

ON THE PARATHYROID GLANDS OF THE CAT : A PRELIMINARY STUDY IN EXPERIMENTAL PATHOLOGY.¹

By D. A. WELSH, M.A., M.D., *Assistant to the Professor of Pathology
in the University of Edinburgh; Pathologist to the Royal Hospital
for Sick Children, Edinburgh.*

(PLATES XXIII. AND XXIV.)

INTRODUCTION.

WHEN it is considered that, bulk for bulk, the amount of thyroid tissue in any one animal is many times greater than the amount of its parathyroid tissue, and when the known therapeutic effects of thyroid administration are remembered, it certainly seems a remarkable fact that an animal will, with its thyroid *in situ*, die of acute symptoms, provided only all its parathyroids have been removed, and a still more remarkable fact that the thyroid may be removed with impunity, provided only a few parathyroids are left. Yet the great body of experimental evidence is altogether in favour of both of these conclusions, and the question for future investigation is not now so much their accuracy as their explanation—a matter of the greatest scientific interest and importance. It was with the latter object that the present research was undertaken. As an essential preliminary, however, it was necessary to repeat the experiments of other observers; but all that will be given in the following paper is a statement of the results observed to follow certain operations, and of the conclusions to which they seem to lead. The further question of how these results are brought about must be deferred. The paper has been published in its present tentative form only because it appeared that, in the uncertainty of our knowledge concerning the parathyroids, any contribution, however slight, might be of value.

A SYNOPSIS OF THE NORMAL ANATOMY OF THE PARATHYROID GLANDS IN MAN.²

The following summary of the normal characters, relation, and

¹ This work was included in a thesis, presented in May 1897 for the degree of Doctor of Medicine of the University of Edinburgh, for which a gold medal was awarded.

² A more detailed account will be found in the *Journ. Anat. and Physiol.*, London, 1898.

structure of the parathyroid glands in man is based upon the examination of over forty cases.

Number.—In man there are, as a rule, four parathyroid glands—two on each side. Occasionally one or more may escape observation, unless a careful and extensive search is made, either owing to some abnormal distribution, so that they do not occupy their usual sites, or owing to a more or less intimate union between two glands, so that they appear externally as a single mass.

General characters.—In shape the parathyroid glands form thin flat plates or discs, of an oval or pyriform outline, and are sometimes attached to the thyroid by a distinct process or stalk. In the ox this stalk is almost invariably present, and on transverse section shows tubular duct-like spaces, lined by a low columnar epithelium; but in man no trace of a duct exists. In size the human parathyroids most commonly measure 6 or 7 mm. in length, 3 or 4 mm. in breadth, and 1·5 or 2 mm. in thickness; but very considerable variations may be met. In the child they are relatively larger than in the adult. The average weight of the fresh parathyroid in the adult is about 0·035 grms. The surface is smooth, and of a yellowish colour, showing a delicate reticulum of small veins immediately underneath the capsule.

Position and relations.—The two parathyroids of each side are quite separate from the thyroid, and cannot be distinguished as internal and external; but, since one is practically always above and behind the other, they may be designated “the posterior-superior” and “the anterior-inferior” parathyroid respectively. *The posterior-superior parathyroid* is the more constant in its position and relations. On each side it is most commonly found lying on the posterior œsophageal wall, in front of the prevertebral division of the cervical fascia, about the level of the lower edge of the cricoid cartilage, immediately internal to the posterior edge of the lateral thyroid lobe, and above and behind the termination of the inferior thyroid artery and the recurrent laryngeal nerve. More rarely it is overlapped by the posterior thyroid margin, and may then come into relation with the outer surface of the lateral thyroid ligament. *The anterior-inferior parathyroid* has more indefinite relations, and is therefore more readily overlooked. It occupies either the postero-lateral surface of the trachea lying below and in front of the inferior thyroid artery, or the antero-lateral aspect of the trachea among the inferior thyroid veins. It may be overlapped by the lower thyroid margin, or situated a considerable distance below it—sometimes as low as the tenth tracheal ring.

Structure.—Each parathyroid is completely invested by a definite fibrous envelope, from the deep surface of which irregular septa are given off, so that an irregular lobule formation may occur. There is never any continuity of parathyroid with thyroid tissue; for even when the former is included in the same capsule as the latter, a fibrous

septum everywhere intervenes between the two glands. Clusters of fat cells are frequently present along the course of the vessels and the connective tissue septa within the gland—a circumstance to which the characteristic yellow tint is probably due. The parathyroids are essentially epithelial structures, and are composed of two distinct kinds of cells.

1. *The principal cells* have a relatively small and homogeneous protoplasmic body, which takes on basic aniline dyes in varying degrees of intensity, and a relatively large and pale nucleus, with an open chromatin network. They are constantly present, and constitute the greater part of the gland tissue. In their arrangement they may show at least four different types—(a) a continuous, uniform cell mass; (b) a continuous cell mass, interrupted at frequent intervals by vascular strands of connective tissue, so that on section the connective tissue strands are surrounded by the epithelial cells; (c) a series of anastomosing columns of cells in a vascular fibrous reticulum, so that on section the epithelial cells appear as discrete masses, completely surrounded by vascular connective tissue; (d) a group of small acini, each containing a small mass of colloidal material in its lumen, and lined by a single layer of epithelial cells. It seldom happens that a parathyroid is composed exclusively of cells arranged according to any one type; more commonly several types are found associated in the same gland.

2. *The oxyphile cells* have, relatively to the principal cells, a large and granular protoplasmic body, the granules of which are highly oxyphile, and a small and darkly staining nucleus, with densely arranged chromatin. They are not present in every case, but were found in the majority of the specimens examined. They rarely form more than a small proportion of the total epithelial tissue in the gland. In their disposition they may show four different types—(a) a uniform cell mass, sharply defined from the principal cells, and situated either deep in the substance of the gland, or immediately beneath its capsules; (b) a few columns of cells which gradually mix with the principal cells; (c) isolated groups of a few cells, without definite arrangement, scattered among the principal cells; (d) a single acinus, lined by oxyphile cells, and containing a colloid globule in its lumen.

In some structural details the parathyroids correspond very closely to the anterior pituitary lobe. (1) The two varieties of epithelial cells found in the parathyroid bear a close resemblance to the “cyanophile” and “erythrophile” cells of the pituitary. (2) In both organs the cells may be arranged in the form of small acini containing a central colloid globule.

When the parathyroid is compared with thyroid tissue, marked differences are apparent. Thus the structure of the adult parathyroid, as above described, is not only dissimilar to that of the adult thyroid, but also quite unlike that of the embryonic thyroid at any stage. In

fact, the parathyroid becomes differentiated from the thyroid at as early a period as the thymus, and at no stage of its subsequent development does it come to resemble the thyroid of the same or of an earlier stage, so that, as has long been maintained by other observers, the parathyroid cannot be regarded merely as a dormant thyroid residue.

