FURTHER OBSERVATIONS ON THE THYROID GLAND (VIII).¹

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IN the last communication² certain experiments were related showing that the administration of calcium in milk or otherwise reduced to a considerable extent the mortality of dogs subjected to total excision of the thyroid and parathyroid glands, and allowed the animals to live for months instead of days, if, that is, the administration of the calcium is continued; if it is reduced or stopped the animals die.

At the time of the last paper one of the dogs therein referred to, dog 17, was alive and well. He had undergone, while taking large quantities of milk (containing calcium), total excision of the thyroid and parathyroids, and at the time of writing, nine months after operation, was alive and well; he was still fed with much milk, and except that he became somewhat thin, he remained lively and well; then on one day—one year, three months, and six days from the date of operation—he showed well-marked tremors; he could walk about, but he refused both milk and meat. The next morning he was found dead in his cage; from the appearance of the straw it seemed probable that the dog had died in a fit. At the post-mortem examination the body was thin, but the organs appeared normal; the urine in the bladder was found to contain a large amount of sugar, it had not been tested during life. The pancreas appeared normal to the naked eye, and under the microscope no definite changes could be made out.

Since the last paper eight more experiments on dogs have been made: they are as follow:—

Dog 1.—This dog was fed on milk for some days, and was also given 15 grains of lactate of calcium twice a day; this would correspond with about 6 additional oz. of milk a day. The thyroid and parathyroids were then excised; slight tremors appeared on the seventh day and the dog died on the eighth; the urine was tested for sugar by Fehling's method during life, but none was found.

Dog 2.—The dog was fed on milk and given 30 grs. of lactate of calcium a day. The thyroid and parathyroids were then excised, slight tremors appeared on the eighth day; on the ninth day convulsions came on, and on the tenth

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² *Journ. Path. and Bacteriol.*, Cambridge, 1910, vol. xiv. p. 288.

day the dog died in them. The urine had been tested for sugar by Fehling's test, but none was found.

Dog 3.—This dog was fed on milk, but instead of lactate of calcium he was given 30 grs. of chloride of magnesium a day, which produced no ill effect. The thyroid and parathyroids were then totally excised; the dog developed convulsions and died on the seventh day. The urine was tested for sugar, but none was found.

Dog 4.—In this dog the thyroid and parathyroids were removed in stages; shortly before the removal of the last parathyroid with a small portion of thyroid adherent, the dog was put on a milk diet. On the fourth day after the operation, tremors and a spastic gait appeared; 9 grs. of lactate of calcium were given intravenously into the leg. In three hours the dog was much better, and the next day there were no tremors and the dog could walk quite well. On the third day the tremors and stiffness recurred, and another intravenous injection of 9 grs. of lactate of calcium was given. The next day the dog was nearly (or quite) well. The sixth day after the second calcium injection the tremors reappeared; he received another intravenous injection of 9 grs. of lactate of calcium, for which he was much better for a time. Five days after this he was given a subcutaneous injection of 10 grs. of a commercial preparation of the pituitary body; this produced no visible effect. Three days later the dog seemed very thin and weak and hardly took any milk; he had, however, no definite nervous symptoms. He was given another intravenous injection of lactate of calcium. The next day he seemed worse, and had tremors; he was therefore destroyed.

Dog 5.—This dog was kept on a diet wholly of milk. After a few days the thyroid and parathyroids were totally removed. On the fourth day he had a severe attack of convulsions. He was given 10 grs. of lactate of calcium intravenously. This relieved the tremors. On the next (sixth) day again 10 grs. of lactate of calcium were given intravenously; the next day he was much better. But the day after (the eighth from the operation) the tremors reappeared. He was now given intramuscularly 2 c.c. of a commercial preparation of pituitary extract; this produced no visible effect. The next day, therefore (the tenth), he was given 10 grs. of lactate of calcium intravenously; this reduced the tremors, but they returned markedly on the twelfth day. He was now given 4 c.c. of the pituitary extract intramuscularly; this, although four times the dose for the human subject, produced no effect. The thirteenth day he was given 9 grs. of lactate of calcium intravenously. This did much good, so that the next day he was running about quite well and had no tremors.

After this the dog remained well, and has remained so till the time of writing, eight months after operation; he has continued his milk diet but not the lactate of calcium.

