

STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

III. THE EFFECTS OF THE THYROID HORMONE AND THYROID DISEASE¹

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INTRODUCTION AND REVIEW OF THE LITERATURE

It is known that the internal secretion of the thyroid gland raises the basal rate of combustion of carbohydrate, fat and possibly protein, and consequently appreciably increases the total heat production of the organism, but its effect on calcium and phosphorus metabolism has not been definitely determined.

Studies of the effect of thyroid secretion on the calcium metabolism have been reported in the literature, but they are inconclusive because unsatisfactory methods were employed and because the data obtained were scanty and contradictory. A short summary of these observations, however, is of interest in this discussion as a background for our experiments on the relation of the thyroid gland to calcium and phosphorus metabolism. As early as 1892, Koeppen (1) reported that there appeared to be a connection between exophthalmic goiter and osteomalacia and other bone diseases. Pierallini (2) in 1906 investigated the possibility of an intimate relation between thyroid function and the metabolism of calcium and phosphorus. In his experiments urinary calcium only was determined; the calcium intake was unknown and unrestricted because he assumed that the urinary content is an index of endogenous calcium metabolism. These assumptions are now known to be incorrect so that his results are of limited value. His figures showed the calcium and phosphorus ex-

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cretions to be normal in Basedow's disease. Another article published in the same year by Scholz (3) gave the results of careful studies of the metabolism of cretins before and after thyroid therapy. The untreated cretin was found to retain phosphorus and to excrete an abnormally large quantity of alkaline earths. Administration of thyroid preparations exerted no marked influence on the phosphorus metabolism, but reduced the urinary excretion of the alkaline earths, particularly that of calcium. The fecal calcium, however, was increased. A year later, Silvestri and Tosatti (4) reported the effect of administration of thyroid extract on the calcium exchange in various diseases. They found that daily ingestion of "one tablet" of thyroid favored retention of calcium. The calcium output was determined in one-day periods during the first six days of thyroid medication, so that their results can probably be explained by insufficient dosage of thyroid and inadequate duration of observation. In referring to work done with Bolaffio and Tedesco, Falta (5) in 1909 mentioned experiments in which administration of thyroid increased the ratio of nitrogen to phosphoric acid in the urine and increased the phosphate in the stools, and concluded that there must be an increase in the fecal excretion of calcium to account for the augmented phosphorus output in the stools. Another series of observations on the effect of thyroid feeding on calcium excretion was made by Parhon (6) in 1912. In this very interesting study the calcium exchange of nine rabbits was determined both before and after administration of thyroid. The first group of animals received 0.05 gram of thyroid daily and suffered a net loss of 0.007 gram of calcium per kilo per week; the second group of three, all of which died within seventeen days, received 0.10 gram of thyroid daily and lost 0.228 gram (average figures) of calcium per week; the last three, which died within five days after the beginning of medication, received 0.3 gram of thyroid daily and lost on the average 0.662 gram of calcium per kilogram per week. These experiments indicate that the thyroid does exert a stimulating influence on calcium excretion. Kojima (7) in 1917 approached the problem from a different angle. He removed the thyroid gland and the parathyroid from rats and then replaced the latter. He then determined the nitrogen and calcium excretions and found that both had been diminished. He could not, however, demonstrate in these experiments that adminis-

tration of thyroid affected the calcium metabolism. The report included no data concerning the adequate functioning of the parathyroid transplants and therefore the reduced calcium excretion after thyroidectomy might be explained by parathyroid deficiency.

Kummer (8) in the same year published data obtained from observation for thirteen days of a patient with exophthalmic goiter. Two and one half liters of milk were given daily, which meant that the calcium intake was approximately 5 grams per day. No determinations were made of the basal metabolic rate and control calcium figures apparently were taken from the literature. The author concluded that the mineral excretion was high but very irregular, both the calcium and phosphorus losses being especially great. Because the quantity of calcium in the urine was normal and that in the feces was large, he attributed the high fecal calcium in Basedow's disease to a difficulty in absorption rather than an abnormal excretion.

Vines (9) stated, without data, in his book on the relation of the parathyroid glands to disease, that calcium is lost from the body during diabetes mellitus and Graves' disease and retained by myxedematous individuals.

In view of the undoubted importance of the thyroid secretion on calcium metabolism and the disagreement in the findings of previous authors, it seemed desirable to reinvestigate this subject.

EXPERIMENTS

We have studied the calcium, phosphorus and nitrogen excretion in a series of patients with various thyroid diseases. The calcium excreted by an individual while on a diet adequate in all respects except in calcium should represent chiefly the endogenous calcium metabolism. Our results demonstrate conclusively that increased thyroid secretion caused a striking accentuation of the calcium excretion and likewise increased phosphorus and nitrogen elimination.

The methods used have been described in a previous communication (10). The daily diets were practically identical for each individual and except for their very low calcium content were well balanced and adequate. There was, however, a temporary negative nitrogen balance in the patients very toxic from exophthalmic goiter. The low calcium diet has a twofold value for it not only permits a more ac-

curate evaluation of the endogenous calcium metabolism, but it also largely eliminates the unknown factor of unabsorbed calcium found in the feces.

RESULTS

Serum calcium

In this series of 14 cases it was found that the serum calcium and phosphorus values remained within the accepted normal limits, though a few cases suggested a slight fall in these values during the period of observation. The serum findings gave no indication of the rate of calcium metabolism, as may be seen when the data on calcium and phosphorus excretion are examined.

Calcium excretion

1. *In exophthalmic goiter.* Our normal standards for calcium excretion have been obtained from thirteen normal individuals who were maintained upon a similar diet inadequate in calcium. These data are to be found in Paper II of this series.

The most obvious conclusions which can be drawn from our data are the marked increase of calcium excretion in exophthalmic goiter and hyperfunctioning adenomata of the thyroid, and the striking decrease found in myxedema. (See table 4 and chart 1.) This increase is out of proportion to the increase in the basal metabolic rate, for though the latter averages only 55 per cent above the normal in our six cases of exophthalmic goiter, the average calcium excretion is 170 per cent above our average control figures. These results are even more striking than they appear, for the average normal calcium excretion of 0.79 gram per three day period is based on the total excretion of men of average weight of 62 kgm., while the thyroid patients were thin individuals, some of them women, with an average weight of 50 kgm. When calculated for three day periods, the average calcium excretion for the normal individual becomes 12.7 mgm. per kilogram of body weight, and for the patients with exophthalmic goiter 42.0 mgm. per kilogram of body weight, which is an increase of 231 per cent above normal. This increase in calcium excretion is shown most strikingly in the case of Norman G. (chart 4), where 4.6 grams of calcium were

excreted in 3 days instead of 0.79 grams, the average found in the normal persons. Expressed in milligrams per kilogram of body weight, he excreted 96.4 mgm., which is 8 times the average excreted by our normal individuals on the same intake. This was out of all proportion to the change in his metabolic rate which was approximately

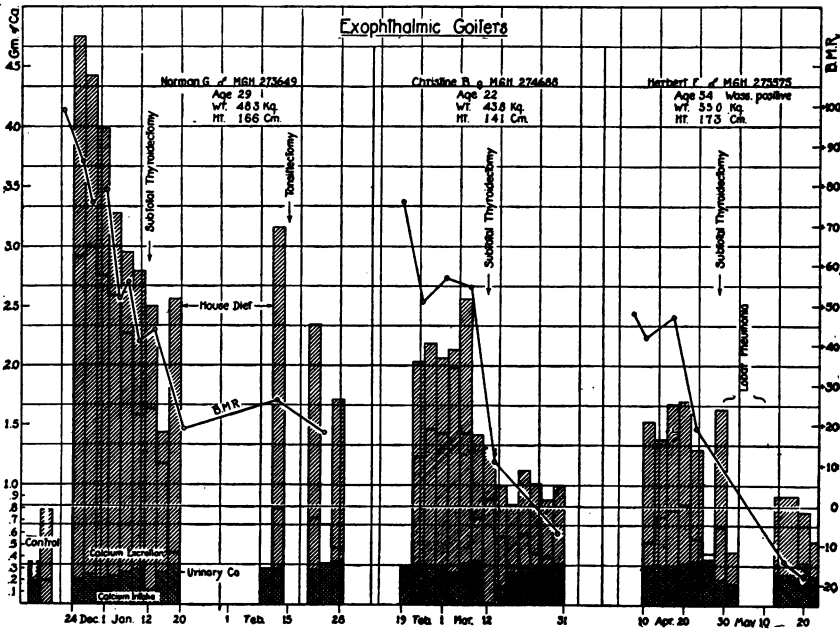


CHART 1. A GRAPHIC REPRESENTATION OF THE CALCIUM METABOLISM DATA GIVEN IN TABLE 4, IN THE CASES OF NORMAN G., CHRISTINE B., AND HERBERT F.

