REPORT OF A DOG MAINTAINED IN GOOD HEALTH
BY A PARATHYROID AUTOGRAFT APPROXIMATELY
ONE FOURTH OF A MILLIMETER IN DIAMETER.
AND COMMENTS ON THE DEVELOPMENT OF
THE OPERATION FOR GRAVES' DISEASE AS
INFLUENCED BY THE RESULTS OF
EXPERIMENTS ON ANIMALS.*

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PLATES 30 AND 31.

PART I.

In a paper on the auto- and isotransplantation, in dogs, of the
parathyroid glandules,1 the histories of two of the dogs (Nos. 8 and
9) reported in the series of experiments were incomplete, the ani-
mal having been kept for further study. One of these dogs (No.
9) was observed for fifteen months and was in good health until
the performance of the final operation at which a parathyroid auto-
graft too small to be visible2 to the naked eye was removed (figures
1 and 2). The death of the dog from hypoparathyroidism occurred
about three months after the removal of the tiny transplant which
was only 0.25 of a millimeter in one diameter and little more than
this in the other.

The history is as follows:

Dog 9. Operation 1.—February 6, 1908. Excision of the right thyroid lobe
and both parathyroids of this side. The right inferior parathyroid was planted
subperitoneally behind the right musculus rectus abdominis.

Operation 2.—March 24, 1908. Excision of the left thyroid lobe with its two
parathyroid glandules. The superior parathyroid, found much lower than usual

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2Fortunately a delicate film of thyroid tissue had been transplanted with the
parathyroid glandule. Were it not for the occurrence of the hypertrophy of the
former, in which the latter was embedded, it would hardly have been possible
to identify this minute, quite invisible parathyroid autograft.

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and lying well exposed but somewhat within the substance of the thyroid, was sliced from the latter so as to include a very thin film of this gland, and immediately transplanted subperitoneally behind the left rectus muscle.

The dog is now deprived of both thyroid glands. He is reduced to the two parathyroid autografts.

To transplant a film of thyroid gland with the parathyroid is a good precaution, because, in our experience, the tendency of the former is to hypertrophy when complete thyroidectomy has been done, and of the latter to disappear, and it might be, as it would have been in this case, impossible to discover the transplanted parathyroid except for the presence of the hypertrophied thyroid tissue in which the tiny transplant was embedded.

March 25. Dog seems unaffected by the second operation.
March 26. Is as lively as ever, but has faint tongue tremors.
March 27. Tongue tremor seen only occasionally.
March 30. Temporal as well as tongue tremors; the latter more marked than at last note. Dog not so well as heretofore.
April 1. Better. No sign of parathyroid privation.
April 4. In usual good spirits. No tremors.
May 23. Has become abnormally stout. Myxedema (?).
June 11. Has greatly increased in size. Hair is thinner. Skin seems thickened. Is quite surely myxedematous. No evidence of hypoparathyroidism. Transferred to Drs. Voegtlin and Strouse for observation and experimentation during the summer.

November 5. Dog has been returned to me by Drs. Voegtlin and Strouse. He seems well, but is not so active and demonstrative as formerly. The myxedema is much less. There is no evidence of hypoparathyreosis.

February 24, 1909. Dog has been quite well since the last note. There is no distinguishable myxedema, although the hair is still thinner than normally.

—February 25, 1909. Assisted by Drs. Gatch and Emmert. Ether. Through a mid-line incision from about 3 cm. below the ensiform cartilage to the same distance below the umbilicus, a careful scrutiny of the peritoneal surface on both sides behind the recti muscles was made. The findings on the right side were negative, as we had expected, for this was the side on which the first parathyroid transplantation was made—a transplantation for which no deficiency had been created. But on the left side, very near the mid-line scar, and shimmering through a locally thickened, almost opaque peritoneum, was a dark spheroidal body about 7 mm. in diameter. In excising this nodule, which was done with the greatest care, and in order that none of the transplant might remain, some of the surrounding tissue was included. Examining the excised piece, I feared that the greatly hypertrophied graft had been shaved too close behind and accordingly cut out a second piece. Both of these pieces were hardened in Zenker's fluid, stained in toto and cut

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I was surprised to find that the graft had in such remarkable degree increased in size and hoped that at last we might have evidence that the parathyroid glandule was capable of hypertrophy. The color of the transplant was the characteristic reddish brown with a slight suggestion of yellow. In consistence, it was hard as if invaded by connective tissue. Its connection with the surrounding tissues, connective and muscular, was intimate, as if considerable reaction had been excited by its presence. It is, of course, possible that on the other side (the right) there may be a remnant of the parathyroid transplanted there at the first operation, but, if so, it is too small to be seen by the naked eye.

