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T H Y R O I D E X T I R P A T I O N.

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- I N T R O D U C T O R Y -

The existence and the gross anatomy of the thyroid gland in man and mammals have been known from the earliest days of Medicine. Certain diseases, more or less directly connected with it, have also been long known, and have led many observers to a close study of the importance and function of the gland.

During the last eighty years the question of its importance has held the close attention of all leading scientists and a vast number of experiments has been performed in the attempt to discover its function and importance to life.

And yet, in spite of the facts that much has been disclosed by those experiments, and fairly reliable cures have been established for diseases that affect the thyroid directly, it must be admitted that the problem in question has not been definitely solved. We do not yet know the true function of the thyroid gland. The question as to its importance to life has not been definitely settled, and the physiological and functional relationship between the thyroid and the parathyroid glands are still matters of doubt.

On reading the accounts of the results obtained by the many scientific workers, who have carried out research work on thyroids and parathyroids, we are at once

confronted with the fact, that many of these are conflicting. It is also very evident that extirpation experiments of thyroid only in most animals, and particularly in some of the carnivora, must be very difficult, owing to the close anatomical relationship between the thyroid and the parathyroids.

In my opinion this accounts, partly at least, for the somewhat indefinite results referred to before. There is further little doubt that results of extirpation of thyroid and parathyroids differ considerably in different classes of animals.

The physiological relationship between thyroid and parathyroids is one of the points upon which scientific workers have not quite agreed in the past. Professor Swale Vincent in his book on "Internal Secretion and the Ductless Glands" states: "Thyroid and parathyroids are to be looked upon as a single physiological apparatus, the two kinds of tissues being intimately associated embryologically, and working together physiologically. When the thyroid is removed the parathyroids appear capable of functionally replacing it to a certain extent, and their histological structure changes accordingly".

This view, though shared by some scientists, has been contradicted by others.

I have attempted to solve the problem by performing a series of experiments on rabbits, the results of which will be submitted after the history of the subject of Extirpation has been briefly reviewed.

H I S T O R I C A L.

During the years 1836-1880 a considerable number of extirpation experiments was performed by different observers. Experiments at this time were, however, often carried out under unsatisfactory or unknown conditions. The existence of the parathyroids was not known, and the records left are in many cases incomplete and unsatisfactory. We may therefore say that the results of those early experiments cannot be considered to have much importance, and a short summary will suffice to indicate the most important points in connection with thyroidectomy, which those experiments have brought to light.

To Raynard (64), a French scientist, belongs the honor of having first performed extirpation experiments upon animals in 1834-1835. He maintains that goitre can be treated in dogs just as in man. "Il réussit," says Raynard, "fréquemment pendant l'âge moyen de la vie. Il est fort advantageux pour les animaux âgés. Quant aux jeunes, depuis le sevrage jusqu'à deux ou trois mois, nous avons fait la remarque qu'il est suivi de la mort peu de jours après, même dès le lendemain de la disparition du goître. Les recherches cadavériques les plus minutieuses ne nous ont fait découvrir jusqu'à ce jour aucune lésion à laquelle on puisse attribuer la mort".

The most important experiments from this period were performed by Schiff (69,70) in 1857-1859. He did a series of thyroidectomies upon different animals, and reports that several dogs, a cat, and a rat died some days after the operation, but that some rabbits, rats, fowls, and dogs survived.

Several other observers extirpated the thyroid from dogs, rabbits, rats and other animals about this time. Generally speaking the animals were not observed to show any ill-effects after the operation with the exception of a few cases in which it proved fatal.

At this time cretinism had long been recognized, and in 1874 a condition later known as myxoedema was described (by Gull). In 1882 some Swiss surgeons noted the symptoms of "operative myxoedema" after an operation for goitre in man.

These early experiments can, therefore, not be said to have yielded definite results, and they left the subject of thyroidectomy open for future research. But they undoubtedly aroused interest in the subject, spurred scientists on to further investigations, and probably drew the attention of surgeons to a possible danger of total removal of the thyroid gland.

The most important experiments performed during the ten following years were done by Schiff and Horsley.

In 1884 Schiff (69) performed a new series of thyroidectomies upon rats, rabbits, cats, and dogs. His results briefly stated were as follows: Rats and rabbits showed no marked symptoms after removal of the thyroid, but in dogs and cats complete removal of the gland at one time resulted in the death of the animal within a few days. In most cases the animals died in the first week after the operation, and one dog only out of sixty survived for fifty days. Schiff thought that removal of the thyroid was not fatal when the two lobes of the gland were removed at different times. He stated, further, that grafting of a portion of the gland into the peritoneal cavity prevented the symptoms that usually followed the operation.

Horsley (36-43) studied the effects of thyroidectomy upon different animals in considerable detail. The results of his experiments agreed fairly closely with those already obtained by Schiff. Thus, he found, that the carnivora - dogs, cats, and foxes - usually died soon after the operation with acute symptoms. In man and the monkey the operation was followed by chronic symptoms, which finally and invariably led to death. The Ungulata -sheep, goats, donkeys, pigs- showed a general cachexia which resulted in death after a more

or less prolonged period. (The Herbivora) Birds and rabbits showed no symptoms.

From these results Horsley came to the conclusion that the different effects of thyroidectomy upon various classes of animals, were due to differences in metabolism.

The general symptoms displayed by animals after thyroidectomy, as noted by these observers, were general malaise, muscular tremors, alterations in sensibility, vaso-motor disturbances, and cachexia.

