REMARKS ON THE FUNCTION OF THE THYROID GLAND: A CRITICAL AND HISTORICAL REVIEW.¹

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THE THEORIES WHICH HAVE BEEN PROPOUNDED CONCERNING THE THYROID GLAND.

In the history of every discovery in physiology or pathology we usually have to wade through the writings of a wearisome number of authors who are ready to occupy space and time in constructing theories as to the probable use or function of an organ without contributing any fact or definite observation to the subject, and that of the thyroid gland affords no exception to this rule. But there is a special point in the hypotheses concerning the present question, only applied to other organs or tissues in the dark ages of medicine, and that is the contention as to whether the thyroid gland has any function at all (Prochaska)² or serves any useful purpose to the economy.

It is universally recognised that: (1) The various organs of the body possess a different value to the economy in different classes of animals and at different ages of the same class or species. (2) If an organ be of importance, then its removal will be followed by constitutional disturbance (subject to the conditions mentioned in (1)) proportionate to the completeness of the loss of the function of the organ. With extremely few exceptions, the results of the investigations of the authors I have consulted show that thus tested the thyroid gland is a structure of importance to the economy and that that importance varies in accordance with the principles stated in (1).

Those who deny that the thyroid gland possesses any importance, or that the symptoms evoked by its removal are due to the loss of its functional activity are Bardeleben, Cambria, Drobnick, Gibson (?), Kaufmann, Munk, Philipeaux, Tauber.

Bardeleben made three experiments in three dogs, of which one gave the usual positive result (*vide infra*). The negative cases, however, were not examined for accessory glands, and consequently cannot be regarded as of weight. Cambria stated that no constitutional disturbance followed removal of the thyroid gland. As however he followed the instructions given by Kaufmann (see below), he probably did not remove the thyroid, but the submaxillary glands, and the negative result of his work is consequently easily understood. Drobnick repeated Munk's experiments in eight dogs, of which three survived. Being, as he admits, for some reason unable to perform the operation aseptically, he naturally was led to believe that irritation of the nerves in the neck was the cause of the cachexia thyroidectomica (*vide infra*). Kaufmann bitterly attacked the views of Schiff and others, and stated that removal of the thyroid glands produces no constitutional disturbance. As, however, it is evident that he removed the submaxillary glands instead, his statement, as it is founded on an erroneous experiment, cannot be accepted. Munk, in his first publication, stated that although his own experiments showed complete and abrupt thyroidectomy in dogs to be almost invariably accompanied by fatal constitutional disturbance, nevertheless in his opinion this was not caused by loss of the function of the thyroid gland, but by certain (indefinite) injuries to the surrounding parts. In his second paper it appeared that these injuries were supposed by him to be lesions of the nerves in the neck, that is, the laryngeal

nerves and the vago-sympathetic trunk. This idea that the symptoms might remotely have been thus produced occurred also naturally to the minds of the earliest experimenters. Schiff had directly examined the nerves in his researches, and I myself had carried out,³ three years before Munk's publication, microscopic investigation of the nerves in my experiments, and had shown that when the thyroidectomy was properly performed, and duly followed by the characteristic symptoms the nerves nevertheless remained quite uninjured. Drobnick, in his experiments, also stated that he found the nerves involved in the scar tissue, which was not unlikely when the fallacies of his septic method are considered. Before Munk and Drobnick's publications, however, Baumgärtner had propounded the same view, and it was then repeatedly put forward (*vide Billroth, etc.*). For many years in England the symptoms of myxœdema had been attributed to lesions of the sympathetic. In consequence of the prevalence of this theory numerous investigators made special experiments on the point.

Munk states that by injecting croton oil into the capsular tissue of the gland he obtained results similar to those of thyroidectomy, though differing in some respects from its characteristic phenomena. As, however, he undoubtedly complicated his experiment by, in some cases, injuring the gland itself seriously by the injections, the mixed result obtained by him, and quoted in support of his theory, is, in truth, only a corroboration of the views he opposes; and his experiment, repeated by Kemperdick, gave equally indeterminate results bearing the same interpretation.

