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Observations on the Occurance and Anlage of the Abberant Thyroid in Dog

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OBSERVATIONS

ON THE

OCCURRENCE AND ANLAGE OF ABERRANT THYROID

IN DOG

A

THESIS

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BY

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INTRODUCTION

The close relation between aberrant thyroid and diseases of the normal thyroid gland demands that we clear the line of demarkation between them. Each year the number of cases of recognized aberrant thyroid gland becomes larger, and the manifestations of the abnormal thyroid gland are different from those of the normal gland. This opens a field for experimentation in practical medicine. I owe a large part of my interest in the problem to this connection between experimental and applied medicine. However, the suggestion of the problem was made by Dr. R. M. Strong of the Department of Anatomy of Loyola Medical School. The idea had its inspiration in the work of Dr. D. J. Davis of the University of Illinois Medical School who, while investigating the periaortic fat body was much impressed by finding thyroid tissue in it, and became curious to know how it had gotten there. The great regularity with which it was found gave prospects of a method by which one might gain important knowledge as to the origin of aberrant thyroid tissue. Each year as more clinical evidence of abnormally located thyroid tissue is found the necessity of knowing the origin of this tissue becomes more acute.

Of all animals in which aberrant thyroid tissue has been reported, the dog seems to show it most constantly. It is located at the base of the aorta, inside of the pericardium, embedded in the periaortic fat body (this thyroid tissue has

been variously reported as present in from fifty to ninety percent of all dogs investigated). It seems advisable, therefore, to depend on dog embryos for knowledge that might be gained in regard to the embryonic origin of aberrant thyroid tissue.

LITERATURE

Conclusions reached by other investigators are necessarily of great importance to us. The outstanding feature of the literature, when aggregated, seems to me to depend mostly on the interpretation of the individual investigator. The evidence in the investigations of the embryology of the thyroid gland are not in themselves conclusive. In the second place there seems to be no literature that has covered aberrant thyroid tissue except in the field of speculation - it is very doubtful if any direct investigation has been made of the subject at all. In fact the anlage of the normal thyroid has been challenged in the last few years. It seems of interest, therefore, to revive our knowledge of the anlage of normal thyroid.

Leech, Smith, and Clute (9) in their article on aberrant thyroid have presented in a very clear manner the important issues that surround the investigation of these stray bits of thyroid gland in the neck and thoracic cavity.

They state that investigations of aberrant thyroid are important for the following reasons:

"1. Because the developmental side of the question is much discussed and far from being settled.

2. Because the frequent occurrence and pathology established it, 'the aberrant thyroid' as a clinical entity of note.

3. Its tendency toward malignant degeneration becomes of serious import to the patient.

4. Because these glands may be greatly influenced by the changes in the normal and pathological thyroid gland itself."

"The older embryologists (His, Born, Prenant, etc.) concluded that the thyroid has a dual origin. They believe that the major part of the gland, including the isthmus is derived from a median caudad growth of epithelium from the floor of the pharynx. They consider the remainder of the gland as arising from the lateral outpocketings of the pharynx which normally fused with the median portion."

It has been suggested by Swartz and Thompson (16) that part of this aberrant thyroid may get into its present location by the early formation of the thyroglossal duct, anterior to the great vessels. To quote from these authors: "The occurrence of thyroid tissue in the pericardial sac of the adult which we have noted in dogs is readily explained by the proximity of the points of origin and early development of the thyroid and the arch and ascending portion of the permanent aorta, and the subsequent migration of the heart into the pericardial sac. In the rabbit and in the human, in which the development of the thyroid has been most carefully studied, the thyroid develops from three fundaments, one medial or unpaired fundament, and two lateral paired ones. In the rabbit the unpaired fundament

arising on the 10th day in the mid-ventral plane from the pharyngeal wall at the level of the second visceral arch grows down from a short stalk into the connective tissue in front of the pericardial cavity. According to Marshall, in the rabbit this small body lies, on the 11th day, embedded in the mesoblast of the floor of the pharynx immediately in front of the truncus arteriosus."

According to Minot: (11) "The thyroglossal duct (median anlage) is an evagination of the floor of the pharynx between the bases of the first and second branchial arches. It lies in a mid line behind the tuberculum impar and the furcula of His (two parts of the tongue). The thyroglossal duct persists up to the 8th week (in man). The vesicular part of the median anlage expands quite rapidly and lies nearly at the level of the 3rd aortic arch (internal carotid)."