Horsley, who first operated on monkeys, records the following train of symptoms in those animals, in the first six weeks: Fibrillary twitchings of the muscles of the limbs (which, however, ceased on voluntary movement), anoemea, and depression, cretinism, and myxoedema. The myxoedema, he states, led to the death of the animal in the sixth or seventh week. Horsley further describes infiltration by mucin into the subcutaneous tissue of the face and abdomen, a hypertrophy of the salivary glands, and a mucous secretion by the parotids. Subsequent observers have not been able to verify those last results (vide infra).

The great majority of scientific observers of this period (1880-1890) agree in the conclusion, that the thyroid gland is an organ essential to life,

basing those conclusions on the experimental evidences discussed above.

A few, however, among whom are Philipeaux (63), Munk (61-62), and Drobnick (5) think, that the symptoms following thyroidectomy in animals are due to entirely different causes, such as injury to nerves, reflex actions etc., and refuse to accept the belief, generally adopted, of the supreme importance of the thyroid. In support of this view, they point to the numerous exceptions recorded by experimenters of different periods, which show that by no means thyroidectomy is always fatal, not even in carnivora such as dogs and cats. Indeed, they remind us that complete thyroidectomy has occasionally failed to produce any ill-effects in those animals.

The next stage in the history of thyroidectomy is marked by the important discovery of the external parathyroids by Gley. He made a detailed study of the subject, and published his observations in a series of papers during the years 1891-1897 (15-22).

In these papers Gley urged that the different results obtained by previous observers in different classes of animals, on removal of the thyroid, were due to anatomical variations, and that, in fact, a different operation was being performed in, for instance the rabbit and the dog. Hence, he claimed,

the thyroid alone was being removed from the rabbit, with no ill-effects; but in the dog, where thyroid and parathyroids were in close contact, the whole apparatus was being removed with fatal results. Thus, he thought that anatomical differences explained the different results obtained in those two cases.

To prove this theory he removed the external parathyroids, along with the thyroid, from a number of rabbits, and came to the conclusion that the operation, when performed in this way, was as fatal in rabbits as in dogs. Out of fifty-five rabbits operated on in this way, twelve lived, however.

Gley also tried to remove the thyroid from dogs, without at the same time taking out the parathyroids, and found that the operation then was no more dangerous than in rabbits.

He further removed the external parathyroids from both these classes of animals, and concluded that the operation was harmless in either case.

The same observer noted, what had previously been learnt, that removal of the thyroid in rabbits gave rise to no symptoms. If, however, the external parathyroids were removed later the animal soon died with acute symptoms. The external parathyroids

upon examination were found to have undergone a compensatory hypertrophy, and, as Gley believed at this time, more or less of a development into thyroid tissue.

Gley's results, though supported by the observations of many other scientific workers, aroused considerable controversy, and later Gley and Nicolas (25) became doubtful of the development of parathyroid into thyroid tissue after thyroidectomy.

Moussu (57) removed both thyroids and parathyroids from nineteen rabbits and only four died.

Hofmeister (32-34) found that removal of the thyroid alone in young rabbits hindered the proper development of the skeleton, and later the same observer and Moussu maintained that removal of the thyroid only gives rise to a cretinoid condition.

It must be borne in mind that up to this time the existance of internal parathyroids had not been known.

These glandules were first discovered by Kohn (47) and in his publication of February, 1895, this author insists, not only upon the presence of two glandules (an external and an internal parathyroid) on each side, but also upon the parathyroids being

organs siu generis.

Two Italian observers, Vassale and Generali (72-73), after making themselves well familiar with anatomical relations of the four parathyroids, proceeded to systematic extirpation experiments.

Ten cats and nine dogs were operated on, all four parathyroids being removed in each case, and the thyroids left behind.

Of the ten cats nine died within ten days after presenting typical symptoms. The tenth cat, though living three months after the operation, showed grave symptoms. The symptoms noted were: fibrillary twitchings, muscular spasms, physical depression, stiff and tottering gait, loss of appetite, tachycardia, rapid emaciation, and lowering of body temperature.

The nine dogs all died within eight days, and mostly on the third and fourth day after the operation, the symptoms as a rule beginning to show on the second day. The symptoms noted in this case were: physical depression, muscular tremors, paresis of the muscles of mastication, trismus, rigidity of the hind limbs, uncertain gait, general muscular feebleness, and convulsions.

Distinct convulsions were not observed until just before death, and the predominating symptoms

were those expressive of diminution of nervous excitability, the paralysis in some cases being rapidly fatal. The autopsy showed that the lungs were normal, but spleen and kidneys congested.

These authors maintain that the death of the animals could not have been due to complications arising from the operation itself, and state that the thyroid suffered little or not at all in the operation.

Vassale and Generali point out that the symptoms presented after removal of all the parathyroids are the same as those presented after removal of thyroid and parathyroids, but that death supervenes earlier after parathyroidectomy alone.

In a later communication Vassale and Generali report that the two parathyroids on one side may be removed with no effects, but when the remaining two are removed some time later, the operation proves rapidly fatal.

Later still the Italian authors observed that tetany after thyroidectomy is more marked in young dogs than in old ones, and that it is particularly well marked when the animals are abundantly fed on a meat diet after the operation.