The hypothesis that the parathyroid may, when necessity arises, become transformed to ordinary thyroid tissue, probably owes its origin to an erroneous interpretation of the frequent occurrence of colloid degeneration of the parathyroid epithelium. Sometimes individual cells become gradually distended to form a small globular mass of colloid matter, surrounded by apparently healthy cells without definite arrangement. More frequently the colloid material is found to occupy the centre of a small acinus lined by epithelial cells, and probably results from degenerative changes taking place in them. Occasionally larger cystic spaces filled with colloid are formed, and to some extent resemble the colloid follicles of the normal adult thyroid, but, so far from representing a higher stage of the glandular development, they must be regarded as essentially retrograde and degenerative in their nature.

HISTORICAL OUTLINE.

The recognition of the parathyroid glands, as distinctive anatomical structures, is of comparatively recent date.

It was not until 1880 that attention was first directed to the existence of such bodies by the Swedish observer Sandström ⁽¹⁾, who, both by the priority of his publications and by the accuracy of his results, has the greatest claim to the honour of this discovery. He observed their constant presence in man and in other mammals, emphasising the occurrence of two on each side in man, and one on each side in the other animals examined. He also described their characteristic structure, and, regarding them as embryonic residues of thyroid tissue, he applied to them the term "*glandulæ parathyroidæ*."

In the following year Cresswell Baber ⁽²⁾ independently observed certain structures intimately related to the thyroid, which indubitably correspond to the parathyroid glands, and to him also, therefore, must be accredited some measure of honour in regard to their discovery. He did not, however, recognise their constant presence in the animals investigated by him; but he, too, compared their structure to that of embryonic thyroid tissue, and regarded them as "undeveloped portions," from which ordinary thyroid tissue might later be formed. A few years later the same bodies were identified and described by Horsley ⁽³⁾.

For an interval of more than ten years no further advance was made; but, in 1892, Gley ⁽⁴⁾ published the first of a series of papers, detailing remarkable experimental results. Under the name "*glandules thyroïdiennes*," he described in the rabbit one parathyroid gland on each side, situated at some distance below the thyroid; so that in previous operations for thyroidectomy in that animal these parathyroids had probably not been removed. In the dog, on the contrary, the corresponding structures were so closely incorporated with the outer surface of the lateral thyroid lobes, that they must almost invariably have been removed along with the thyroid itself. To these different anatomical arrangements, he suggested, might be attributed the fact that the rabbit had

been found to be relatively insusceptible to removal of the thyroid, while the dog suffered acutely. He accordingly undertook the removal of both thyroid and parathyroid glands in the rabbit, with the result that, in the majority of cases, acute symptoms, and speedy death ensued, just as in the dog. On the other hand, he found that removal of the thyroid alone, the parathyroid being left *in situ*, produced in the dog and the rabbit alike little or no result. Excision of these glandules alone produced in neither animal any appreciable effect. To Gley is due the credit, not only of having redirected attention to a long-forgotten subject, but also of having initiated the experimental study of the question, and thus opened up a fresh field for research. It must not be forgotten that the existence of internal glandules was not yet known, and that Gley's work refers only to the external parathyroids.

From this time onwards a considerable amount of work has been devoted to the investigation of these organs, both from an experimental and from an anatomical point of view. Unfortunately, however, by far the greater part of the experimental work was undertaken before an accurate account had been given of the number and disposition of these glands in the animals used for research, and much of it is, therefore, of little value. This indispensable condition was not furnished until 1895, when Kohn (⁷), by the publication of his elaborate monograph on the thyroid gland of the cat, demonstrated the fallacies underlying all previous operations, and, for the first time, supplied a reliable anatomical basis for subsequent experiment. Among other results, he found that in the cat, dog, rabbit, and possibly in other mammalia, there were in all four parathyroid glands—one external (relatively to the thyroid), and one internal, on each side—whereas formerly only the two external glandules had been recognised. He further differed from most previous writers in regarding these bodies, not as potential thyroid reserves, but as independent specific structures, and designated them “the external and internal epithelial corpuscles of the thyroid.”

Two Italian observers, Vassale and Generali (¹²) were the first to take advantage of the opportunity thus presented; and the record of their experimental work, published in 1896, marks a distinct advance. They removed all the four parathyroid glands, leaving the thyroid *in situ*. This operation was performed on ten cats and nine dogs. Of the cats, nine had succumbed by the tenth day, and one had been living for a month at the time of writing; while of the nine dogs, all died within eight days, and, on an average, between the third and fourth day. The symptoms, both in the cat and in the dog, were analogous to those which had previously been recorded as the result of simple thyroidectomy—an operation which had probably involved simultaneous removal of the thyroid and parathyroids. As a rule, however, convulsive attacks were wanting, or were only slightly marked; but, on the other hand, there predominated phenomena of diminished nervous excitability, and forms of paralysis which rapidly killed the animal.

The same authors performed a second series of operations on the dog, in order to test the functional significance of the parathyroids relatively to each other and to the thyroid. Their results are in essential agreement with those previously obtained by Gley. A short account of their work has recently been given by Robertson (⁹).

The only other papers which take cognisance of the internal parathyroids were published early in 1897 by Rouxau, Gley, and Moussu; but they do not contain such uniformly successful operations, or such uniformly consistent results.

Rouxau (¹⁰) performed for the rabbit what Vassale and Generali had done for the dog and the cat. He removed all the parathyroids, leaving the thyroid intact; and, although all the animals did not succumb, he came to the conclusion that in the rabbit this operation is infinitely more serious than removal of the thyroid alone.

Gley (⁴), too, repeated the same experiment on one cat, three dogs, and nine rabbits; but, in spite of his great experience in such work, he frequently failed to find all the parathyroids, and his results were contradictory. He emphasised the experimental difficulties to be encountered, and the urgent necessity for histological examination of all structures removed or left *in situ*.

Moussu (⁸), from his own and from other researches, concluded that two distinct functions exist—the one thyroidal, suppression of which leads only to chronic troubles; the other parathyroidal, suppression of which induces acute symptoms. He also claimed to have induced experimental cretinism in the dog and cat, and in birds by the removal of the thyroid, the parathyroids being left *in situ*.

In this country only one observer, Edmunds (²) has as yet published any experimental work on this subject; and, although his results have reference only to the external parathyroid, they afford valuable confirmation of Gley's original discoveries.¹

GENERAL PROCEDURE.

