasmobranchs, but not with a structure which develops like a seventh pouch. Unless, as Kingsbury suggests, one assume—and that without basis—that intermediate pouches have vanished leaving no trace, I cannot agree with the statement of Camp ('17) that, if one admits the ultimobranchial body to be of branchiogenetic origin, it would appear then without justifiable doubt that this structure could be homologized with similar branchiogenetic organs of lower forms, including the suprapericardial body of selachians. The interpretation of the ultimobranchial body as a structure formed as an expression of continued growth tendency in the caudal pharyngeal region, perhaps to be correlated with further pouch-forming potentialities, serves to emphasize the probably analagous circumstances of origin, while obviating the necessity of assigning the structure to a definite pouch.

The ultimobranchial body of the cat is without doubt a structure whose degeneration is apparent; its fate in other forms is probably a matter of variation. It may persist in various cysts within the thyroid (Verdun, Prenant); it may contribute to the parenchyma of the median thyroid, a view recently supported by the work of Badertscher on the ultimobranchial body of the pig, it may seemingly degenerate leaving no trace (Kingsbury).

In the ultimobranchial body of the cat, however, conditions are such as to suggest degeneration from early stages onward; following an early growth period there occur in successive phases reticulation, cellular degeneration, cyst formation, the ingrowth of thyroid cords, and lastly a lymphocyte infiltration, the structure thus formed constituting the internal thymic lobule of the thyroid. Furthermore, so far as one may determine in view of the results indicated in previous paragraphs, the branchiomic concept of the pharyngeal region has lost value. No reason has been found for believing a thymus-forming potentiality inherent only in the cells of the diverticulum ventrale of the fourth pouch, the latter being a structure of transient occurrence which never, so far as could be determined, exhibited evidence for regarding it alone as the anlage of the internal thymic lobule of the thyroid.

The question of the lymphocyte invasion is an interesting one not merely as to the origin of the cells, but rather as to the fundamental nature of the reaction. It seems not unlikely that the lymphocyte reaction is to be regarded as a reaction of degeneration. In view of the conditions existent in the tissue just previous to its infiltration, it is difficult to view it in another light. The circumstances prompting the invasion of a tissue by lymphocytes are largely unknown. Suffice it to say, consideration of the nature of the origin of the ultimobranchial body places the structure in so far as the lymphocyte reaction is concerned, in line with certain other lymphoid organs, notably amphibian tonsils. A lymphoid infiltration attending the absorption of epithelium and a lymphoid infiltration in a tissue which by virtue of the mechanism of its origin is essentially

foreign would seem fundamentally similar in nature. Indeed, instances of similar phenomena are by no means lacking in recent pathological findings. The histological findings of Murphy ('12, '15) accompanying the development of resistance to implanted sarcoma are not unlike those encountered in the histogenesis of such a normally occurring structure as the thymus.

I believe the similarity between thymus infiltration and the reaction toward foreign tissues further enhanced by features occurring in the formation of the corpuscles of Hassall. The statement of Bell ('05) that there is no evidence connecting the development of the Hassall's corpuscles with the involution of the thymus, because their formation is begun before the lymphoid transformation is complete and because they are most numerous when the thymus is at the height of its development, is perhaps open to question. It is difficult to define the height of development of a regressive structure. Bell's 'height of development' probably refers to the period of maximum lymphocyte infiltration. According to my own interpretation, this point is to be regarded as well along on the descending limb of the curve. On the basis of the theory of the degenerative nature of the lymphocyte reaction, Bell's observation may indicate that maximum degeneration of the epithelial anlage is the feature of maximum lymphocyte infiltration and as such one might expect it. My own suggestion would be that the corpuscles of Hassall are in some degree comparable with the degenerative remains of foreign growths as observed by Murphy.

SUMMARY

1. The ultimobranchial body of the cat develops essentially as a fifth pharyngeal pouch, although as such it does not make ectodermal contact. There is some suggestion of the involvement of a still more caudal region.

2. No reason is seen for directly homologizing the ultimobranchial body of mammals with the structure as found in lower vertebrates. It is regarded as a structure which develops as the result of continued growth in the caudal pharyngeal region,

which growth is probably to be correlated with further tendencies towards pouch formation.

3. The internal thymic lobule of the thymus is not to be regarded as a branchiomic structure; the so-called diverticulum ventrale of the fourth pouch is a structure of transient occurrence and may not alone be considered the anlage of the intrathyreoid thymus, but rather——

4. The whole of the ultimobranchial body or all of that portion which does not undergo degeneration as a purely epithelial structure contributes to the internal thymic lobule.

