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VOLUME VI

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CHAPTER ONE

DISEASES OF THE THYROID GLAND

WILLIAM FRANCIS RIENHOFF, JR., M.D.

Twenty-three years have now elapsed since this chapter on Diseases of the Thyroid Gland was originally published in *Lewis' Practice of Surgery*. That year of publication was 1926 and the task of revision and correction has proved to be interesting as well as instructive. In general there have been surprisingly few fundamental advances in our knowledge of the thyroid gland itself or of the maladies which befall it. The morbid conditions which affect the thyroid are essentially as obscure now as they were 23 years ago. The advances in our knowledge that have been made in the field of embryology and anatomy as well as the lymphatic system have been recorded in quite some detail. The employment of the antithyroid drugs is discussed as fully as it is possible to do so in our present state of knowledge. Definite statements in regard to these drugs cannot at present be made. Their mode of action is unknown and their employment too recent to draw conclusions as to the permanence of their effect.

Advances in our knowledge of the pathologic and clinical phenomena encountered in hyperthyroidism have thrown considerable light upon the pathogenesis of many of the morbid changes occurring in diseases of the gland which are not associated with hyperthyroidism. Following a short introduction, a review of the embryology, anatomy, histology and physiology, including the physiologic chemistry of the normal thyroid gland, is given in detail. The morbid conditions which may be encountered are then taken up in the following order: 1. Hyperthyroidism. 2. Goiter, Simple or Endemic. 3. Hypothyroidism and Cretinism. 4. Abnormalities in Development and Position of the Thyroid Gland. 5. Infections and Inflammations of the Thyroid Gland. 6. Tumors of the Thyroid Gland. 7. Treatment, Medical and Surgical.

The Earlier Literature of the Thyroid Gland.—So far as is known, antiquity possesses but one passage which undoubtedly points to the thyroid gland. This passage occurs in *De Voce*, a work which is attributed to Galen but exists only as a Latin translation (Tractatus II):¹ "The neck has two glands in which moisture is generated, and in the epiglottis a thick and viscid humor is secreted for the moistening of that organ. But from the true glands which are in the neck and from the substance of the epiglottis are no ducts through which the humor may flow, as is the case in the two glands of the tongue. But those which are in the neck are of a spongy nature and from them the humor oozes out and trickles down, there being no necessity for ducts (which the others need) whereby the fluid may be carried." After Galen, there is a long lacuna. Among the moderns the first mention of the thyroid gland was made by Vesalius² in 1543 in his *De Corporis Humani Fabrica*, Book VI, Chapter 4. "This incision also shows two

glands, one on each side of the root of the larynx, and these are large and somewhat fungous, and almost of the color of flesh, but rather darker, with many prominent veins." Further on in the same chapter he suggests as a function of the thyroid, "This also do the glands which lie at the root of the larynx perform for the trachea, since they moisten its orifice with a humor not indeed fluid, but rather viscid and thick, for the glands themselves are thicker and denser than the rest of the glands which secrete a humor." In Book II, Chapter 21, Vesalius depicts the thyroid in four of his diagrams of the larynx. It appears as two rounded bodies, one on each side of the base of the larynx.

The world was content with his description for 100 years, all writers speaking of it in the terms of Vesalius—*Glandulae ad laryngis radicem adnatae*. Colombus³ in 1562 pointed out for the first time that the thyroid gland was relatively larger in women than in men. Casserius⁴ was the first to describe the thyroid as a single organ. In his *First Dissection of a Man* there is a drawing in which the gland figures as an oblong body stretching across the top of the trachea and is called *corpus glandulosum ad laryngem ipsam situm*. He concluded that it had no duct. Fabricius ab Aquapendente⁵ in 1619 was the first definitely to localize the thyroid gland as the anatomic seat of goiter. In his work *Chirurgia fol.*, Venitiis, 1619 (Hieran Fabinic), he differentiates bronchocele, which arises from the trachea, and gozzo (goiter), which always springs from the glands at the sides of the trachea immediately below the larynx. So far the thyroid gland was known as "the gland," "the unnamed glands" or "the bronchial glands." However, Wharton,⁶ in his erudite *Adenographia*, London, 1656, called it the "thyroid gland," the name being suggested by its anatomic location beside the thyroid cartilage. Eustachius⁷ described the organ as single and gave to the structure joining the lateral lobes the name of "isthmus."

