CALCIUM METABOLISM AFTER THYRO-PARATHYROIDECTOMY.*

By OLAF BERGEIM, Ph.D., F. T. STEWART, M.D., and P. B. HAWK, Ph.D.

(From the Laboratory of Physiological Chemistry of Jefferson Medical College, Philadelphia.)

That the thyroid apparatus, particularly the parathyroids, either directly or indirectly exerts considerable influence over the metabolism of calcium has been clearly shown in a number of ways by several authors. Probably the most striking of these experiments are those made by Erdheim (1) on rats. He observed that after parathyroidectomy the dentine of the rapidly growing incisor teeth ceased to calcify. After successful transplantation of the glands the calcification process again commenced and a zone of uncalcified dentine marked the period during which the parathyroids were absent. Erdheim and Canal (2, 3) also found that callus formation was greatly retarded, due almost entirely to deficient deposition of calcium salts. He also cites the relative frequency of parathyroid hyperplasia in osteomalacia, as well as changes in the teeth in this disease, similar to those noted by him in the animals mentioned.

Biedl (4) found that thyroidectomy prevented the normal development of the bony skeleton in animals, and Bircher (5) showed that treatment with thyroidin in these cases led to a more rapid formation of bone and a hastened process of calcification. Towles (6) found no special peculiarities in the calcium metabolism of exophthalmic goitre. Analyses of the blood and of various tissues have been made after parathyroid removal but these show a lack of uniformity. MacCallum and Voegtlin found a decrease of calcium in the blood and brain of dogs killed in parathyroid tetany, but not after incomplete removal (7). This has been confirmed by Pexa (8) and Aschenheim (9). Analyses by Cooke (10), however, indicate an increased calcium content of the brain under these conditions. This author found little change in the calcium metabolism. Leopold and von Reuss (11), in their studies of the calcium content of the tissues of normal and parathyroidectomized rats, found little change with adults and some decrease in young animals. The soft tissues were poorer in calcium and the bones were richer in this element. Similarly Morel (12) found that parathyroid extracts favored the growth of bone in young, but not in old animals. Neurath (13) found an increase in the calcium precipitable by oxalate in the blood in animals after parathyroidectomy. Most authors claim that an increased excretion of calcium in the urine follows this operation. Among these are MacCallum and Voegtlin (14) and Frouin (15). Musser and Goodman (16), however, found a marked decrease in the urinary calcium, as did also von Reuss and Welde. Cooke likewise found no increased excretion of calcium in the urine.

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The relation of calcium metabolism and the parathyroids has been studied most extensively in connection with the tetany brought on by their removal. The finding by MacCallum and Voegtlin that injection of calcium salts caused a temporary disappearance of the symptoms has been confirmed by a number of investigators. Some doubt is expressed as to any actual prolongation of life by this treatment. Arthus and Schaffermann (17) apparently obtained somewhat more persistent results in rabbits with calcium chloride ingestion. That this power is not restricted to calcium salts has been shown by Berkeley and Beebe (18) and by Canestro (19), who obtained similar results with magnesium and strontium salts, by Frouin (20) with lanthanum and thorium salts, and by Joseph and Meltzer (21) for sodium chloride solution. Further, simple bleeding decreases the symptoms. On the other hand, it has been shown that the injection of calcium precipitants causes a more rapid oncome of tetany (22).

Numerous attempts have been made to correlate the above findings with the tetanies of man presumably of parathyroid origin. In infantile tetany von Cybulski (23) found a much less calcium retention during the period of tetany. Schwarz and Bass (24) obtained similar results. Schabad (25) in a case of rachitis with tetany found no changes from the metabolism of rachitis alone, nor were the symptoms alleviated by treatment with calcium salts. Phosphorized oil, however, caused a retention of calcium and an improvement of the tetany. Haskins and Gerstenberger (26) could not show that in man parathyroid and calcium salts favored calcium retention. The theory of Stoeltzner (27) that tetany is due to a heaping up of calcium in the organism has met with much objection. On the other hand, Cattaneo (28) found a decreased calcium content of the blood in six cases of spasmophilia, and it has been suggested that the tetanies of pregnancy may be due to the drain on calcium that occurs at this period. Parathyroid tetany also develops very quickly in lactating animals (Carlson (29)).

The therapeutic application of calcium treatment of tetany in human beings has met with some success (30, 31, 32). The relation of infantile tetany to calcium metabolism is further supported by the work of Quest (33) who found a low calcium content of the brains of children who died in tetany. This was confirmed by Silvestri (34) but not by Cohn (35) or by Leopold and von Reuss.