The operation was in every case conducted on strictly aseptic principles. The instruments, ligatures, etc., were all sterilised by boiling. No antiseptic was employed during the dissection, or for any purpose other than cutaneous disinfection, both before the incision was made, and again after the wound had been closed. By this means the tissues in the deeper parts were exposed to a minimum of irritation. After each operation the wound healed by first intention. In one case, however, which showed no symptoms of thyroidectomy, a later suppuration resulted from scratching. It has been maintained by Munk, Drobnick, Billroth, Baumgartner, and more recently by Argand and Magon, that the symptoms which followed thyroidectomy are really due to accidental lesions of the vagus, or sympathetic or other structures in the neck. I have not specially concerned myself with this hypothesis, beyond taking every precaution to avoid irritation, and making, in one of the cases which died with acute symptoms, a histological examination of both vagus and sympathetic, the result of which was entirely negative.

The skin, platysma, and pre-tracheal fascia having been incised, the knife was entirely discarded, and the subsequent exposure of the thyroid effected by means of a blunt dissector. It is essential that all hæmorrhage in the deeper parts of the wound should be avoided, otherwise the recognition of the parathyroid, which is never easy, becomes well-nigh impossible.

The external parathyroid is usually very distinctly visible as a whitish ovoid body, about 3 mm. long and 2 mm. broad, situated in the upper (oral) half of the outer surface of the lateral thyroid lobe, and most frequently quite near its upper extremity. Sometimes the glandule is found perched in the oral pole of the thyroid and just separate from it. A relatively large leash of vessels, which enters and

¹ A more complete account of the literature relating to the parathyroid glands will be found in the *Journal of Anatomy and Physiology*, 1898.

leaves the outer surface and anterior margin of the glandule, often affords a clue to its position in an otherwise doubtful case—when, for example, as sometimes happens, the thyroid and parathyroid are not well differentiated in colour.

The recognition of the internal glandule presents much greater difficulty, and is, in fact, the crux of any operation for the removal of all the parathyroids. This is due to several factors—(1) the internal glandule is, as a rule, considerably smaller than the external; (2) it occupies the internal or tracheal surface of the thyroid, which is not so easily examined as the external surface; (3) it is almost invariably deeply placed in the substance of the thyroid, and not uncommonly entirely covered over by thyroid tissue. In spite of these adverse circumstances, the glandule may be identified—(1) by its whiter colour, or at least its lighter tint, as compared with that of the thyroid; (2) by its frequent association with a small mass of thymus tissue, which is very constantly present on the inner thyroid surface (the “internal thymus lobule” of Kohn), and which, being larger than the glandule, often affords a guide to its position; (3) as in the case of the external glandule, by its relatively greater vascularity. Occasionally no other indication of its site may be had beyond the presence of a leash of vessels, somewhat larger than the other, coursing in the internal surface, and yet, on excising a small mass of tissue about 3 mm. in diameter, immediately beyond the termination of these vessels, the glandule may be found embedded in it.

Enough has been said to show how absolutely essential it is to supplement all operative procedure by histological methods, before any conclusion can be drawn as to what has, or what has not been removed, and enough also to illustrate the difficulties that attend these operations, not so much in the mere technique, which with a little care is easily acquired, but in the identification of the glandules, more especially of the internal ones, an undertaking which in my experience has rarely been other than tedious and uncertain.

The animals were fed partly on milk, but chiefly on the lungs of oxen or of sheep. It is important, in view of Breisacher's experiments, to note that the lung tissue was always boiled for at least an hour, in order that no disturbing factor might be introduced. Thyroid tissue was, of course, never administered with the food, the entire larynx and adjacent tissues being rejected.

RECORD OF EXPERIMENTS.

The experiments were twelve in number and were all performed on cats. They may be briefly summarised as follows:—

First series.—Removal or destruction of all the four parathyroids without removal of the thyroid—three operations (one doubtful).

No. 1.—Acute symptoms, died within five days.

No. 2.—Very severe symptoms, died within four days.

No. 3.—(Doubtful) delayed symptoms, died within twenty-one days.

Second series.—Removal or destruction of less than four parathyroids without removal of the thyroid—four operations.

No. 4.—Removal of three parathyroids, acute symptoms for ten days, recovery, no subsequent symptoms, killed after four months.

No. 5.—Removal of three parathyroids, no symptoms, killed after five months.

No. 6.—Removal of three parathyroids, no symptoms, killed after two months.

No. 7.—Destruction of two parathyroids, no symptoms, killed after five and a half months.

Third series.—Removal of the thyroid and some of the parathyroids, the remaining parathyroid being retained—three operations.

No. 8.—Retention of one parathyroid, acute symptoms, died within six days.

No. 9.—Retention of two parathyroids, no symptoms, killed after one month.

No. 10.—Retention of two parathyroids, no symptoms, killed after three and a half months.

Fourth series.—Removal of the thyroid and all the four parathyroids together; mouth administration of fresh ox parathyroid—two operations.

No. 11.—Severe symptoms in spite of treatment, died in eleven days.

No. 12.—Died of acute bronchitis in three days.

First series.—Removal of all the four parathyroid glands, the thyroid remaining intact—three operations (one doubtful), resulting in each case in death.

CAT No. 1 (Operation 7).—White adult female.

25th February 1897.—The thyroid lobes were both larger than is common in the cat, measuring more than 30 mm. in length, and about 5 mm. in breadth. The parathyroids were not correspondingly enlarged. Subsequent microscopic examination showed that all had been successfully removed.

The method of excising the parathyroids was—(1) to catch up each organ by its capsule with fine forceps; (2) to snip it carefully off with fine curved scissors, the greatest care being taken to remove no thyroid tissue along with it; (3) to lightly cauterise the raw surface with a stout wire, heated to redness in order to arrest any hæmorrhage. It is better to identify both the parathyroids on one side before beginning to remove either of them, as the slightest ooze of blood utterly obscures their position. It is also better to remove the internal before the external, since the latter is much more easily recognised.

26th February.—The animal was depressed and disinclined to leave its cage. When taken out it could walk fairly well, but shook its paws as it raised them from the ground, so that it had a peculiar gesticulating gait. This symptom was noted by Lorrain Smith⁽¹³⁾ as a result of thyroidectomy in the cat, and appropriately likened by him to the action of shaking water off its paws. There was also a slight degree of rigidity of the muscles of the

hind-limbs, most noticeable when the animal stood still. There were no tremors to be either seen or felt in any of the muscles. Slight anorexia was present.

27th February.—The animal was much more depressed and lethargic. It appeared to be in distress, and was continually emitting a loud petulant cry, which I have very frequently noted at the onset and during the course of the acute symptoms. It walked unsteadily, with the posterior limbs slightly but distinctly rigid, occasionally taking a few tottering steps, as if the anterior limbs showed slight paresis, and always shaking its paws as it raised them from the floor. It could not stand without swaying slightly from side to side, and the hind-feet were kept wide apart. There were no noticeable muscular tremors. It absolutely refused to take any food.