Results of experiments carried out by several other scientists about this time agreed with those obtained by Vassale and Generali, and there was a

marked tendency at this period to emphasize the importance to life of the parathyroids, while, at the same time, the importance of the thyroid itself was being underestimated. This view received support from the fact that several observers had failed to notice any ill-effects -especially in rabbits- after removal of the thyroid.

This, as pointed out by Professor Swale Vincent, may be due to two causes: (1) The presence of accessory parathyroids, (2) the fact that the thyroid is of less functional importance in the adult than in the young animal.

Moussu (60) suggests that there may be two distinct functions for thyroids and parathyroids, and that interference with the functions of the thyroid will give rise to chronic troubles, while interference with the functions of the parathyroids will lead to acute symptoms.

Most observers hitherto mentioned speak of the removal of the thyroid apparatus, or any part of it, as if it were quite a simple matter. Vincent and Jolly (68), however, seem to realize fully the difficulty of the operation in most of its variations, and comment as follows upon that point: "From the writings of the authors who have supported the modern view (i.e. the supreme importance of the parathyroids)

it would appear to be a simple matter to remove, in some cases, the parathyroids, leaving the thyroid intact, and in others the thyroid, leaving the parathyroids *in situ*. Variations of these experiments would seem to be equally simple. Welsh, indeed, who worked with the animal in which this operation is most easy, admits some difficulties in performing complete thyroidectomy. Our experience has convinced us that he has understated rather than otherwise these difficulties. The obstacles in the way of success in this operation are mainly anatomical. The parathyroids are extremely variable in position. The external pair may as a rule be easily seen and removed, but the internal are, in the great majority of cases, embedded deeply in the substance of the thyroid. When it is remembered how vascular thyroid tissue is, how slightly the parathyroid differs from it to the naked eye, and how this difference, slight as it is, entirely disappears when there is any bleeding, it will be seen that the operation of digging out the internal parathyroid is one of extreme delicacy. A further difficulty presents itself in the fact that there is a nodule of thymus also embedded in the thyroid lobe, frequently in close proximity to the internal parathyroid, resembling it on naked

eye examination, and therefore easily mistaken for it in the course of the operation. Bearing all these difficulties in mind, we can hardly hesitate to say that, except in very favourable cases , where the internal parathyroid chances to lie near the surface of the thyroid lobe, the operation is an impossible one. The injury caused to the thyroid in endeavouring to excavate an almost invisible body from its substance, combined with the accompanying profuse haemorrhaege, may, we venture to think, account fo some of the deaths which other experimenters have attributed to parathyroid insufficiency. It will be obvious that the other operation, viz. the removal of all the thyroid tissue, while leaving the parathyroids with their blood supply uninjured, is still more difficult, and we have not even attempted it, though we have succeeded, in some cases, in leaving one or two external parathyroids".

Vincent and Jolly performed about 100 experiments upon cats, dogs, foxes, monkeys, rats, guinea-pigs,and rabbits.

Total thyroidectomy was performed on fifteen cats. Of these five survived the operation but three out of the five showed grave nervous symptoms. A careful post mortem (examination) dissection of neck, thorax, and abdomen failed to disclose the presence of any accessory thyroid or parathyroid tissue.

Symptoms usually began to show on the second day after the operation, and appeared in rapid succession in the following order: paw-shaking and malaise, muscular tremors, stiffness of gait, and convulsions. Hallucinations, conjunctivitis, and respiratory catarrh were also observed.

On nine other cats these observers did a series of variations upon the original experiment. Where one thyroid lobe was left and one parathyroid, the cats remained well. When parathyroids alone were left the cats also remained well until these, too, were removed. In the opinion of these scientists the fact that cats survive (where when) the thyroid gland has been removed, if one or more parathyroids are suffered to remain in situ, points to the probability that parathyroid tissue, whether ~~hmr~~ active or not where thyroid tissue is present, can, in its absence, functionally replace it, and there is, they think, a change in the structure of the parathyroids, which supports this view.

The experimenters think, however, that the parathyroids cannot in all cases entirely replace the thyroid in function, and record a case of a young cat, which, after removal of the thyroid, showed no increase in size or weight for 76 days after the operation.

In nine cats where the thyroid was left and all

four parathyroids removed only 33 per cent proved fatal, and of the three cats which died one did not show typical symptoms. In the other two cases which proved fatal the thyroid glands were found to be extensively damaged on post mortem examination. "In the great majority of cases", they say,"it will be seen that no ill-effects of any kind resulted from the operation".

From this the authors concluded that simple parathyroidectomy in the cat, where the thyroid gland is left uninjured is not necessarily fatal - a view directly opposed to that of Vassale and Generali.

Out of five dogs operated on by those experimenters, the complete operation produced no symptoms in one, the animal living in good health for 91 days after the operation. The other four dogs died, and the symptoms observed were similar to those described above as occurring in cats.

In foxes, the most purely carnivorous animals employed, the operation produced acute symptoms which in all of four cases led to death.

In their general observations upon the experiments on Carnivora the authors remark: "We cannot assail the logic of the position, that the thyroid which may frequently be removed with impunity is not "essential to life", and our results force us to extend this observation to include the parathyroids also. But we consider that the

thyroid has undoubtedly a specific function, which can be performed in its absence by the parathyroids.. Symptoms when they occur are thus to be attributed to the absence or interference with the functional integrity of both sets of glands. We are convinced that the theory of accessory thyroids or parathyroids is insufficient to account for cases where perfect health is regained after operation; and we must conclude that the functions of these glands can be otherwise performed or, indeed, dispensed with. If this is the case in Carnivora, it is, as we shall see later, more emphatically so in other groups of Mammals. In no Carnivora have we seen any condition resembling myxoedema".