Properly to test the point, a very thorough series of experiments was carried out by Ewald, Fano, Fuhr, Herzen, Carle, and Weil, and a few observations were made by Breisacher. In these experiments not merely the special glandular nerves derived from the sympathetic observed by Liebrecht and others, but also the trunks of the laryngeal nerves and even the vago-sympathetic trunk were subjected to every conceivable form of irritation by extensive traumatism, septic inflammation, even by direct inoculation of septic microbes, chemical irritation, electrical excitation—all producing intensely the conditions supposed by Munk to cause the cachexia thyroidectomica, but with absolutely no result. Finally, other observers have examined the condition of the nerves after thyroidectomy, and have found them uninjured. This has been done by Schiff, Fuhr, von Eisselsberg, Ewald, Loeb, and myself. The weight of evidence is so obviously against the view that the cachexia and acute symptoms following thyroidectomy are evoked as the result of irritation of the nerves in the neck, that it is now never seriously advocated, with the few exceptions before named; and the view that the thyroid gland is of some functional value, and not an "indifferent organ" (Bollinger), prevails.

Philipeaux stated that he removed completely the thyroid glands in four dogs 1 year old, and that a month later they showed no symptom. The observations of Tizzoni, Ughetti, Alonzo, among others, indicate that even in dogs a month or six weeks is too short for observation, and that at the end even of several—for example, seven to nine—months dogs have shown the fatal cachexia. In any case, moreover, in view of the immense number of positive results on dogs by so many investigators, these four negative observations are difficult to understand. Tauber made the remarkable statement that in an extremely large percentage—about 66 per cent.—of cases, he could find no thyroid gland at all in his animals.⁴ This is so completely at variance with the observations of every other observer that his work cannot be accepted.

THEORIES OF FUNCTION.

We have occupied sufficient space and time in the consideration of this very fundamental question, and must turn at once to discuss what theories have been formed as to the true function and importance of the gland. The theoretical modes of regarding its duties may be enumerated as follows:

1. That it is for the purpose of preserving the contour of the neck. 2. That it acts as a mechanical cushion to protect the important vessels and nerves from compression effects exerted by the contracting muscles. 3.

¹ A German version of this paper was published in *Virchow's Festschrift*, 1891. I have given the references in full in that publication, but considerations of space forbid their reproduction here.

² For example, such a classical work as Leisring and Müller's dismisses the subject in a few words, saying that the gland is not known to possess any function, but that recently (*sic*) the idea of its being a regulator of the cerebral circulation has been suggested.

³ My original publication, *in extenso* in the BRITISH MEDICAL JOURNAL in 1885, was evidently not known to Munk or to the large majority of my fellow workers abroad until recently.

⁴ The account is so imperfect that it is not stated what kind of animal; possibly they were rabbits.

That it acts mechanically to support the larynx and improve the voice. 4. That it acts mechanically, and protectively causes anæmia of the brain, etc. 5. That it acts mechanically, and protectively prevents anæmia of the brain, etc. 6. That it manufactures some substance specially necessary to the integrity and proper functional activity of the central nervous system. 7. That it is directly a blood-forming organ. 8. That it is indirectly a blood-forming organ. 9. That it plays a special part in the metabolism of the sexual organs. 10. That it modifies or destroys substances which, circulating in the blood, are harmful to the general economy. *Corollary*.—That it secretes some substance useful to the general metabolism of the body.

Passing over the first of these, a teleological theory originated by Wharton, we turn to the second, which was advocated by Luschka; but since not only is there no proof forthcoming in support of it, but also the experience of thyroidectomy directly negatives it, we may proceed to the third hypothesis, which, though supported by Boerhaave, Martyn, and Merkel, is nevertheless so directly contradicted by every observation of extirpation—hundreds of which have now been performed—as to call for no further discussion.

The next views which I shall consider are those which have been put forward by the anatomists, and it is a striking comment on the fallacy into which an observer is easily led if he ventures to argue from structural details alone as to the function of an organ, unaided by the only true method of inquiry, namely, experiment, that the anatomists are divided into two exactly opposite schools on this very point. One party believes that the thyroid acts mechanically to produce anæmia of the brain either by compressing the carotid arteries—Guyon; or, as a diverticulum of part of the blood stream—Rush, Waldeyer, Grashey. The other party, the opponents of this view and supporters of the fifth hypothesis—Schrager, Meuli, Liebermeister—believe that the duty of the gland is to prevent anæmia of the brain. Even the swelling of the gland in the recumbent position, which is put forward by the supporters of the fourth hypothesis, is claimed by their opponents as favouring their own view. It is very strange that so much should have been written and argued upon these fourth and fifth hypotheses without any of the authors testing their worth by simple experiment, which would have at once settled the matter.