28th February.—The animal was very much depressed, and continually uttered the loud cry previously noted. It walked with great difficulty, the posterior limbs being very stiff and rigid, the anterior limbs obviously very weak but not rigid. In walking it took a few staggering steps, showing a great tendency to fall to the right side, and, after a few steps more, it fell. When raised to its feet, it stood at first very unsteadily with rigidly extended hind-limbs. It then tried to walk, but, after a few steps, it again fell, and would not stand even when raised up, but simply collapsed on the floor. Still no tremors could be felt in any of the muscles. Complete anorexia continued, and artificial feeding was resorted to, warm milk being used.

1st March.—It did not appear quite so depressed. Its loud petulant cry had ceased. It could walk without much difficulty, proceeding rather quickly with an anxious restless expression. It did not show any tendency to fall. There was very little unsteadiness in standing, but some rigidity of the posterior limbs. There was now present for the first time marked twitching of the shoulder muscles, especially of the trapezius and latissimus dorsi. The twitching was distinctly felt before the animal was removed from its cage, and was not aggravated by exercise. It still refused to eat, and was fed as before.

2nd March.—The animal was found dead this morning with all its muscles rigid.

Autopsy.—The incision was completely closed, and there was not the slightest trace of sepsis. The thyroid appeared quite healthy, apart from the shallow cauterised depressions from which the parathyroids had been removed. The central nervous system and the peripheral nerves showed no naked-eye change. The skeletal muscles, especially those of the back, appeared wasted, paler than in health, dry, sticky, and anæmic. The other organs showed no noteworthy change.

CAT NO. 2 (Operation 12).—A very large, fat, striped male (testes absent).

21st April 1897.—The thyroid was very large, each lobe measuring 30 mm. in length, 8 mm. in breadth, and about 5 mm. in thickness. The left external glandule was the largest I have ever seen in the cat, measuring 6 mm. in length and 4 mm. in breadth; the left internal was relatively small. The parathyroids in the right side were both very large. Excision was effected in much the same way as before, but, owing to their size, the leash of vessels passing to and from each glandule was caught up by fine catch-forceps, which were left on until the glandule had been enucleated and the cautery lightly applied. It was afterwards found that all the parathyroids had been removed without any thyroid tissue adhering.

¹ NOTE.—The * in this and subsequent temperature charts indicates that the mercury would not rise above the bulb of the clinical thermometer.

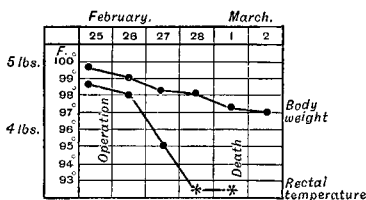


FIG. 1.¹

22nd April.—The animal showed some depression, but uttered no cry. It could walk without any appreciable abnormality of gait, but it appeared very unwilling to undergo any exertion, repeatedly tried to return to its cage, and was very impatient of handling. It refused to eat anything until evening, when it took some milk, but vomited soon afterwards.

23rd April.—When first seen at 10 A.M. the animal was found to be acutely ill. It kept moving round its cage in a state of great restlessness, stretching its limbs out against the sides. It gave utterance to a loud incessant cry, and its attention could not be attracted. In about a quarter of an hour the restlessness passed off, and it lay extended on the floor of its cage in a collapsed and semicomatose condition. It showed the most intense dyspnoea and extreme polypnoea, the respiration varying in frequency from 140 to 160 per minute. There were distinct fine tremors in all the muscles of the anterior and posterior limbs, most marked in the muscles passing to them from the trunk. There were no tremors in the masseters or in the temporal muscles. There was slight rigidity of the posterior limbs, noticeable on passive movement, but not of the anterior.

When taken out of its cage it had a very dazed expression, and stood unsteadily swaying from side to side. It walked with great difficulty, and had a shuffling unsteady gait, as if all the limbs were parietic. The paralysis appeared to be specially marked in the extensors of the anterior limbs, and to be associated with spasticity of the muscles of the posterior limbs. It still refused food, and was artificially fed on warm milk. On opening the jaws some muscular rigidity was noted.

About noon it had another attack of great restlessness and excitement, dashing itself about in its cage with loud petulant cries. This lasted six or seven minutes, and gradually passed off. Soon the animal lay prostrate and comatose, breathing about 160 times per minute, and showing fine tremors in muscles of thigh and upper fore-limbs. At 2 P.M. it lay quiet, and the number of respirations had fallen to 40 per minute. No subsequent change was observed. It vomited after being artificially fed at 4 P.M.

24th April.—It showed extreme hebetude. There was no cry. It roused itself a little on being handled, but, when taken out of its cage, it simply collapsed on the floor. As it lay, two remarkable phenomena were noted—(1) the respiratory movements were characterised by marked arhythmic contractions of the abdominal muscles, and by great irregularity in their extent, and in the time interval between each. Their frequency varied from 32 to 40 per minute. There was no apparent dyspnoea. (2) There were peculiar undulatory movements of the upper crural and brachial muscles, not, however, resulting in any movements of the limbs. When placed on its feet, it adopted a crouching attitude with its neck rigidly extended. It was photographed in this position, and remained quite motionless, as if cataleptic. It showed extensor paralysis of the anterior limbs, with spasticity of both anterior and posterior limbs. It took a few staggering steps, then fell down and would not rise. The muscles of the jaw and neck were extremely rigid.

25th April.—It was found dead and perfectly rigid this morning. Body weight, $7\frac{1}{2}$ lb.

Autopsy.—The wound was closed and free from septic changes. The thyroid appeared quite healthy, apart from the cauterised sites of the parathyroids. There was a considerable amount of adipose tissue throughout the body. The muscles were somewhat dry and sticky, but not very pale. The nervous system showed no recognisable change. The lungs were anæmic

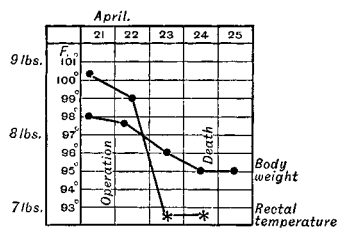


FIG. 2.

and emphysematous. The other organs showed no important morbid change.

CAT No. 3 (Operation 10).—Large, tawny, lean male (testes present).

12th April 1897.—The two external parathyroids were readily identified. The two internal glands could not with certainty be found, but two small pale areas about 3 mm. in diameter, indicated by their relative vascularity, were excised. It was afterwards found that only the two external parathyroids had been removed; the nodules taken for the internal parathyroids were composed entirely of thyroid tissue. The case is included here, because no trace of the internal parathyroids could be found on a careful histological examination of the thyroid after death. In all probability, therefore, the tissues removed from the internal surface were really in the vicinity of the parathyroids, which would then be wholly or partially destroyed by the cautery. It must be confessed, however, that there is considerable uncertainty as to what had or had not been destroyed.

For the next twelve days the animal remained extremely well. It ran about purring quite naturally. The body weight had slightly increased, the temperature showed no essential variation.