With regard to the inevitability of the oncome of tetanic symptoms in various animals and in man after complete removal of the thyroid apparatus there has been much dispute, although the opinion more generally held seems to be that the results are always fatal and that any other termination is to be ascribed to the incompleteness of the operation, or insufficient length of observation. Much evidence has, however, accumulated in support of the view, emphasized particularly by Vincent (36), that a considerable percentage of animals of different species may survive total extirpation for prolonged periods and may show no specific symptoms of any kind; and also that the operation produces very different results in different species, in general the carnivora being much more sensitive than herbivorous animals. Vincent concluded that in monkeys neither thyroids nor parathyroids were essential to life. Breisacher (37) found that dogs fed on a milk diet suffered less than those on a meat diet. Vassale and Generali (38) found further that the tetany induced by thyroidectomy is

less marked in old than in young animals. In hunger the tetany was much less marked also than on a meat diet.

Marine (39) apparently goes so far in the belief that the parathyroids are essential as to make the absence of symptoms after removal a test for the presence of accessory glands. Parathyroidectomy extending over a long period was less often fatal and calcium salts sometimes tided an animal over an otherwise fatal tetany. Why this should be taken as a sign of compensation by accessory tissue rather than by some other gland or set of glands does not seem clear. Paton (40) has suggested that "the variations in symptoms may be due to the fact that removal of parathyroid reduces the stability of the central nervous system but that some other disturbing factor, for example, pregnancy, is required to upset it sufficiently to cause the manifestation of the symptoms."

The observations of Gozzi (41) and others (42, 43), that thyroparathyroidectomy was less rapidly fatal than removal of parathyroids alone, do not agree with the findings of Halpenny (44), Wiener (45), and Biedl (46). Other work done along this line will be mentioned in the discussion of our results.

In connection with the calcium metabolism the findings of Greenwald (47) should be mentioned. This author found an increase in the total phosphorus of the blood and serum after parathyroidectomy, the phosphorus being mainly in an ether-insoluble, acid-soluble form. He found likewise (48) a decrease of the phosphorus of the urine after operation with an increase as tetany came on. A pronounced increase in the creatinin content of the urine was noted. Frontali later observed (49) a decreased urinary creatin output after thyroidectomy. The latter also found a decrease of creatinin in the muscles and an increase in the blood.

Considerable study has been made of the nitrogenous metabolism after parathyroidectomy, particularly with the idea in view of proving or disproving an intoxication as the basis of the symptoms.

MacCallum and Voegtlin found a great increase in the ammonia content of the blood. Similar results were obtained by Cooke, Morel (50), and Medwedew (51), but could not be confirmed by Carlson and Jacobson (52), Albertoni (53), Greenwald, Musser and Goodman, and von Reuss and Welde. Increases of the ammonia content of the urine have been found by Berkeley and Beebe, Frouin (54), Cooke, and Morel. Greenwald found only a slight increase of ammonia but a larger increase of nitrogen of unknown character. Other abnormalities noted by Cooke were increases in the excretion of magnesium, and the presence of lactic acid due probably to the muscular work of tetany.

After thyroidectomy alone there is usually a reduction of organic as well as inorganic metabolism. However, Falta, Bolaffio, and Tedesko (55) found a pronounced increase in the nitrogen: phosphoric anhydride ratio, due to increased nitrogen excretion and decreased phosphorus excretion in the urine. Thyroidin treatment brought about an increased excretion of calcium in the feces. Similarly Scholz (56) found in man that such treatment brought about an increased phosphorus excretion in the feces. Kottmann (57) found a lowering of the freezing point of the blood in Basedow's disease, due supposedly to abnormal content of metabolic products.

The present study was carried out on a patient in the Jefferson Hospital.