The double cross hatching represents the calcium intake, the single cross hatching up to the heavy dark line represents the urinary calcium excretion, the single cross hatching above the heavy black line represents the fecal calcium excretion.

twice normal. As his basal metabolic rate returned towards normal, the calcium excretion also approached normal. This was found to be true in all our other cases also. The calcium excretion in the *urine* alone was far higher than the *total* excretion found in our control cases. The increased calcium excretion in both urine and feces in thyrotoxic patients was about proportional. Because of the inade-

quate calcium intake on our routine diet, this increased calcium excretion must represent largely calcium loss from the body.

2. *In toxic adenomata.* Added evidence of the effect of thyroid on calcium metabolism was furnished by two typical cases with hyperfunctioning thyroid adenomata in which the basal metabolic rates were not as high as in those suffering from exophthalmic goiter. The

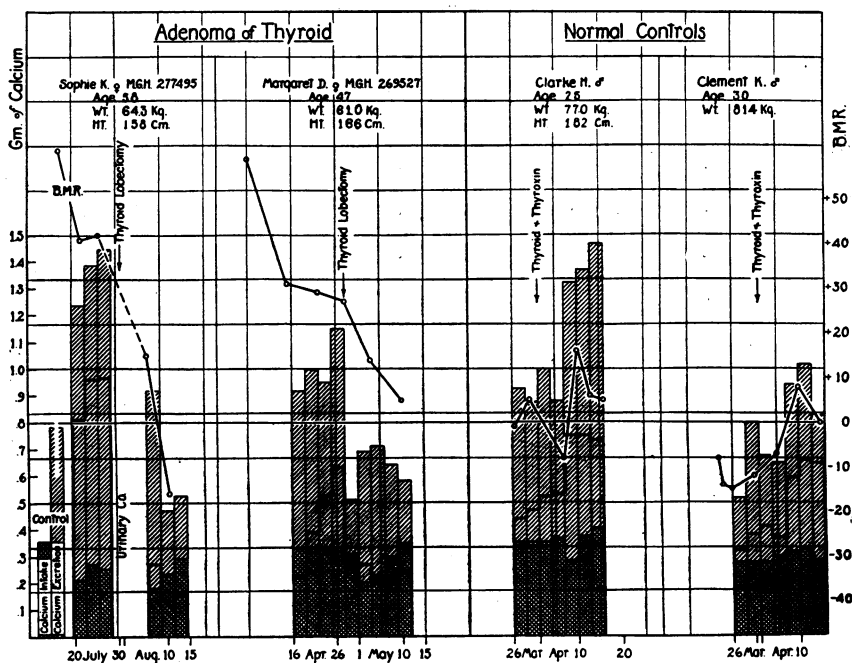


CHART 2. A GRAPHIC REPRESENTATION OF THE CALCIUM METABOLISM DATA SHOWN IN TABLES 5 AND 7

The calcium intake, urinary calcium excretion and fecal calcium excretion are represented in the same manner as shown in chart 1.

calcium, phosphorus and nitrogen excretions were likewise less elevated than in the series of patients with Graves' disease. (See table 5.) With this small number, however, it is impossible to say that there is any fundamental difference in the calcium excretion in the two diseases. The calcium excretion in these two cases was above normal and fell definitely after the adenomata were removed (chart 2).

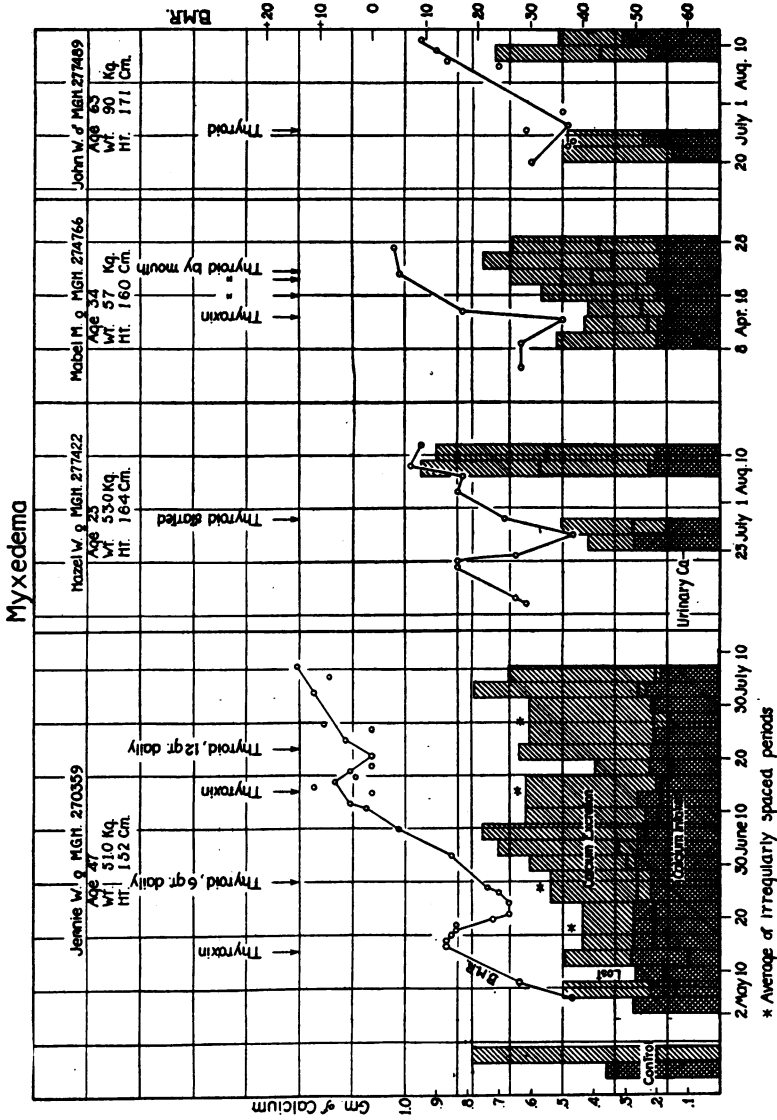


CHART 3. A GRAPHIC REPRESENTATION OF THE CALCIUM METABOLISM DATA GIVEN IN TABLE 6, IN THE CASES OF JENNIE W., HAZEL W., MABEL M., AND JOHN W.

Here again the calcium intake, urinary calcium excretion and the fecal calcium excretion are represented as in chart 1.

3. *During thyroid medication.* The foregoing observations were corroborated by the feeding of thyroid extract to two normal individuals.

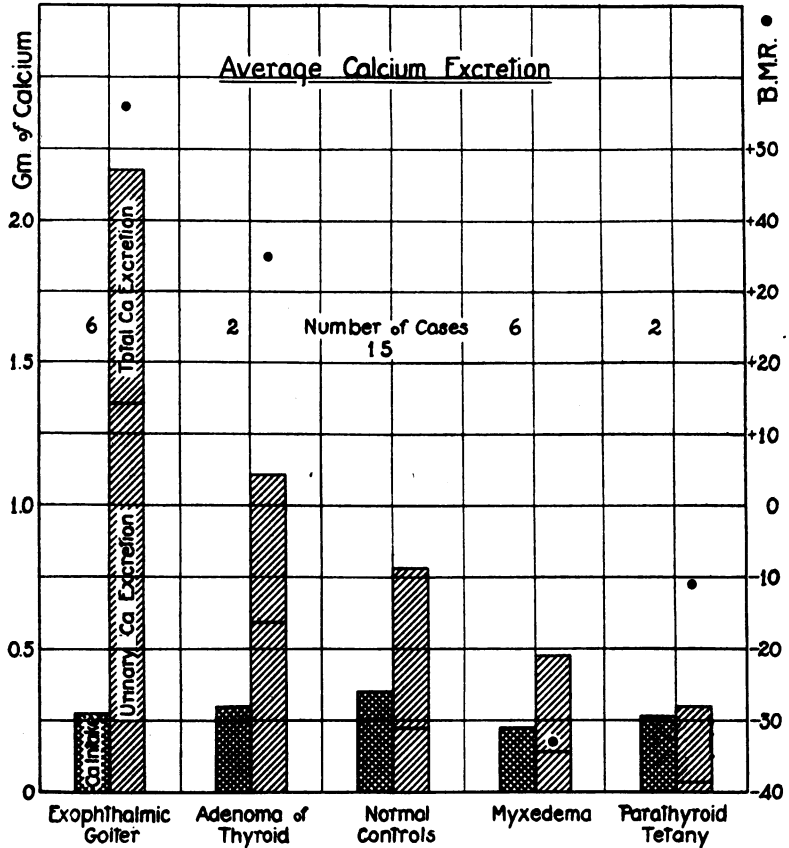


CHART 4. A COMPOSITE CHART SHOWING THE AVERAGE CALCIUM METABOLISM IN 6 CASES OF EXOPHTHALMIC GOITER, 2 CASES OF ADENOMATA OF THE THYROID, 15 NORMAL INDIVIDUALS, 6 CASES OF MYXEDEMA AND 2 PATIENTS SUFFERING FROM PARATHYROID TETANY

The calcium intake is represented by double cross hatching, the urinary calcium excretion by the single cross hatching below the heavy line, and the fecal calcium excretion by the single cross hatching above the heavy black line.