25th April.—Morbid symptoms were present for the first time. It refused to take any food until evening, and it showed well-marked spasticity of the posterior limbs. It had also a very unsteady reeling gait, and almost fell whenever it tried to shake itself. It did not appear to be in the least distress, but purred continuously. There were no muscular tremors.

26th to 29th April.—Very little alteration could be observed in its condition beyond a gradual increase in the rigidity of the posterior limbs.

30th April.—There was a distinct aggravation of the rigidity. In walking, the posterior part of the trunk was elevated and jerked about from side to side within each step. There were no tremors and no obvious implications of the fore-limbs. The animal did not show any distress, and purred when stroked. Its appetite remained poor, but it never required artificial feeding. The rectal temperature for the first time fell below 95° F. No change occurred on 1st and 2nd May, and it was found dead on the morning of the 3rd.

Second series.—Removal or destruction of less than four parathyroids, the thyroid and the remaining parathyroids being left *in situ*—four operations; none of the animals died.

In illustration of the experimental difficulties to be encountered, it may be mentioned that in each of these cases an attempt was made to find all the parathyroids, and only where a prolonged search proved futile, was it decided to remove less than four.

CAT No. 4 (Operation 9).—An adult grey female.

11th March 1897.—The thyroid was of moderate size. On the right two small bodies were isolated in close relation to the upper thyroid vessels, from which they were freed as far as possible, then caught up by fine forceps, ligatured off, and cut out close to the ligature. The pedicle was then touched with a hot wire, to destroy any traces of tissue left beyond the ligature. In this operation the superior thyroid vessels were subjected to considerably more interference than usual. A third body was removed from the inner surface of the thyroid and its site cauterised, but it proved to be only a small piece of thyroid tissue. On the left side two small bodies were removed by excision and cauterisation. Subsequent examination showed that the left internal parathyroid had not been removed.

12th March.—The animal was somewhat depressed and lethargic, refusing

to take any food. There were no tremors in any of the muscles, and no noticeable rigidity.

13th March.—It was found to be very acutely ill, and showed marked hebetude and depression. It was in considerable distress, and had a loud piercing cry. There were distinct twitchings of the muscles of the shoulder and of the anterior part of the trunk, but not elsewhere. There was distinct rigidity of the posterior limbs. Artificial feeding was required.

14th March.—It showed considerable improvement, and ate greedily for a short time. There were now no distinct muscular tremors, but still marked posterior rigidity. It could walk much better, but with straddling hind-limbs, shaking its paws as it raised them from the ground. When put back into the cage, it continued to raise its hind-paws and give them a shake, and, while it was doing so, a series of rapid clonic spasms occurred in both hind-limbs simultaneously, and the animal was thrown on its side. This attack was of short duration, lasting only about a minute.

15th to 20th March.—There was no recurrence of the clonic spasms, and no muscular tremors were observed during this period. The stiffness of the hind-limbs became gradually less from day to day. The appetite continued poor; since the operation it has lost slightly in weight, but the temperature has been maintained at its normal level.

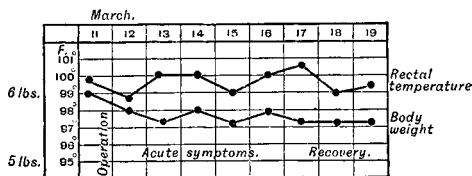


FIG. 3.

21st March.—A distinct improvement was observed in its condition. It had a better appetite than it had ever had since the operation. The rigidity of the hind-limbs had almost entirely disappeared.

22nd March.—No abnormal symptoms of any kind could be detected, and the animal continued in good health, until it was killed on the 2nd July, four months after operation.

CAT No. 5 (Operation 4).—A large striped female.

8th February 1897.—The right internal glandule could not be detected, and, as no indication of its position was obtained, no tissue was removed from the inner thyroid surface. In the course of this prolonged search the thyroid lobe was more severely handled than usual. The right external glandule was destroyed *in situ* by repeated cauterisation with a hot wire until a small cavity was made in the thyroid—an unsatisfactory method of procedure, as it does not permit histological examination. The two parathyroids in the left side were excised and their site cauterised.

This animal showed absolutely no symptoms after the operation. It was always quite lively and had a good appetite. The body-weight showed a slight fall during the second month, but no subsequent loss occurred. The temperature remained practically unaltered throughout. The nutrition of the skin was never affected; the fur was always sleek and glossy; the hair never fell out to any appreciable extent. Apart from its slightly thinner appearance, the animal did not appear to have undergone any change whatever after the operation. It was killed five months later, on the 3rd July.

CAT No. 6 (Operation 11).—A large white and striped male (testes absent).

20th April 1897.—The two right parathyroids were included in the same ligature, and excised together. The ligature, on being tied, slipped and included a considerable mass of thyroid tissue, which was also removed. It may be noted that this was the only case in which trouble was experienced with the recurrent laryngeal nerve. It was so closely bound up with the vessels that the effort to isolate it resulted in considerable hæmorrhage, and had to be

abandoned. Part of it was included in the same ligature as the parathyroids, and excised along with them.

The left external parathyroid was cut out and its site cauterised. The left internal parathyroid could not with certainty be identified. Ultimately, a small piece of tissue was removed from the upper end of the inner surface. It was afterwards found that the left internal parathyroid had been left *in situ*.

In spite of all the complications of the operation the animal showed no morbid symptoms whatever. Even before the operation it appeared to be somewhat morose, and used to sit moping in its cage. This it afterwards continued to do, but not to any greater extent than before. Its appetite remained good, and the body-weight and temperature showed no important alteration. It was killed two months later, on the 16th June.

CAT No. 7 (Operation 2).—Large striped female.

15th December 1896.—The two external parathyroids were destroyed *in situ* by the cautery. The internal parathyroid could not be recognised on either side, even after a long search, and no attempt was made to remove or destroy any portion of tissue in the internal surface, but the thyroid underwent considerable handling.

About the middle of March a circular patch of baldness, about $1\frac{1}{2}$ in. in diameter, was observed in the mid-dorsal region, but during April the hair began to grow over it again.

On the 31st May, five and a half months after operation, the animal was killed, having never shown the slightest derangement, and being in a state of perfect nutrition.

Third series.—Removal of the thyroid together with—(a) three parathyroids—one operation resulting in death; (b) two parathyroids—two operations resulting in recovery.

A. Retention of the Right External Parathyroid alone.

CAT No. 8 (Operation 5).—Striped adult female.

15th February 1897.—The left thyroid lobe was removed along with the left parathyroids. The right thyroid lobe and the right internal parathyroid were also excised, after the right external glandule had been dissected out and left in position. The leash of vessels supplying the parathyroid was first freed from the thyroid capsule by means of sharp-pointed scissors. The capsule of the parathyroid was then caught up by fine forceps, and the glandule severed from the thyroid with fine curved scissors, care being taken not to injure the parathyroid, and at the same time to avoid removing any thyroid tissue with it. A ligature was then passed, so as to include all the vessels going to the thyroid at that part, and at the same time preserve all the parathyroid vessels intact. The thyroid lobe was then excised and the parathyroid alone left suspended by its vascular connections.