Clinical History.—G. H., aged 32 years, colored; laborer. Admitted to the surgical ward of the Jefferson Hospital, Oct. 19, 1913. Fourteen months before this he began to experience difficulty in breathing, which increased steadily for two months, when a low tracheotomy was performed by a surgeon in Florida, where the patient was then residing. The condition evidently was thought to be syphilis of the larynx, as the patient was subsequently given salvarsan, and later neosalvarsan, potassium iodide, and inunctions of mercury. After coming to Philadelphia the patient entered Dr. D. Braden Kyle's ward at the Jefferson Hospital. Dr. Kyle found a growth in the larynx and removed a portion of this growth for microscopic examination. Histologic study of the excised fragment revealed a typical picture of papilloma. From a clinical standpoint, however, Dr. Kyle regarded the growth as malignant, and because of its extent transferred the patient to the surgical ward. There was nothing relevant in the family history. The patient had had gonorrhea about five years before his laryngeal trouble, but had never had a chancre or other evidence of syphilis. The Wassermann reaction was negative. There had never been much pain, never any hematemesis. The tracheotomy tube was worn constantly, and when this was closed with a finger the patient was able to whisper. The man was well nourished; the temperature, pulse, and respiration were normal. The pupils reacted to light and accommodation. There was a large cauliflower-like mass filling the glottis and extending up into the epiglottis and into the esophagus. On palpation the larynx was found to be considerably expanded, measuring three inches at the widest part. It could be moved laterally, and it moved when the patient swallowed. The thyroid gland was enlarged and hardened. Examination of the thorax, abdomen, extremities, and urine showed nothing abnormal.

An operation was performed on Oct. 21, 1913, intratracheal insufflation of ether being employed to maintain anesthesia. A median incision was made from above the hyoid bone to the tracheotomy opening, and a transverse cut made at each end of this incision, thus forming lateral flaps, which were turned outward. After separating the larynx from the soft parts on each side, it was discovered that the growth had invaded the thyroid gland, the trachea, and the esophagus. The sternohyoid and sternothyroid muscles were severed near the sternum, the omohyoid beneath the sternomastoid, and the trachea in the episternal notch below the tracheotomy opening. A tube was then passed into the esophagus through the mouth, and the anterior half of the esophagus, from the sternum to the pharynx, separated by sharp dissection while the specimen was dragged upwards to facilitate the incisions in the esophagus, which incisions were continued up into the pharynx to meet in the median line above the hyoid bone. The excised mass of tissue included a portion of the pharynx, the anterior half of the esophagus as low as the sternum, the hyoid bone, the epiglottis, the larynx, the trachea as far as the sternum, the entire thyroid gland, and of necessity the parathyroid glands, although it must be stated that owing to the neoplastic infiltration neither Dr.

Coplin nor myself could identify the parathyroids in the excised tissue. After the growth had been removed, the esophagus and the pharynx were sutured over the tube with catgut, and the skin flaps brought together except at the points corresponding to the outer angles of the lower transverse incision, where gauze drains were inserted. The tracheal stump was anchored to the skin with heavy silk thread. The operation lasted one and one half hours, and was followed by little shock. The patient sat up the next day and was out of bed at the end of the first week. Liquid food was given through a tube which reached to a point just below the lowest suture in the esophagus. On the eighth day the lower part of the esophageal wound began to leak and some of the food passed into the trachea. Subsequent to this nourishment was administered through a long tube which passed through the nose, pharynx, and esophagus into the stomach. The tube was not removed between feedings, because of the difficulty of guiding it past the opening in the lower cervical esophagus. During the first postoperative week the patient coughed only occasionally, but subsequent to the entrance of food into the trachea the cough became more frequent, the expectoration being tough stringy mucus. On Nov. 4, 1913, two weeks after the operation, sharp pain due to pleuritis was felt in the right chest. The respirations increased in frequency and fever developed. Later signs of fluid in the pleural cavity became evident, but none could be obtained by aspiration. On Nov. 21, 1913, an incision was made into the pleural cavity and a large quantity of foul pus evacuated. One week after this and thirty-eight days after the laryngectomy the patient died.

Autopsy.—A septic pneumonia of the right lung and gangrene of the right pleura were revealed. The laryngeal growth proved on microscopic examination to be a squamous-celled epithelioma.

METHOD OF STUDY.

The patient was kept in a private room in the Jefferson Hospital and under charge of a private nurse throughout the period of study.

On account of the necessity of feeding the patient through a nasal tube the food given was all in liquid form. It consisted of soup, eggs, milk, orange juice, and water. No attempt was made to have the amount of each food uniform from day to day but the amounts fed were accurately measured and aliquot portions were taken at each meal for analysis. The food samples for the day were mixed in the proportions as fed, evaporated to dryness, ground to a fine powder in a mortar, and thoroughly mixed. Portions of these powders were taken for analysis. Water was analyzed separately. The urine was carefully collected in twenty-four-hour periods, and calcium determinations were made in each day's output. Feces separation was made by means of carmin and was not attended with

difficulty. Feces were kept in a friction top can in a frozen condition until the end of the period when they were thoroughly mixed and portions taken for analysis. McCrudden's (58) method for the determination of calcium was employed.