Their calcium excretion was first determined for two control periods on a low calcium diet and then thyroxin and thyroid extract were given in doses sufficient to raise their basal metabolism and produce

some of the symptoms of thyrotoxicosis. (One of them (Clark H.) complained of fever, malaise, rapid pulse and nervousness for two days.) The administration of thyroid raised definitely their calcium excretion (chart 2 and table 7), although prolonged observations on patients with tetany indicate that these two control experiments were not continued sufficiently long to observe the maximum effect of thyroid on calcium metabolism. This observation does not agree with the findings of Boothby and his co-workers (11) who found no increase in calcium excretion after a single dose of 7 mgm. of thyroxin, but this

TABLE 1
Patients with thyroid disease

	Age	Height	Weight	Basal metabolic rate	Caloric intake	Metabolic balances			Total nitrogen output
						Calcium	Phosphorus	Nitrogen	
		cm.	kgm.	per cent	grams	grams	grams	grams	grams
Hazel W., myxedema, ♀	23	164	52.8	-32	2,400	-0.27	-0.01	+1.4	12.2
Eliz. B., exophthalmic goiter, ♀ *	27	163	49.5	+70	4,330	-1.39	-1.60	-19.3	42.8
Eliz. B., exophthalmic goiter, ♀ †				+40	7,850	-1.36	-1.01	-1.4	24.3
Chris. B., exophthalmic goiter, ♀ *	22	140.5	42.9	+54	7,530	-1.81	-0.37	-1.2	33.5

* Periods II and III during which no medication was given.
 † Periods V and VI in which Lugol's solution was being taken.

discrepancy is probably due to the smaller thyroid dosage given in Boothby's case.

4. *In myxedema.* If the thyroid secretion increases calcium excretion, then myxedema may be expected to be associated with a diminished calcium output. This was clearly established in our six cases, for their average excretion was 40 per cent below the normal average. With an average weight of 66.3 kgm. they excreted 7.2 mgm. per kilogram of body weight—as compared to 12.7 mgm. in our normal controls. Without any change in their dietary intake, feeding thyroid to these patients resulted in an increase both in metabolism and in calcium excretion. (See table 6 and chart 3.) This demonstrates

TABLE 2
Metabolic studies in cases with a high metabolism due to fever and leukemia

Period number	Phosphorus			Calcium			Nitrogen			Total caloric intake	Blood serum			Basal metabolic rate	Average temperature (rectal)	Diagnosis
	Output			Output			Output				Date	Calcium mgm. per 100 cc.	Phosphorus mgm. per 100 cc.			
	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total							
Christian L.	I	1.307	1.070	2.377	1.759	0.348	0.492	0.840	0.323	36.32	2.7	39.02	26.5	5.353	103	Lymphoblastoma Tertiary syphilis
	II	1.392	1.099	2.491	2.146	0.386	0.420	0.806	0.350	30.23	4.0	34.23	28.9	5.910		
	III	1.289	1.013	2.302	2.342	0.343	0.649	0.992	0.382	58.49	4.2	62.69	31.8	7.302		
	Average		
Myron G. B.	I	2.795	1.100	3.895	2.460	1.105	0.893	1.998	0.356	34.52	3.53	38.05	35.3	6.633	98	Myelogenous leukemia
	II	2.448	1.143	3.591	2.478	1.053	0.673	1.726	0.366	67.00	3.55	70.55	35.5	6.693		
	Average		
Charles A.	I	1.196	0.635	1.831	1.301	0.239	0.510	0.749	0.223	29.96	2.33	32.29	23.3	5.356	102	Subacute bacterial endocarditis
	II	0.675	0.513	1.188	1.134	0.317	0.368	0.685	0.239	26.8	2.43	29.23	24.3	4.864		
	Average		
Jennie R.	I	1.520	0.430	1.950	1.240	0.305	0.248	0.553	0.161	23.85	2.16	26.01	21.6	2.831	99	Myelogenous leukemia
	II	1.478	0.714	2.192	2.077	0.271	0.498	0.769	0.228	27.20	2.96	30.16	29.6	4.663		
	III	1.368	0.634	2.002	2.160	0.242	0.421	0.663	0.244	26.84	3.20	30.04	32.0	5.647		
	Average		

again that thyroid increases the endogenous calcium metabolism, for the extra elimination must come from the tissues, and presumably mostly from the bones. Similarly, two cases of parathyroid tetany with very low calcium levels in both their blood and excreta responded to thyroid therapy by a distinct elevation not only of their calcium excretion but also of their serum calcium level. This effect was prolonged and greatly benefited their general condition (12).

It is thus definitely established that increased thyroid secretion augments the excretion of calcium. This effect of thyroid secretion on calcium excretion is greater than its effect upon total metabolism. Thus the percentage variations from the normal controls, as shown in chart 4, indicate this marked difference, although the limits of variation of calcium metabolism are not as definitely established as those for the basal metabolic rate. The differences, however, exceed greatly the limits of variation in our normal series.

The marked effect of thyroid activity in three women can well be compared (Elizabeth B. and Christine B., who had Graves' disease, and Hazel W. who had myxedema). They were all young, and Elizabeth B. and Hazel W. were remarkably similar in age, height and weight. The thyroid effects are obvious from table 1.

5. *In other states of increased basal metabolism.* Is the high calcium excretion of hyperthyroidism dependent on the increased thyroid secretion, or is it merely an accompaniment of an increased metabolism? This question could only be answered by determining the calcium excretion in cases with a high metabolism due to factors other than the thyroid, such as prolonged fever and leukemia. Three such cases—two suffering from subacute bacterial endocarditis, and one from lymphatic leukemia—showed a normal calcium excretion on our routine diet. A fourth case (M. G. B.), suffering from myelogenous leukemia, showed an elevated calcium excretion approaching that found in hyperthyroidism. Three of the four cases, therefore, demonstrated normal calcium excretion in spite of an elevation of general metabolism. The basal metabolic rates in these four cases varied from plus 21 to plus 41 per cent. We may conclude therefore that an increased calcium excretion is not necessarily a function of an elevated metabolic rate alone.