Norris states: (12) "The earlier well known stages in the development of the (median) thyroid anlage in the human embryo becomes detached and is transformed into a small epithelial plate, well shown in the 6mm. embryo. This epithelial plate soon presents irregularities, as shown in a 7.5 mm. embryo, and rapidly becomes transformed into what appears in cross section to be a network of anastomosing epithelial cords. One feature of the end result is that the cord-like appearance seen in the sections is largely an illusion, the end results are plates not cords. Fundamentally, the plate-like structure

of the thyroid anlage persists for a considerable time, although modified by a complicated process of fenestration, splitting, and budding. This type of structure, with varying degrees of complexity is found in various pre-follicular stages of embryos from 10 mm. in length."

Grosser (6) gives the following description of the thyro glossal duct. "Almost contemporaneously with the formation of the first pharyngeal pouch or slightly later there appears the anlage of the thyroid glands, usually termed the anlage of the median thyroid; the term median, however, now seems superfluous since it probably represents the only anlage of the thyroid tissue. The anlage is recognizable before the firs pharyngeal pouch has come into contact with the ectoderm as a prominence in the ventral wall of the pharynx. It then becomes constricted to form a stalked vesicle, and its stalk, whose lumen becomes obliterated, persists for some time as an epithelioid cord. The thyroid anlage belongs primarily to the medial region between the first two ventral pharyngeal grooves, i.e. to the oral portion of what is later the area mesobranchialis."

"The thyroid anlage, before its separation from the pharynx becomes bilobed with a divided lumen. At about the time when the thyroglossal duct becomes broken it loses its lumen, undergoing a continuous displacement caudally, and develops into a broad structure composed or irregular cords of cells,

disposed for the most part transversely."

In reviewing the literature regarding the paired lateral anlage of the thyroid, we must keep in mind that the later anlagen have been variously called ultimobranchial, postbranchial or suprapericardial bodies. It is these pharyngeal pouches, or parts of pouches that have caused so much difference of opinion regarding the origin of the thyroid gland. So far as I can learn all of the embryologists have recognized their presence but the relation to the thyroid gland remains doubtful. This doubt is due to a number of causes, some of which Badertscher (1) has clearly described:

"1. The possibility of a variable developmental behavior of these structures in different mammalian types.

2. Inadequate series of successively older embryonic stages (especially in the larger mammals).

3. Faulty technique (principally poor fixation of the thyroid gland in the older embryos of the larger mammals, especially man)."

Grosser (6) believes that the ultimobranchial bodies do not take part in the formation of the adult human thyroid. He describes the ultimobranchial bodies as outpocketings of the fifth visceral pouch. He also states that they will come to lie in the area of the thyroid gland, and eventually will be surrounded by cells from the median thyroid anlage. Grosser makes the following statement: "The derivatives of the caudal

pharyngeal pouch complex apply themselves to the somewhat dorsally bent lateral portions of the anlage and become partly enclosed by it. This is the case with the ultimobranchial bodies which then lose their lumina, but further than this they apparently do not always behave in the same manner. While in some cases they appear as compact bodies, in others they separate into an irregular group of small cells with strongly staining nuclei. In man, however, no cell formation that can be referred to the ultimobranchial bodies can be distinguished after a time; up to the present, no evidence has been advanced in favor of the widely accepted view that the bodies become converted into thyroid tissue, and such a transformation is rendered highly improbable by the results of comparative investigation."

Minot (11) espouses a view in direct contrast; "The lateral anlages are derived from the entodermal epithelium of the fourth pharyngeal pouches. The fourth entodermal pouch develops a ventral prolongation (human embryo of 10 mm.). His, makes a distinction between the diverticulum and the pouch. In an embryo of 12.5 mm. His found the diverticulum a closed vesicle entirely separated from the pharynx; the vesicle curved forward and there was just beginning to form a thyroid anlage. The median anlage at this stage is situated further oral and ventral. In an embryo of 13.8 mm. the lateral anlages have moved nearer the median, and take such a position that they prolong the me-

dian anlage forward and upward on each side." A diagram by
Minot shows that the lateral thyroid anlagen (ultimobranchial
bodies) lie a little below the fourth aortic arch, whereas, the
median ventral anlage lies cranial to the third aortic arch
(carotid artery). This may have a later bearing on the location
of the aberrant thyroid.

The outstanding work pertaining to the relation of the
ultimobranchial bodies and the thyroid gland has been that of
J. A. Badertscher (12) who investigated it in the pig. He is
able to state very definitely that the ultimobranchial bodies
form a part of the thyroid gland in the pig. The ultimobranchi-
al bodies may vary in size, shape, and in degree of transform-
ation, but their location in general is in the lateral half of
the gland. He was able to see colloid in the thyroid gland in
embryos of 75 mm. in length, but saw the colloid in the ulti-
mobranchial bodies only at 125 mm. length embryos.