Even the most recent anatomists, who have devoted attention to it, namely, Waldeyer, Staehel, Zeiss, etc., have trusted only to the revelations of structure, and in so doing have laid themselves open to the successful attack by the same weapons of a representative of the opposite anatomical camp, namely, Rüdinger. A corollary to the anatomical views is the theory of Forneris, who considered that the gland swelled during sleep, with the evolution of which condition he considered it to be connected.

All the hypotheses, therefore, which merely rest on a point of general import, such as the vascularity of the gland, etc., should claim no further consideration.

The sixth hypothesis, namely, that the thyroid gland manufactures some substance specially required for the proper nutrition and functional activity of the nervous system, is one which has been advanced by some authors—John Simon, Weil, Sanguirico, with Canalis—but is not strongly supported. The fact that the nervous system suffers so prominently in the cachexia thyroidectomica is no proof in favour of this restricted creed of the function of the gland; it is only one expression of the general disturbance of metabolism caused by loss of the thyroid tissue.

The seventh hypothesis has long been in favour, owing to the theoretical hæmopoietic action of the gland having only of late years been more defined. In fact it has usually been confused with the eighth hypothesis, of which more will be said immediately. Direct hæmopoiesis may be imagined to occur (a) in the manufacture of leucocytes, (b) of red corpuscles, (c) of the constituents of the plasma.

As yet the hæmopoietic influence of the gland has only been investigated as far as (a) and (b) are concerned. The first observations, those of Crede, Zesas, and others showed that consequent upon the loss of the spleen the thyroid gland underwent hypertrophic changes or *vice versa*, upon which the disappearance of previous leucocytosis was noted. All the experimental observers who have witnessed the cachexia thyroidectomica have noted the remarkable anæmia characteristic of this condition. I myself, in 1884, devoted special attention to this subject, and found that in monkeys the red blood corpuscles diminished steadily from the time of the

thyroidectomy for a fortnight, and then reached an oligæmic equilibrium which persisted to death. The leucocytes, on the other hand, became treble in number, but when the oligæmic condition of the red corpuscles began to be marked the leucocytes steadily diminished to below normal at death. In accord with the observations of Crede and Zesas on man, I found that in some cases of thyroidectomy in monkeys the spleen was also enlarged, but this fact has been only exceptionally observed in the carnivora, although a very large number of experiments have been performed. For a further discussion of the vicarious action of the spleen and thyroid gland as regards hæmopoiesis I must for brevity refer to the writings of Zesas.

There remains a line of research which has not to my knowledge been followed up; that is the question of the presence of lymphoid tissue and the enumeration of the leucocytes in the thyroid artery and veins respectively. In 1886 I showed that in addition to the embryonic gland tissue described by Baber and Wölfler there was definite lymphoid tissue of a distinctly splenic character; further, that leucocytes were present in notably greater proportion in the veins than in the arteries, and that this proportion was greater than that to be found in the vessels of the limbs.

There is no evidence that the thyroid gland is directly hæmopoietic as regards the red corpuscles or the blood plasma, but Kohlrausch has found that in the acini are bodies closely resembling blood plates. This introduces us at once to the eighth hypothesis, according to which the thyroid gland is indirectly hæmopoietic. It has always seemed to me obvious that its influence must be exerted first on the chemical metabolism, especially of the albuminoid constituents of the blood, and that while there was no positive evidence that the normal effect is a constructive one, it is perfectly clear that the absence of the gland must very markedly alter the constitution of the blood, and so, indirectly, hæmopoiesis must be dependent on the integrity of the thyroid. This is a point of considerable importance in view of the fact that all observers who have examined the condition of the blood after thyroidectomy have found it notably altered in its constitution and function, even apart from the changes in the corpuscles already referred to. (Sanguirico, with Canalis.)

The changes in the blood apart from the alteration in the numbers in the corpuscles are as follows: (a) Increased vascosity (all observers, especially Herzen, Hofrichter, and Rogowitsch). (b) Great diminution⁵ in the amount of oxygen (Albertoni and Tizzoni) which may in the arterial blood fall below the normal proportion in the veins. This condition has been termed by Herzen "anoxæmia." (The connection of this condition⁶ of the blood with the activity of the respiratory centre is given below). (c) Presence of abnormal constituents of the plasma. Halliburton has found mucin in the blood of monkeys on which I had performed thyroidectomy.

It requires no insistence to point out that such changes in the blood gravely altering its constitution and functional activity must evoke a considerable degree of anæmia both by destructive changes in the fluid itself and by the effect which it, thus altered, necessarily exerts on the blood-forming tissues—for example, marrow.