5. The latter is of almost constant occurrence in the cat, having been found in all but one of upwards of twenty embryos and adults examined, of 74 mm. and over in length.

6. The Hassall's corpuscles are formed from the reticulum and are therefore of epithelial origin. They are regarded as regressive structures.

7. The ultimobranchial body of the cat is believed to be an essentially regressive structure due to evidences of degeneration as found in cellular disintegration, reticulation and cyst formation. The early evidences of degeneration and the invasion of the structure by lymphocytes to form an internal thymic lobule are regarded as phases of a single process.

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LIST OF ABBREVIATIONS

<i>CHH</i> , complex III.	<i>P.IV</i> , parathyreoid IV.
<i>CIIV</i> , complex IV.	<i>Ph.</i> , pharynx.
<i>C.M.</i> , main cavity of complex.	<i>R.</i> , caudal pharyngeal complex reticulum.
<i>Cav.IV</i> , cavity of IVth pouch.	<i>R.C.</i> , reticular-lined cyst.
<i>D.br.IV</i> , ductus branchialis IV.	<i>S.br.III</i> , third pharyngeal pouch.
<i>D.ph.br.IV</i> , ductus pharyngo-branchialis IV.	<i>S.br.IV</i> , fourth pharyngeal pouch.
<i>D.v.III</i> , diverticulum ventrale III.	<i>S.br.V</i> , fifth pharyngeal pouch.
<i>D.v.IV</i> , diverticulum ventrale IV.	<i>T.</i> , thyroid.
<i>E.</i> , esophagus.	<i>Th.</i> , internal thymic lobule.
<i>Epi.IV</i> , epibranchial placode IV.	<i>Tr.</i> , trachea.
<i>H.</i> , Hassall's corpuscle.	<i>U.</i> , ultimobranchial body.

PLATE 1

EXPLANATION OF FIGURES

- 1 Drawing: reconstruction of caudal pharyngeal entoderm of cat embryo of 5.5 mm. \times 130.
- 2 Drawing: same model. \times 87.
- 3 Drawing: left caudal pharyngeal complex of cat embryo of 7 mm. \times 125.
- 4 Drawing: reconstruction of right caudal pharyngeal complex of cat embryo of 8.5 mm. \times 130.