To Morgagni⁸ belongs the credit for having first described the slender vertical column of gland which usually arises from the isthmus. He called this the "appendix" and later it was called by Lalouette,⁹ in 1750, the "pyramid." He concluded that the thyroid was a secretory gland because of its abundant blood supply and that the secretion was carried away by lymphatics. In 1722 Ruysch¹⁰ expressed the opinion that the secretion was carried away by the veins, but Lalouette,⁹ after injecting the veins, never found the injection mass in the follicles of the gland and therefore opposed this view.

Ruysch¹⁰ was also the first to suggest that some special fluid was elaborated and separated from the blood by this organ, this fluid passing into the general circulation through the lymphatics and veins. Haller¹¹ described for the first time the *arteria thyroidea ima* which arose directly from the aortic arch.

Development of the Thyroid, Parathyroid and Thymus Glands in Man.—There are several classical reports in the literature concerning the embryologic development of the thyroid, parathyroid and thymus glands. In order to have a proper comprehension of the development of the thyroid and parathyroids one must include also a study of the origin of the thymus. This is intimately connected with the characteristic and intricate method of transformation of the

pharynx and its derivatives. It is impossible, because of limited space, to enter into a detailed discussion of this most interesting subject and, therefore, only the salient features of the development of these structures can be pointed out.

Among the early papers dealing with this subject which are of particular interest are those of Tourneaux and Verdun,¹² based upon a series of eight human embryos and five fetuses. A second most important work was that of Hammar who studied 50 embryos and fetuses. The latest and perhaps the most excellent reports are those by Weller¹³ and also Norris.¹⁴ These articles have been freely drawn upon for the substance of this discussion. A greater number of human embryos than ever before studied for this purpose, 24 in Weller's¹³ series and 139 in that of Norris,¹⁴ was made available by the Carnegie Embryological Laboratory under the direction of Dr. G. L. Streeter. Such a considerable number of embryos has been accumulated that progression in the development of both embryos and individual organs could be arranged to form a finely graduated series. Also, it may be said that under the direction of highly trained technicians, such as O. O. Heard, Chester Reather and J. F. Didusch, the methods of reconstruction, photographing and illustrating have been modified so that models of the highest accuracy have been produced.

The following terms employed in this study are defined in order to preclude any possibility of confusion which might arise. In general, it is believed that as soon as the organ contains all of the tissue required for successful subsequent growth and differentiation, it should be designated as such. Previous to such a time "primordium" seems appropriate. In the case of the "parathyroid" glands, it seems embryologically more correct to discontinue the distinction between parathymus and parathyroid glands through postuterine life.

Parathyroid Glands—Either epithelial structure, the primordium of which arises in close association with the primordium of either lateral thyroid component of the thyroid gland; the two upper or superior "parathyroid" glands of postuterine life, the primordium of which arises in close association with that of the thymus; the two lower or inferior "parathyroid" glands of postuterine life.

Median Thyroid Component—That portion of the thyroid gland which arises as a single median pharyngeal derivative.

Lateral Thyroid Component—Either primordium of the thyroid gland which arises from the lateral wall of the pharynx, from the fourth pharyngeal pouch.

Definitive Thyroid—That structure formed at and after the time of union of the lateral and median thyroid components.

Pharyngeal Pouch—Pharyngeal pouch is a morphologic term used to designate the lateral branchiomic expansions of the pharyngeal entoderm, which intervene between the aortic arches so as to come in contact with the ectoderm. Various bilateral primordia arise in the region of these pouches; these, however, are not strictly branchiomic. One, two or more primordia can compose any given pouch.

Development of Median Thyroid Components.—The first evidence of the presence of the median thyroid component is a well defined fold in the ventral wall of the pharynx. This occurs before the