W. M. Rogers (14) in his studies on the ultimobranchial
bodies in the rat makes the following statement: "Although my
previous description shows that the ultimobranchial bodies are
transformed into cords and the cords into colloid-forming
follicles which do not differ morphologically from those in the
rest of the thyroid, still the possibility remains that the
colloid in these follicles is physiologically different, as
Herrmann et Verdun ('00) and Kingsbury (8), ('14) suggested.

Swartz and Thompson (16) states; "The paired fundaments

of the thyroids arise in mammals a day or so after the unpaired fundaments arise, as two hollow evaginations of the ventral epithelium of the throat behind the last visceral arch and in connection with the last visceral cleft. By the 16th day in the rabbit embryo the thyroid anlagen have grown out into numerous cylindrical cords from which the lateral buds extend. By the union of these cords with one another a network is formed into which connective tissue and blood vessels grow. From these epithelial cords the alveoli of the thyroid are formed."

Other factors which the literature reveals are, the relation of the developing thyroid to other organs in the neck and thorax, and the exact location of the thyroid glandules within the pericardium.

Swartz and Thompson (16) have described the relations of the thyroid anlage to the other organs in the neck and thorax. "The anterior median anlage lies anterior to the truncus arteriosus/will become at later stages the pulmonary artery and the ascending part of the arch of the aorta. The fourth aortic arch of the left side, which by the 11th day runs through the 2nd left visceral arch, will become the permanent arch of the aorta. About the 10th day of gestation in the rabbit after the visceral arches have been closed, the pericardio-thoracic cavity extends as far forward as the last visceral arch. The heart gradually slips down into the thoracic cavity and in so doing

"The anterior median anlage lies anterior to the truncus arteriosus and to the pericardial sac. The embryonic heart is formed in the region that will become the adult neck in the mid-ventral line. From the cephalic end of the embryonic heart the truncus arteriosus arises. This truncus arteriosus will become at later stages the pulmonary artery and the ascending part of the arch of the aorta.

draws down the pericardial mesoblast which will become the epicardium, and at the same time drawing down the ascending arch of the aorta."

These authors also give a very brief description of the location of the thyroid tissue in the pericardium. They state; "We have found in addition to the thyroid tissue in situations which have previously been described (normally located thyroid gland) accessory thyroid tissue in the pericardial sac of 24 dogs out of 30 examined in succession. A total of 68 grandules in these 24 animals was found situated on the ventral and dorsal aspect of the ascending portion of the aortic trunk growing into the pericardial cavity." "The pericardial accessory thyroid grandules, with but one exception, were in the sub-epicardial fat anterior to the ascending portion of the aorta, or were attached to the sub-epicardial fat or connective tissue on the posterior aspect of the ascending portion of the aorta."

Davis (5) in his investigation of the fat bodies within the pericardium noticed that; "small reddish-brown bodies are often seen immersed in the fat-bodies." He also noticed that they varied in size (from a pin point to 1 cm. in diameter), in number and appeared either on the surface or deep in the fat-tissue. Out of 50 dogs that he examined 22 showed the presence of these thyroid grandules, which were checked by means of microscopic sections. Microscopically these sections showed that they might or might not have a capsule. "They are rich in colloid and are supplied with blood by rather ~~large~~

large prominent vessels, often by one at each end. The acini are uniform in size and are lined by typical normal thyroid cells." Their chief location was in the "anterior and posterior fat bodies. These anterior and posterior fat bodies are located anterior and posterior to the ascending part of the aorta. On gross examination Davis failed to note thyroid tissue in the pericardial cavity of the cat, hog, sheep, cow, rat, mouse, guinea-pig, or the rabbit.

Swartz and Thompson (16) failed to note the presence of thyroid tissue within the pericardium in their examination of human material.