X-rays of bones in exophthalmic goiter

It is not to be expected that all cases of hyperthyroidism would show osteoporosis of the bones because of this increased calcium elimina-

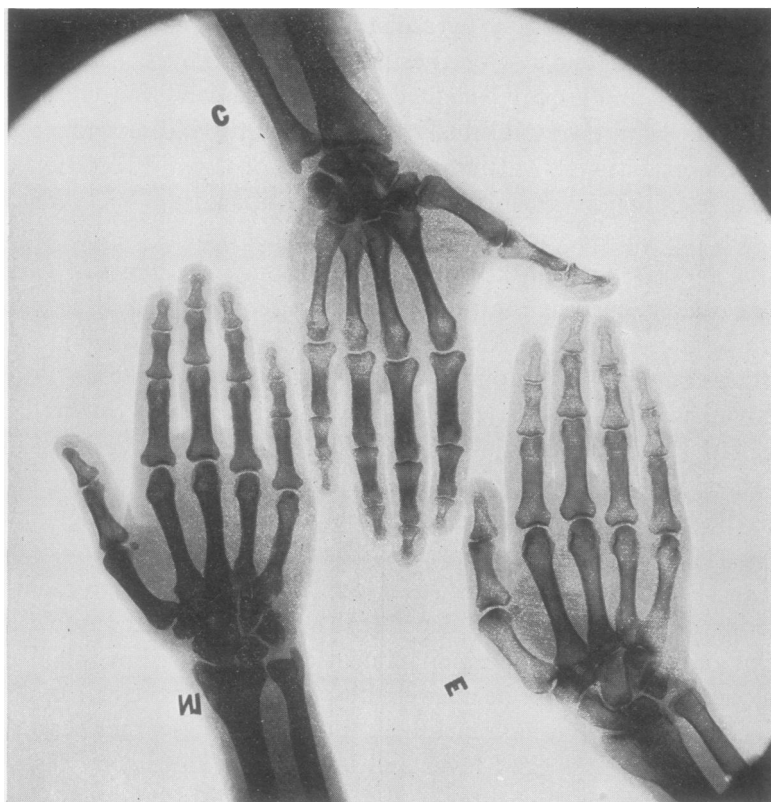


FIG. 1. SINGLE X-RAY OF THE HANDS OF THREE WOMEN OF SIMILAR AGE, SIZE AND WEIGHT

C is a normal control; *E* is the hand of a patient who is known to have had exophthalmic goiter for seventeen years; *M* is the hand of a case of severe myxedema.

tion, which could probably be compensated for by a diet containing an adequate amount of calcium. In some cases of long duration, however, this increased calcium loss from the bones may be apparent in x-ray pictures. This is obvious in the x-ray pictured in figure 1, where

the hands of a patient with exophthalmic goiter of 17 years' duration, a case of myxedema, and a normal control are all shown in the same exposure. These individuals (all women) were approximately the same as regards age, weight and the shape of the hands. The marked

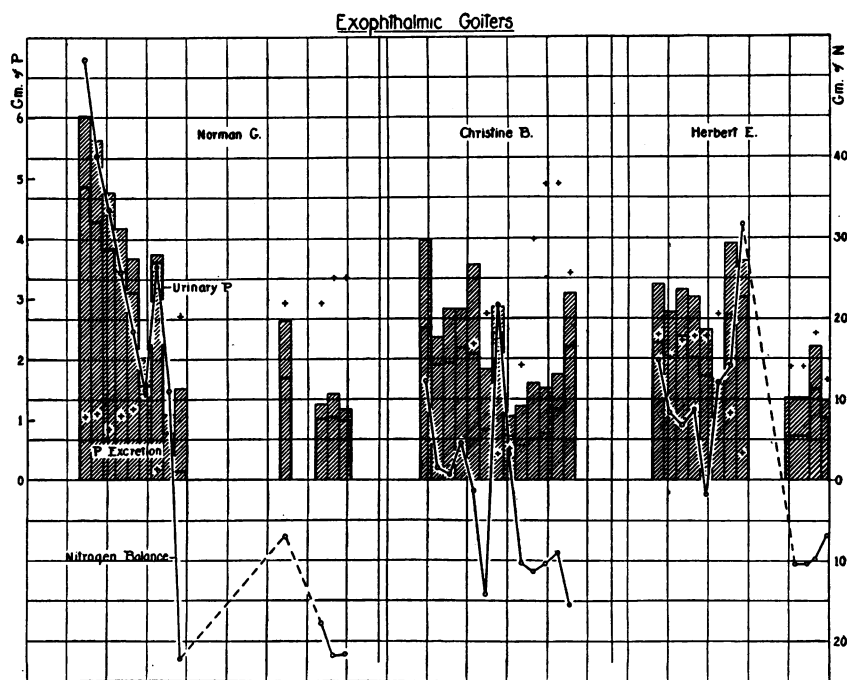


CHART 5. A GRAPHIC REPRESENTATION OF THE PHOSPHORUS METABOLISM DATA GIVEN IN TABLE 4 IN 3 CASES OF EXOPHTHALMIC GOITER

The phosphorus intake is represented by a cross, the heavy black line divides the fecal and urinary phosphorus excretions, the part of the column below being the urinary phosphorus excretion, and the part above being the fecal phosphorus excretion. The nitrogen balance is represented by \circ ----- \circ ; that above the zero line represents a negative nitrogen balance, and that below, a positive nitrogen balance.

loss of calcium in this case of hyperthyroidism is very striking. We have seen one similar case, although less marked. This observation of osteoporosis in thyroid disease has recently been confirmed by Plummer (13).

Phosphorus metabolism

Phosphorus metabolism determinations were made in connection with those of calcium in all of these experiments. This gave us an opportunity to find out whether the calcium loss from the body as a result of thyrotoxicosis represents calcium phosphate withdrawn from the bones. If that were the case there should be a ratio such that the calcium loss to the phosphorus loss would equal that of calcium to phosphorus in tertiary calcium phosphate ($\text{Ca/P} = 1.93$). In addition a correction should be introduced for the phosphorus liberated

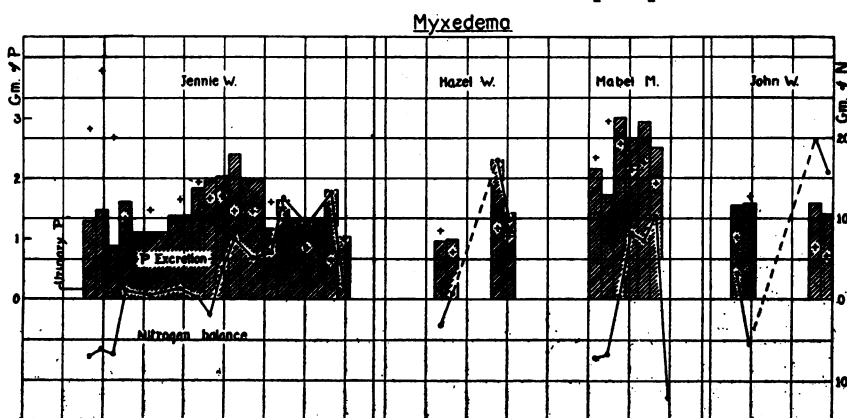


CHART 6. A GRAPHIC REPRESENTATION OF THE PHOSPHORUS METABOLISM DATA GIVEN IN TABLE 6 ON FOUR CASES OF MYXEDEMA

The phosphorus intake, urinary phosphorus excretion and fecal phosphorus excretion are represented as in chart 5.

in protein metabolism ($\text{N/P} = 17.4$). In table 3 there is included the actual phosphorus balance and the theoretical phosphorus balance calculated from the calcium and nitrogen balances as above described. In general the actual and theoretical balances agree as closely as could be expected. This supports the supposition that the increased calcium excretion represents, for the most part at any rate, calcium phosphate withdrawn from the bones. That some of this calcium may represent calcium carbonate withdrawn from the bones as suggested by Goto (14) is of course possible.

TABLE 3
Phosphorus excretion

Period number	Phosphorus excretion		Phosphorus calculated from		Basal metabolic rate	Weight	Remarks	
	Actual	Calculated	Endogenous calcium	Endogenous nitrogen				
Exophthalmic goiter								
Norman, G. Age 29 (see Table 4)	II	-4.99	-5.37	-2.37	-3.00	+86	56.3	Lugol's solution started
	III	-4.52	-4.39	-2.08	-2.31	+76		
	IV	-3.92	-3.81	-1.88	-1.93	+79		
	V	-3.10	-3.01	-1.52	-1.49	+52	48.3	
	VI	-2.50	-2.40	-1.34	-1.06	+56	48.3	
	VII	-0.60	-1.88	-1.24	-0.64	+41	48.2	Subtotal thyroidectomy
	VIII	-3.55	-2.72	-1.19	-1.53			
	IX	-0.06	-1.21	-0.58	-0.63	+44		Lugol's solution discontinued
	X	+1.21	+0.19	-1.11	+1.30	+19	46.0	House diet for 3 weeks
	XI							
	XII	+0.285	-1.03	-1.43	+0.40	+26	48.0	Tonsillectomy. House diet, for 1 week
	XIII	+1.667	-0.35	-1.02	+0.67			
	XIV	+1.925			+1.27	+18		
	XV	+2.180	+0.57	-0.68	+1.25		48.3	
	Elizabeth, B. Age 27 (see Table 4)	II	-0.61	-1.20	-0.73	-0.47	+70	49.0
III		-2.59	-2.40	-0.65	-1.75			
IV		-1.15	-1.28	-0.40	-0.88	+40	46.7	
V		-1.13	-0.59	-0.59	0	+43	45.5	
VI		-0.95	-0.94	-0.77	-0.17			
VII		-0.71	-0.88	-0.57	-0.31	+16	46.5	
VIII		-0.06	+0.07	-0.33	+0.40			Subtotal thyroidectomy
IX		+0.16	+0.30	-0.30	+0.60			
X		-1.16	-0.71	-0.29	-0.42			
XI		+0.01	-0.36	-0.30	-0.06			
XII		+1.06	+0.22	-0.32	+0.54	+7	43.9	
XIII		+1.32	+0.67	-0.12	+0.79			
XIV		+0.69	+0.15	-0.43	+0.58			
XV		+0.45	+0.39	-0.42	+0.81	+8	53.4	