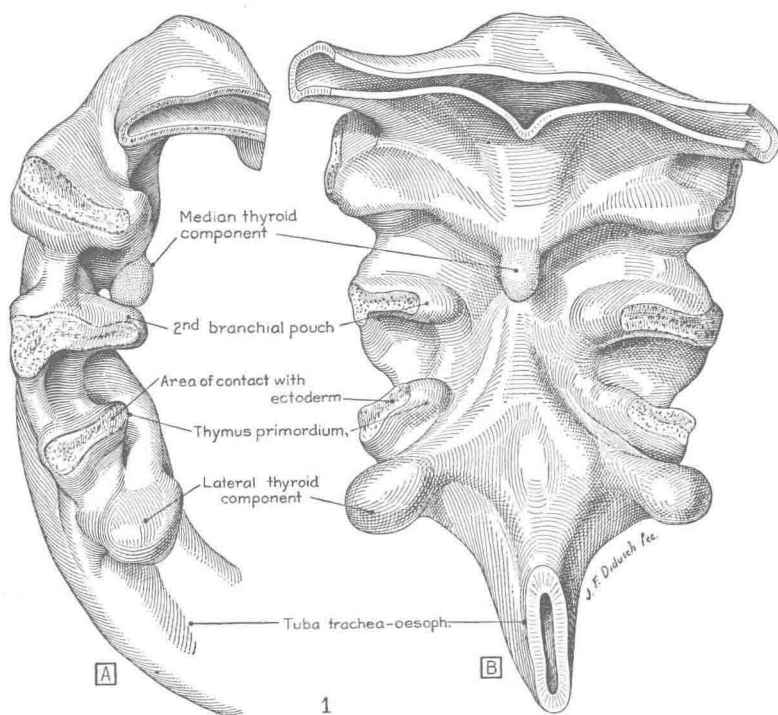


FIG. 1.—A. Lateral aspect of pharyngeal and primordial epithelium of 4 mm. embryo, No. 836. Median and lateral thyroid components located much farther ventrally than other primordia. B. Ventral aspect of same. Primordium of median thyroid is located just anterior to and midway between those of tonsils. Primordia of lateral thyroids extend far laterally beyond those of thymus components but are not in contact with ectoderm as are the latter. (From G. L. Weller, Jr.)

second pair of somites has been definitely separated off and consists in a proliferation, rather than primarily a differentiation, of pharyngeal cells. In addition, there is also present the first pair of pharyngeal pouches. Previous to the time when such pharyngeal cells begin to proliferate they are definitely pharyngeal entoderm cells; after that, because they have just begun to proliferate, they are median thyroid cells. Proliferation is just as good a criterion of the presence of a primordium as is cytologic differentiation. As Roth¹⁵ contends, the median thyroid undergoes changes chiefly in its external form as a result of which it assumes a spherical shape. In a 4 mm. embryo, for instance, the median thyroid has the appearance indicated in Figure 1. It is located on the ventral aspect of the pharynx midway between the primordia of the tonsils. Its walls and lumen, continuous with those of the pharynx, are composed of two types of cells. The first of these is a small cell with deep-staining nucleus, typical of pharyngeal entoderm, while the second is an elongated cell which contains more cytoplasm and a vesiculate nucleus. The cells of the latter type are arranged with their long axes along the radii of the sphere (Fig. 2). As would be expected, the median thyroid presents numerous morphologic differences in development, some of which are evident at this period. With further growth of the embryo, the distance between the