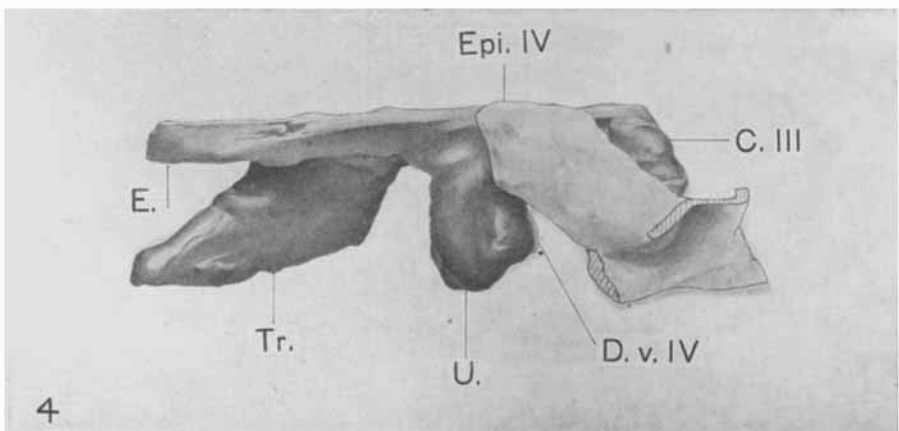
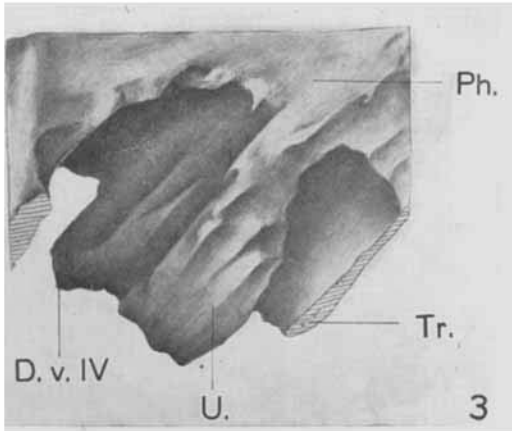
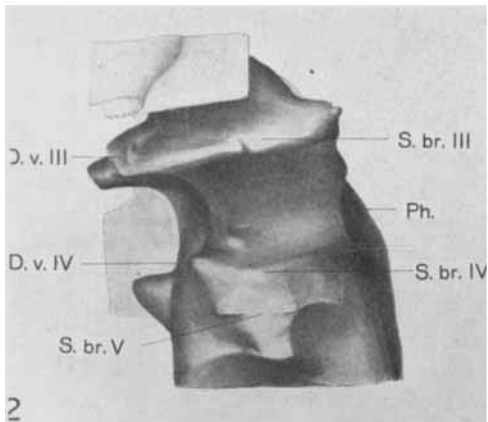
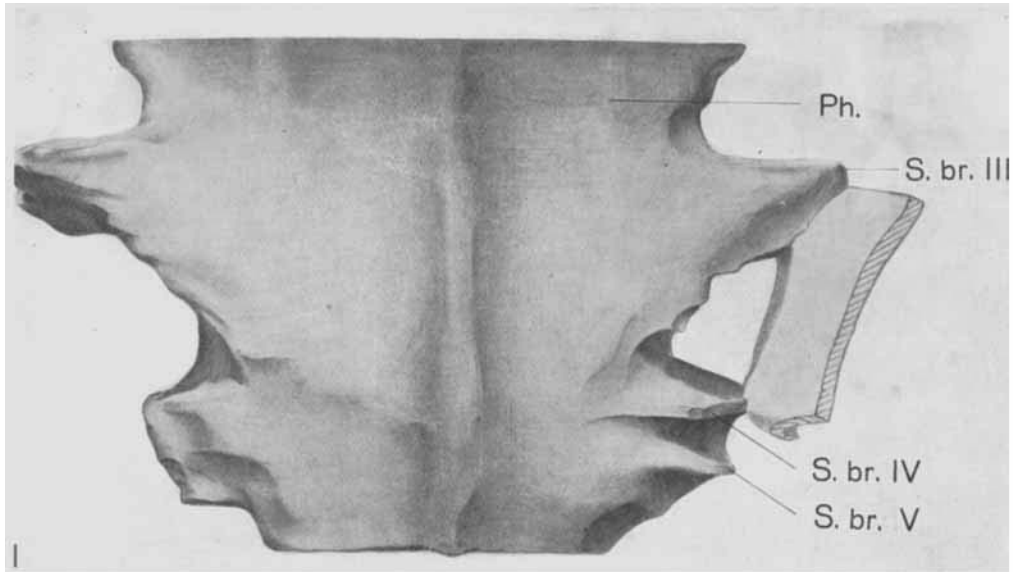


PLATE 2

EXPLANATION OF FIGURES

5 Drawing: reconstruction of caudal pharyngeal complex of cat embryo of 9.5 mm. \times 130.

6 Drawing: reconstruction of caudal pharyngeal complex of cat embryo of 13 mm. \times 125.

7 Photograph: section through caudal pharyngeal complex of 13-mm. cat embryo. \times 177.

8 Photograph: section through caudal pharyngeal complex of 105-mm. cat embryo. A stage just preceding fusion with the thyreoid. Magnification not determined. Connection with pharynx broken at a very early period.