The work of Broman (3) revealed the following facts; "The development of the thyroid is visible in a 2.5 mm. embryo and therefore belongs to the anlage of the young embryo. It appears as a ventral evagination of the foregut. Around this part the tongue anlagen are marked between which the origin of the thyroid occurs. The thyroid anlage now grows caudally into the cranial wall of the pericardial cavity, where it comes to lie in the immediate neighborhood of the truncus arteriosus. During the later caudal dislocation of the heart this epithelial cord is considerably elongated. The epithelial vesicles, how-ever, cannot follow the heart entirely, but remain on the cranial end of the trachea while the heart sinks into the tho-racic cavity. At the beginning of the fifth embryonic week the vesicle separates into two lateral lobes, which show a

lumen for the first time. By this time the thyroglossal duct has generally two lumina. This ductus thyroglossus will soon be elongated and become thin. It loses its lumina and by the fifth embryonic week will atrophy completely. At its origin from the mouth cavity it partially has the foramen caecum; and in exceptional cases other parts of the ductus thyroglossus may persist during life (as the so called "median Nebens-childruesen" respectively lobus pyramidalis). The two lateral lobes soon also lose their lumen. They begin to be cut into strands in the 8 mm. embryo. These epithelial cords - surrounded by a rich vascular connective tissue - remain compact for a time as such, particularly in the center of the lobes. But already in a 3 cm. embryo some of these strands may show lumina and secretion (Hammar 1925). These cell cords which thus appear beaded are then cut into individual cell groups, the follicular anlage. The development of follicles goes on and finally gives to the entire gland its characteristic aspect in a seven millimeter embryo.

The median connecting part of the thyroid gland is early retarded in its growth and is changed into the isthmus. The lobes soon bend over dorsally and caudally so that the entire gland assumes a horseshoe shape."

MATERIAL AND METHOD

Dog material was used almost exclusively.

As a check on the gross picture that Davis had found, we investigated serial sections of pig embryos, ranging from

the internal senses, and say that these are the channels
by which impressions, received by the outer senses, are
transmitted to the intellect. In some writers, then,
reason is considered to be a part of the sensitive soul,
and in others, as part of the highest, or <u>intellective</u>
soul. Pecock calls the five inward bodily wits common
wit, imagination, fantasy, estimation and mind. The
common wit presents the sensations received through the
outer senses to the imagination, which in its turn refers
them to the fancy or "fantasy". The image, in its turn,
is given over to the estimation, or judgment, and then
is presented to the intellect to be loved as Good or
rejected as Evil. The will is a power by which one
chooses what the reason, or <u>understanding</u>, deems to be
good. He says in <u>The Donet</u>,

> Free will is a power with which may
> freely be loved and chosen that thing which
> reason knoweth and deemeth to be good--and
> which may command to all other witty and
> moving powers of the soul and to all members
> of the body such moving proper workings as
> she wills that they be commanded. [11.]

Pecock held that living morally was identical with living
reasonably. If one lives reasonably, he necessarily lives
according to faith. Thus reason is the ultimate crite-
rion for action, the guardian and perfecter of con-
science. Phineas Fletcher says that conscience is a

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11. See Note 8.

The result was difficulty in obtaining serial sections. The second method was to make our blocks of celloidin. The trouble here was to keep the sections in serial order. We put 4 to 6 sections between filter paper and in this way we were able to keep the sections straight. It was necessary, therefore, to stain the sections through the filter paper. This was not satisfactory because the stain did not penetrate to the sections near the center of the pack in a sufficient manner to make a clear differentiation possible. The third method was a combination of the above two.

We tried various methods of staining, but found that the routine method of Hemotoxalin and Eosin was the best. The sections were cut 10 u. in thickness.

From our collection of slides we noted the following: A cross section series of a 10 mm. pig embryo showed that the thyroid took origin from a median ventral outpocketing, the thyroglossal duct. It extended caudad through 12 sections, ending in a double pouch, which rested on the 3rd aortic arch. No thyroid tissue was noted in the pericardial cavity because the embryo was too young.

In a 15 mm. rat embryo that was sectioned serially in a longitudinal direction there was no thyroid tissue in the pericardial cavity. The normal thyroid gland was located at the level of the first 4 tracheal rings. The sections demonstrated a very large blood supply, but showed no capsule devel-

opment around the thyroid gland. We were able to identify two lobes and an isthmus.

Our next series was of the pericardial thyroid taken from an adult dog. The histology was that of a normal adult thyroid gland with a slight excess of colloid.

We tried the double embedding process on an embryo of 8.5 cm. crown-rump length. The sections stained exceptionally well, but we were unable to cut a complete series and therefore we were unable to make a statement about the aberrant thyroid located in this animal.

We have a series of 477 sections of an average thickness of 10 u. which were made from tissue of a dog embryo 17.5 cm. in length. The area between the mandible and diaphragm was removed and all of the cartilagenous material dissected out before the process of embedding was started. The evidence given from these serial sections were such as to cause one to conclude that an actual migration of the cells is possible but not established.