TABLE 3—Continued

	Period number	Phosphorus excretion		Phosphorus calculated from		Basal metabolic rate	Weight	Remarks
		Actual	Calculated	Endogenous calcium	Endogenous nitrogen			
Normal controls								
		<i>grams</i>	<i>grams</i>	<i>grams</i>	<i>grams</i>	<i>per cent</i>	<i>kgm.</i>	
Clark H. Age 25 (see Table 7)	I	-1.69	-1.08	-0.30	-0.78	0		
	II	-0.04	-0.36	-0.27	-0.09			
	III	-1.13	-0.80	-0.34	-0.46	-6		Thyroid started
	IV	-1.83	-0.89	-0.27	-0.62			
	V	-1.08	-2.00	-0.54	-1.46	+16		Thyroid stopped
	VI	-0.85	-1.19	-0.51	-0.68			
	VII	-4.03	-1.46	-0.55	-0.91	+48		
Clement I. K. Age 27 (see Table 7)	I	-0.11	-0.43	-0.12	-0.31	-15		
	II	-0.57	-0.60	-0.27	-0.33	-12		
	III	-0.85	-0.62	-0.22	-0.40	-7		Thyroid started
	IV	-1.13	-0.66	-0.18	-0.48			
	V	-0.80	-0.81	-0.33	-0.48	+8		Thyroid stopped
	VI	-1.34	-1.88	-0.36	-1.52			
	VII	-0.68	-0.94	-0.29	-0.65	+2		
Myxedema								
Hazel B. W. Age 23 (see Table 6)	I	+0.18	+0.09	-0.10	+0.19	-38	52.3	
	II	+0.19	-0.20	-0.17	-0.03	-25		Thyroid, grs. VI daily
	III	-0.75	-0.52	-0.30	-0.22	-16	50.6	
	IV	-1.12	-1.36	-0.36	-1.00	-7		
	V	-0.40	-0.93	-0.35	-0.58	-9	50.7	

DISCUSSION

Thyroid secretion has been shown to increase markedly calcium excretion. The cause of this is as yet undetermined. There are several possibilities:

1. *A stimulating effect on the parathyroid glands directly or through their sympathetic innervation.* The absence of any marked rise in the serum calcium is very much against this, although Hunter and Aub (15) reported a case in which the administration of Collip's parathyroid extract increased the calcium excretion without appreciably rais-

ing the serum calcium level. Work now in progress will probably determine this possible relationship.

2. *A method of neutralizing the acid products of an increased metabolism.* The neutralization of the phosphorus set free as a result of the increased protein metabolism might account for the increased calcium excretion. Such an explanation would be analogous to the increased calcium output following the injection of phosphates found by Greenwald (16). However, unpublished observations (14) from this laboratory, on normal people following the administration of large amounts of acid phosphate, showed that a large part of this neutralization was accomplished by ammonia. The increased calcium excretion in these cases was not as marked as was observed in our cases of exophthalmic goiter. The other acid products resulting from an increased protein metabolism might call upon the calcium deposits in a similar manner. Studies on the total acid-base metabolism in hyperthyroidism and myxedema are now being made and should help decide this point.

3. *The remaining explanation, namely a direct stimulating catabolic effect on the calcium deposits in the bones,* seems the most likely one, and this would be in agreement with the general action of thyroid on other body tissues. It remains, however, for future work to establish this.

CONCLUSIONS

1. The calcium excretion in patients with exophthalmic goiter and in those with hyperfunctioning thyroid adenomata is increased markedly above the normal. This increase (231 per cent) is far greater than the increase in basal metabolic rate (55 per cent).

2. The ingestion of thyroid by normal individuals likewise increases the calcium elimination.

3. The calcium excretion in myxedema is markedly diminished below that found in normal individuals.

4. A marked increase in phosphorus excretion was also found. This increase was quantitatively such as to suggest that most of the calcium excreted came from tertiary calcium phosphate in the bones.

5. This high rate of calcium elimination is not obvious in the blood,

TABLE 4

Exophthalmic goiter

Dates of period	Period number	Phosphorus			Calcium			Nitrogen			Total caloric intake	Blood serum		Basal metabolic rate		Weight		Treatment and remarks			
		Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total		Intake	Output	Intake	Output	Intake	Output		Intake	Output	
IV/10	I	2.28	0.96	3.24	2.40	0.53	0.99	1.52	0.32	33.9	7.4	41.3	26.5	8.215	IV/10	111.5	2.8	IV/7 +48	IV/10 +42	IV/10	56.2
IV/13	II	2.06	0.74	2.80	2.02	0.73	0.66	1.39	0.32	29.8	8.5	38.3	29.9	8,516	IV/10	111.5	2.8	IV/10 +42	IV/10 +42	IV/10	56.2
IV/16	III	2.36	0.79	3.15	2.32	0.79	0.91	1.70	0.33	38.8	3.6	42.4	35.5	8,222	IV/17	9.6	2.8	IV/17 +47	IV/17 +47	IV/17	55.0
IV/18	IV	2.02	0.99	3.01	2.37	0.83	0.87	1.70	0.35	35.3	7.1	42.4	33.7	8,652	IV/22	9.6	2.8	IV/23 +19	IV/23 +19	IV/22	54.8
IV/22	V	1.73	0.76	2.49	2.38	0.56	0.74	1.30	0.36	26.1	5.2	31.3	33.1	9,132	IV/22	9.6	2.8	IV/23 +19	IV/23 +19	IV/22	54.8
IV/26	VI	1.66	0.75	2.75	2.04	0.43	0.38	19.5	3.5	23.0	35.3	9,632	IV/22	9.6	2.8	IV/23 +19	IV/23 +19	IV/22	54.8		
IV/28	VII	2.74	1.18	3.92	1.11	0.65	0.99	1.64	0.21	26.8	10.1	36.9	12.6	3,471	IV/30	10.5	3.4	IV/29, lobar pneumonia until V/9	IV/28	55.4	
V/1	VIII	3.03	0.61	3.64	0.47	0.09	0.35	0.44	0.17	33.6	3.3	36.9	5.3	2,398	IV/30	10.5	3.4	IV/29, lobar pneumonia until V/9	IV/28	55.4	
V/11	IX	0.75	0.62	1.37	1.89	0.21	0.70	0.91	0.30	12.3	3.9	16.2	22.5	5,731	V/14	8.9	2.5	V/15 +14	V/15 +14	V/17	52.0
V/16*	X	1.51	0.70	2.21	2.43	0.26	0.52	0.78	0.36	18.5	4.7	23.2	33.1	8,929	V/14	8.9	2.5	V/15 +14	V/15 +14	V/17	52.0
V/18*	XI	1.04	0.29	1.33	1.66	0.14	0.39	0.53	0.24	12.4	3.5	15.9	22.7	6,220	V/21	9.7	3.3	V/20 +18	V/20 +18	V/21	53.6
V/21	XII	1.04	0.29	1.33	1.66	0.14	0.39	0.53	0.24	12.4	3.5	15.9	22.7	6,220	VI/12	9.7	3.3	VI/12 +5	VI/12 +5	V/21	53.6
V/23																					