The statement of these points relating to the influence of the thyroid gland as regards hæmopoiesis will serve, I trust, to make clearer the position I have always held, and which Professor Virchow has done me the honour to criticise. The final solution of the questions raised will be rendered easy by future researches.

The ninth hypothesis which directly connects the function of the gland with the functions of the female sexual organs is many centuries old. Of late years the subject has been so carefully considered by Freund⁷ in its chief bearings that it is hardly necessary for me here to do more than point out how the truth of the conjunction of the functional activities of

⁵ Michelson and Tarchanoff say that the whole gas exchange of oxygen and carbonic acid is increased; according to the latter to three times the normal amount.

⁶ Pisenti and Viola consider that the secretion of the thyroid may by being constantly supplied to the blood prevent the development therein of some toxic product, which poisons the system if the gland be removed.

⁷ For the special literature of this necessarily indeterminate point consult Freund's valuable paper.

these parts is confirmed by the far greater liability of the female sex to suffer from myxœdema. The harmony between the two sets of organs is evinced by the enlargement of the thyroid occurring when active changes happen in the sexual organs. What is the nature of the change which requires the increased activity of the thyroid is not yet known, but that such a need should arise is comprehensible from the altered condition of the blood in pregnancy and menstruation. The widespread alterations in metabolism, which are frequently noted in these conditions, would naturally create a necessity for increased activity in a metabolist organ like the thyroid. As an indirect confirmation of the relationship, Schönlein shows that there are two maxima for the appearance of goitre—namely, the development of puberty and of senile involution respectively.

There remains the tenth hypothesis, which is the most important of all, and the demonstration of which is necessary to the proof that the thyroid gland is the active agency in metabolism that has been suggested in these pages. The task before us is first to review the facts accumulated during the last decade in the investigation of the following conditions—first, thyroidectomy in birds, rodents, ruminants, solipedes, carnivora, monkeys, men, and its relation to (1) myxœdema, (2) cretinism; and, secondly, to summarise the general level of knowledge thus attained for the purpose of categorically stating the present position of the subject.

NATURE OF THYROID TISSUE.

We must preface the demonstration of what happens when the function of the thyroid glands is lost by some consideration of the circumstances under which the normal gland tissue exists in functional activity. Having already alluded to the hæmopoietic action of thyroid tissue, and having shown the error of believing that its rich blood supply merely suggests a mechanical appendage to the cerebral circulation, we are able to discuss its proper glandular structure. It was suggested by Morgagni and some of the older writers that the thyroid secreted a colloidal or glairy substance. These hypothetical ideas, however, were worthless until King showed that gentle pressure on the lobes of the gland caused the contents of the gland acini or vesicles to flow into the peripheral lymphatics. After he had thus filled the lymphatics, he coagulated their contents *in situ*, and thus readily demonstrated the mode of exit of the secretion, which he thus recognised the colloidal product of the gland to be. Boéchat and Baber first showed microscopically that the periacinous lymphatics contained the colloidal material seen in the acini, and thus anatomically confirmed the experimental demonstration of King as to the connection between these cavities. I also found the same condition constantly to exist, and determined the obvious truth of Baber's view that the acinous epithelium was a true secretory gland tissue which separated the colloidal material from the blood, and that this found its way into the circulation by means of the lymphatics. Quite recently the subject has again received attention from Langendorff, Biondi, and Kohlrausch, all of whom have reconfirmed these views. They have also acceded to the opinion that the vesicles in part intercommunicate, and Langendorff has dwelt particularly on the secretory character of the epithelium, and especially on the intimate connection between the protoplasm of the cell and the colloid material. The secretory character of the epithelium has been further exhibited by the experiments of Wyss, who, inspired by Gaule, injected pilocarpin with the result of increasing remarkably the secretion of the colloidal substance, as well as of producing extra colloidal change, extension, etc., in the epithelial cells, after the toxic action of the drug had become well established.

As to the colloidal secretion of the gland, that was shown in 1826 by Babington to be albuminous and not mucin. The same opinion was formed by Gorup Besanez, who showed that, unlike mucin, it was soluble in acetic acid. Langendorff's micro-chemical experiments also yielded the same facts. Besides various forms of alkali-albumin, water, salts, etc., according to Moscatelli, paralactic acid must be specially mentioned among its constituents. The same substance has been also found by Hirschler in those lymph glands which receive lymph from the thyroid gland.