The same reporters then report on experiments performed on monkeys. Both thyroid and parathyroids were removed from seven of these animals and it is interesting to note that they all recovered completely after the operation, and lived in perfectly good health for several weeks afterwards. In some cases, however, transient nervous symptoms were observed, and the authors think that probably removal of the thyroid gland leaves monkeys, as well as other animals, in a condition in which they are less capable of resisting disease. In no case was there any sign of myxoedema, nor in fact, any symptoms which could be attributed to it.

Rats and guinea-pigs showed no ill-effects after removal of both thyroid and parathyroids.

Thus in a series of experiments upon cats, dogs, foxes, monkeys, rats, and guinea-pigs, more than 51 per cent servived the operation for a prolonged period,and of these more than 68 per cent showed no specific symptoms of any kind. But, as these writers state: "There is a fundamental difference of behavior, as Horsley taught, between different classes of animals, and this is as true when the parathyroids enter into the discussion, as when omitted".

Speaking of the entire series of experiments,the authors' conclusions are as follows: "It cannot be truly said that either thyroids or parathyroids are essential for life, since it is frequently possible to remove either or both without causing death. Rats and guinea-pigs do not seem to suffer at all as the result of extirpation. Monkeys only show transient nervous symptoms. Dogs and cats frequently but by no means invariably, suffer severely, and die. In foxes, symptoms come on with very remarkable rapidity, and death is correspondingly early. The diversity of results obtained in different classes of animals is not to be attributed to anatomical, but to physiological differences. In no animals have we been able to induce symptoms resembling

those of myxoedema. In young animals, although extirpation of the thyroid causes a temporary cessation of growth, we find that this is not necessarily accompanied by symptoms of a cretinoid nature. Myxoedema and cretinism must then, we think, be due to causes more complex than simple thyroid insufficiency. When the thyroid is removed, the parathyroids appear capable of functionally replacing it to a certain extent, and their histological structure changes accordingly".

The results of a second series of experiments done by Vincent and Jolly (79) were entirely in accord with those cited above. Monkeys, cats, dogs, prairie-wolves, badgers, and rats were operated on. The experiments on monkeys, six in number, confirmed those previously recorded. Two only showed transient nervous symptoms, and all the animals lived. There were never any signs of myxoedema.

Wolves, after the extirpation of their thyroids, behaved precisely as did dogs. Badgers and rats did not seem to be affected at all.

In discussing the significance of the results of these experiments the authors remark: "When parathyroidectomy proves fatal, this is probably due to the severe damage simultaneously done to the thyroid, and it is pos-

sible that there may be a difference between the results of severe damage to the thyroid apparatus and its total removal. Thyroid and parathyroid are to be looked upon as a single physiological apparatus, the two kinds of tissue being intimately associated embryologically, and working together physiologically. When the thyroid is removed, the parathyroids appear capable of functionally replacing it to a certain extent and their histological structure changes accordingly".

Forsyth (10,11) is in entire accord with Vincent and Jolly as regards the extreme difficulties of the operation of parathyroidectomy, and, after enumerating the various difficulties invariably met with in the operation he comes to the conclusion that we are not justified in maintaining that the parathyroid glands have been proved to possess a function of such vital importance that their suppression invariably leads to rapid death. He believes that the parathyroids are a portion of the main thyroid gland, which has assumed functional activity, but has not yet formed vesicles.

MacCallum (49-51) has a different opinion. He states: "At least we know well that the destruction of all the parathyroid glands results in the death of the animal with symptoms of tetany, which is not in the least depen-

dent, as was once taught, upon the destruction of the thyroid gland".

MacCallum and Voegtlin (54:) utilize the theory of a separate and supreme function of the parathyroids to explain the pathogeny of different forms of "tetany" which occur in clinical observations, and in recent years many scientists have seemed inclined to connect diseases of a tetanoid nature with lesions of the parathyroids.

MacCallum and Voegtlin state that the effect of the extirpation of the parathyroid glands may be annulled by the introduction of an extract of these glands even from an animal of a widely different character. According to these authors the effects of the extract in counteracting tetany appear some hours after inspection, and last several days. They think that tetany is an expression of hyperexcitability of nerve-cells due to deficiency of calcium salts.

Berkley and Beebe (1) confirmed these results, and found that salts of strontium had a similar effect. Biede (2), however, finds that these salts do not prolong the life of animals suffering from tetany, despite the fact that they suppress the symptoms of excitation.

Carlson and Jakobson (4) put forward the theory

that, with the exception of parathyroid transplantation, the action of all measures which suppress the excitation symptoms can be accounted for by decreased excitability of the nervous tissues. The excitability is decreased directly by the drug action of the Calcium and Strontium salts, and by hypertonicity. Indirectly by substances or measures which cause partial anoemia of the brain through vaso dilatation. None of these measures have, therefore, any specific significance as regards the cause and nature of parathyroid tetany.

In 1907 MacCallum, Thomson, and Murphy (53) performed a series of experiments upon sheep and goats, removing the parathyroids from both the thyroid and the thymus.

Practically no effect was produced in five sheep. In eight goats there were fairly definite twitchings without actual convulsions in four. Two showed no symptoms at any time, while two developed violent and typical tetany.

From these experiments they admit that there indeed is a very marked difference in the results obtained by parathyroidectomy in the dog and those in such animals as the sheep and goat.