Herbert E. Age 34

Norman G. Age 29

XII/24	II	4.87	1.16	6.03	1.04	2.92	1.82	4.74	0.21	56.6	4.9	61.5	9.3	3.096	XII/23	9.9	4.1	XII/19	+99	XII/19	56.9	XII/18, complete rest in bed, low calcium diet
XII/27	III	4.29	1.33	5.62	1.10	3.00	1.41	4.41	0.25	44.3	5.49	8.9	7.7	5.260	XII/28	9.7	4.0	XII/24	+86	XII/24	56.3	XII/27, began Lugol's M x t.i.d.
XII/31	IV	3.84	0.93	4.77	0.85	2.75	1.23	3.98	0.22	36.5	6.2	42.7	9.1	4.114			XII/30	+79				XII/28, Lugol's M xx t.i.d.
I/2	V	3.49	0.69	4.18	1.08	2.58	0.70	3.28	0.24	35.0	4.2	39.2	13.2	4.240			I/2	+52	I/3	48.3		
I/5	VI	3.12	0.58	3.70	1.19	2.27	0.68	2.95	0.27	30.3	3.2	33.5	15.0	4.607			I/4	+56	I/4	47.8	I/4, Lugol's M x t.i.d.	
I/8	VII	1.59	0.44	2.03	1.43	1.58	1.20	2.78	0.29	20.5	7.3	27.8	16.6	5.365			I/7	+41	I/8	48.2		
I/13	VIII	3.62	0.13	3.75	0.19	1.64	0.86	2.50	0.12	30.1	0.4	30.5	3.8	1.783			I/13	+44			I/10, subtotal thyroidectomy	
I/14	IX	0.79	0.29	1.08	1.02	1.18	0.25	1.43	0.27	22.2	1.1	23.3	12.3	4.254			I/13				I/13, Lugol's stopped	
I/17	X	0.16	1.35	1.51	2.73	0.44	1.13	1.57	0.33	8.8	5.4	14.2	36.8	8.877			I/18	+19			I/17 to II/7, house diet	
I/20	XI																I/17		I/17	46.0	I/27, tonsillitis, temperature, 104.5°	
II/13	XII	1.68	0.95	2.63	2.92	0.80	2.36	3.16	0.30	23.1	8.7	31.8	38.8	8.559			II/8		II/8	48.0	II/13, tonsillectomy and adenoidectomy	
II/22	XIII	1.02	0.24	1.26	2.92	0.72	1.61	2.33	0.29	19.1	6.8	25.9	38.8	8.559			II/23	+18			II/14, soft solid, high caloric diet (3000 calories) to II/19	
II/25	XIV	1.06	0.36	1.42	3.35	0.68			0.34	19.4	2.3	21.7	43.8	9.702			II/27	+16			II/20, low calcium diet	
II/28	XV	1.00	0.17	1.17	3.35	0.48	1.23	1.71	0.36	15.0	7.1	22.1	43.8	9.702			II/27		II/27	48.3		

* The average of two uneven periods.

TABLE 4—Continued

Dates of period	Period number	Phosphorus			Calcium			Nitrogen			Total caloric intake			Blood serum		Basal metabolic rate		Weight		Treatment and remarks	
		Output		Intake	Output		Intake	Output		Intake	Date	Calcium	Phosphorus	Date	Percent	Date	Kgm.				
		Urine	Feces		Total	Urine		Feces	Total									Urine	Feces		Total
II/21*		gm.	gm.	gm. cc.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm. cc.	gm. cc.	gm. cc.	gm. cc.	gm. cc.	gm. cc.			
II/25	I	2.51	1.48	3.99	1.23	0.80	2.03	0.33	24.6	11.7	46.3	34.1	7,437	10.0	2.9	II/17	+76	II/19	42.9	II/19, transferred to Metabolism Ward, complete rest in bed, low calcium diet	
II/28	II	1.91	0.45	2.36	1.48	0.71	2.19	0.30	27.3	6.5	33.8	32.3	7,630			II/24	+51	II/24	43.5	II/28, 2 grams calcium lactate by mouth	
III/3	III	1.93	0.89	2.82	1.46	0.61	2.07	0.32	28.3	5.0	33.3	32.5	7,846			III/3	+57	III/3	42.9	III/6, began Lugol's M.x.t.i.d.	
III/6	IV	2.20	0.62	2.82	1.98	0.36	2.34	0.27	26.1	4.3	30.4	25.8	7,224			III/10	+55	III/10	41.9	III/12, subtotal thyroidectomy	
III/10†	V	2.09	1.50	3.59	2.25	1.47	1.09	2.56	0.35	28.5	11.2	39.7	8,253			III/16	+11	III/16	41.9		
III/12††	VI	0.84	1.00	1.84	2.75	0.72	0.69	1.41	0.37	13.0	6.4	19.4	33.0	9,127							
III/16	VII	2.42	0.44	2.86	0.44	0.88	0.43	1.31	0.02	19.5	3.8	23.3	1.8	651							
III/18	VIII	0.71	0.35	1.06	0.50	0.57	0.42	0.99	0.16	8.0	2.1	10.1	6.9	3,221							
III/22	IX	0.59	0.62	1.21	1.92	0.31	0.54	0.85	0.27	7.2	3.3	10.5	20.8	6,345							
III/24	X	0.68	0.72	1.40	3.99	0.58	0.52	1.10	0.32	12.2	4.7	16.9	28.1	9,150							
III/27	XI	0.79	0.74	1.53	4.88	0.42	0.59	1.01	0.31	13.1	4.8	17.9	28.3	9,378							
III/30	XII	1.19	0.56	1.75	4.88	0.40	0.48	0.88	0.31	14.1	5.1	19.2	28.3	9,378							
IV/2	XIII	2.21	0.88	3.09	3.42	0.34	0.66	1.00	0.32	11.9	0.9	12.8	28.3	9,124							
IV/3**	XIV	0.68	0.70	1.38	3.97	0.19	0.41	0.60	0.29	6.6	1.8	8.4	27.3	9,378							

Christine B. Age 22

* Period I is 4 days, reduced in the above table to the equivalent of 3 days.

** Period XIV is 1½ days, results being multiplied by 2 to give equivalent 3-day amounts.

† Period V Urine: About 500 cc. may belong to period VI.

†† Period VI Stool: Contains 400 cc. of urine.

TABLE 4—Concluded

Dates of period	Period number	Phosphorus			Calcium			*Nitrogen			Total caloric intake			Blood serum		Basal metabolic rate		Weight		Treatment and remarks
		Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Date	Calcium	Phosphorus	Date	Per cent	Date	
IV/3	I	2.00	0.47	2.47	0.54	0.88	0.92	0.32	29.5	2.6	32.1	27.8	7,874				III/12	+58	III/12	56.5
IV/6	II	1.92	0.92	2.84	0.72	0.62	1.34	0.32	28.2	7.0	35.2	27.8	7,874				III/29	+49	III/29	55.4
IV/9	III	1.76	0.67	2.43	0.68	0.50	1.18	0.32	28.5	3.3	31.8	29.6	8,026		10.5		IV/5	+31	IV/5	54.1
IV/13	IV	1.81	1.04	2.85	1.91	0.67	1.02	1.69	0.36	28.6	6.4	35.0	33.2	8,632			IV/7	+23	IV/7	53.9
(IV/16)*	V	1.20	0.88	2.08	2.44	0.51	0.70	1.21	0.37	13.4	4.2	17.6	33.7	9,396			IV/10	+15	IV/10	53.8
																	IV/12		IV/12	52.9

George R. A. Age 24

III/30, transferred to Metabolism Ward, rest in bed, low calcium diet

IV/10, Lugol's begun

IV/15, transferred to Ward D

IV/17, subtotal thyroidectomy, good recovery

* Period V, a 2-day period, multiplied by 3/2.