Blood samples of fifty cubic centimeters each were obtained on the first and final days of the test period. Coagulation was prevented by means of potassium oxalate. The calcium was determined gravimetrically with platinum crucibles, by a modification of McCrudden's method for pure solutions.

The results obtained are given in table I.

TABLE I.

Ten-Day Calcium Balance after Thyroparathyroidectomy.

Day.	Calcium oxide in food.	Calcium oxide in urine.		Calcium oxide in feces.	Total excretion.
		Volume.	Calcium oxide.		
1	1.0923 gm.	635 c.c.	0.0051 gm.		
2	0.7610 gm.	870 c c.	0.0074 gm.		
3	1.6355 gm.	865 c c.	0.0091 gm.		
4	1.5258 gm.	900 c.c.	0.0131 gm.		
5	0.7036 gm.	740 c.c.	0.0078 gm.		
6	1.6912 gm.	1,160 c.c.	0.0145 gm.		
7	2.3261 gm.	940 c.c.	0.0193 gm.		
8	2.2882 gm.	1,125 c.c.	0.0169 gm.		
9	1.9273 gm.	1,110 c.c.	0.0244 gm.		
10	2.7847 gm.	1,765 c.c.	0.0159 gm.		
Period	16.7357 gm.		0.1335 gm.	16.1444 gm.	16.2779 gm.
Daily average...	1.6736 gm.		0.0134 gm.	1.6144 gm.	1.6278 gm.

Balance.

10 days ..... 0.4578 gm. of calcium oxide retained.

Balance.

Daily average ..... 0.0458 gm. of calcium oxide retained.

Retention ..... 2.74 per cent. of calcium oxide.

Blood.

First sample... 0.0087 per cent. of calcium oxide.

Second sample. 0.0100 per cent. of calcium oxide.

DISCUSSION.

It will be noted that there was a retention during the ten-day period of 0.4578 of a gram of calcium oxide, or 0.0458 of a gram per day. This corresponds to a percentage retention of 2.74 per cent. of an ingestion of 1.6736 grams of calcium oxide per day. A retention as slight as this on a comparatively high intake cannot be said to show after operation a distinct tendency of the body to take up

calcium salts. In fact it is probable that a normal individual on such a diet would tend to retain more rather than less calcium oxide than was noted in this case. The figures must therefore be taken to show an approximate calcium equilibrium. They have a certain negative significance in that they certainly give no support to any assumption of a pronounced calcium loss to the body in this condition.

The relation of the excretion of calcium in the urine to that in the feces was found to be approximately 1 to 121. This proportion is lower than was found by us in osteitis deformans or by McCrudden and Fales (59) in intestinal infantilism. It is in fact one of the most striking facts brought out by this table. Taken in connection with the low figures for calcium in the blood the most plausible interpretation is that absorption of calcium by the intestine must have been very slight. That there was a demand by the body for calcium salts to fight off infection or toxemia is indicated by the fact that three times as much calcium was retained as was excreted in the urine, small as this amount was. There must have been deficient absorption which must be attributed to the thyroid and parathyroid removal. How such an effect could be produced is problematical. In the apparently somewhat related intestinal infantilism McCrudden and Fales could not find that the poor absorption was secondary to the overproduction of phosphate, fatty or volatile acids, nor could they determine the form in which about one half of the calcium of the feces was combined. Of course the diet employed in our case, consisting largely of eggs and milk, contained considerable organic phosphorus and the possibility of a faulty digestion of these substances on calcium absorption must be considered, particularly in view of Dibbelt's experiments (60). He found that the introduction of sodium bicarbonate or disodium phosphate directly into the intestine of animals caused an increased excretion of calcium in the urine. He assumed that excessive amounts of these calcium-precipitating agents might be formed by decomposition of undigested casein and from carbohydrate fermentation and believes that the etiology of rachitis must be of this nature. We are not, however, aware of any evidence proving that this actually occurs. The fact that Keeton (61) has shown in

cats that parathyroidectomy greatly diminishes gastric secretion is of interest in this connection. A lack of hydrochloric acid secretion might operate in two ways to decrease calcium absorption. First, it decreases the amount of calcium chloride or acid phosphate formed from the carbonate or phosphate of the diet. Secondly, intestinal fermentation and putrefaction processes of a nature calculated to form calcium precipitants would be increased due to the decreased antiseptic power of the gastric juice. It would be of interest to know whether an achylia exists in intestinal infantilism, rickets, and allied disorders. It is our intention to investigate this point.