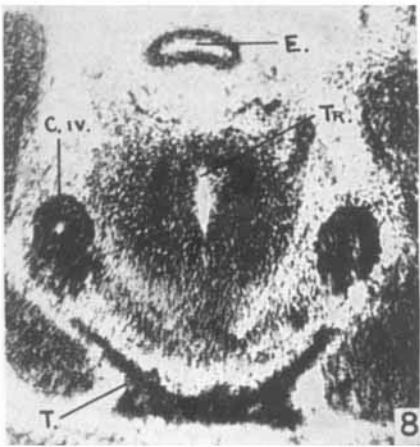
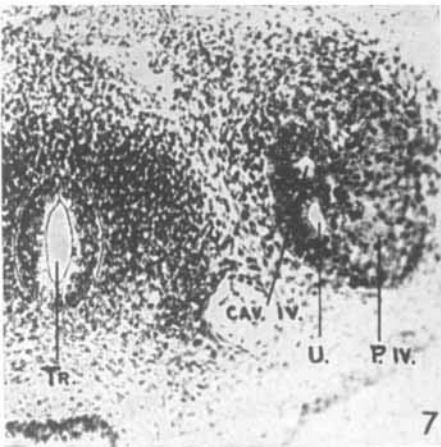
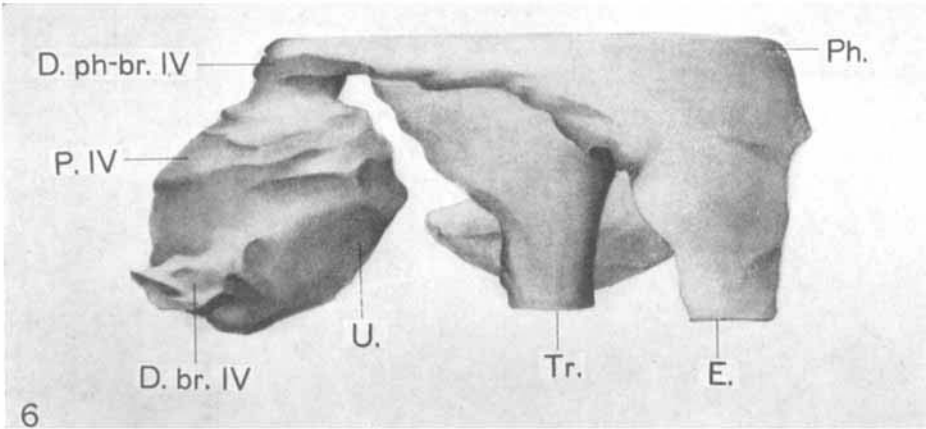
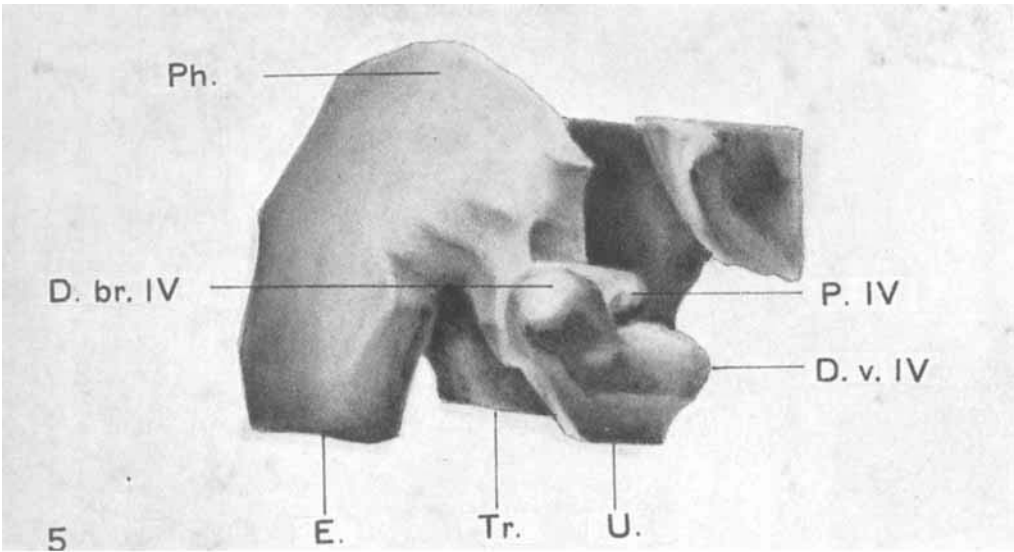


PLATE 3

EXPLANATION OF FIGURES

9 Photograph: an early stage of fusion of the caudal pharyngeal complex with the thyroid, showing altered position of the cavity of the complex. Embryo of 16 mm. \times 120.

10 Photograph: caudal pharyngeal complex in a 37-mm. cat embryo. \times 177.

11 Photograph: Reticulated portion of ultimobranchial body within the thyroid. Marked area of compression at left of figure. From cat embryo of 40 mm. \times 620.

12 Photograph: Extrathyroid caudal pharyngeal complex. From cat embryo of 47 mm. \times 150.

13 Photograph: Caudal pharyngeal complex on surface of thyroid; showing denser and reticular ultimobranchial tissue. From cat embryo of 52 mm. \times 177.