March 8, 1909. The dog seems to be very little affected by the removal of the graft.

March 10. Is still, apparently, quite as well as before the last operation, although occasionally there is a fairly definite fibrillar tremor of the tongue.

March 20. Dog has gradually failed in vigor since the last note. He is becoming myxedematous again.

This is interesting as indicating that the disappearance of the rather excessive myxedema which occurred at the second operation, after the removal of the remaining thyroid lobe, was due, at least in considerable measure, to the hypertrophy of the delicate and very small thyroid film included in the parathyroid graft.

April 2. Dog is exhibited before the Interurban Medical Society at one of my clinics. Tongue and temporal tremors are pronounced. The Trousseau phenomenon is readily obtainable on both sides by pressure over the femoral arteries. He is becoming definitely weaker although still lively and demonstrative.

May 1. Observed each day, since the previous note, by Dr. Gatch or myself. The dog has been steadily failing and is now quite weak. The tremors have become general and are almost constantly present. He sniffs in the manner characteristic of extreme hypoparathyroidism, and the upper lip, on handling, draws up as in snarling, on one or both sides.

May 15. Dog is so nearly dead that I asked Dr. William G. MacCallum to see him with a view to killing him at once to insure having fresh tissues for the autopsy. We finally decided to postpone this and to watch him carefully.

May 24. Having almost expired, the dog is killed under an anesthetic.

in serial sections by an expert technician. All the sections were preserved, and all those of the main piece mounted in proper order. As the sections of the underlying second piece contained no parathyroid tissue, only every tenth section was mounted. Dr. W. G. MacCallum studied all the mounted sections with the result given by him further on.
Dr. MacCallum performed the autopsy with exceeding care. I am greatly indebted to him for the following admirable report:

"May 24, 1909. Autopsy on Dr. Halsted's dog (dog 9) in which a parathyroid had been transplanted (more than a year ago) and later removed.

Dog is emaciated. The hair is irregular—has dropped out or become thin in places. Anesthetized and bled to death from femoral. Dissection of neck as shown in diagram (figure 3).

Sutures and ligatures healed imperfectly. There was absolutely no solid body of tissue in the region of the superficial wound. Muscles carefully stripped apart and each mass of the tissue labeled and preserved. Larynx separated into various parts, trachea examined throughout. Tongue removed and sectioned. Hyoid region carefully studied as well as the original thyroid regions; also the lateral and median portions of the neck throughout. Four or five small masses, apparently hypertrophied accessory thyroids, found near the trachea below the cricoid cartilage. No definite structures of this sort found elsewhere. No obvious parathyroid remains. Careful search made in the substernal tissues and in the tissues about the pericardium and the arch of the aorta and pulmonary vessels; no further thyroid found. Lungs and heart normal. No abnormality seen in the liver, kidneys, pancreas, adrenals, or in the intestinal tract.

Testes seem small—one sectioned appeared fibrous.

Hypophysis showed no macroscopical abnormality. Brain externally normal. Wound in abdomen behind rectus searched with negative result.

Microscopical Examination of the Tissue Removed.—(A) is a mass of hypertrophied thyroid tissue. This is surrounded by a dense fibrous capsule and is composed of alveoli empty of colloid or containing only traces of it. They are extremely irregular in outline, and some are so small as to show no lumen whatever. They are lined by high columnar epithelium. In other words, they present the appearance described by Dr. Halsted as arising in the course of hypertrophy of the thyroid.

(B) is a small lymph-gland.

(C) is a large lymph-gland. It shows no particular lesion.

(D) is a mass of hypertrophied thyroid showing the same characteristics as (A) with beautiful, irregular alveoli and containing a glassy looking, ragged colloid.

(E) is a mass of thyroid tissue. The alveoli are not nearly so irregular as in the case of (A) and (D) and contain a good deal more pink-staining colloid material. The epithelium is not quite so high and is more smoothly arranged. There is no parathyroid tissue to be observed.

(F) is a mass of thyroid tissue containing very large, irregular alveoli with columnar epithelium and relatively little colloid. At one corner there is a solid mass of cells which do not closely resemble any normal tissue, but are in all probability thyroid cells, although they form no alveoli. They have not the appearance of parathyroid tissue.