They do not know, however, how to explain satis-

factorily the negative results in so many of their animals unless it be that, in spite of their extremely careful and concientious search, there were still other masses of parathyroid tissue hidden away somewhere in the neck or the thorax.

Accessory parathyroids, it must be admitted, have been found occasionally in different classes of animals. Their position, however, is by no means constant, and in the great majority of cases a careful search fails altogether to reveal their presence.

The question of their importance is therefore at least a doubtful one and as Professor Vincent remarks: "The insistence upon the necessary presence of remaining parathyroids somewhere or other in all cases where symptoms did not occur, in investigations made to discover whether or not parathyroids are essential to health, is a distinct case of reasoning in a circle.. And, further, if accessory glands be so usually present, then the question as to the importance of the glands ceases to have the value hitherto attached to it".

Gley (24) remarks that after parathyroidectomy one may sometimes observe symptoms usually attributed to simple thyroidectomy (cachexia), and puts these facts forward in support of his theory of a functional

relationship between thyroids and parathyroids.

Halsted (30) seems to believe in a totally separate and distinct function for thyroid and parathyroids, and thinks that parathyroidectomy is always fatal. Yet he records some observations which tend to prove quite the contrary: "Mere handling of the thyroid lobes", he says, for instance, "may give rise to symptoms of parathyroid privation. Manipulation, not excessive of the thyroid gland in dogs has several times in my experience produced fatal tetany". This is quite plainly a support to the view urged by Vincent and Jolly, Forsyth, and others, that thyroid and parathyroids are to be looked upon as one apparatus. For how could "mere handling of the thyroid lobes" give rise to the same symptoms as parathyroidectomy, if thyroid and parathyroids are to be looked upon as entirely separate and distinct organs, with no physiological connection?

THE RELATIONSHIP BETWEEN THYROID AND PARATHYROIDS.

In 1880 Sandström (67) discovered "a new gland in man and various mammals," which he called parathyroid gland. He found two of these glandules invariably present in the immediate neighbourhood of the thyroid, one on each side. Their situation, he noted, was somewhat variable though in the majority of cases they lay in close relation to the posterior part of each lateral lobe of the thyroid.

The parathyroid glands, as we know now, are reddish-brown or yellowish-brown ductless glands which are invariably present in all animals. They are somewhat bean shaped or kidney shaped with the long diameter in the supero-inferior direction, and flattened antero-posteriorly. They vary greatly in size and position, the average length in the rabbit being about 5-6 mm. The reddish-brown color of the glands is due to their rich blood supply.

Each gland is made up of solid irregular masses of epithelium cells divided into lobules by connective tissue. Each gland is also surrounded by a capsule of connective tissue which is always present and from the inner surface of which pass numerous processes

which make up the framework for the gland substance proper.

The parathyroids are usually four in number, but there may be as many as six or eight, and there are occasionally only two or three.

The location of the glands varies in different animals, but generally speaking there is an external and an internal pair. In most animals the external pair is in close contact with the lateral or posterior aspect of the thyroid lobes. In rabbits, however, they are entirely separated. The internal parathyroids on the other hand are frequently embedded in the substance of the thyroyd, and in no animal are they quite separated from it. Neither pair is constant in position.

The close anatomical relationship between the thyroid and the parathyroids, as well as their morphological similarity, seems to suggest that there may possibly also be a functional relationship.

This question of functional relationship between thyroid and parathyroids has aroused considerable controversy between scientific observers in the past. Some think that when the thyroid is removed the parathyroids are capable of functionally replacing

it to a certain extent, and that there is an alteration in their structure accordingly.

The majority of writers, however, consider the two bodies quite distinct and separate organs morphologically, physiologically, and pathologically.

Professor S.Vincent has been one of the chief supporters of the theory of functional relationship between thyroid and parathyroids. He says:

"The theory that parathyroids develop into thyroid after thyroidectomy is based upon three kinds of proof. (1) CHEMICAL: Gley found in the parathyroids of the rabbit about twenty-five times more iodine than in the thyroid, in the dog six times more, and suggested that the parathyroids prepare the secretion which is then stored in the thyroids, and utilized according to the needs of the economy. If the iodine be not rendered harmless by elaboration in the parathyroid (as when these are extirpated), we get acute symptoms. If the iodine be subjected to preparation in the parathyroid,but is not distributed to the body by way of the thyroid (as when this is extirpated), we get nutritive troubles from the absence of assimilable iodine in the body. (2) PHYSIOLOGICAL: Occasionally complete

parathyroidectomy leaving the thyroid in situ, gives rise, not to acute symptoms, but to slowly progressive changes in the bodily nutrition. Thus, we get symptoms commonly associated with thyroid insufficiency induced by absence of parathyroids. It is alleged by Lusena (48) and also by Vassale and Generali (72-74) that parathyroidectomy kills more rapidly than thyro-parathyroidectomy. This is explained by Vassale and Generali by supposing that, when the parathyroids are removed, the animal is in a toxic condition, which is the more marked when the nutritive changes of the body generally are more pronounced. The tetany then will be more or less serious, according as the thyroid is more or less active, and therefore, logically, will be much less marked after ablation of the thyroid. (3) HISTOLOGICAL: According to Edmunds (6,7) and Vassale and Generali (72,73,74), there is a disappearance of the colloid substance in the thyroid after removal of parathyroids".