Dog 6.—The dog was fed exclusively on milk to which 30 grs. a day of lactate of calcium was added; the thyroid and parathyroids were then totally excised. The day but one after the operation the dog had severe tremors, so severe that he could hardly stand; 9 grs. of lactate of calcium were given intravenously. The next day the dog was nearly well; he was running about, and seemed quite bright. He continued well (on milk diet) for four months and eleven days from the operation; then the gait was affected and the hind limbs seemed stiff. There was no sugar in the urine. The next day the dog seemed dull, ran about only slowly, and could not jump up on his hind legs. Two days later the dog died. The post-mortem examination did not show any naked-eye changes of any of the organs.

Dog 7.—This dog was fed for many days on a purely milk diet, then subjected to total excision of the thyroid and parathyroids; the milk diet was continued, and there was added to the milk 30 grs. a day of lactate of calcium. Up to the time of writing (fifty-four days after operation) the dog has remained well.

Dog 8.—This dog has been fed for many days on a purely milk diet; then he underwent a total excision of the thyroid and parathyroids. The milk diet was continued, and there was added to the milk 30 grs. a day of lactate of calcium. At the time of writing (forty-six days after operation) dog is well, but has received three intravenous injections of lactate of calcium, 9 grs. in each.

Thus in the eight experiments on dogs here related we have four recoveries under the calcium treatment. If the similar experiments related in the previous paper are added in, we have altogether in twenty-one experiments nine recoveries, or 45 per cent. This is greatly more than the 4 per cent. recoveries said to occur in untreated animals. Some of the animals died after months, and it is not maintained that their deaths were not late results of the operations, in fact they were; all that is said is, that the administration of calcium wards off the acute and fatal tetany coming on in the first week. It will be noticed that the pituitary extract had no similar effect; for this purpose it seems useless.

Somewhat similar experiments were made on cats.

CAT No. 1 was fed on normal goat's milk, and later on normal cow's milk; it was then subjected to total excision of thyroid and parathyroids. This produced no ill effects, and the cat remained well for about six months; it then died of cirrhosis of the liver and ascites.

CAT No. 2 was fed on normal goat's milk; it was then subjected to total excision of thyroid and parathyroids. The cat remained well for ten months. There was no sugar in the urine. The death of the cat was from an independent cause.

CAT No. 3.—This cat was fed on normal goat's milk; then underwent total excision of thyroid and parathyroids, and did well for two months; then it had an attack in which it seemed stupefied and also breathed rapidly. There was no sugar in the urine. From this attack the cat recovered, and remained well till seven months after the operation; the animal then had an altered gait and walked with its legs apart. There was still no sugar in the urine. The next day the animal was worse and could hardly stand; it was therefore destroyed.

CAT No. 4 was fed on normal cow's milk, and was also given lactate of calcium in the milk. The cat remained well for about four months, when it seemed ailing and died somewhat suddenly; there were no tremors. At the autopsy the internal organs were normal to the naked eye.

It will be noticed that all these four cats escaped the tetany which is usually fatal in the first few days, and that they survived for months. Two of them died of independent causes and two of them of the late effects of the total operation, and this although they were fed on milk throughout.

In the former paper (VII.) it is stated that three cats were fed on normal goat's milk—one died shortly after the total operation and two survived—and that six cats were fed on milk from thyroidless goats; all six cats died. In the present paper we have three cats fed on normal goat's milk, all three surviving. Thus, adding the experiments in the two papers together, we had six cats fed on normal

goat's milk, and five of them surviving for weeks and one dying; whereas of the six cats fed on thyroidless goat's milk, all six died. Those cats which survived for months, escaped death from tetany due to aparathyroidea; therefore it seems probable they were saved (unless the results were a coincidence) by the parathyroid secretion in the milk of the normal goats.¹ Of the cats which survived for months, two died of the late effects of athyroidea or aparathyroidea, or both, notwithstanding they were being fed on the milk of normal cows.

In Graves's disease we appear to have an excess of thyroid secretion, and at the same time compensatory hypertrophy of the thyroid gland. This suggests an absence of one of the constituents of the thyroid secretion; which that may be we do not know. The weight of evidence is against the parathyroids being affected in the disease; but it has recently been stated that dried parathyroid tissue is of benefit in the treatment of Graves's disease.²

CONCLUSIONS.

1. That the early death from tetany which almost always follows total excision of the thyroid and parathyroids in dogs and cats can often be prevented by the administration of calcium in large doses.
2. That pituitary extract has no such effect.
3. That if the calcium be stopped the animals die.
4. That even if it be continued the animals eventually die of the effects of the operation.

¹ The removal of the thyroid does not alter the percentage of calcium in the milk of a goat. See *Lancet*, December 9, 1911, p. 1619.

² "Quinquennium of Medicine and Surgery," 1906-1910, p. 287.