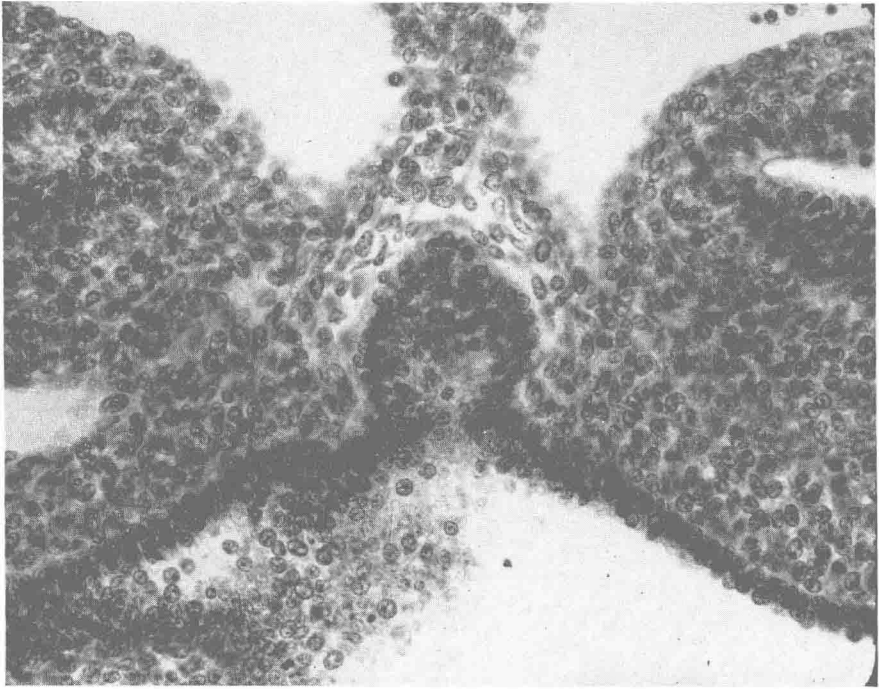


FIG. 2.—Frontal section of median thyroid of 4 mm. embryo, No. 836. Its cells and those of pharynx are very similar in that nuclei of both are vesicular and amount of cytoplasm scant. Thyroid epithelium somewhat thicker than that of pharynx. $\times 300$. (From G. L. Weller, Jr.)

median thyroid and ventral wall of the pharynx increases. Simultaneously, there occurs a change in the shape of the median thyroid component so that it assumes (Figs. 3, 4) an inverted Y appearance. Of the factors responsible for this, the chief one is that of growth—growth, however, not only of the median thyroid component but also of the mesenchyma surrounding it. The connective tissue cells in this region maintain the same appearance as those throughout the embryo generally. There are no condensation and subsequent demarcation of certain areas of mesenchyma, such as occur, for instance, around the epithelium of the submaxillary gland.

The chief factor which contributes to the change in the shape of the median thyroid component is the direction in which the epithelial cells are proliferating. This action can only occur when the direction in which the epithelium is proliferating is strictly regulated because under the alternate circumstances, namely, equal growth in all directions, the spherical median thyroid would persist. There is thus present (Fig. 4) for the first time, as a result of such growth, a structure which may be identified as median thyroid component. One is able also to identify two lateral lobes as well as the isthmus as a part of this median thyroid component.

An interesting feature of the cytology of the median thyroid in this period of development is the arrangement of the cells in two layers which are in close approximation. Their nuclei are situated along the

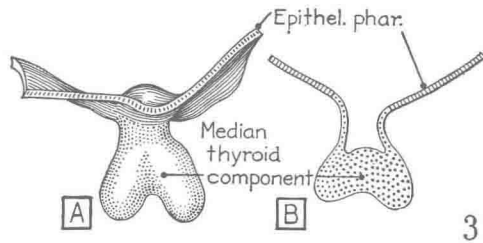


FIG. 3.—*A.* Embryo, 6.5 mm., No. 800. Bilobed median thyroid component now attached to pharynx by short pedicle. *B.* Single large cavity within pedicle communicated with lumen of pharynx. (From G. L. Weller, Jr.)

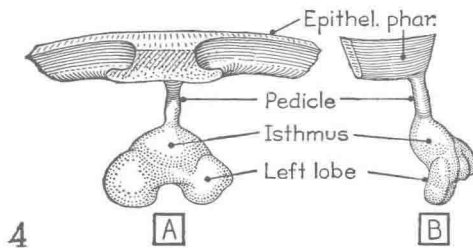


FIG. 4.—*A.* Embryo, 8.2 mm., No. 4672. Ventral aspect showing further development of median thyroid. Bilobed body still connected with pedicle with epithelium of pharynx. *B.* Right lateral view of same showing its attachment to ventral ridge of pharynx. (From G. L. Weller, Jr.)

periphery of the epithelial sheets, thus leaving a clear space of cytoplasm between them (Fig. 5). This indicates clearly how the follicles will arise although none are yet formed. Follicles only form after cleavage takes place between such rows of cells.

By the time the embryo has become 14 mm. in length, the median thyroid assumes the U shape which is of so much importance in the formation of the definitive thyroid gland. It is still impossible to designate the lateral portion as true lobes, nor is the isthmus composed of the tissue which it will contain in the adult. The structure, sheet-like in form, is draped across the pharynx and curled around the external carotid arteries. It is located just above the primitive subclavian arteries. These epithelial sheets are usually two cells in thickness (Fig. 6). The continuity of the median thyroid component with the pharynx has become interrupted and the primordium is molded to the configuration of adjacent structures, particularly the carotid arteries.