The physiological influence of the secretion has also been directly investigated, first by Ewald, who found that the

juice expressed from the thyroid gland of a dog produced in another such animal coma after three hours, and, further, that the extract from other animals was not so toxic at all. I repeated the experiment with the gland of the sheep, and obtained only negative results, as also was the case with Alonzo's experiments. Langendorff noted drowsiness to follow such injections in rabbits. As I pointed out some years ago, this experiment is complicated by the presence of tissue fibrinogens (Wooldridge), which are very toxic. In accordance with this, it is important to note that several experimenters (Langendorff, etc.) have seen intravascular clotting to occur as the result of their injections. Wagner finds that injections of mucin determine in cats tremors and tetanoid spasms resembling those of the cachexia thyroidectomica. Closely connected with this point is one which is discussed on page 219, namely, the effects of injecting the secretion of the gland in animals from whom the glands have been removed, and at the same time the source and mode of improvement in myxœdema caused by transplantation of gland tissue.

FUNCTION OF THE THYROID.

We must conclude, it seems to me, that the thyroid gland is a structure essentially connected with the metabolism of the blood and tissues; that in fulfilment of its functions it is hæmopoietic both directly and indirectly, and that it forms, that is, secretes from the blood a colloidal substance, which is transmitted *via* the lymphatics from the acini of the gland to the circulation.

Importance of Thyroid Tissue to the Economy.

The relative importance of a gland in its service of the needs of the organism is well shown by its developmental history. This is particularly true of the thyroid gland in both its normal physiological relations, and under morbid conditions. I have myself found that in the human foetus the gland tubes, or rather cylinders of epithelium, during the interval from the sixth to the eighth month commence their secretory function. Huschke showed that in proportion to the body weight the gland was heaviest at birth, and notably diminished towards the end of life. Not only is the mass of the gland greater in early life, but histological research (Canalis and Tizzoni) shows that whereas karyokinetic changes are very frequently to be seen in the epithelial cells of the glandular acini in young animals, they are correspondingly very rare in the acinous epithelium of old individuals.

In strict accord with these proportional estimates are (1) the anatomical degenerative changes which occur in consequence of senility and (2) the anatomical changes witnessed in general wasting diseases in which the metabolism of the body is generally lowered. (1) Those alterations which are due to old age are widely known—namely, fibrocystic degeneration, etc.—but have been well described by Hale White and Pilliet, who find cystic degeneration, interstitial cirrhosis, great diminution of the colloidal secretion, and retrogressive changes in the glandular epithelium, the acini being filled with broken-down *débris* of the cells. (2) Defaucamberge, working under Cornil, has found that in phthisis the secretory activity of the gland is very notably decreased, and consequently the colloidal substance disappears from the acini, which come to resemble the epithelial cylinders of the embryonic stage.

The thyroid gland, therefore, is in functional activity before birth, and is of special metabolic importance in early extra-uterine life, while its value falls as the general vital processes decrease. This position is finally confirmed by the crucial experiments of pathology as follows:—

(a) Experimental thyroidectomy is very much more fatal to young animals than to adults. This I have found to be markedly so in monkeys; Schiff, Wagner, Ewald, and others in the carnivora. Cooper's two experiments are the only ones to my knowledge which oppose this general conclusion, and they must be considered to be imperfect, since the animals were not kept for a sufficiently long period nor examined for accessory glands. Sanguirico and Orecchia state that in ruminants the removal of the gland in 3 lambs was not followed by the cachexia. Judging from my own experience of adult sheep, I do not think that in these cases the animals were observed for a sufficient length of time. It would, therefore, be very advisable that the experiments should be repeated and largely extended. Conversely,

Hegar, Simon, and myself have found that removal of the gland in aged carnivorous animals is not followed by the usual rapid cachexia.

(b) Cachexia strumipriva has been found by all observers to occur with far greater frequency when the thyroidectomy has been performed in young individuals. This is well shown in the accompanying table which is copied from Bourneville and Bricon's valuable paper on Sporadic Cretinism:—

Liability to Cachexia Strumipriva after Total Thyroidectomy.			
Age.			Cases observed.
10 to 20 years	...	...	18
20 " 30 "	...	...	14
30 " 40 "	...	...	3
40 " 50 "	...	...	2
50 " 60 "	...	...	1
60 " 70 "	...	...	1

This table shows that the liability to constitutional disturbance following the loss of the function of the thyroid gland is extremely marked in early life, and almost abruptly ceases at about the 30th year. The observations of anthropologists have for a long time tended to show conclusively that active growth—that is, increase—also ceases at the 30th year. The concordance of these two facts strikingly illustrates the bearing of the gland's function on the general vital activity. Kocher, who has had so large an experience, is of the opinion that total thyroidectomy performed before puberty will inevitably be followed by the cachexia.