16th February.—The animal was somewhat depressed, and there were distinct fine tremors in the muscles passing from the trunk to the anterior limbs. There were no tremors in the other skeletal muscles, and no rigidity of the hind-limbs.

17th February.—It showed great depression, and had an incessant wailing cry. There was complete extensor paralysis of both anterior limbs, so that, when the animal was placed on the floor, the two fore-paws became doubled up, and each fore-limb rested on the dorsal surface of the carpus. If the fore-limbs were straightened out, they remained in that position so long as the animal stood perfectly still; but, as soon as it tried to move, the fore-paws doubled up again. The tremors in the shoulder muscles had entirely ceased. There was no rigidity anywhere noticeable. The appetite was poor.

18th February.—It was still more depressed and collapsed, but otherwise in much the same condition. The rectal temperature for the first time fell below 95° F.

19th and 20th February.—It remained greatly depressed and collapsed. The extensor paralysis continued as before, but there were no tremors or rigidity. On the 19th it took a little milk at intervals all day, but on the 20th artificial feeding was begun.

21st February.—It was found dead and rigid this morning.

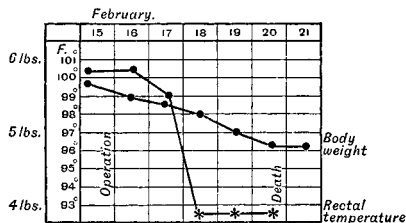


FIG. 4.

B. Removal of Thyroid and Internal Parathyroids—Retention of the Two External Parathyroids.

CAT No. 9 (Operation 6).—Medium-sized striped female.

24th February 1897.—The thyroid lobes were very small, not exceeding 10 mm. in length. The right external parathyroid was perched on the upper end of the thyroid lobe. It was, therefore, very readily isolated by simply ligaturing it off from the thyroid, the capsule having previously been incised all round, so that, when the ligature was tightened, the glandule was not unduly crushed. The external parathyroid was thus left adherent to the superior thyroid vessels when the thyroid and internal parathyroid were removed. The left external parathyroid was not quite so favourably placed, but it was dissected off, as described in the preceding case. The thyroid lobe, together with the internal parathyroid, was then excised.

Next morning the animal was very lively and had an excellent appetite. It continued in this condition of perfect health, showing not the slightest abnormality for the next three weeks.

On the 20th March a copious vaginal discharge of pus and blood was observed. As this could not be controlled, and as the animal appeared to be in some distress, a lethal dose of chloroform was administered on the 24th March. During this latter period it was somewhat depressed and did not eat well, but it showed no symptoms suggestive of thyroidectomy.

Autopsy.—There were found lying on the trachea two small oval bodies, which afterwards proved to be the parathyroids, without any thyroid tissue adherent. An exhaustive search was made in the neck and thorax for accessory thyroids, and the structures removed were histologically examined, but the result was absolutely negative. Both horns of the uterus were full of pus, and the uterine mucous membrane was thickened and rugose. There was no peritonitis. The other organs appeared quite healthy.

CAT No. 10 (Operation 8).—A half-grown, black and white male (testes present).

9th March 1897.—Operation. On the left side the external parathyroid could be isolated at the upper extremity of the thyroid lobe by simply tying a ligature as before. On the right side the corresponding glandule had to be dissected off along with its leash of vessels. Both thyroid lobes, together with the internal parathyroids, were then removed, the two external glandules being retained.

On the day after the operation there was slight anorexia, but otherwise no derangement could be detected. On subsequent days absolutely no morbid symptoms occurred, and the animal remained in apparently perfect health until it was killed on 23rd June, three and a half months after operation. At the autopsy two parathyroids were found, but not the slightest trace of thyroid tissue.

Fourth series.—Removal of the thyroid and parathyroid glands at the same time, the animal being fed with fresh ox parathyroid—one operation, resulting in death.

This series was undertaken with the object of investigating the effect of mouth administration of fresh parathyroid tissue, after removal of (*a*) the parathyroid glands alone, (*b*) the thyroid and parathyroid glands together. So far as I am aware, this has never previously been attempted, probably owing to the great difficulty of obtaining these glands in sufficient quantity. I did not, however, succeed in carrying out this scheme in its entirety, for the removal of all the parathyroid glands, leaving the thyroid *in situ*, proved to be a more difficult operation than I had been led to anticipate from the statements of Vassale and Generali. Not only so, but it was impossible to be certain that all the parathyroids had actually been removed, until a histological examination had been made of the tissues excised at the operation. In this state of uncertainty it would have been necessary to operate on a very large number of animals, to make a rapid microscopic examination of the parts removed, and to have a large supply of parathyroid ready for use. I was accordingly obliged to limit my observations to the effect of parathyroid feeding after the more certain operation of removal of the thyroid and the parathyroid glands together. For the purpose of feeding, the parathyroid glands of the ox were used, since in that animal the glandules are fairly large and not very hard to find, though the dissection is troublesome, on account of the dense bed of fat in which they lie between the lateral thyroid lobes and the pharynx. In the ox they are distinguished from nodules of thyroid tissue by their lighter brown colour, by their pyriform shape, and by the fact that they are attached by a distinct stalk or duct-like process to the tracheal surface of the thyroid.

CAT No. 11 (Operation 3).—A small, young, striped female.

29th January 1897.—The thyroid and all the parathyroids were removed together.

30th January.—Two ox parathyroids (weighing 2 grs.) were given. The animal showed slight tremors in the shoulder muscles, and slight rigidity of the posterior limbs, so that it had an unsteady gait.

31st January.—Three ox parathyroids (weighing $2\frac{1}{2}$ grs.) were given. There were now distinct twitchings of the shoulder muscles and greater rigidity of the hind-limbs. There was also complete anorexia, and artificial feeding was required.

1st February.—The dose was increased to six ox parathyroids (weighing 6 grs.). The animal was very depressed and had developed a loud, incessant cry. Marked twitchings of the shoulder muscles and rigidity of the posterior limbs were still present. Anorexia was still complete.

2nd February.—Four ox parathyroids (weighing 4 grs.) were given. There was no change in its condition.

3rd February.—Eight ox parathyroids (weighing 7 grs.) were given. It had a short convulsive attack, which lasted about fifteen seconds. Some cessation of the muscular twitchings occurred in the afternoon, but by evening they were again very violent.

4th February.—Eight ox parathyroids (weighing 7 grs.) were again given. It appeared rather less depressed. Only slight tremors were present in the shoulder muscles, and the hind-limbs were rather less rigid. Anorexia was still complete.

5th February.—Five ox parathyroids (weighing 5 grs.) were given. No change was observed.

6th February.—The dose was increased to twelve ox parathyroids (weighing 9 grs.), but the animal continued in much the same condition.