Development of Lateral Thyroid Components.—The lateral thyroid components, in a manner similar to the median thyroid components, are evidenced first by proliferation of certain cells of the pharyngeal entoderm; however, not until the embryo shows more than 20 somites. There are outpouchings of the pharyngeal wall formed by the proliferation of the pharyngeal epithelium lining the fourth pharyngeal pouch. These form the lateral thyroid primordia (Fig. 1).

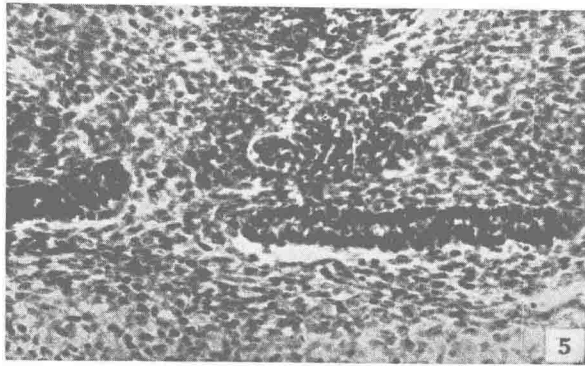


FIG. 5.—Transverse section of median thyroid of 10 mm. embryo, No. 623. Nuclei of its cells are arranged along periphery of lobes, leaving clear cytoplasmic space in center. $\times 200$. (From G. L. Weller, Jr.)

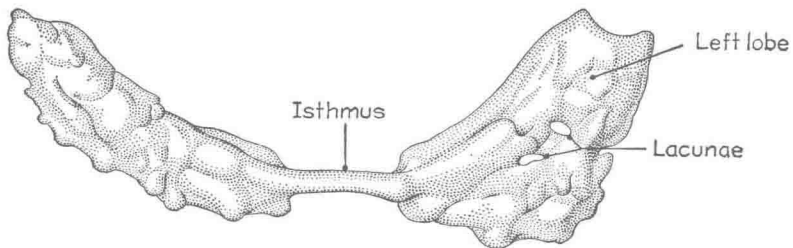


FIG. 6.—Ventral view of median thyroid component of 13.5 mm. embryo, No. 695. The two lobes are now thin sheets curving around carotid arteries. Isthmus forms a delicate bridge between them across midline of neck. Several lacunae present but should not be confused with lumina of follicles. (From G. L. Weller, Jr.)

With additional growth the lateral thyroid components present an external form similar, in general, to that of the median thyroid at the same stage. Thus, at the outset, the chief difference between these two thyroid primordia is one only of location. This similarity is emphasized by the configuration of the floor of the pharynx in this region. There is a definite triangular area (Fig. 1, *B*) raised above the surrounding tissue, which contains at each apex a thyroid primordium. Further, each of the components is hollow and its lumen is continuous with that of the pharynx. Each of these primordia is surrounded by mesenchyma. The cells of the lateral thyroid components are very similar in appearance and arrangement to those of the median thyroid primordium of the same embryo. As growth of the embryo proceeds, the lateral thyroids undergo changes which differ from those of the median components, chiefly because of the difference in location. They become increasingly further removed from the pharynx so that at the time the embryo reaches a length of 10 mm. (Fig. 7, *A, B*) the lateral thyroid primordia are shaped, in general, like rounded long-necked flasks. By this time there is present, approximated to either lateral thyroid, a parathyroid primordium. These three primordia, the median and two lateral components, grow in a longitudinal direction,

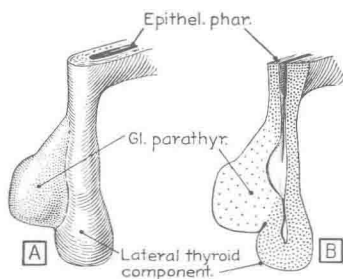


FIG. 7.—A. Ventral view of right lateral thyroid of 10 mm. embryo, No. 623. Dorsally its epithelium is continuous with that of pharynx. Parathyroid gland is attached to its lateral surface. B. Section of same to show extent of its lumen, and relationship between parathyroid gland and lateral thyroid component. (From G. L. Weller, Jr.)

their pedicles become severed and a layer of mesenchyma develops between them and the pharynx.

HISTOGENESIS OF THE LATERAL THYROID.—Due to the fact that the development of the lateral thyroid component is so intimately associated with the embryogenesis of parathyroid IV, or the future superior parathyroid gland, further discussion and illustration of the later stages of the morphologic changes of this component will be found in the description of the development of the parathyroid glands.