(c) Intrauterine cretinism is now (Virchow, Barlow, Shatlock, Eberth, Bowlby, Sutton) well recognised, although for a long time it was described under the title of fetal rickets. In this condition either the thyroid gland does not develop normally or it undergoes atrophic changes, so that at the time of birth usually not a trace of it is to be found, very rarely it has been described as normal, but no microscopical examination made. Under these circumstances the cretinic and myxœdematous cachexia is excessively advanced during the intrauterine life of the fetus, so that it is almost invariably born dead.

(d) To this may be added the well known fact that in countries where cretinism is relatively rare—for example, England—there occurs a myxœdematous form which follows morbid changes in the thyroid gland in children, producing what is spoken of as "sporadic cretinism" or "*idiotie pachydermique*" (Bourneville and Bricon). In the present paper, however, I cannot deal with these conditions except so far as they illustrate points like the present, emphasising the apparent importance of the gland in early life.

The conclusion therefore affirmed above concerning the relative value of the gland according to the age of the individual need not be further insisted upon.

The Distribution of Thyroid Tissue in the Body and its Relation to the Pituitary Body.

The occurrence of thyroid tissue in other parts than the lobes of the gland in front of the trachea is, as will be subsequently seen, a matter of far more than embryological interest, and the coexistence of the pituitary body may conveniently be considered at the same time. The development of the thyroid gland proper can not be entered upon here, but not only are the position, early appearance and relations of the gland in the embryonic life of the higher animals evidence of importance, but as shown by Julin and others the same appears to be true of the lower vertebrates; for example the *Ammocetes*.

The principal fact, however, of importance to the present question is the existence^a of additional masses of thyroid tissue or accessory thyroid glands as these have been termed. Since Gruber described the proportional frequency of accessory glands in man, numerous authors (Callender, Bruch, Kadyi, Zuckerkandl, Madelung, Streckeisen, Wolf and Porta) have considered the subject in all its anatomical bearings and collected the literature upon it. This last duty has been specially carefully performed by Madelung and Semon. Briefly summarised, these accessory glands may be grouped in man as follows:

Region of the Hyoid Bone: Supra-hyoideal, Pre-hyoideal, Infra-hyoideal.
—Of these the infra-hyoideal gland has long been known as the middle or pyramidal lobe of the thyroid body. This Callender showed to be really

a free mass of tissue, and in 2 per cent. of the cases examined by Gruber, he regarded it as a superior accessory gland. Streckeisen subdivides the remaining two kinds thus: (1) Pre-hyoideal, (2) supra-hyoideal, (3) epihyoideal, and (4) infrahyoideal, but these were not only found in man.

Region of the Thyroid Gland.—Porta, Gruber, and Bruch found accessory glands termed lateral or posterior either under or behind the lateral lobes of the thyroid body and the gullet, and these have been repeatedly found enlarged and removed by operation (Wolf, Barker).

Region of the Aorta and Great Vessels.—In the dog, Piana stated that accessory thyroid tissue was present situated close to the aortic arch in 66 per cent. of all cases examined by him. Ewald similarly found that in every one of five dogs which suffered from goitre there happened to be also enlarged aortic thyroid glands. Other authors, Wölfler, Wagner, and Carle have also determined the existence and relative constancy of these accessory glands, and it will be remembered that according to Kölliker the thyroid gland in its development commences close to the bulbous aortæ (in the rabbit). In the carnivora accessory thyroid glands have been found in other situations (Fuhr, Autokratow). Munk states that although he has looked in general for accessory glands in animals, he has never found one.

As of course positive evidence must always outweigh negative evidence we nevertheless are compelled to conclude that accessory glands occur with notable frequency.

The bearing of all these facts will be seen further when the question of compensatory action of other tissues arises in cases where the thyroid is lost, but it seemed more proper to discuss the prevalence of this specialised tissue at the moment when the general importance of the gland as a metabolising organ was under consideration.

The Pituitary Body.

Attention must now be directed to the pituitary body, inasmuch as from the development of the anterior lobe, as well as from its structure, it is evidently closely allied to the thyroid body, and, like it, plays probably a more important part in the economy than has previously been attributed to it.