7th February.—No parathyroids could be obtained. It seemed somewhat less depressed this morning. The tremors of the shoulder muscles and the rigidity of the hind-limbs were both less marked; but the rectal temperature for the first time had fallen below 95° F.

8th February.—Twelve ox parathyroids (weighing 10 grs.) were given. It was more depressed, but the other symptoms were not aggravated.

9th February.—Eight ox parathyroids (weighing 7 grs.) were given. Practically no change could be noted in its condition.

10th February.—It was found dead and rigid this morning, with its limbs naturally extended.

Autopsy.—The wound was in process of healing by first intention. No remains of thyroid or parathyroid tissue were found. The central nervous system showed no obvious lesion. The muscles of the shoulder were specially pale, yellowish, and dry, but all the skeletal muscles showed to some extent the same change. The other organs showed slight changes, which need not be detailed.

CAT No. 12 (Operation 1).—An ill-nourished, adult, black and white female.

12th December 1896.—The thyroid and parathyroids were removed together, preparatory to feeding, but the animal died three days later of an intercurrent attack of acute bronchitis.

REMARKS AND CONCLUSIONS.

From the conditions under which the above work was done it was not possible to operate on a greater number of animals or to keep the survivors alive for longer periods, and one must be extremely guarded in drawing any inferences from so limited a number of observations, extending over so limited a space of time. Yet it is possible to indicate a few conclusions which these experiments tend at least to support if not entirely to justify.

1. *Removal of all the four parathyroids in the cat leads to acute and severe symptoms, with a rapidly fatal issue, even though the thyroid be retained practically uninjured.*

In two cases of the first series (Cats No. 1 and No. 2) it was definitely proved, by microscopic examination, that all the four parathyroids had been removed without any gross lesion of the thyroid. In both cases the tissues removed at the operation (the parathyroids), and the thyroid lobes removed after death were weighed, after having been subjected to precisely similar methods of fixation and hardening. It was thus possible to obtain the relative weights with some degree of certainty. In Cat No. 1 all the four parathyroids together weighed 0.019 grms., and the two thyroid lobes together weighed 0.257 grms.

Hence the ratio of the weight of the tissues removed to that of the thyroid retained was less than $\frac{2}{5}$, *i.e.* less than 8 per cent. In Cat No. 2 all the four parathyroids together weighed 0.060 grms., while the two thyroid lobes together weighed 0.405 grms.; so that the ratio of the weight of the tissues removed to that of the thyroid retained was less than $\frac{3}{20}$, *i.e.* less than 15 per cent. Now it is a well-known experimental result (cf. Horsley, ⁶) that in the lesser carnivora two-thirds of the thyroid may be removed without inducing symptoms of thyroidectomy, though individual results vary probably according to the number of parathyroids left behind. When only half the thyroid is removed, the animals almost never die. One is therefore bound to conclude that Cat No. 1, which lost less than 8 per cent., and Cat No. 2, which lost less than 15 per cent., did not die on account of the quantity of tissue recovered from the thyroid.

It may be noted that both these animals were advantageously placed as regards susceptibility to thyroidectomy—the one being a female, the other a castrated male, both of which classes are said by Kent (¹⁴) and others to be less susceptible than the uncastrated male.

It might be urged that the animals died owing to interference with the thyroid nutrition, through damage to either its vascular or its nervous supply. But against this objection must be set the following facts:—(1) Owing to the difficulty experienced in finding the parathyroids, most of the animals in the second series were exposed to more prolonged and more drastic manipulation, and yet none of them succumbed. (2) In the case which died with most severe symptoms (Cat No. 2), the great size of the parathyroids rendered their identification the easiest and the operation the briefest of all.

In regard to local necrosis of thyroid tissue, at the sites of excision of the parathyroids, it must be remembered that an equal number of pieces of tissue were excised from most of the animals of the second series, and further that, in the Cats No. 1 and No. 2, the thyroid lobes were unusually large, and therefore the destruction of an equal amount of tissue would be proportionately less hurtful.

In fact, any difference between the first two animals of the first series, which died of acute symptoms, and the animals of the second series, none of which died, was all in favour of the former, with the single exception of the fact that in those of the first series all the parathyroids had been removed, whereas in those of the second series at least one parathyroid had been left behind.

In regard to the remaining animal of the first series (Cat No. 3) it is not possible to speak with certainty. The facts of the case are, that only two parathyroids could be found among the tissues removed at the operation, that the animal died with less acute symptoms after a longer interval of time, and that after death no parathyroid tissue could be found in relation to the thyroid.

2. *Removal of three parathyroids does not lead to death, but may*

cause transient symptoms, similar to those which result from removal of all the glandules; loss of two parathyroids does not produce any appreciable change.

This conclusion is supported by the results of the second series of experiments, although most of the animals underwent a more severe operation, and lost a greater proportion of tissue from the thyroid than did those of the first series.

3. *Removal of the thyroid and some of the parathyroids may lead to death with acute symptoms, if only one parathyroid is left; but may not induce any obvious derangement, if two parathyroids are retained, at least not for several months.*

Had it been possible, it would have been a point of great interest to allow the survivors of this third series to live, in order to see whether any chronic changes resulted from the loss of the thyroid. It may again be stated that in these animals accessory thyroid tissue was carefully sought for post-mortem, but that no trace of any could be found.

4. *Mouth administration of the fresh parathyroid of the ox has no effect, either in mitigating the symptoms, or in averting death, after removal of the thyroid and parathyroids in the cat, even though relatively enormous doses are given.*

It must be remembered, however, that similar administration of thyroid tissue itself may fail to avert death after thyroidectomy. The great difficulty of obtaining parathyroid tissue in sufficient quantity has so far prevented me from trying the effect of subcutaneous injection of parathyroid, both after complete thyroidectomy and after removal of the parathyroids alone.

I have great pleasure in recording my indebtedness to Professor Greenfield, for having afforded me every facility for the prosecution of this research. My thanks are also very specially due to Dr. W. F. Robertson, who was the first to bring the subject of the parathyroid glands under my notice, and to Mr. G. C. Low, M.B., who rendered me much assistance in the experimental work.

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DESCRIPTION OF PLATES XXIII. AND XXIV.

PLATE XXIII.

- FIG. 1.—Section through part of the internal parathyroid (*a*) of the cat, and through the entire internal thymus lobule (*b*) associated with it, to illustrate differences in their structure. ($\times 45$ diam.)
- FIG. 2.—Parathyroid of cat, showing compact arrangement of cells. ($\times 100$ diam.)
- FIG. 3.—Parathyroid of cat, showing less compact arrangement. ($\times 100$ diam.)
- FIG. 4.—Transverse section through thyroid, parathyroid, and thymus on one side of neck of sheep embryo (11·5 cm.) to illustrate the early differentiation of structure, and complete separation from each other by embryonic connective tissue: (*a*) part of wall of trachea, (*b*) of œsophagus, (*c*) of carotid artery, (*d*) thyroid, (*e*) parathyroid, (*f*) thymus. ($\times 70$ diam.)

PLATE XXIV.

- FIG. 5.—Human parathyroid, showing part of a wedge-shaped mass of granular oxyphile cells, situated immediately beneath the capsule, and abruptly demarcated from the surrounding principal cells. ($\times 200$ diam.)
- FIG. 6.—Human parathyroid, showing a few columns of oxyphile cells mingling with the principal cells. ($\times 200$ diam.)
- FIG. 7.—Human parathyroid, showing early colloid changes in some of the principal cells. ($\times 200$ diam.)
- FIG. 8.—Human parathyroid, showing unusually large cystic spaces filled with colloid matter, and somewhat resembling thyroid follicles. ($\times 200$ diam.)

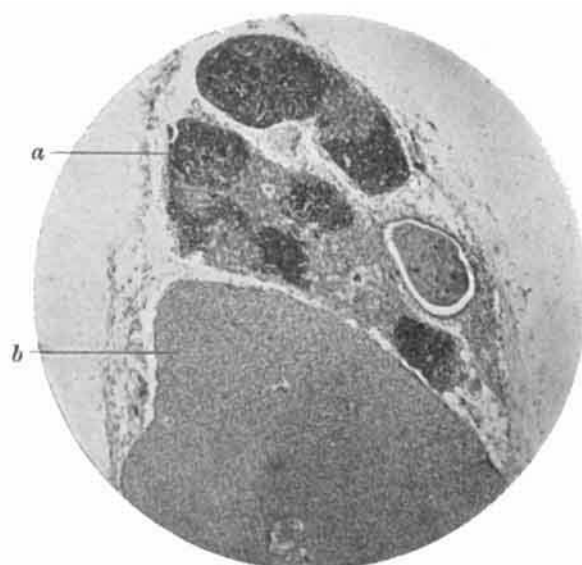


FIG. 1.



FIG. 2.

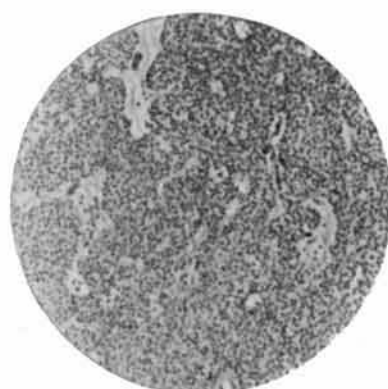


FIG. 3.

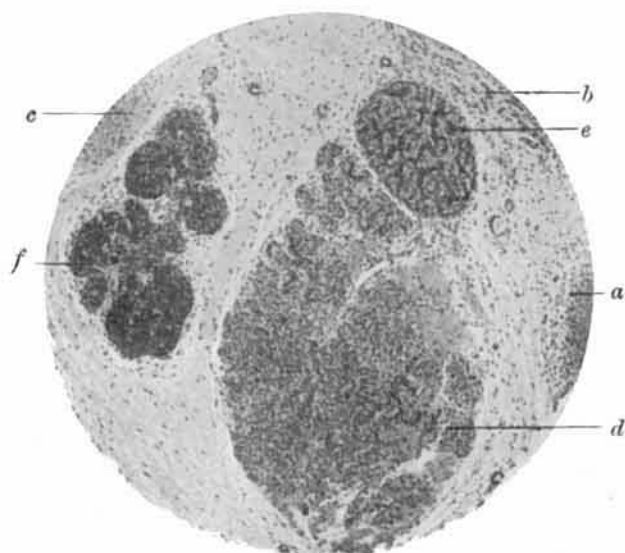


FIG. 4.

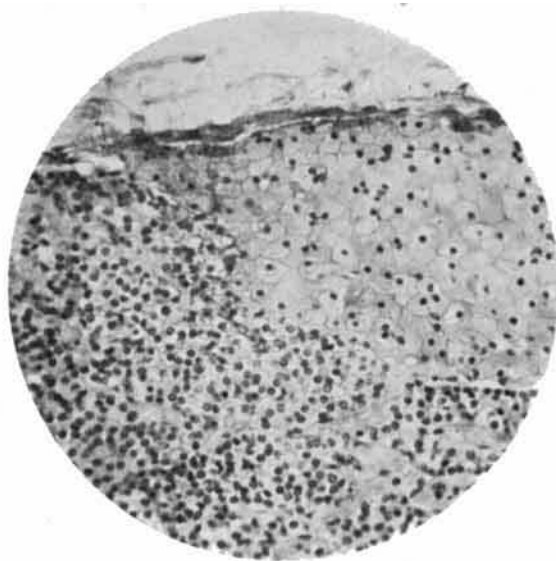


FIG. 5.

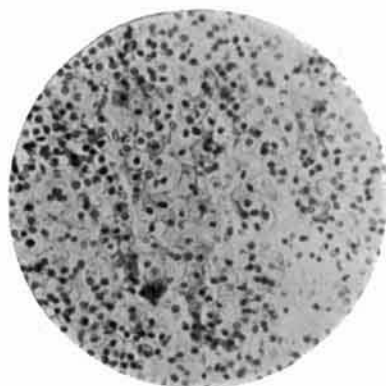


FIG. 6.

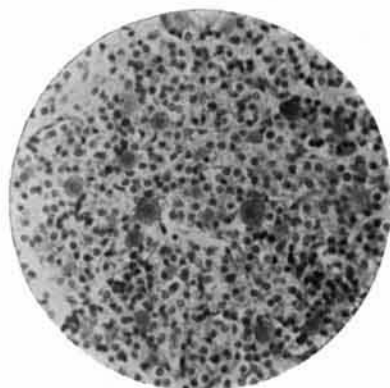


FIG. 7.

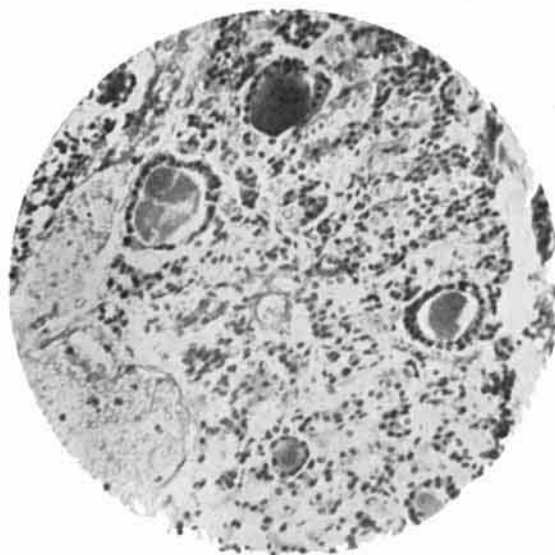


FIG. 8.