TABLE 5
Hyperfunctioning adenomas of the thyroid

Dates of period	Period number	Phosphorus			Calcium			Nitrogen			Total caloric intake		Blood serum		Basal metabolic rate		Weight		Treatment and remarks	
		Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Intake	Output	Intake	Calcium	Phosphorus	Date	Per cent	Date		Kgm.
Margaret Catherine D. Age 47																				
IV/16																				
IV/19	I	1.67	1.10	2.77	2.48	0.22	0.70	0.92	0.33	24.6	5.8	30.4	35.57	551	IV/5	+59	IV/16	62.6		
IV/23	II	2.05	1.08	3.13	2.84	0.39	0.61	1.00	0.34	29.9	6.4	36.3	39.78	491	IV/15	+31	IV/16	62.6		
IV/25	III	1.82	0.89	2.71	3.58	0.52	0.42	0.94	0.34	31.4	6.3	37.7	40.19	210	IV/22	+29	IV/23	61.8		
IV/28	IV	1.69	1.05	2.74	4.69	0.63	0.52	1.15	0.32	26.6	7.1	33.7	39.09	306	IV/28	+27	IV/28	62.0		IV/28, operation—lobectomy
V/1	V	2.28	0.44	2.72	0.13	0.26	0.25	0.51	0.81	25.4	4.4	29.8	0.9	714	IV/30	3.2	IV/28	62.0		
V/4	VI	1.14	0.60	1.74	1.09	0.27	0.42	0.69	0.20	19.2	2.9	22.1	15.2	3,918	V/3	+14	V/12	62.4		
V/7	VII	0.71	1.00	1.71	0.37	0.20	0.51	0.71	0.23	17.7	4.3	22.0	29.3	6,460	V/7	2.5	V/12	62.4		
V/10	VIII	0.46	0.88	1.34	2.96	0.21	0.43	0.64	0.30	13.0	5.5	18.5	29.7	6,535	V/10	+5	V/12	62.4		
V/13	IX	0.73	0.71	1.44	3.15	0.24	0.34	0.58	0.35	14.7	4.5	19.2	30.2	6,537	V/25	+18	V/12	62.4		
Sophie Jonine K. Age 58																				
VII/20																				
VII/23	I	2.08	0.74	2.82	1.52	0.81	0.45	1.26	0.21	29.8	4.8	34.6	20.83	977	VII/3	+67	VII/17	64.1		Low calcium diet
VII/26	II	1.92	0.75	2.67	1.61	0.96	0.42	1.38	0.27	26.8	5.7	32.5	29.54	823	VII/22	+41	VII/22	62.3		
VII/29	III	1.72	0.60	2.32	1.49	0.97	0.48	1.45	0.68	31.5	3.9	35.4	20.83	806	VII/26	+42	VII/26	62.1		Lugol's M xv t.i.d.
VIII/5	IV	0.89	1.00	1.89	1.39	0.27	0.65	0.92	0.18	12.9	2.2	15.1	15.63	306	VIII/5	+15	VIII/5	60.7		VII/31, operation—lobectomy
VIII/8	V	0.81	0.93	1.74	1.90	0.13	0.35	0.48	0.23	10.7	7.6	18.3	16.63	430	VIII/10	-16	VIII/10	61.5		VIII/3, Lugol's discontinued
VIII/11	VI	0.49	0.57	1.06	1.21	0.15	0.37	0.52	0.29	9.7	7.6	17.3	21.74	668	IX/15	+4	IX/15	61.5		

* Two-day period. Results multiplied by 3/2.

TABLE 6—Continued

Dates of period	Period number	Phosphorus			Calcium			Nitrogen			Total caloric intake		Blood serum		Basal metabolic rate		Weight		Treatment and remarks			
		Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Intake	Phosphorus	Calcium	Date	Per cent	Date	Kgm.					
IV/11	I	1.41	0.74	2.15	2.36	0.07	0.45	0.52	0.20	18.9	4.0	22.9	30.1	5.589	IV/7	9.9	3.3	III/13 IV/8	-29 -29	IV/6	61.4	Previous basal metabolic rate: III/20/26, minus 17 per cent; II/25/26, minus 25 per cent
IV/15	II	1.18	0.53	1.71	2.97	0.13	0.32	0.45	0.19	19.6	3.9	23.5	30.4	5.954	IV/14	10.6	3.2	IV/14	-36	IV/11	60.8	IV/7, low calcium diet
IV/17	III	2.75	0.25	3.00	2.58	0.25	0.19	0.44	0.16	23.2	2.2	25.4	25.1	5.108	IV/14	10.6	3.2	IV/15	-17	IV/14	61.6	IV/14, thyroxin 10 mgm. i.m.
IV/20	IV	2.22	0.43	2.65	2.13	0.27	0.29	0.56	0.20	34.9	3.5	38.4	30.3	5.878	IV/22	10.9	3.6	IV/22	-5	IV/17	59.8	IV/18, thyroxin 5 mgm. i.m.
IV/23	V	2.59	0.35	2.94	2.28	0.41	0.26	0.67	0.23	34.8	2.7	37.5	30.4	6.378	IV/23	10.9	3.6	IV/22	-5	IV/17	59.8	IV/21, thyroxin 5 mgm. i.m.
IV/27	VI†	2.02	0.50	2.52	1.90	0.34	0.42	0.76	0.19	31.3	4.4	35.7	25.6	5.323	IV/27	10.9	3.6	IV/27	-4	IV/24	58.0	IV/23, thyroid grains iv i.d.
IV/29	VII*	0.18	2.00	2.18	2.00	0.38	0.27	0.65	0.21	16.4	1.0	17.4	29.6	5.425	V/12	10.9	3.6	V/12	+13	IV/29	58.0	

* Period VII—Two days and a little over. Results multiplied by 3/2 for 3 day period.

† Period VI—Lost one small stool and small amount of urine.

Mabel M. Age 34

TABLE 7
Normal controls

Dates of period	Period number	Phosphorus			Calcium			Nitrogen			Total caloric intake	Blood serum		Basal metabolic rate		Treatment and remarks		
		Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total		Date	Calcium	Date	Per cent			
March 26	I	3.11	1.92	5.03	3.33	0.44	0.48	0.92	0.35	54.1	45.5	8.622	March 29	9.4	2.7	March 26	-1	March 24, low calcium supper.
March 29													March 31	8.1	2.8	March 30	-5	April 1, thyroid gr. xss i.d.
April 1	II	2.45	0.92	3.37	3.33	0.47	0.41	0.88	0.35	43.1	47.1	45.5	April 2	10.2	3.5	April 6	-8	April 7, thyroxin 10 mgm. i.v.
April 4	III	3.41	1.05	4.46	3.33	0.52	0.48	1.00	0.35	47.6	53.5	45.5	April 14	9.4	2.6	April 10	+16	April 9, thyroid stopped
April 7	IV	3.74	0.85	4.59	2.76	0.53	0.36	0.89	0.37	52.0	56.2	45.5	April 12	10.6		April 16	+48	
April 10	V	3.98	0.92	4.90	2.82	0.75	0.57	1.32	0.28	56.1	61.4	36.1	April 14	9.4	2.7			
April 13	VI	3.44	0.95	4.38	3.53	0.75	0.61	1.36	0.38	56.4	59.9	48.1						
April 16	VII	6.25	1.31	7.56	3.53	0.73	0.74	1.47	0.39	56.7	63.9	48.1						

Clark H. Age 25

Clement I. K. Age 27

March 26													March 23	8		March 23, a.m., low calcium diet.
March 28	I	2.70	0.44	3.14	3.03	0.32	0.20	0.52	0.28	39.3	41.3	36.0	March 26	9.2	2.2	
													March 31	8.0	2.7	March 31, thyroid gr. viid.

April 1	II	2.39	0.92	3.31	2.74	0.38	0.43	0.81	0.28	34.8	6.9	41.7	36.0	6,273	April 2	9.7	3.1	April 5	-7	April 5, thyroid gr. xvid.
April 5	III	3.05	0.54	3.59	2.74	0.41	0.26	0.67	0.28	39.1	3.9	43.0	36.0	6,273				April 10	+8	April 9, thyroid stopped
April 7	IV	3.24*	1.01	4.25	3.12	0.37*	0.28	0.65	0.30	44.3	3.7	48.0	39.6	8,829						
April 10	V	3.30	0.69	3.99	3.19	0.59	0.36	0.95	0.31	50.8	3.2	54.0	45.6	7,519						
April 13	VI	3.57	0.67	4.24	2.90	0.66	0.36	1.02	0.32	53.4	4.3	57.7	30.9	7,308	April 13	8.3	2.3			
April 15	VII	2.89	0.33	3.22	2.54	0.65	0.19	0.84	0.29	49.8	2.3	52.1	40.5	6,687	April 15					

*Period IV urine: estimated 600 cc. lost on April 1.

Urine period stops the morning after carmine has been given—9 a. m.

Feces period stops when carmine shows.

for essentially normal values for calcium and phosphorus are found in the serum.

6. X-ray evidence is presented which indicates that marked osteoporosis may develop in the bones from prolonged hyperthyroidism.

7. The increased calcium excretion is not dependent upon the elevated metabolism alone, for three out of four cases with high metabolism due to leukemia or fever had normal calcium eliminations.

PROTOCOLS

Norman G. No. 273649. Age 29 years, white, male, married. Admitted: December 17, 1925. Discharged: February 28, 1926.

History. One brother had a goiter with hyperthyroidism. Patient has been married nine years. He has three children. One child died at age of 2 months. Nine months previous to entry patient noticed nervousness, palpitation, and tremor of extremities. Dyspnea and headache were present on exertion. There was a gradual progression of symptoms until four months previous to entry when swelling of neck and prominence of eyes was noticed with slightly increased sweating. One month previous to entry he had a sense of constriction in his throat and slight constipation. He has had nocturia for five or six months.