The theory of functional relationship between thyroid and parathyroids is also supported by structural changes already referred to. Vincent and Jolly found a conspicuous alteration in structure, on microscopic examination of parathyroids left in situ after

removal of the thyroid. These authors think that parathyroid tissue when left behind, approximates in appearance to ordinary thyroid tissue, so that final product in some cases cannot be distinguished from the latter.

In later papers (76,77) Professor Vincent points out that the parathyroid glands are developed from the epithelium of the third and fourth gill-clefts, while the thyroid is derived from a median- rudiment from the central wall of the embryonic pharynx, and ephasizes the fact that the two structures are thus derived from very similar sources. He also lays stress upon the fact that even in the fully developed state there is no fundamental difference between the constituent cells.

Forsyth (10,11) and Mrs. Thompson (71) have investigated the subject from the side of comparative anatomy and histology. Forsyth thinks that the parathyroid is essentially thyroidal in nature, and that it is engaged in the active secretion of the same substance as the thyroid gland. Mrs. Thompson's views agree largely with those of Forsyth, though she is not ready to admit that parathyroids "are part of the main thyroid gland".

Halpenny and Thompson (28) report marked structural changes in a parathyroid of a dog left behind after removal of the thyroid, and Halpenny (26) also reports the same phenomenon in a rabbit.

Professor Biedl (3) thinks that hyperterophy of the parathyroids is by no means always accompanied by structural changes, although he does not deny that such changes may possibly take place after thyroidectomy. He states: "Die Hypertrophy der Epithelkörper ist keineswegs immer mit wesentlichen Abänderung ihrer Struktur verbunden, wenn auch drüsenähnliche, mitunter mit Kolloid gefüllte Hohlräume im allgemeinen häufiger in hypertrophen, als in normalen Epithkörperchen vorgefunden werden. Ob diese Kolloidbildung in den Epithelkörpern nach Wegfall der Schilddrüse als kompensatorischer Sekretionsvorgang zu betrachten ist, möge vorerst dahingestellt bleiben".

He has not, however, abandoned the theory of functional relationship between thyroid and parathyroids, although, he admits, it is not yet weal understood: "Die angeführten Daten, erstens der günstige Einfluss der Schilddrüsenmedikation auf den Verlauf der parathyreopriven Tetanie, zweitens die sicher festgestellte Hypertrophie der äusseren Epithelkörper nach Extirpation der Schilddrüse und drittens

die von manchen Autoren konstatierte Hypertrophie der Schilddrüse nach Entfernung der Epithelkörperchen kommen als hinreichende Beweise für den functionellen Zusammenhang zwischen Schilddrüse und Epithelkörperchen betrachtet werden. Sie geben allerdings keine klare und eindeutige Antwort auf die Frage, auf welche Art und Weise dieser Zusammenhang zustande kommt".

The majority of writers, however, as I stated before, and notably all the American scientists, prefer to consider the two bodies as quite distinct, both morphologically and physiologically.

MacCallum is very positive about this. He states: "At least we know well that the destruction of all the parathyroid glands results in the death of the animal with symptoms of tetany, which is not in the least dependent, as was once taught, upon the destruction of the thyroid gland".

Marine also states that his observations are in harmony with those who hold that the thyroid and parathyroid are independent structures. He remarks: "Such observations when compared with the experiences of others -Simpson (68) with tetanies in sheep; Halsted (29), MacCallum (50), Erdheim (8), and others with

tetanies in dogs; Kocher (46), Reverdin (65),and Fuhr (12) with total thyroidectomy in man; Maresch (55). Erdheim (9), and Getzowa (13) with congenital defects; and Roussy and Clunet (66) with spontaneous myxoedema-, leave no doubt that as regards myxedema and tetany the parathyroids and thyroids are anatomically, physiologically, and pathologically independent structures".

This, I think, will suffice to indicate that there exists, even at the present time, considerable controversy as regards the relationship between thyroid and parathyroids.

The series of experiments, which I undertook to perform, was done with the object of ascertaining whether or not parathyroids undergo any structural changes after thyroidectomy.

As already stated Vincent and Jolly, Halpenny,, and others have maintained that this is so, while many other scientists have contradicted their view.

The rabbit was selected for the experiment owing to the fact that in this animal the external parathyroids are entirely separated from the thyroid, and on this account the removal of the thyroid with the internal parathyroids presents less difficulties in a rabbit than in most other animals.

THE OPERATION.

The removal of the thyroid with the internal parathyroids is by no means an easy operation, not even in the rabbit. Dr. Halfpenny admits that it is "a difficult surgical procedure", and points to the close anatomical relationship between the thyroid lobe and the recurrent laryngeal nerve in many instances as causing the difficulty of separating the latter without injury.

I therefore proceeded to make myself thoroughly familiar with the anatomy of the rabbit's neck before attempting the operation. This I did as follows:

After rinsing out the arteries of the head and neck with normal saline solution injected by means of a syringe, I injected a mass of calcium sulphate and red lead suspended in water. When this was properly hardened I dissected out the arteries of the neck very carefully and noted their relations to the thyroid, and external parathyroids. I also studied carefully the position of the recurrent laryngeal nerve and its relations to the thyroid lobe and the inferior thyroid vein. Details of this preliminary examination are omitted as they would take up consider-

able space if written in full, but the knowledge which I obtained in this way proved of great value to me later. Three rabbits were thus examined before the first operation was performed.

Every operation was carried out under strictly aseptic conditions, the anterior aspect of the animals neck was carefully shaved after the anaesthetic had been administered, and an incision of from 2 to 2½ inches was made in the median line. When access had thus been gained to the thyroid by cutting through the skin and the pre-tracheal muscles the superior thyroid artery (which is the chief artery of supply to the gland) was ligatured in order to prevent the gland from becoming distended with blood. It is important that this be done at once because even the slightest bleeding makes the dissection of the recurrent nerve from its close relation with the thyroid lobe very difficult. It is therefore best to cut the gland completely off from its blood supply before the dissection is commenced if that is possible. It is a fairly easy matter to shell out the gland with its capsule when this has been done, and it is not necessary to use the knife at all for that purpose, which does away with the danger of cutting the recurrent nerve

or other important structures.

My own observations of the position of the recurrent laryngeal nerve do not permit me to support the statement, which has been made by some previous observers, that it frequently passes through the substance of the thyroid lobe laterally and the trachea and larynx medially, and then its relation to the thyroid is of course an intimate one. In my opinion the nerve very rarely passes through the connective tissue capsule of the thyroid gland proper. On no occasion did I find it necessary to cut the nerve or even to pinch it in order to be able to remove the thyroid completely.

When the thyroid with the internal parathyroids had been removed the pre-tracheal muscles were stitched together by a broken suture. The superficial incision was also carefully stitched and the wound thoroughly bandaged. In every case the wound healed by first intention.

DISCUSSION OF THE RESULTS OF THE EXPERIMENT.

I shall make no attempt to give a complete historical account of the discussion of this subject. Such an account up to the year 1912 has been given by Vincent (75), and up to 1913 by Biedl (3).

The earlier investigators looked upon the parathyroids as embryonic thyroids, and a belief in some kind of morphological and physiological relationship between the two glands has persisted up to the present time, but since the appearance of the papers of Vassale and Generali (72, 73, 74) the majority of authors have regarded the parathyroids as organs sui generis.

The experimental evidence for and against this view has been somewhat contradictory. Vincent and Jolly found that on microscopic examination of parathyroids left in situ after removal of the thyroid an alteration in structure had occurred. The parathyroid approximated in appearance to ordinary thyroid tissue. Their experiments were carried out on cats. Similar

changes after thyroidectomy were found by Halpenny and Thompson (28) in the parathyroid of a dog, and Halpenny (26) later reported a somewhat more doubtful instance occurring in a rabbit.

These results have not been generally accepted although the rabbit among laboratory animals lends itself in a special way (from anatomical considerations) to the special experiment bearing upon this problem. I can find in the literature very few detailed accounts of work directed towards this point carried out upon the animal in question.

It was in rabbits that Gley first discovered the external parathyroids, and in his earlier experiments supported the view that the parathyroids could develop into thyroid tissue when the latter gland had been extirpated. Later on he changed his view though he has continued his belief in some sort of relationship between the two structures. Biedl (3) reports that although he has noticed very considerable hypertrophy of parathyroids (in the rabbit) left behind after

removal of the thyroid, yet he has never noticed any structural changes in the former under these circumstances.

The present series of experiments has been carried out upon rabbits of different ages, some of them being full-grown, some only half-grown. The thyroid has been carefully extirpated under aseptic conditions, and with it both internal parathyroids leaving one or more external glandules. The animals have been kept under the best possible conditions after the operation for periods varying from 7 days to 115 days. Out of 16 animals which survived the operation for more than 24 hours two have died within a few weeks from septic conditions which are so common after thyroidectomy. The rest to the number of 14 have survived for periods varying from 44 to 115 days after which time the parathyroids were removed and examined microscopically. In some instances the animals were allowed to live after the second operation.

My results are briefly as follows:-

In all cases the parathyroids were found

to be considerably hypertrophied, but in none have we found any distinct traces of vesicle formation. It is possible that there were changes of other kinds and of less significance in the glandules which had been left behind, but on this point I do not wish to be positive.

This series of experiments then does not lend support to the view that parathyroids left behind after thyroidectomy become converted into thyroid tissue. It is of course possible that in rabbits a still longer period than I have allowed is necessary for such changes to occur. It is also possible that the anatomical differences between rabbits on one hand and dogs and cats on the other involves also a difference in regard to the potentiality of a change from parathyroid to thyroid tissue. Notwithstanding these considerations and notwithstanding the fact that negative results in such cases are of less value than positive ones, we must confess that these experiments have led us to suspect the possibility that there were some errors of observation in the cases reported by Vincent and Jolly (78), Hal-

penny and Thompson (28), and Halpenny(26). It is clear that in dogs and cats where the parathyroids are in close proximity to the thyroids there is great danger that a shred of thyroid tissue might be left behind at the operation for thyroidectomy, and might subsequently be mistaken for a transformed parathyroid. This suspicion is at any rate strong enough to suggest that further careful experiments upon animals other than rabbits ought to be carried out.

A few observations of another character bearing upon the functions of the thyroid-parathyroid apparatus have been made in the course of these experiments. In the first place it may be desirable to call attention to the fact emphasized by Vincent and Jolly (78) and other observers that after thyroidectomy animals are particularly prone to various infective diseases. Particularly of the respiratory tract. Again stress must be laid upon the observation that none of our animals suffered from a condition which resembled in the remotest degree myxoedema in the human subject. It is true that some of them suffered from falling out of hair

and other skin diseases, but it is also true that many controll animals suffered in the same kind of way. In none of the animals young or adult was there any puffiness of the face or swelling of the subcutaneous tissue of any part of the body.

It is important to note that we have not seen distinct tetany in any of the animals, and some have survived a removal of the remaining parathyroids for several weeks without symptoms. We are aware that tetany sometimes occur in rabbits, but the precise conditions which determine its onset are by no means clear.

-P R O T O C O L S.

Experiment 1.

Nov.11th 1916.

Rabbit female full-grown. Thyroid with both internal and left external parathyroids removed. On Feb. 22nd (103 days) the animal was killed and the right parathyroid removed. Gland considerably hypertrophied but no structural changes found on microscopical examination.

Experiment 2.

Nov.17th 1916.

Rabbit male full-grown. Thyroid with both internal parathyroids removed, both external parathyroids left behind. Animal remained well till jan. 6th (50 days) when the two external parathyroids were removed under aseptic precautions and the animal allowed to live until Jan. 17th when it was killed. The parathyroids removed on Jan. 6th showed no structural changes. At the post mortem examination no accessory bodies could be found.

Experiment 3.

Nov.18th 1916.

Rabbit male full-grown. Thyroid with both internal parathyroids removed along with the right external parathyroid. Animal remained well until Jan. 18th, when the left external parathyroid was removed for microscopic examination. The animal was allowed to live until Jan. 31st when it was killed. The left external parathyroid showed no structural changes though it was considerably hypertrophied. No symptoms of tetany developed after its removal and on post mortem examination no accessory parathyroids could be found.

Experiment 4.

Nov.22nd 1916.

Rabbit male full-grown. The thyroid with both internal parathyroids was removed, and the external parathyroids left in situ. The animal remained well till Feb.1st (71 days) when a second operation was performed and both the external parathyroids, which were found to be distinctly hypertrophied, removed. No symptoms of

tetany developed and the animal was killed on Feb. 20th. Neither parathyroid showed any marked structural changes on microscopic examination.

Experiment 5.

Nov.23rd 1916.

Rabbit female, full-grown. The thyroid with both internal parathyroids was removed, while both the external parathyroids were left in situ. On Dec. 9th the animal died of intercurrent disease. The parathyroids were taken out and examined but there were no signs of any vesicular formation in either.

Experiment 6.

Nov.23rd 1916.

Rabbit female,half-grown. The thyroid with both internal and the right external parathyroid was removed. The rabbit died on Dec. 1st (7 days) of broncho-pneumonia.

The remaining parthyroid showed no structural changes when examined microscopically.

Experiment 7.

Nov.25th 1916.

Rabbit male, full-grown. The thyroid and both the internal parathyroids were removed and both external parathyroids left behind. The animal remained in good health till Feb. 28th (95 days) when it was killed. Both parathyroids were distinctly hypertrophied, but no vesicular formation could be detected under the microscope.

Experiment 8.

Dec.1st 1916.

Rabbit male, full-grown. The thyroid and both internal parathyroids were removed, both external parathyroids left in situ. The animal remained in good health till March 27th (115 days), when it was killed. The parathyroids when cut out were found to be about double their original size. No vesicluar formation could be observed on microscopical examination.

Experiment 9.

Dec.2nd 1916.

Rabbit male, full-grown. Thyroid with both internal parathyroids removed, both external parathyroids left behind. The animal remained well till March 27th (114 days) when the two external parathyroids were removed. They were much hypertrophied but showed no structural changes.

Experiment 10.

Dec.4th 1916.

Rabbit male, full-grown. Thyroid with both internal parathyroids removed, both external parathyroids left *in situ*. On Feb. 28th (86 days) the animal was killed, having remained well till then. A microscopical examination revealed no changes in the structure of the parathyroids.

Experiment 11.

Dec.7th 1916.

Rabbit female, half-grown. Thyroid with both internal and the left external parathyroidx removed. On Feb. 20th (75 days) the animal was killed and the right external parathyroid removed. Gland considerably hyperthophied but no structural changes were found on microscopical examination.

Exprfment 12.

Dec. 7th 1916.

Rabbit male, full-grown. The thyroid and internal parathyroids removed, both external parathyroids left in situ. On Jan. 28th (52 days) the animal died of intercurrent disease. The parathyroids showed no structural changes.

Experiment 13.

Dec.18th 1916.

Rabbit female, full-grown. Thyroid with both internal parathyroids removed. Left external parathyroid also taken out. The animal was killed on March 27th (99 days) and the remaining parathyroid removed. No colloid vesicles were found in it on microscopic examination.

Experiment 14.

Dec.18th 1916.

Rabbit male, full-grown. Thyroid with both internal parathyroids removed. Right parathyroid also removed. The animal died on March 2nd (74 days) of broncho-pneumonia. During the last month the hair had been falling out gradually, first in patches around the neck, then on one side. The parathyroid left at the operation was distinctly hypertrophied, but showed no structural changes.

Experiment 15.

Feb.3rd 1917.

Rabbit male, half-grown. Thyroid with both internal parathyroids removed, both external parathyroids left behind. The animal remained well till March 26th (52 days) but did not increase in size nor weight. The parathyroids showed no structural changes when examined with the microscope.

Experiment 16.

Feb.10th 1917.

Rabbit male, half-grown. Thyroid with both internal parathyroids removed, both external parathyroids left behind. The animal remained well till March 26th (44 days) but did not increase in size nor weight. The external parathyroids showed no structural changes when examined under the microscope.

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