The description of the development and histology of the pituitary body (anterior lobe), which is given in most textbooks, has been notably supplemented by several authors, especially Rogowitsch, Pisenti and Viola. From these researches it is obvious that the anterior lobe of the pituitary body is an epithelial structure, the cells of which are arranged cylindrically, and that there is a series of lacunar spaces surrounding them which, together with the blood vessels contain, in the normal state, colloidal material.

As yet but little research has been directed to the relation between the thyroid and pituitary bodies, apart from similarities of structure, but there is some direct evidence on this point, and what there is goes to show that the pituitary body responds (in a compensatory manner (?)) when the thyroïdal function is lowered. Thus Rogowitsch has found that after thyroidectomy in dogs the pituitary gland is swollen, and the cells become vacuolated and ultimately disintegrated the longer the animal survives the thyroidectomy. Finally, in sporadic cretinism, where the thyroid gland is lost, the pituitary body has been found to be enlarged (Bourneville and Bricon).

INDIRECT EVIDENCE OF THE IMPORTANCE OF THE THYROID GLAND.

In accordance with the well-known laws of gland physiology, the thyroid, upon loss of one lobe, shows compensatory hypertrophy of the other. This "hypertrophy" has been observed under different circumstances.

When Half the Whole Gland has been Removed.—Wagner was the first who recognised enlargement of one lobe to occur if that of the opposite side were removed. In the following year I confirmed his statements, but like subsequent investigators—von Eisselsberg, Breisacher, who also obtained the same result—I noticed that it did not always occur. It soon became evident to me that this inconstancy was apparently due to the variable condition of the animals so far as their constitutional state was concerned. Where the active metabolism of the tissues was lowered from any reason, and the animal neither grew nor increased in weight, the remaining lobe of the gland did not hypertrophy, but when the animal was not old at the time of operating and developed normally, then the thyroid tissue hypertrophied in an apparently parallel degree to the needs of the metabolism of the body. This view has been confirmed by the observations of von Eisselsberg, who found the hypertrophy only to occur in young individuals. There are many points, especially in regard to the histology of this hypertrophy, which are well worth of an

^a Von Eisselsberg could not detect any accessory glands in the cat.

extended study,⁹ but the observations are too scanty to admit of further consideration in detail.

Hypertrophy of Accessory Thyroid Glands.—It has been observed after complete thyroidectomy in man that other islands of thyroid tissue became enlarged, and that whereas temporary symptoms of cachexia (Reverdin) may appear, they improve in proportion apparently to the degree of swelling of the accessory thyroid glands. In one interesting case (Shattock), destruction of the thyroid by a neoplasm led apparently to hypertrophy of an accessory thyroid gland. Following closely on the evidence afforded by hypertrophy of the remaining thyroid tissue when part is lost is the remarkable series of experiments on transplantation of thyroid tissue commenced by Schiff, and so thoroughly elaborated by von Eisselsberg. Schiff found in the dog that transplantation (intra-peritoneally) of the healthy gland shortly before the operation of thyroidectomy was sufficient to protect the animals from the fatal cachexia, although they appear to have constantly suffered from the tetany. Carle found that transplantation a week after the thyroidectomy was inefficient to ward off the cachexia. This experiment repeated a few times by other investigators, however, did not yield the same positive result until von Eisselsberg renewed the research on a larger scale, and found that in cats, if the transplanted gland underwent atrophy and degeneration, the usual cachexia supervened. If, on the other hand, the gland became properly vascularised and resumed its functional activity, then the cachexia did not show itself. This very conclusive evidence suggested to me the advisability of introducing the practice of transplantation as a rational treatment of myxœdema and cretinism. I was not aware until some months later, by the subsequent publication of Bircher, that this had already been performed by him as treatment of cachexia strumipriva, and I afterwards learnt, through the kindness of Professor Kocher, that he had commenced it as long ago as 1883. In France it has been taken up, and operations by Lannelongue, Merklen and Walther, Bettencourt and Serrano have been performed in myxœdema and sporadic cretinism. The sum of all these operations is unquestionably a notable improvement in the patients and amelioration of the symptoms in those cases where the grafted gland survived.