Early Differentiation Stage.—The lateral thyroid is made up of small dark cells with but a small amount of cytoplasm and relatively large nuclei, and these cells as compared with those of the parathyroid have indistinct outlines (Fig. 8). A vestige of the lumen of the fourth pouch may be present in this body until the embryo is about 20 mm. in length, but with the exception of this vestigial lumen the lateral thyroid is essentially a solid ball of cells. When the embryo is about 15 mm. long, a reticulation of the parenchyma begins and this is followed by an invasion by mesenchymal elements. This reticulation and invasion give the lateral thyroid a less dense structure and, when the embryo is about 20 mm. long, a process of differentiation and proliferation begins. The cytologic picture is altered so that the individual cells of the lateral thyroid come to have an appearance exactly like the individual cells of the median thyroid. They may be differentially recognized only by their arrangement. The cells of the median thyroid are disposed in plates two cells in thickness, whereas those of the lateral thyroid adhere to no typical pattern. That there is a rapid proliferation of the parenchymal cells in the lateral thyroid is evidenced by the not infrequent appearance of mitotic figures. A striking picture is produced by the fact that although at the actual points of contact between the tissue of the lateral thyroid and that of the median thyroid there is a union which in places amounts to a fusion of surfaces, there nevertheless remains for a time a certain distinctness of the two tissues (Fig. 9). Gradually with the invasion of more mesenchyma, the dense epithelial body gives place to one whose parenchyma is made up of isolated cells or groups of cells that are separated by a few connective tissue whorls.

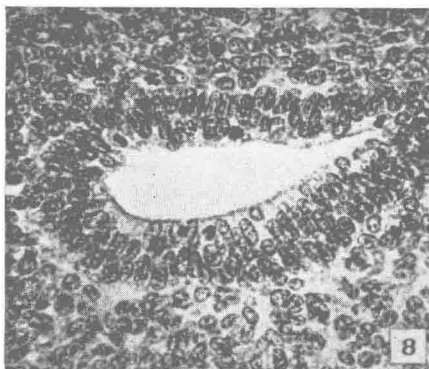


FIG. 8.—Transverse section of lateral thyroid component of 4 mm. embryo, No. 836. These cells are more prismatic in shape than those of median thyroid. Like those of median thyroid, their nuclei are located away from lumen. $\times 300$. (From G. L. Weller, Jr.)

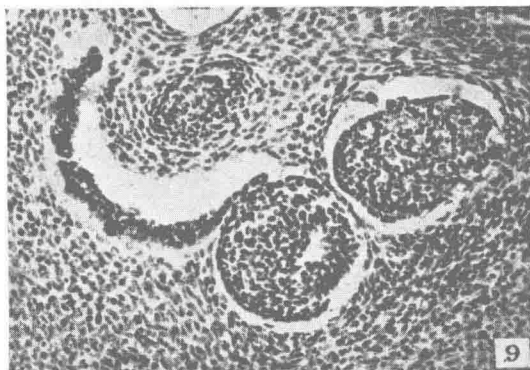


FIG. 9.—Transverse section of definitive thyroid of 13 mm. embryo, No. 175. Median thyroid component approximated to lateral one without intervention of connective tissue. Large mass to right of lateral thyroid is parathyroid (see Fig. 12). Clear spaces surrounding various structures are results of fixation. $\times 150$. (From G. L. Weller, Jr.)

Late Differentiation Stage.—In the period represented by embryos from 40 to 65 mm. in length very important changes occur in the structure of the lateral thyroid. The parenchymal elements exist as tiny groups or clusters of a few cells which are scattered irregularly and separated by a small amount of connective tissue. At no time in the differentiation of the lateral thyroid is there a “plate stage” or any semblance of the formation of plates which is comparable to those of the prefollicular period for the median thyroid. During this period the cell groups show a tendency to become organized and the individual cells shift their relative positions so that whorls are formed. These whorls have the sectional appearance of primitive follicles and are to be found scattered irregularly through the lateral thyroid area. After these primitive follicles have made their appearance, the further development of the follicles appears to be in all respects like that of the follicles derived from the plates of the median thyroid.

The problem of the lateral thyroid may be summarily stated in the following interrogations: