The Journal of Clinical Investigation

CALCIUM AND PHOSPHORUS METABOLISM IN DISEASES OF THE THYROPARATHYROID APPARATUS. II. CALCIUM AND PHOSPHORUS BALANCE (*A*) FOLLOWING THERAPEUTIC RADIATION OF THE HYPERPLASTIC THYROID GLAND, AND (*B*) IN HYPERTHYROIDIC PATIENTS TREATED WITH IODINE

F. S. Hansman, W. A. Carr Fraser

J Clin Invest. 1938;17(5):543-554. https://doi.org/10.1172/JCI100979.

Research Article

CALCIUM AND PHOSPHORUS METABOLISM IN DISEASES OF THE THYROPARATHYROID APPARATUS. II. CALCIUM AND PHOSPHORUS BALANCE (*A*) FOLLOWING THERAPEUTIC RADIATION OF THE HYPERPLASTIC THYROID GLAND, AND (*B*) IN HYPERTHYROIDIC PATIENTS TREATED WITH IODINE

By DR. F. S. HANSMAN,[1] WITH A STATISTICAL ANALYSIS BY DR. W. A. CARR FRASER [2]

(*From the Department of Biochemistry, Royal Prince Alfred Hospital, Sydney, Australia*)

(Received for publication October 2, 1937)

In a previous publication (1) the details of a series of experiments on seven patients suffering from hyperthyroidism, two of whom had an associated hypoparathyroidism, were given. The following conclusions were drawn:

> Seven patients suffering from hyperthyroidism have been carefully studied. An analysis of their experimental data provides definite evidence in favour of an associated hyperparathyroidism being the direct cause of the excessive mobilization and excretion of calcium and phosphorus.
>
> Two patients suffering from hyperthyroidism with an associated hypoparathyroidism were studied. Both patients were in calcium and phosphorus equilibrium.
>
> Though hyperthyroidism is frequently accompanied by a negative calcium and phosphorus balance, it is not invariably so. It is possible for calcium and phosphorus equilibrium or a positive calcium and phosphorus balance to be present.
>
> Hyperthyroidism *per se* has no specific effect on calcium and phosphorus metabolism.

The present study presents further evidence that in hyperthyroidism the state of the calcium and phosphorus balance is independent of the amount of circulating thyroxin and demonstrates that several months subsequent to radiation of the hyperplastic thyroid gland the calcium and phosphorus balance becomes positive though the clinical and laboratory evidences of hyperthyroidism are still present.

This study was primarily undertaken with three objectives: (*1*) To see if the information obtained by estimating the calcium and phosphorus balance for one period of four days would be of value in the treatment of hyperthyroidism. (*2*) To try to correlate the signs and symptoms of hyperthyroidism with the state of calcium and phosphorus balance; it was thought that the degree of so-called "sympatheticotonia" present in any individual case may be proportional to the negative calcium and phosphorus balance. (*3*) To ascertain the calcium and phosphorus balance at various periods after radiation of the hyperplastic thyroid gland.

The practical value of estimating the calcium and phosphorus balance for a period of four days

The same experimental diet was employed as that used formerly (1). In this diet the same articles are used for each patient and the amounts of each article of the diet are increased or decreased proportionally; in this way a constant calorie-nitrogen-calcium-phosphorus ratio is maintained. The caloric requirements of each patient are ascertained from the basal metabolic rate and from the appetite of the patient, and a preliminary four days are used to stabilize the patient on the diet before the actual period begins. A 2500-calorie diet contained approximately 60 grams of nitrogen, approximately 0.45 gram of calcium and approximately 0.88 gram of phosphorus. A 3000-calorie diet contained six-fifths of these amounts, a 2000-calorie diet four-fifths, etc. The amounts of calcium and phosphorus actually present were estimated for each period. The nitrogen content was taken as the average of a large number of periods of the previous study. It is known that fluctuations in the calcium and phosphorus balance may be considerable in consecutive periods, but the fluctuations are not so great that a patient would have a gross negative balance in one period and be in calcium and phophorus equilibrium in another. From our results we consider that

[1] Senior Honorary in the Department of Biochemistry, Royal Prince Alfred Hospital, Sydney.

[2] Fellow Royal Statistical Society, London; Statist, Commonwealth Advisory Council on Nutrition, University of Sydney.

for clinical purposes where a large number of patients are to be studied one period may be considered adequate to give a fair idea of the state of the calcium and phosphorus balance, provided the patient is in nitrogen equilibrium.

The correlation of the state of the calcium and phosphorus balance with the signs and symptoms of the individual patient

The attempt to give quantitative values to signs such as exophthalmos, tremor, hypotonus and degree of nervous instability, by using plus and minus signs, was unsuccessful. Each patient was examined independently by three physicians of the Senior Honorary Medical Staff, but the physical signs of the patients were not constant. Factors influencing the state of the patient were: (*1*) Time of day the examination was made. In general the patients were much more composed in the morning than at the end of the day, but it was not practicable to have the examinations always at a standard time. (*2*) Unexplained variations in the patient from day to day. (*3*) Visitors. The patient's signs tended to become exaggerated following the effort of entertaining relatives and friends. (*4*) Different responses of the individual to the personality of the three examiners. The same examiner would apparently compose one patient and upset another. The sister-in-charge of the cases frequently remarked on this phenomenon. As we were unable to develop a satisfactory technique to give standardized findings, this aspect of the study will not be further considered.

Calcium and phosphorus balance (a) following therapeutic radiation of the hyperplastic thyroid gland, and (b) in hyperthyroidic patients treated with iodine

This paper gives the results of studies on the calcium and phosphorus balance of twenty-seven patients suffering from hyperthyroidism. The patients are divided into four groups:

Group 1.—Five patients examined before any treatment for hyperthyroidism.

Group 2.—Six patients examined while iodine was being administered.

Group 3.—Twelve patients examined after therapeutic radiation of the thyroid gland.

Group 4.—Four patients examined before and after therapeutic radiation of the thyroid gland.

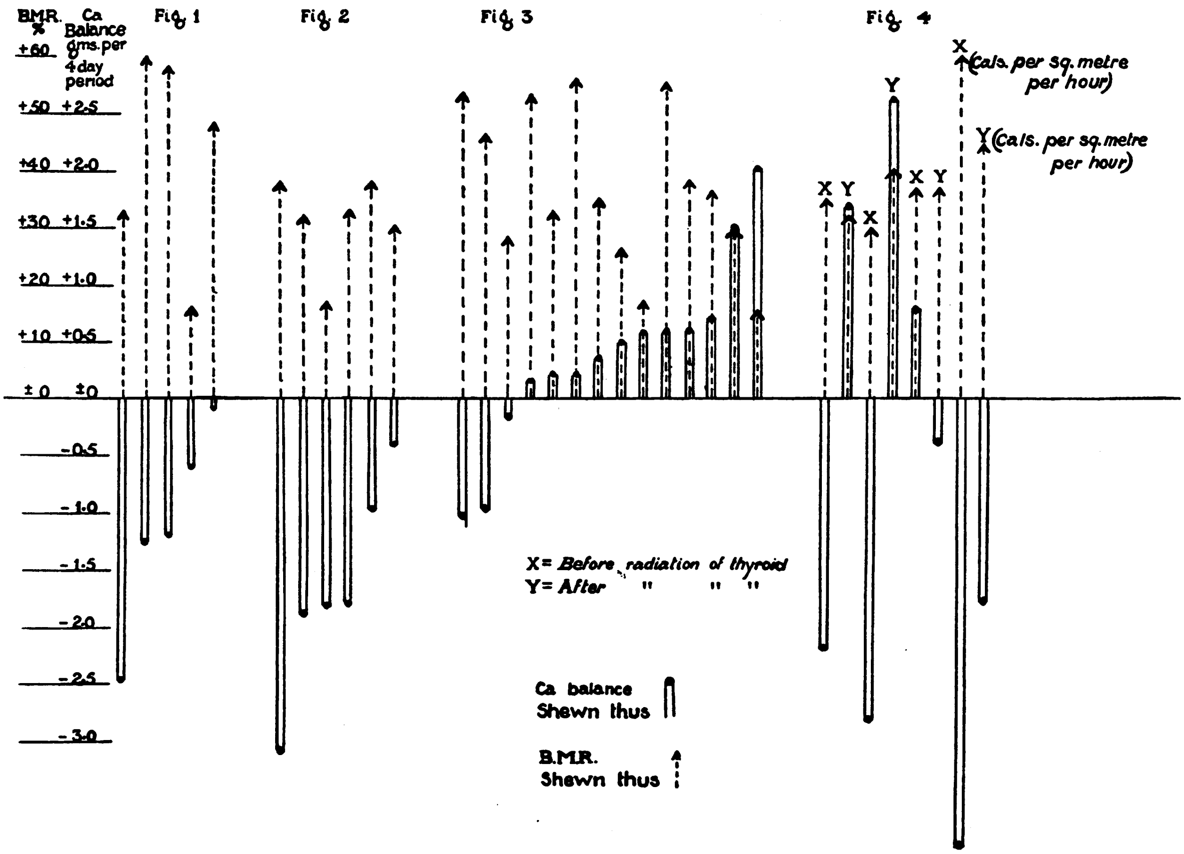
Group 1. Cases examined before treatment (5 cases)

Cases I and II were in definite negative calcium and phosphorus balance. Both were subsequently operated on, and the histology of the tumors removed showed diffuse hyperplasia. Case III was in slight negative calcium balance but in positive phosphorus balance. Case IV was approximately in calcium and phosphorus equilibrium. Case V was in definite negative calcium balance and in approximate phosphorus equilibrium. This patient had an extremely large goiter. It consisted of multiple adenomata, some of which showed definite hyperplasia. Soon after the experimental period the patient died. The postmortem findings of the thyroid are shown in the protocol. The size of the tumor can be judged from its weight (590 grams).

The basal metabolism of the patients in this group at the time of the examination ranged from + 16 to + 60 per cent, but there was no relationship between the level of the basal metabolism and the state of the calcium and phosphorus balance. This can be seen by referring to Figure 1, in which the basal metabolic rate and the calcium balance are shown.

Group 2. Patients examined while on iodine therapy (6 cases)

Of these, Cases I, II, III, and V were in definite negative calcium and phosphorus balance. Case IV was in slight negative calcium and phosphorus balance. Case VI was practically in calcium and phosphorus equilibrium. Case III showed a typical hyperplastic thyroid histologically, while the tissue removed at operation in Cases V and VI had multiple adenomata associated with hyperplasia (histologically) of the adenomatous tissue. In this group also there was no relationship between the level of the basal metabolism at the time of the experimental period and the extent of the negative calcium balance (see Figure 2).



FIGURES 1 TO 4

Figures 1, 2, 3, and 4 correspond to Groups 1, 2, 3, and 4 respectively. These figures show the state of the calcium balance and the level of the basal metabolic rate (during experimental period) on the same ordinate. The cases are charted in descending order of negative calcium balance. In Figure 4, in the last case, the results are expressed as calories per square meter per hour.

In Case IV the iodine was suspended at the beginning of the experimental period. In all the other cases it was given throughout the period.

In Groups 1 and 2 there were three cases of multiple adenomata (confirmed histologically), two of which (Case V, Group 1, and Case V, Group 2) had a definite negative calcium balance, while Case VI, Group 2, was practically in calcium equilibrium.

Group 3. Patients who had had x-ray before the experimental period (12 cases)

Of these, Cases I to IX had had deep x-ray therapy to the thyroid gland but each still had a raised metabolism, range + 15 to + 56 per cent, at the time of the experimental period. Cases I to VIII inclusive were in positive calcium balance and either in positive phosphorus balance or approximately in phosphorus equilibrium. Case IX was a private patient who was examined on two occasions; (*a*) three months after a dose of 1400 r. to the thyroid he was in slight negative calcium balance, and (*b*) five months after the application of a radium collar to the thyroid region he was in positive calcium balance. Case X was examined during her first course of x-ray therapy and was in negative calcium balance. Cases XI and XII had been treated with superficial x-ray; at the time of the experiment they both had a raised basal metabolism, + 26 and + 53 per cent respectively, both were in very slight positive calcium balance.

The cases of Group 3 were selected for experimental study because they had remained hyperthyroidic in spite of x-ray therapy. Their after-histories are shown in the protocol. Three cases were subsequently operated on. Cases VII and VIII had definite hyperplasia histologically. Case X was a doubtful lymphadenoid goiter. A study of Figure 3 will show the total lack of relationship between a raised metabolism in hyperthyroidism and mobilization of bone salt as evidenced by the state of the calcium and phosphorus balance.

Of the twelve cases only one had a negative calcium balance, and this case was having the first course of radiation at the time of the experimental period.

The result of the studies on calcium and phosphorus balance on these cases indicates that thyroxin cannot be the cause of the mobilization of bone salt in hyperthyroidism.

Group 4. Patients studied before and after radiation of the thyroid (4 cases)

Cases I and II were in definite negative calcium and phosphorus balance before and definite positive calcium and phosphorus balance after radiation. Case III was in positive calcium and phosphorus balance before but in negative calcium and phosphorus balance after two courses of deep radiation. This patient was subsequently operated on, but within six months of operation had another course of deep radiation because of a recurrence of the hyperthyroidism. On the evidence of the clinical condition and the basal metabolism, the x-ray seemed to stimulate the whole thyroparathyroid apparatus in this patient.

The fourth case was aged 14. She was in gross negative calcium and phosphorus balance before x-ray and was still in definite negative calcium and phosphorus balance after x-ray, but as only two months had elapsed since the radiation it was probably too early to get the final effect of the rays on the parathyroid glands.

Nitrogen balance in the material studied

We endeavored to have each patient in nitrogen equilibrium but were not always successful; this is the most serious objection to using a single four-day period experiment. If such a means of investigation should become a routine, larger nitrogen intakes are essential. In our material, out of thirty-four periods there was positive nitrogen balance or equilibrium (less than — 1.0 gram per day) in twenty cases and a loss of 2 grams or less a day in eight cases. The greatest loss was in the 14-year-old patient, who lost 5 grams of nitrogen a day. There can be little doubt that a definite negative nitrogen balance disturbs calcium metabolism and introduces complications into the interpretation of the results. However, in the present study if we excluded from our data all the patients who had a negative nitrogen balance greater than 2 grams a day—Group 1, Case I; Group 2, Case II; Group 3, Case IX (two periods out of five); Group 4, Cases II and IV—the general tenor of the results would in no wise be affected.

DISCUSSION

There is in general a negative calcium and phosphorus balance in untreated hyperthyroidism. The negative calcium balance, however, is not invariable, and its extent bears no relationship to the amount of circulating thyroxin as measured by the level of the basal metabolism. The administration of iodine, provided it does not bring the metabolism to normal, has no apparent influence on the state of the calcium and phosphorus balance. Therapeutic radiation (deep or superficial) to the neck determines in the majority of cases a profound change in the calcium and phosphorus metabolism; two to three months after irradiation the calcium and phosphorus balance tends to become positive irrespective of the level of the basal metabolism at the time the balances are estimated. In the series of patients presented in this paper the calcium and phosphorus balances were positive in twelve out of fifteen patients. The experiments were conducted two or more months after irradiation and at the time the basal metabolism was definitely raised in each case.

The most probable explanation of the negative calcium and phosphorus balance in untreated hyperthyroidism and the shift towards a positive balance in cases who have received radiation is that in hyperthyroidism the parathyroid glands undergo varying degrees of hyperplasia and that radiation has a more profound effect on hyperplastic parathyroid tissue than on hyperplastic thyroid tissue. Another possible explanation is that the thyroid gland secretes a second hormone and that the cells responsible for its production are more radio-sensitive than the acinar cells that produce thyroxin. It seems unnecessary to discuss the possibility of the pituitary gland being involved.

Cope and Donaldson, in a recent article in this Journal (2), discussed the calcium and phosphorus metabolism of a patient who had a recurrent hyperthyroidism (postoperative) associated with hypoparathyroidism. This patient was found to be in calcium and phosphorus equilibrium at a time when the basal metabolism, as a result of the administration of potassium iodide, was somewhat below normal, and in negative calcium and phosphorus balance when the basal metabolism rose after the potassium iodide was left off.

The authors interpret their findings as follows: "The studies of the calcium and phosphorus balance made on this patient confirm the findings of Aub and his coworkers. The marked increase in calcium and phosphorus excretion to above normal, occurring during the time of increased metabolic rate with signs of thyrotoxicosis and continued tetany, lends substantial support to the belief that the increased excretion in hyperthyroidism is not due to a concomitant overactivity of the parathyroid glands."

There is an obvious increase in the calcium and phosphorus excretion in Cope and Donaldson's patient when the basal metabolism was raised, but there are possibilities to be considered other than that this increased excretion of calcium was due to a mobilization of calcium resulting from the "specific effect of the thyroxin circulating in excess" (3). Firstly, the diet being practically the same as that given when the basal metabolism was low led to an increased negative nitrogen balance, and a consequent large mobilization of phosphorus to which Cope and Donaldson refer; the increased acidity of the organism thereby determined would affect calcium metabolism. The degree of tetany was not the same on the two occasions; during the experi-

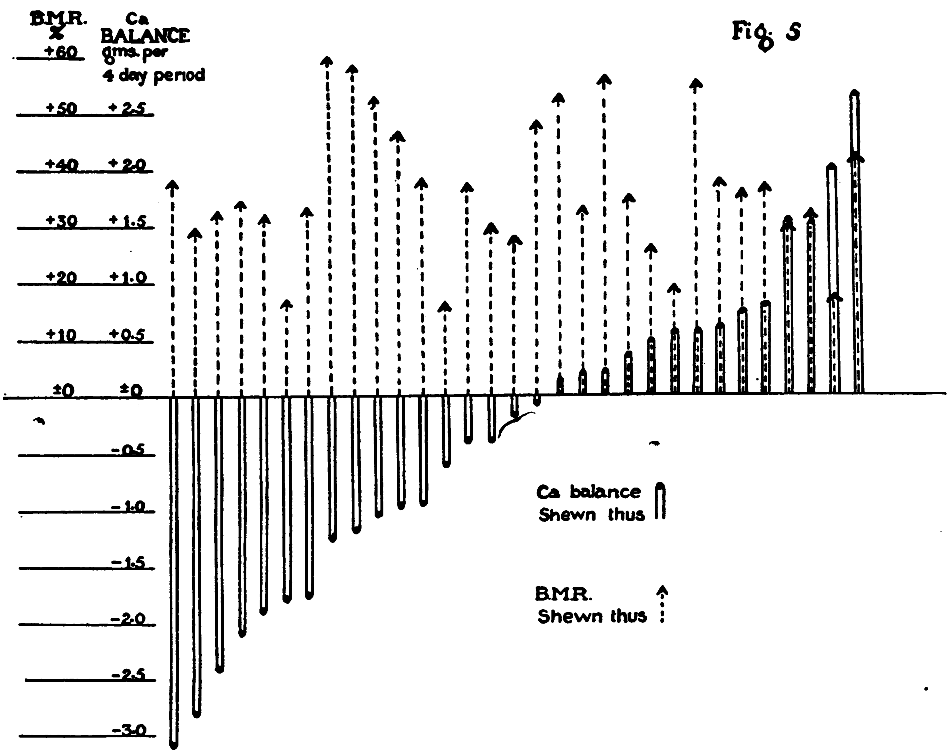


FIG. 5. STATE OF CALCIUM BALANCE AND BASAL METABOLIC RATE (DURING THE EXPERIMENTAL PERIOD) ON THE SAME ORDINATE. 31 OBSERVATIONS ON 26 CASES, GROUPS 1 TO 4 INCLUSIVE. THE CHILD, AGED 14, CASE 4, GROUP 4, EXCLUDED.

The cases are charted in descending order of calcium loss. This graph demonstrates the absence of correlation between the state of the calcium balance and the degree of hyperthyroidism as measured by the basal metabolic rate.

mental period when the basal metabolism was low there was active tetany, during the period when the basal metabolism was raised the tetany was practically absent.

The results of the experiments on this patient are equivocal; they may denote a specific effect of the increased circulation of thyroxin on bone salt, as Cope and Donaldson interpret them, or the results may be simply an expression of the summation of three other factors, undernutrition, acidosis, and increased activity of the parathyroid glands, each of which of themselves are conducive to calcium loss.

When the results obtained in the present study are considered, the same ambiguity does not arise. Here we have a range of calcium balances from — 3.1 grams of calcium per four-day period to + 2.65 grams per four-day period, with an excess of circulating thyroxin in each of the thirty-five experimental periods. The results of all the observations are charted in Figure 5. Statistically[3] there is no correlation between the level of the basal metabolism and the state of the calcium balance. The evidence is complete that thyroxin *per se* has no effect on calcium catabolism. The results do not prove that variation in parathyroid function is the true explanation of the observed phenomenon, but in the present state of our knowledge it is the most logical thesis.

Physiological requirements of diets for use in calcium and phosphorus studies on human beings

It is important to consider the physiological requirements of diets for use in calcium and phosphorus studies on human beings. In experimental work, standard conditions are essential, but in metabolic studies there must be variables; if a constant diet is used that is inadequate in various ways, the nutrition of different individuals suffers to a varying extent, and in turn the metabolism of substances under investigation may be disturbed. If the components of the diet are kept constant, but change quantitatively though proportionally to meet caloric requirements, a variable is introduced, as the subjects are not examined on the same diet.

The calcium content of the diet of the present study approximates that of "normal diets," and is greater than that employed by Bauer, Albright, and Aub (3). Its use demonstrates that in hyperthyroidism a wide range of calcium balance is possible. The state of the calcium balance is independent of the degree of hyperthyroidism or the actual calcium content of the diet, *i.e.*, the state of calcium balance is apparently not directly influenced by the calcium content of the diet. In some patients in whom the metabolism remained at a comparatively constant elevation, and the calcium content of the diet also remained constant, the calcium balance was observed to pass from gross negative to definite positive balance. When hyperthyroidism is associated with a negative calcium balance, there is an apparent inability to assimilate the calcium of the food quite apart from the mobilization of calcium from the bones, or in other words, there is calcium diarrhea.

A standardized procedure for use in various laboratories would be very valuable, as the results of experiments on calcium and phosphorus balance must vary when diets are used as divergent in principle as that of the Boston School and that of the present study.

SUMMARY AND CONCLUSIONS

1. Untreated hyperthyroidism is generally but not invariably associated with a negative calcium and phosphorus balance.

2. There is no relationship between the level of the basal metabolism and the amount of calcium and phosphorus excretion.

3. The oral administration of Lugol's iodine has no specific effect on calcium and phosphorus metabolism.

4. Irradiation of the thyroid region in hyperthyroidism leads to profound changes in calcium and phosphorus metabolism. In the majority of patients calcium and phosphorus equilibrium or a positive calcium and phosphorus balance occurs two months or more after the irradiation.

5. The change in calcium and phosphorus balance that follows irradiation of the thyroid region is independent of the activity of the thyroxin-producing mechanism.

6. The most likely explanation of the changes in calcium and phosphorus metabolism in hyperthyroidism and of the effect of irradiation is that in hyperthyroidism there is an associated hyperparathyroidism and that the hyperplastic parathyroid glands are radio-sensitive.

[3] See appendix for statistical analysis of this data.

TABLE I

Calcium and phosphorus balance of hyperthyroidic patients before treatment and on iodine therapy

Case number and patient's name	Age (*years*)	Sex	Date of experimental period	Before experimental period: Basal metabolic rate (*per cent*), Months									Experimental period: Calcium (*grams per 4-day period*)				Experimental period: Phosphorus (*grams per 4-day period*)				Nitrogen balance	After experimental period: Basal metabolic rate (*per cent*), Months										Remarks
				12	9	6	5	4	3	2	1	0	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance		0	1	2	3	4	6	12	15	24	27	
GROUP 1—BEFORE TREATMENT																																
I—Ho.	21	♀	Jan. 10–13, 1936								+62	+33	3.17	2.27	3.34	−2.44	4.23	4.47	1.92	−2.16	−12.3											Treated with iodine after experimental period, and then thyroidectomy. Histology—diffuse hyperplastic goiter.
II—Bu.	31	♀	Feb. 3–7, 1935				+39				+76	+60	3.23	0.95	3.54	−1.26	4.06	3.05	1.81	−0.80	+ 1.2									+41	+19 Iodine	Thyroidectomy June 6, 1937. Histology—patchy hyperplasia.
III—Mu.	36	♀	Dec. 5–8, 1934								+21	+16	3.93	1.25	3.28	−0.60	5.09	2.93	1.34	+0.82	+17.3					+31						Had deep x-ray, but no further B.M.R. after the one shown.
IV—Bu.	36	♀	Jan. 26–29, 1935								+75	+48	3.66	0.99	2.93	−0.05	4.74	3.21	2.07	−0.56	+ 2.9											Patient lost sight of.
V—Do.			Aug. 19–22, 1935								+58		2.93	1.55	2.57	−1.19	3.87	2.83	1.53	−0.49	+ 2.0											Death on Sept. 27, 1935. This patient had a very large goiter consisting of multiple adenomata. She had chronic bronchitis and severe myocarditis with auricular fibrillation. Autopsy: Thyroid gland weighed 590 grams, surface was very lumpy, several of the lumps felt calcified. On section the thyroid gland was made up of very numerous adenomata which were of colloid type. They contained many large alveoli full of thin, sticky colloid as well as some small alveoli. Some were fibrous and calcified in the center. One series of adenomata in the upper pole of the right lobe contained some cysts full of thin brown fluid with cholesterol crystals. The thymus was enlarged. Histology of thyroid gland: Multiple adenomata, many of colloid type; some showed hyperplasia. Tissue removed as ? parathyroid glands turned out histologically to be lymph glands.

TABLE I—*Continued*

Case number and patient's name	Age (*years*)	Sex	Date of experimental period	Before experimental period: Basal metabolic rate (*per cent*), Months									Experimental period: Calcium (*grams per 4-day period*)				Phosphorus (*grams per 4-day period*)				Nitrogen balance	After experimental period: Basal metabolic rate (*per cent*), Months										Remarks
				12	9	6	5	4	3	2	1	0	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance		0	1	2	3	4	6	12	15	24	27	
GROUP 2—ON IODINE THERAPY																																
I—McL.	28	♂	July 28–31, 1935						←		+32 Iodine	+38 →	3.48	2.78	3.91	−3.21	4.38	5.00	2.48	−3.10	− 1.5		+59	+64 Deep x-rays	+58	+67						This patient had iritis and a corneal ulcer. He became extremely ill. B.M.R. rose to +67 per cent 4 months after experimental period. Deep x-ray to thyroid and later to pituitary region was tried. Ligation of superior thyroid arteries.
II—Da.	42	♀	Dec. 14–17, 1935							←	Iodine	+32 →	2.92	0.97	3.85	−1.90	4.00	3.50	2.37	−1.87	−12.3		+63	+47								Patient died of acute thyrotoxicosis with mental symptoms. No autopsy allowed.
III—Wa.	28	♀	Dec. 31, 1935–Jan. 3, 1936						Iodine		+74 Iodine	+33	3.56	1.77	3.58	−1.79	4.55	3.66	2.18	−1.29	− 6.7	←	+8	+30 Iodine	+9 →							Operation when B.M.R. fell to +9 per cent. Histology—hyperplastic goiter, not quite diffuse—some fibrosis.
IV—Va.	22	♀	Jan. 18–21, 1935	←			Iodine				→	+38	3.54	0.90	3.48	−0.84	4.63	3.32	2.27	−0.96	− 0.2		+35	+25								Deep x-ray therapy after experimental period.
V—Co.	43	♀	Jan. 10–13, 1936								+20 ←Iodine→	+17	3.17	1.26	3.72	−1.81	4.23	3.86	2.41	−2.04	− 7.6											Operation Jan. 21, 1936. Histology—multiple adenomata with some hyperplasia.
VI—Du.	47	♀	Dec. 31, 1935–Jan. 3, 1936							+37 ←	+47 Iodine	+30 →	3.56	1.01	2.59	−0.04	4.55	3.50	1.60	−0.55	+ 0.3	+40										Auricular fibrillation. Operation Jan. 21, 1936. Histology—multiple adenomata with some hyperplasia.

TABLE II

Calcium and phosphorus balance of hyperthyroidic patients after therapeutic irradiation of the thyroid region and before and after therapeutic irradiation of the thyroid region.

Case number and patient's name	Age (years)	Sex	Date of experimental period	Before experimental period: Basal metabolic rate (per cent) Deep x-ray (dose to each lobe), Months															Experimental period: Calcium (grams per 4-day period)				Phosphorus (grams per 4-day period)				Nitrogen balance	After experimental period: Basal metabolic rate (per cent) X-ray (dose to each lobe), Months									Remarks
				36	30	24	21	18	15	12	9	6	5	4	3	2	1	0	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance		0	1	2	3	6	12	18	24	36	
GROUP 3—AFTER THERAPEUTIC IRRADIATION OF THE THYROID REGION																																					
I—Ca.	29	♀	July 7–10, 1935								+57 1400 r.	+44	+64 1400 r.	+33	+69		+29	+15	4.09	0.38	1.61	+2.10	4.67	2.31	0.98	+1.38	+18.1										Developed symptoms of hypoparathyroidism, relieved by vitamin D. Went to England 2 months after experimental period.
II—St.	20	♀	July 7–10, 1935				+65	+80 1400 r.	+68	+38 2800 r.	+57							+30	4.09	0.22	2.36	+1.51	4.67	3.21	1.56	−0.10	+ 6.0	+32				− 1		−10			Seen 2 years after experimental period. Thyroid palpable, not vascular. Patient very well. This patient had been too ill for operation before x-rays.
III—O'C.	25	♀	Nov. 24–27, 1935					+36 1200 r.	− 4		+60 1500 r.							+36	3.19	0.96	1.50	+0.73	4.21	3.49	0.94	−0.22	+ 1.6										This patient did well after 1st course of deep x-ray and then relapsed. Was referred from another hospital. B.M.R.'s done at Royal Prince Alfred Hospital.
IV—Pe.	45	♀	Nov. 24–27, 1935	+80 1200 r.	+66 1600 r.			+19	1200 r.	+33					+25			+38	3.19	0.61	1.99	+0.59	4.21	3.49	0.97	−0.25	− 5.7										
V—Wi.	47	♀	Sept. 28–Oct. 1, 1935							+46	1400 r.	1400 r.						+55	3.93	0.60	2.76	+0.57	5.14	2.70	1.41	+1.03	+12.4							1200 r.			Clinically this patient was still hyperthyroidic 20 months after experimental period. We could not get co-operation for a B.M.R. owing to mental deterioration.
VI—Fa.	29	♀	Feb. 16–19, 1935							+78		1500 r.		1400 r.			+57	+35	3.52	0.99	2.18	+0.35	4.48	3.64	1.24	−0.40					+59		+33 1600 r.	+43			Private patient, extremely "highly strung." Ultimately did very well.
VII—Sh.	26	♂	Oct. 12–15, 1935							+50 2000 r.		+43				1800 r.		+56	4.18	0.40	3.57	+0.21	5.53	4.36	1.96	−0.79	− 0.4	+33	+23								Originally this patient had been extremely ill and deep x-ray was given as a "forlorn hope." Thyroidectomy Nov. 5, 1935. Histologically, moderate to pronounced hyperplasia (patchy).

TABLE II—*Continued*

Case number and patient's name	Age (*years*)	Sex	Date of experimental period	Before experimental period: Basal metabolic rate (*per cent*) Deep x-ray (dose to each lobe), Months															Experimental period: Calcium (*grams per 4-day period*)				Phosphorus (*grams per 4-day period*)				Nitrogen balance	After experimental period: Basal metabolic rate (*per cent*) X-ray (dose to each lobe), Months									Remarks
				36	30	24	21	18	15	12	9	6	5	4	3	2	1	0	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance		0	1	2	3	6	12	18	24	36	
VIII—Be.	41	♀	Nov. 15–18, 1935	+33 ↑ opn.	+59 1000 r.	+66 1400 r.		+36 1000 r.	+36		+22			+23				+33	3.22	0.47	2.54	+0.21	4.51	2.77	1.50	+0.24	+ 4.1										Thyroidectomy Mar. 7, 1933, 2½ years before experimental period (diffuse hyperplastic goiter). Three courses of deep x-ray, first soon after operation which was not successful as it was followed by further hypertrophy of thyroid. Not seen after experimental period.
IX—McI.	41	♂	Aug. 2–13, 1935											+50	1400 r.			+46	4.37 4.34 4.21	0.84 0.67 0.69	4.50 3.80 3.68	−0.97 −0.13 −0.16	5.57 5.36 5.54	4.12 4.10 3.99	2.13 2.07 2.14	−0.68 −0.81 −0.59	− 9.1 −15.3 − 1.0	+28 ↑ Radium collar to thyroid for 9 days. B.M.R. 19 days after.		+28		+23					Was an outpatient before experimental period. Fall in B.M.R. probably influenced by rest in bed.
																			2d admission for Ca & P Balance 5 months after application of radium collar. Was having iodine during experimental period.																		
																		+17	4.81 4.93	0.53 0.62	3.71 3.58	+0.57 +0.73	6.08 6.45	4.83 3.83	1.73 1.70	−0.48 +0.92	− 8.0 − 6.9						+29				On 2d admission required 3500 calories to satisfy appetite though B.M.R. definitely lower on Jan. 19, 1937. Felt very well. Still definitely hyperthyroidic.
X—De.		♀	July 24–27, 1935															1400 r.	3.89	1.85	3.08	−1.04	4.23	3.13	1.82	−0.72	− 8.4	+53	+17	+43 ↑ opn.	+ 3						Experimental period during x-ray therapy. Thyroidectomy Sept. 4, 1935. Histology—?lymphadenoid goiter.
XI—O'H.	41	♂	Aug. 10–13, 1935										+52	5 Superficial x-rays 140 K.V. 4 min. to both lobes			+34	+26	3.86	0.44	2.93	+0.49	5.09	4.25	1.48	−0.64	− 1.7		+48 Superficial x-ray 140 K. 4 min. to both lobes	+73	+52		+27				This patient had superficial x-rays. He is still under treatment. Had no iodine at any time.
XII—Ca.	46	♀	Aug. 31–Sept. 3, 1935									+53			+53 3 Superficial x-rays 140 K.V. 4 min. to each lobe	+56	+75	+53	3.48	0.59	2.74	+0.15	4.34	2.89	1.74	−0.29	+ 0.1		+53 3 Superficial x-rays 140 K.V. 4 min. to each lobe	+70	+42	+20					Examined during x-ray therapy, after 3d treatment.

TABLE II—*Continued*

Case number and patient's name	Age (*years*)	Sex	Date of experimental period	Before experimental period: Basal metabolic rate (*per cent*) Deep x-ray (dose to each lobe), Months												Experimental period: Calcium (*grams per 4-day period*)				Phosphorus (*grams per 4-day period*)				Nitrogen balance	After experimental period: Basal metabolic rate (*per cent*) X-ray (dose to each lobe), Months										Remarks
				21	18	15	12	9	6	5	4	3	2	1	0	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance		0	1	2	3	4	5	6	9	12	15	
GROUP 4—BEFORE AND AFTER THERAPEUTIC IRRADIATION OF THE THYROID REGION																																			
I—Gr.	17	♀	Dec. 5–8, 1934											+47	+35	2.65	2.42	* 2.43	−2.20	3.80	3.19	* 1.51	−0.90	* +13.3											* A good deal of food was refused by this patient on this occasion. The nitrogen balance is not accurate, as the nitrogen in the food refused was not estimated.
			July 16–19, 1935						+35	1400 r.				1400 r.	+32	3.73	0.09	2.12	+1.52	4.22	2.67	1.23	+0.32	+ 3.6		±0									
II—Th.	18	♀	Dec. 15–18, 1934											+31	+30	3.02	2.96	2.87	−2.81	4.28	5.20	0.90	−1.82	−14.0											
			Sept. 28–Oct. 1, 1935					1400 r.		1400 r.					+42	3.93	0.25	1.03	+2.65	5.14	2.72	0.65	+1.77	+16.3											
III—Co.	19	♀	Oct. 12–15, 1935											+27 I	+37 No. I	2.89	0.14	1.96	+0.79	3.83	2.79	0.95	+0.09	± 0											This patient was on iodine for a time, but iodine was suspended before the experimental period.
			May 5–8, 1936						1400 r.			1400 r.		+59	+37	3.26	0.68	2.98	−0.40	3.88	3.83	1.38	−1.33	− 6.3	Optn.						1400 r. (post-operative)				Operation May 28, 1936—diffuse hyperplastic goiter.
IV—Ca.	14	♀	Dec. 3–6, 1935	Cals. per sq. meter per hour										60	52.2	3.19	3.11	4.03	−3.95	4.06	6.11	1.56	−3.61	−19.4											This was a very sick girl—note after-treatment.
			Feb. 22–25, 1936										1400 r.		44.4	3.34	1.36	3.78	−1.80	4.12	3.81	1.80	−1.49	− 8.3		42.6 ↑ Optn.(*a*)	39.6	↑ Optn.(*b*)							Had one course of deep x-ray therapy, then experimental period. Then ligation of superior thyroid vessels at (*a*). Thyroidectomy at (*b*) (histology—diffuse hyperplastic goiter). Comment—Ca and P balance too soon after x-rays for the full effect on the parathyroid glands to be observed.

STATISTICAL ANALYSIS

(By W. A. Carr Fraser)

Correlation between the state of the calcium balance and the basal metabolic rate of the material of the present study

The thirty-one experimental periods can be divided into two groups according to the state of the calcium balance: (*1*) 14 periods showing positive calcium balance per four-day period. (*2*) 17 periods showing negative calcium balance per four-day period. The correlation between the state of the calcium balance and the basal metabolic rate of these two groups can be investigated. Following Fisher's method (Section 34 (4)) significance can be attributed to a value of a correlation coefficient derived from a sample when a correlation coefficient as large as the one found would be obtained at most once in every twenty or more random samples of similar size from an infinite population which showed zero correlation.

Subjects in positive calcium balance per four-day period

The correlation coefficient between the state of calcium balance and the basal metabolic rate is — 0.33. A correlation coefficient as large as this would be obtained in one out of every four random samples of the 14 pairs of observations drawn from an infinite population showing zero correlation. On the evidence, therefore, there is zero correlation between the basal metabolic rate and the state of the calcium balance per four-day period for subjects in positive calcium balance.

Subjects in negative calcium balance per four-day period

The correlation coefficient between the state of calcium balance and the basal metabolic rate is + 0.18. A correlation coefficient as large as this would be obtained in approximately one out of every two random samples of 17 pairs of observations drawn from an infinite population showing zero correlation. On the evidence, therefore, there is zero correlation between the basal metabolic rate and the state of the calcium balance per four-day period for subjects in negative calcium balance.

Combination of the two groups

Having shown that each group is equivalent to a random sample drawn from an infinite population showing zero correlation between the state of the calcium balance per four-day period and the basal metabolic rate, we can estimate the weighted correlation coefficient of the two samples according to the method of Fisher (Section 35, example 33 (4)). This estimate gives — 0.05 for the correlation between the state of calcium balance and the basal metabolic rate. A correlation coefficient equal to this figure would be obtained in eight out of every ten random samples of this size by sampling an infinite population of which the correlation is zero.

CONCLUSION

This investigation shows that there is no correlation between the state of the calcium balance per four-day period and the basal metabolic rate.

BIBLIOGRAPHY

1. Hansman, F. S., and Wilson, F. H., Calcium and phosphorus metabolism in diseases of the thyroparathyroid apparatus. I. Calcium, phosphorus and total metabolism in hyperthyroidism and the part played by the parathyroid glands. M. J. Australia, 1934, 1, 37.
2. Cope, O., and Donaldson, G. A., Relation of thyroid and parathyroid glands to calcium and phosphorus metabolism. Study of a case with coexistent hypoparathyroidism and hyperthyroidism. J. Clin. Invest., 1937, 3, 329.
3. Bauer, W., Albright, F., and Aub, J. C., Studies of calcium and phosphorus metabolism. II. The calcium excretion of normal individuals on a low calcium diet, also data on a case of pregnancy. J. Clin. Invest., 1929, 7, 75.
4. Fisher, R. A., Statistical Methods for Research Workers—Oliver and Boyd, London, 1936, 6th ed., revised and enlarged.