(G) is a rounded mass of thyroid tissue showing the same general characteristics as (F). Its alveoli contain a good deal of rather ragged colloid material. There is a sympathetic nerve ganglion nearby and the vascular supply seems to be very good.
"(H), the nodule on the surface of the heart inside the pericardium, is also thyroid tissue. It is surrounded by a thick capsule and composed of very irregular alveoli. Many of these contain granular colloid, while others are practically solid and have no lumen.

"(I) is a lymph-gland situated along the brachiocephalic artery.

"(J) is a hemolymph-gland situated near the first rib on the left side.

"(K) is a lymph-gland near the first rib on the right side.

"(L) is a small lymph-gland.

"(M) is the tissue just under the arch of the aorta. It is composed chiefly of fat with many nerves and some ganglia. In connection with one of these ganglion-like masses there is a small, glandular-like structure which is not thyroid and not parathyroid, but which is probably a mass of chromaffine tissue. It is composed of acini in which the cells have a ragged protoplasm. They do not leave a very distinct lumen; their rounded vesicular nuclei lie near the base of the cell. Other masses of a similar character are scattered in the tissue.

"Another section marked retrosternal lymph-gland shows a normal lymph-gland surrounded by fat.

"The hypophysis shows rather distinct alterations. The pars nervosa is practically surrounded in the section by the pars intermedia which is perhaps slightly thickened and contains one or two alveoli full of colloid. The pars anterior is in part very deeply stained with eosin, but one portion, and that the major part, is sharply marked off from this eosin-stained tissue by its lilac color. It contains only a few of the bright staining cells, but for the most part is made up of swollen, faintly granular, palely stained cells. These resemble very closely the section obtained by Dr. Honans after injecting pilocarpin. The cleft in the glandular part of the hypophysis is here seen to open into the subarachnoid space.

"The adrenals show no abnormality.

"The spleen seems normal.

"The testicle shows absolutely no sign of spermatogenesis. The cells which line the tubules are in single rows and are not in process of mitosis. They are drawn out into long filaments which are entangled in the wide lumen of the tubules, but there is no sign of a spermatozoön. The whole testis has an atrophied appearance and looks spongy. The interstitial cells of Leydig are inconspicuous. Some are seen, at least, which lie in their position, which are taken to be interstitial cells. They are large and very much vacuolated as if containing large globules of fat. It gives one the impression that these cells, too, which are supposed to preside over secondary sexual
Parathyroid Autograft in a Dog.

characters, are markedly influenced by the loss of the thyroid, although their changes are by no means so striking as the changes in the spermatogenic tissue. They are still in abundance even though a rather degenerated appearance of their protoplasm suggests that they have undergone some change. At best, however, the interstitial cells have a very irregular protoplasm. It seems that perhaps the most interesting result of this microscopical study lies in the determination of the complete loss of spermatogenic function of the testicle.

"No trace of parathyroid tissue is to be found anywhere.
"The pancreas shows no abnormality.
"The kidney shows no special abnormality except for the almost complete shriveling up of some of the glomeruli.
"The liver shows no abnormality.
"There is quite abundant thymus tissue. In the thymus there are some cysts, one quite large, one lined by ciliated epithelium. Such ciliated cavities of small size are found quite frequently through the tissue. I do not see any Hassall's bodies unless these might represent them. The thymus is not in the acme of its development but has undergone a certain amount of atrophy.

"The sections of the little body removed at the third operation at the site of the transplanted parathyroid gland are composed chiefly of thyroid tissue. This tissue closely resembles the human thyroid in cases of exophthalmic goiter, so large are the alveoli and so great the amount of convolution. A small mass of parathyroid tissue is found, but only on a limited number of slides and right at the edge of the sections. It first makes its appearance in the middle of slide 2; extends, then, through all the sections of slide 3, and disappears finally in the last section of slide 4—that is, extends through 32 sections. These sections are not perfectly uniform in thickness but will probably average 10 to 15 microns. This would make the mass of parathyroid tissue measure from 320 to 480 microns in thickness, that is, less than ½ mm. Transversely, the mass measures not more than ¼ mm. measured by a stage micrometer. It is almost inconceivable that so small a mass could have been so sufficient to carry on the function of the gland. It is enclosed in a dense fibrous tissue which is abundantly vascular and has the usual structure of a parathyroid gland. It shows no degenerative changes, but at one point there are tubular structures embedded in the gland which are rather difficult to interpret. These are lined by flattened
epithelium and are really not directly in contact with the gland tissue but are surrounded by a hyaline connective tissue. The cells of the parathyroid and the nuclei are pretty well preserved. The thyroid tissue round about is composed of alveoli of the most varying size, lined with high, columnar epithelium and extremely irregular in outline, so that folds are thrown up into the lumen of each alveolus. Some of the alveoli are very small and contain no colloid, while the larger ones are filled with homogeneous colloid (figures 1 and 2)."