It must be borne in mind, however, that we know little with regard to the mechanism of calcium absorption. If we assumed that calcium was absorbed largely as chloride or acid phosphate in the stomach or upper intestine, the problem would be simplified. We have, however, noted in a study on acromegaly (61) that urinary excretion of calcium increases when calcium-rich feces accumulate in the intestine, indicating absorption of this element from the large intestine. It appears that in the present state of our knowledge we cannot bar out a more direct parathyroid action, through the intermediary of a nuclein metabolism or on the intestines themselves.

The slight increase in urinary calcium during the period may be considered as largely due to a higher calcium ingestion, possibly also to a slight constipation. The somewhat higher blood calcium content at the close of the period may be attributed to similar causes. Possibly also there has been a greater demand on calcium for antitoxic purposes and deficient excretion of calcium phosphate.

Why in the case of complete thyroid and parathyroid removal under consideration did not tetanic symptoms develop during the period of thirty-nine days after operation? Some authors who have worked particularly upon carnivorous animals, such as the dog, would unhesitatingly answer that accessory parathyroids must have been present. From the nature of such an assertion, precluding, as it does, either proof or disproof, and assuming as it does the point in question, it follows that this argument must be given not first but last consideration, and resorted to only if other explana-

tions are not forthcoming. Unfortunately the explanation of the absence of tetany in the present case cannot be given with any certainty. Possible explanations only can be suggested.

Our patient was on a high calcium diet. Absorption was not satisfactory, but there was a retention and not a loss of this element. Certainly these facts are significant. Calcium salts delay the oncome of tetany. Most observers have, however, found this inhibiting effect of calcium salts to be temporary. It could hardly be expected to extend over a period of more than a month.

The patient was further kept quiet and thus untoward influences were avoided. The suggestion of Paton that parathyroid removal reduces the stability of the central nervous system, but that other disturbing factors may be required to upset it sufficiently to cause symptoms, has already been mentioned. The facts that carnivora are more sensitive than herbivora, that dogs fed on a milk diet suffered less than on a meat diet, and that in old animals the tetany was less marked than in young animals, have already been considered.

Bircher (62) has reported complete and permanent recoveries from tetany following partial removal of thyroids and parathyroids, by means of temporary treatment with parathyroid extracts. Schneider (63) reports a case of neck tumor of the thyroid in a woman of 46 years, in which apparently complete thyroid and parathyroid removal was followed by acute tetany which was overcome by treatment with parathyroid extracts. This case as well as ours may of course be explained on the basis of the supposed presence of supernumerary parathyroids. It would seem more plausible that this compensation was brought about by hypertrophy of some other of the ductless glands, probably the hypophysis. This view is supported by the known relation of this gland to calcium metabolism, its rapid hypertrophy in the calcium-mobilizing period of pregnancy, and after thyroid removal, as shown by Rogowitsch (64) and others (65); also after parathyroid removal as reported by Thompson (66), Pepere (67), and Halpenny (68). It may be more than an interesting coincidence that hypophysectomy (Crowe, Cushing, and Homans (69)) is much more rapidly fatal in old than in young animals, while parathyroidectomy (Vassale and Generali (70) and others) has a higher mortality in the young when apparently the compensatory mechanism is not so well developed. Ott and Scott (71) have further found that pituitary extracts temporarily inhibit parathyroid tetany. The observations of Thompson, Leighton, and Swarts (72) are of interest in this connection. They found that ligatures producing slow interference with the blood supply led to no tetanic symptoms, but that slow wasting occurred.

The fact that the parathyroids in our case were so infiltrated as

to be unrecognizable is very important as suggesting that there had probably been a gradual decrease in parathyroid activity with sufficient lapse of time for a compensatory mechanism to develop sufficient to prevent the oncome of tetany at least for a considerable period of time, but not sufficient to preserve a normal metabolism of calcium.

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CONCLUSIONS.

The metabolism of calcium was studied in a man after complete removal of the thyroid and parathyroid glands. A slight retention of calcium (0.4578 of a gram of calcium oxide in the ten-day period) was noted. The urinary calcium excretion was low, averaging 0.0134 of a gram per day on a daily ingestion averaging 1.6736 grams of calcium oxide. A slight increase was observed during the period of study in the calcium content of the blood.

No symptoms of tetany were noted in the patient, who survived operation thirty-nine days.

The low urinary and blood calcium values are taken to show deficient absorption of calcium, which may bear some relation to the decreased gastric secretion after parathyroidectomy.

Attempts are made to explain the non-occurrence of tetany as due to the high calcium intake and to the development of a compensatory mechanism in which the pituitary body may play a part.

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