Amount of Gland which in the Carnivora must be left for Functional Purposes.—In accordance with what has been said, it will be recognised that a valuable point in connection with this branch of the subject is the question as to how much of the gland is necessary to meet the needs of the organism. The statements of investigators (Colzi, von Eisselsberg, Fuhr, Sanguirico, with Canalis, Weil) are pretty close, and show that in dogs and cats there must be at least one-third, or in some cases one-fourth of the gland left to prevent the onset of the fatal cachexia. It follows from what I suggested above that the value of this remnant will be very different according to the constitutional state of the animal. Coupled directly with this point of residual portions of thyroid tissue being available for the metabolic necessities is the question whether gradual extinction of the gland (thus anticipating the effect of senility) could be accomplished without causing the fatal cachexia. Schiff first attempted this by successive extirpations at considerable intervals in dogs, but he found that as a rule the procedure was only occasionally survived. In his and all the various methods of gradual extinction of the thyroid gland, a remarkably constant feature appears, and that is the outbreak of many of the initial symptoms of the cachexia, that is, tetany, hebetude, etc. These are developed (Schiff, Colzi, Fuhr, Fano, with Zanda) in proportion to the destruction of the gland tissue, and disappear when the metabolic equilibrium is regained, often by hypertrophy of accessory tissue. Colzi and Fano (with Zanda) found, further, that transfusion of healthy blood caused these preliminary symptoms to diminish. Munk stated that if the gland were isolated, shelled out of its bed, but left *in situ* with the vessels ligatured and primary union secured, the animal would probably recover, but that if suppuration occurred, as seems to have happened in the large majority of his cases, death ensued. His experiment has been repeated, however, by several

observers—Weil, von Eisselsberg, Fano, Ewald—who state, on the contrary, that the effects are the same as thyroidectomy. Munk's own description, moreover, shows that where the nutrition of the gland substance and contents was completely destroyed by the operation, the cachexia inevitably followed, and the same conclusion is arrived at by the above-mentioned investigators, who have repeated his experiment, as well as by Tarchanoff, who ligatured all the vessels supplying the gland. A further point is raised by these experiments, namely, the temporary warding off of the unfavourable symptoms by the animal absorbing the secretion, yet remaining available in the residual gland structure. This was the view taken by Schiff of his transplantation experiments. A positive observation in its favour is the result of the experiments conducted by Vassale on nine dogs. This author found that if, immediately after thyroidectomy, the expressed juice and secretion of the glands were injected into the animal, the cachexia was thereby considerably diminished, that is, the venosity of the blood improved, as also the conjunctivitis, etc.¹⁰ Von Eisselsberg, however, saw no such improvement in cats similarly treated.

Evidence of Active Growth, that is, Regeneration of Thyroid Tissue when this has been in part removed.—Active growth or regeneration on the part of the thyroid tissue, if it existed, would be in support of the opinion that its integrity is a metabolic necessity. As a matter of fact, the true thyroid glandular tissue does show a strong tendency to regeneration, especially in the peripheral regions (*cf.* also Wölfler). Canalis, Ribbert, and Neumeister have found that in dogs and rabbits the removal of portions of the gland was followed in a few (two to three) days by, first, the appearance of mitotic figures in the epithelial cells of the nearest acini; and, secondly, the growth of the epithelium as cylinder masses, which subsequently formed new acini in the supporting tissue of the scar.

Summary.—To sum up the indirect facts, we see that they afford very weighty evidence in favour of the view that the thyroid is in truth the important origin of metabolic influence that the general results of thyroidectomy would lead us to believe it to be.

(To be continued.)

REMARKS ON GALL STONES AND ON

THEIR TREATMENT BY THE ADMINISTRATION
OF LARGE DOSES OF OLIVE OIL.

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THE uncertainties of medicine are so great that my sympathies have ever gone out to that candidate for a degree of whom it is told that his examiner, after appealing in vain to several lines of, as he hoped, dormant genius only to meet with disappointment, tossed him the corner of a blotting pad, with the scathing request that he would write down all he knew. In a sense we are not so far removed from that poor young man, for while we can most of us talk to any extent upon what we think, how few things are there that we really know! But a discourse upon ignorance in the abstract will not help us much, so I have selected the liver as our *locus niger*, and as our *locus nigerrimus* I will take gall stones.

We all know that gall stones produce a great deal of distress, not to say agony, that they lead to various serious changes in the liver, and in one way or another are by no means an infrequent cause of death. But it is not with points of this kind that I wish to deal at present. The question I wish to ask is a much more searching one, namely, what do we know about the why and the wherefore of the formation of gall stones, because clearly, unless we do know why and how they form, we are in no position to treat them to any good

⁹ I very greatly regret that the details of the splendid work by Professor Halsted and Professor Welch are not available for this report. I anticipate much will be learnt from their researches on this very question of "hypertrophy."

¹⁰ Compare the gratifying results obtained by Dr. G. Murray in treating myxœdema by this method. BRITISH MEDICAL JOURNAL, October 10th, 1891 p. 796.