It is interesting to note how slowly the tetany developed and for how long a time the animal lived after the removal of the almost microscopic transplant. The final operation was performed the 25th of February and the first definite sign of parathyroid privation was not observed until March 10, fourteen days later. This is in great contrast to the prompt appearance of privation symptoms, one or two or three days after the simultaneous removal in dogs of all the parathyroid bodies, but in accord with observations made by me in 1887 and 1888, that when these glands are removed two at a time with a considerable interval between the operations, the outbreak of tetanic symptoms may be delayed by several days. Dog 9 lived three months absolutely without parathyroid tissue, so far, at least, as it was possible with the most painstaking search, to determine this fact. Whether or not there was somewhere in the animal's body a particle of parathyroid tissue remaining at the time of its death will, of course, never be known, but it is quite certain that the removal of an "epithelial body" so small as to be practically invisible produced the almost inconceivable effect described, namely, death from tetany in an animal whose condition prior to the removal of the few cells had been excellent.

The dog's organism had, it seems, in some way accommodated itself to the loss of all of its parathyroid tissue except the quite invisible remnant in the graft; so that on the removal of this minute fragment, the impression produced was neither so immediate nor so profound as it is after the excision of these glandules in the animal unprepared for their loss.

In confirmation of the story of dog 9 is that of another dog (No. 8) operated upon three times in precisely the same way, on approxi-
mately the same dates, and affected in an almost identical manner. The differences observed in the two dogs tend to strengthen rather than weaken the argument which has been advanced.

In dog 8 both thyroids and all the parathyroids had been removed in two operations, and one parathyroid transplanted extraperitoneally at each of these. But the myxedema in dog 8 became excessive after the removal of the second thyroid lobe (second operation) and remained so to the end of its life a year later. Furthermore, mild symptoms of parathyroid privation persisted throughout, and finally, prolonged and thorough search (third operation) for the parathyroid autograft was negative in result although the sites of the transplantation of these bodies had been accurately recorded. Unfortunately, the non-resistant myxedematous tissues of this dog became infected in the course of the prolonged third operation and death from peritonitis followed so quickly that there was not time for the development of lethal tetany. The slight previous symptoms of hypoparathyroidism became, however, definitely intensified. At the autopsy no accessory thyroid could be found and not a trace of the transplanted epithelial bodies. The persistence of the myxedema in this case is to be explained by the facts that the parathyroid glandule transplanted at the second operation was devoid of thyroid film, and that accessory thyroid glands were wanting. That the search for the parathyroid transplants in dog 8 should have been negative the findings in dog 9 explain; for had it not been for the hypertrophied thyroid film in this dog it would probably have been impossible, as I have said, to discover the remnant of the parathyroid graft.

PART II.

Although thousands of operations have been performed, the world over, for the cure of Graves' disease, we are not as yet in a position to state how much of the thyroid gland should be removed in any given case. Some of the severest cases have been sufficiently cured by the removal of one lobe, and in some of the mildest the excision, almost total, of both lobes has been necessary to bring about a cure or a satisfactory condition. But we find ourselves gradually coming to the conclusion that more than one lobe of the
thyroid gland must be removed in certain cases of Graves' disease, so that at present in quite a considerable number of these cases we excise the greater portion of both lobes (usually in two acts)\(^4\) provided the excision of one lobe has not been attended with the desired effect, without waiting, as formerly, one or more years to observe the result of the removal of the single lobe.

In two of my cases, in which three and four arteries respectively had been tied and both lobes almost totally excised, severe symptoms of thyroid intoxication persisted; and only after removal of all but a fragment of one lobe was satisfactory relief obtained.

One case died in the convulsions of a thyroid toxemia, one and a half years after the final of four operations at which three thyroid arteries, one lobe, and two thirds of the other had been excised.

This accords with the observation, recorded above, that the hypertrophy of hardly more than a film of transplanted gland plus, perhaps, the hypertrophy of minute accessory thyroids sufficed in the dog to cause the disappearance of myxedema.

That a very small, seemingly quite negligible part of a thyroid gland with disordered function might be responsible for severe toxic symptoms is quite as comprehensible as that the removal of the little thyroid autograft (dog 9) should account for the reappearance of myxedema.

The surgeon must, therefore, not despair of being able to effect a cure, approximate or complete, so long as any portion of the thyroid gland, functioning so riotously, remains.

I believe that, in the present state of our knowledge, the operation upon the first lobe should be conducted just as if the operation on the second lobe were definitely contemplated. Therefore, a small portion of each lobe must probably be left in order to preserve with sufficient certainty the parathyroid glandules. In twenty (?) of our cases of Graves' disease in which both lobes have been removed in this manner, which is with us at present typical, four cases of hypoparathyreosis have occurred, two of these with pronounced tetany. The symptoms of tetany disappeared promptly on administration of calcium lactate, only one case requiring the giving of this drug for a period longer than ten days. These cases

\(^4\) Occasionally both lobes are excised at one operation.
of hypoparathyroidism in which certainly not a single parathyroid
gland was removed and in which the circulation of these epithelial
bodies was protected with the greatest care by the preservation of
a slice of thyroid tissue at the hilus of the lobe, these cases, I say,
stand in interesting relation to the results which we have obtained
in transplantation of the parathyroid glandules in dogs. It is more
than likely that the epithelial bodies died on the side first operated
upon in these cases of hypoparathyreosis in the human subject, and
that, if this is the case, these parathyroid glands had been reduced
to the condition of autografts. This inference is defendable for the
reason that in the dog a tiny fragment of parathyroid tissue is
sufficient to preserve the health of the animal and that it is improb-
able that tetany would have supervened in our patients at the second
operation if one or both or considerable portions of either of the
parathyroid glands had survived on the side first operated upon. As
a result of our experiments on dogs, we might have prophesied the
death of such autografts inasmuch as an inconsiderable or insuffi-
cient deficiency had been brought about. For the past five years we
have been in a position to state, provisionally, that in the transplan-
tation of the parathyroid glandules, the following law seems to
exist; namely, that unless considerable deficiency in parathyroid
tissue has been created, the autografts do not live. So, too, in the
human subject in which first one and then, later, the second thyroid
lobe is removed, the "epithelial bodies" if reduced to the condition
of autografts would be more likely to die on the side first operated
upon than on the side of the second operation. Conversely, the
epithelial bodies on the second side would be more likely to live than
those on the first because, by the loss of the glandule as a result of
the first operation a sufficient deficiency had been created to insure,
as a rule, the life of one or perhaps both of those upon the other
side, however completely their circulation might have been cut off.
It is important to state that all of the cases in which post-operative
tetany developed were so highly toxic before operation that the
ligation of two or more thyroid arteries in from one to three acts
was made as a preliminary to the lobectomies. The ligation of these
arteries, plus the thyroidectomy and plus the connective tissue for-
mation resulting from three to five operations may have been a
decisive factor in the determination of the tetany. If this is true, it would be an argument, other things being equal, in favor of omitting the preliminary ligation and excising at the first operation as much of both lobes as seemed likely to be indicated. But I am, and alas, with good reason, decidedly opposed to the view that the intensified toxemia which occurs after lobectomy in cases of Graves' disease is due solely to the overactivity of the lobe which remains and that, consequently, in the desperate cases, the safer procedure, so far as mortality is concerned, should be the removal of both lobes at one operation. It would probably be out of place to discuss this matter more fully in this Journal, hence, it must suffice, at this time, to say that I feel justified in firmly endorsing the view of Kocher that we have a great safeguard in the preliminary ligation of the arteries in the serious cases of exophthalmic goiter. Quite as important as the improvement in the patient's condition, which usually, for a time at least, follows the ligation of one or more thyroid vessels and enables the operator to proceed with greater safety to the excision of a lobe, is, in my opinion, the indication which the operation of ligation gives the surgeon of the relative intensity of the reaction likely to occur after lobectomy in the particular case.

EXPLANATION OF PLATES.

PLATE 30.

Fig. 1. Section of the entire graft (five diameters) removed from dog 9, fourteen months after the transplantation.

Fig. 2. The parathyroid and surrounding tissue from figure 1 enlarged (100 diameters).

PLATE 31.

Fig. 3. Diagrammatic representation of the findings at autopsy in dog 9.