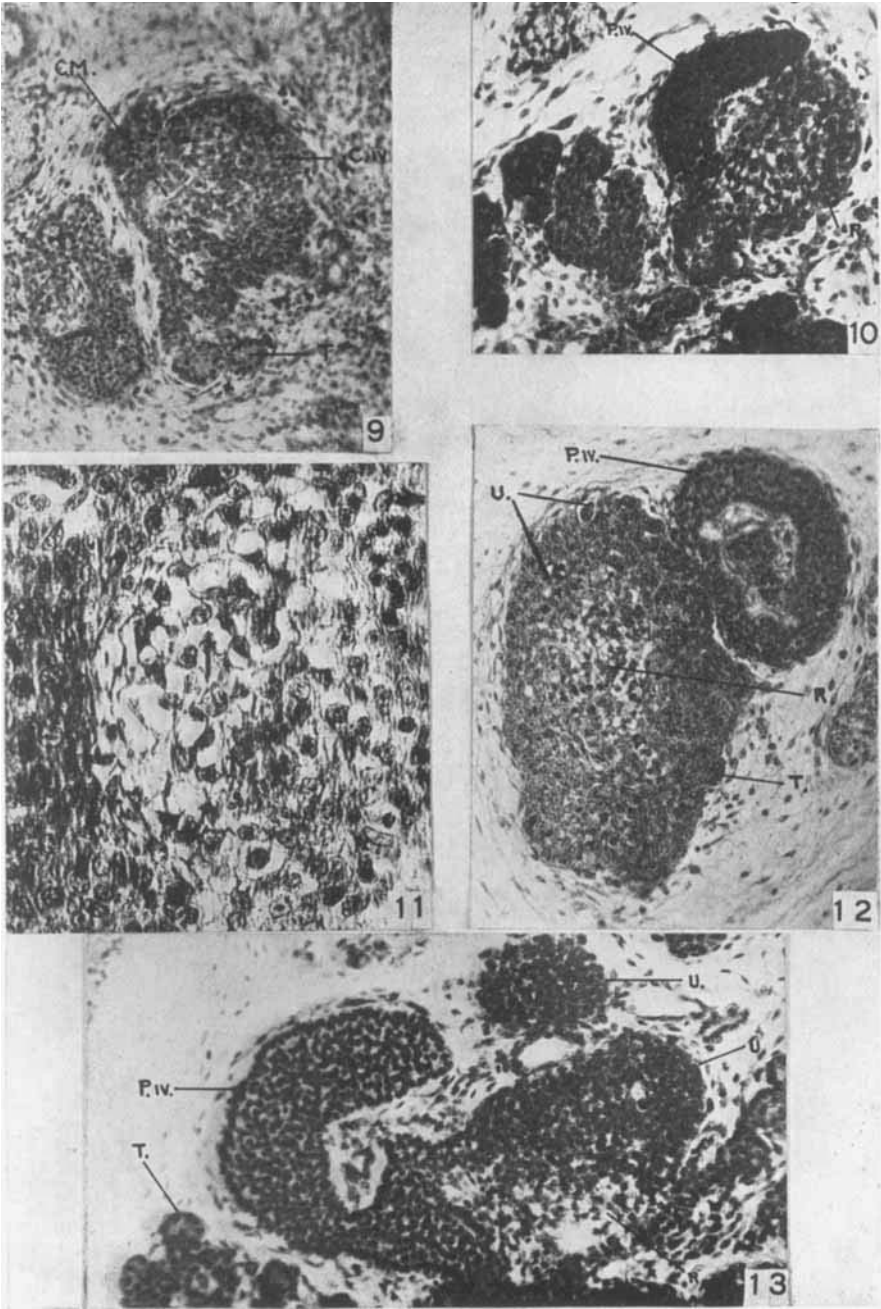


PLATE 4

EXPLANATION OF FIGURE

14 Photograph: Showing an early proliferation of lymphocytes in the reticulum. From cat embryo of 77 mm. $\times 177$.

15 Photograph: Internal thymic lobule from cat embryo of 83-mm. Shows a dense lymphocyte infiltration of the surrounding mesenchyme. $\times 177$.

16 Photograph: Internal thymic lobule from cat embryo of 120-mm. An early stage in the development of a Hassall's corpuscle, with the indication of the concentric arrangement of surrounding epithelial cells. $\times 177$.

17 Photograph: Cyst identified as the probable remains of the ultimobranchial body in a kitten of 26 days. $\times 275$.

18 Photograph: Parathyroid IV and internal thymic lobule in an adult cat. $\times 40$.