The total length of the thyroid gland was 432 u. There was no evidence of an isthmus connecting the two rather large lobes situated more toward the posterior sides of the trachea. There appeared no definite capsule surrounding either lobe of the thyroid gland. There was considerable connective tissue around the gland, but it had not formed into the dense cap-sule that was expected. In one of the sections (slide 22)

of the left thyroid there seemed to be a tendency of the cells to wander away from the compact mass of acini. These cells that are drifting away at the periphery are of two types; large cells in which the nucleus tends to be a little to one side, and small cells that have no evident cytoplasm. The right lobe ends caudally at slide 24 by a scattering of the acini and the cells accompanying them. In this same section there is a large collection of cells near the trachea and esophagus which present a primitive undifferentiated cell structure. The heart is definitely present in slide 143. In the posterior part of slide 135 just anterior to the esophagus we have evidence of a (glandular?) structure. It is composed of some very large cells with a large amount of cytoplasm and a relatively small eccentrically located nucleus. This structure is surrounded by a definite capsule. There is a nerve just anterior to this glandular structure which can be seen in a series of sagital sections made on another dog. In slide 136 the above mentioned collection of cells tends to form into cords. This type of structure is noted on both sides of the trachea, but they are not connected. These two structures extend caudad for some distance. In slide 143 we note that the cells in the glandular structure on the right side become arranged around numerous capillaries. The main body of the heart does not show in this section. In section 147 there is a very strong tendency for the cells to migrate in a dense fibrous tube around the left pulmonary artery. No other glandular structure presents itself

in this series.

A series of sagital sections were made of another animal of the same litter. They revealed the following picture. On slides 17-18-19 there is a group of cells with an acinar structure located 2 mm. caudal to the lower end of the thyroid gland. It seems to be headed down between the common carotid artery and the internal jugular vein. The trachea first becomes evident in the second section on slide 19. The main body of the thyroid remains lateral or posterior to the trachea in all of these sections. There is no evidence of an isthmus to connect the two lateral lobes of the thyroid gland in this series. Slides 24-29 show a very small amount of thyroid tissue anterior to the trachea 1 cm. below the first tracheal ring or about 3 mm. below the glandular material noted in slides 17-18-19. This material seen in section 24 has a very definite acinar structure. It is 10 u. long and about 2 u. wide. In section 29 it has lost its acinar structure and has traveled so that it is now 1.4 cm. below the first tracheal ring. It continues to travel as a group of individual cells on the anterior surface of the trachea until it arrives close to the arch of the aorta (slides 35-36-37). Slide 37 shows two cell groups located within the connective tissue that will make up the attachment of the pericardium to the arch of the aorta. They present the appearance of a developing lymph node or some similarity in arrangement to the developing thyroid gland.

since, so far as I know, there have never been any definite lymph nodes noticed within the pericardium it would appear that this would at least be negative evidence of the presence of thyroid cells.

DISCUSSION

From a general review of the literature and slides, I believe that the thyroid glandules are migratory elements from the main body of the thyroid gland. This tendency to migrate may be caused by the descent of the heart and great vessels into the thorax, but I am inclined to believe the contrary.

If this migration was due to the descent of the heart or the great vessels (aorta), we would expect to find thyroid tissue resting on the heart or aorta in a more well developed state than is presented in the slides.

There is progressive lack of acinar formation of the thyroid glandules as they pass down around the trachea, to become located on the aorta near its base.

In the formation of the thyroid gland at its earlier stages it rests upon that part of the aorta which will become the distal part of the aortic arch. Other investigators have found that the periaortic thyroid is located at the base of the aorta. At no time in its early formation is the main body of the thyroid in close proximity to the aorta at its base.

If the surmise of Swartz and Thompson is correct, then some migration must also be necessary before the thyroid could

arrive at its adult location.   In this case we would expect to find rather well developed thyroid structure located at various positions along the medial section of the arch of the aorta. This evidence is not present in the sections that I have investigated.   It is my opinion, therefore, that the migration of thyroid tissue into the pericardium is not due entirely to the change in position of the heart and aorta in the embryo.

SUMMARY

1. There is evidence of a migration of cells from the thyroid gland of a dog embryo

2. This migration occurs after there is a definite acinar formation in the thyroid gland and also after the heart and great vessels have descended into the thorax

3. The migration of the cells from the thyroid gland begins in relation to the carotid sheath and more caudad is seen in relation to the pretracheal fascia

4. These cells migrate in small groups. The cephalad groups show an acinar structure, the caudal groups appear as irregular cell clusters.

5. The groups as a whole resemble a beaded sting that travels spirally about the trachea from left to right

6. The similarity of the cells found in the pericardium to this beaded chain would indicate the presence of aberrant thyroid gland in that region

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