Physical examination. He was a nervous, restless, sweating, flushed young man with slight prominence of the eyes. There was slight lid lag. There was a fine tremor of fingers and tongue. Tonsils were very large and cryptic. Thyroid was symmetrically enlarged, firm and smooth, with definite bruit. Heart showed no enlargement. There was a systolic murmur over the precordium. There was a palpable thrill at the apex. Skin was warm and moist.

Laboratory findings. Urine was examined five times—there were a few red blood cells on three occasions and sugar was slightly positive on three occasions; otherwise urine was negative. Blood—red count was 4,450,000; white count 7100; hemoglobin 80 per cent. Differential count showed polymorphonuclears 45 per cent, small lymphocytes 48 per cent, large lymphocytes 6 per cent, and mast cells 1 per cent. Wassermann was negative. Non-protein nitrogen was 34 mgm. per 100 cc. Phthalein excretion was 35 per cent. Basal metabolic rate on December 19, 1925 was plus 99 per cent with a weight of 48.3 kgm.

Treatment and progress. He had complete rest in bed and after ten days, Lugol's solution was started. On January 8, 1926, he had a sub-total thyroidectomy with uneventful recovery. On January 26, 1926, he had an attack of acute tonsillitis with a fever of 104.5 degrees F. which lasted ten days. On February 3, 1926, he had a tonsillectomy and adenoidectomy performed.

Impression. This was a most severe case of exophthalmic goiter, greatly improved but not cured by operation. This condition was complicated by severely infected tonsils.

George R. A. No. 275358. Age 24 years, white, male, married, truck driver. Admitted: March 24, 1926. Discharged: April 29, 1926.

History. For years he has had frequent frontal headaches. For three years he has had shortness of breath and severe palpitation on exertion which has gradually become more intense. He also has had an occasional, non-radiating, stabbing, precordial pain. For one year he has noticed an increasing weakness, emotional instability, and a feeling of heat with marked sweating. He had a markedly increased appetite but good digestion and regular bowels. His neck was growing larger.

Physical examination. He was well developed and nourished. Skin was moist. There was tremor of the hands. There were visible pulsations in his neck. Thyroid was enlarged with marked bruit. There were no eye signs. There was a diastolic murmur heard at the left border of the sternum. Blood pressure was 210/75. There was a capillary and corrigan pulse. Heart rate was 130.

Laboratory findings. Urine and blood were normal.

Treatment and progress. He had complete rest in bed and after two weeks Lugol's solution was started. On April 17, 1926, a sub-total thyroidectomy was done. He had an uneventful recovery. Pathological report showed follicular hyperplasia.

Impression. This was a case of aortic regurgitation with a very mild Graves' disease. Operaton was advised largely because of the heart lesion and it produced a marked general improvement.

Herbert B. E. No. 275575. Age 34 years, married, white, male, mail carrier. Admitted: April 5, 1926. Discharged: May 23, 1926.

History. He has been married ten years and has three children. One child died at 5½ months from lobar pneumonia. His wife has liver enlargement and some cardiac decompensation. He had a Neisserian infection fifteen years ago. For a year he has noticed prominence of his eyes. Gradually he noted definite nervousness and irritability, excessive perspiration with a voracious appetite but loss of strength and 22 pounds in weight. For two weeks he has noticed a much enlarged thyroid with increased tremor of his hands, palpitation, and dyspnea on exertion. He has had three transient attacks of precordial pain in the past month.

Physical examination. He was fairly well developed and nourished and in no distress. He was very nervous. Skin was moist and warm, with tan pigmentation. There was marked bilateral exophthalmos and lid lag. Thyroid was symmetrically enlarged. There was lumbar lordosis. Heart showed a forceful apex impulse but was not enlarged. Sounds were rapid and regular. Blood pressure was 175/75. There was a fine tremor of the hands.

Laboratory findings. Urine was normal. Blood showed a red count of 4,680,000; white count 8,150, and hemoglobin of 75 per cent. Differential count showed polymorphonuclears 61 per cent, small lymphocytes 12 per cent, large lympho-

cytes 25 per cent, and eosinophiles 2 per cent. Non-protein nitrogen was 29 mgm. per 100 cc. Wassermann was strongly positive on two examinations. Basal metabolism on April 7, 1926 was plus 48 per cent.

Treatment and progress. He had complete rest in bed and Lugol's solution was started after two weeks. On April 29, 1926 a sub-total thyroidectomy was done. Pathological report showed follicular hyperplasia. Following operation he had typical lobar pneumonia of the left lower lobe with a crisis on the eighth day. Basal metabolic rate on May 20, 1926 was minus 18 per cent.

Impression: Exophthalmic goiter; tertiary syphilis.

Rose Lee K. No. 275699. Age 63 years, female, white, married, housewife. Admitted: April 12, 1926. Discharged: May 23, 1926.

History. Patient has had fourteen children of whom seven died from obstetrical operations and three died in infancy. She has had no miscarriages. She has had recurrent tonsillitis. She also has had pleuritis and pneumonia. She had her menopause at 53 years of age.

Present illness. She was always a hard worker. For the past year she had noticed increasing fatigue, nervousness, palpitation, and trembling of hands. Swelling in her neck was noticed ten months previous to entry. Appetite became poor and she had epigastric distress relieved by food, and difficulty in swallowing. For six months she has had shortness of breath and orthopnea. She was easily irritated and perspired easily. She has lost 57 pounds in weight.

Physical examination. Patient was poorly developed and nourished, apprehensive, and nervous. There was slight exophthalmos, blepharitis, and slightly congested pharynx. Her thyroid was asymmetrically enlarged, nodular, and very firm. There was local glandular enlargement. Heart was enlarged to the left. Rate was rapid and regular. Liver edge was palpable. Blood pressure was 180/70.

Laboratory findings. Urine was normal. Blood showed red count of 5,200,000; white count 15,000; and hemoglobin 70 per cent. Differential count showed polymorphonuclears 63 per cent, small lymphocytes 29 per cent, large lymphocytes 7 per cent, and mast cells 1 per cent. Non-protein nitrogen was 26 mgm. per 100 cc. Wassermann was negative. Basal metabolic rate on April 15, 1926 was plus 87 per cent.

Treatment and progress. She had complete rest in bed and after eleven days Lugol's solution was started. On May 6, 1926, a sub-total thyroidectomy was performed. Pathological report showed follicular hyperplasia. Basal metabolic rate on discharge was plus 27 per cent.

Impression. Exophthalmic goiter.

Christine B. No. 274688. Age 22 years, female, white, married, hospital ward maid. Admitted: February 15, 1926. Discharged: April 3, 1926.

History. She was separated from her husband. She had had no pregnancies. She was strong and well up to present illness. She noticed a goiter one year

previous to entry and had been easily upset emotionally with crying and nervous spells. For one month she had noticed palpitation, slight prominence of her eyes, increased sweating, and slight difficulty in swallowing.

Physical examination. She was a well developed and nourished, very short young woman who felt hot. There was definite exophthalmos. There was a fine tremor of hands and tongue. Thyroid was symmetrically enlarged, firm, with bruit. Heart was rapid and regular with no enlargement.

Laboratory findings. Urine was negative. Blood showed red count 5,656,000; white count 8,000, and hemoglobin 80 per cent. Smear showed polymorphonuclears 78 per cent, small lymphocytes 20 per cent, and large lymphocytes 2 per cent. Non-protein nitrogen was 32 mgm. per 100 cc. Wassermann was negative. Basal metabolic rate on February 17, 1926 was plus 76 per cent, pulse 116, and weight 43.8 kgm.

Treatment and progress. Patient had complete rest in bed and Lugol's solution was started at the end of two weeks. On March 12, 1926, a subtotal thyroidectomy was done. Her basal metabolic rate at time of discharge was minus 7 per cent. Patient was apparently cured by the operation.

Impression. Severe exophthalmic goiter.

Elizabeth B. No. 274040. Age 27, female, white, single, stenographer. Admitted: January 9, 1926. Discharged: March 3, 1926.

History. Rheumatic fever at eight years for six months. She had two attacks of tonsillitis. Catamenia was somewhat irregular. For ten years she had been nervous, marked by very easy excitability, crying and insomnia. She had grown worse in the last three months and had lost 15 pounds in spite of an increased appetite. She had a feeling of warmth, fatigue, and palpitation. For ten days she had noticed swelling in her neck. She felt quite tired.

Physical examination. Patient was nervous and twitchy. She was well developed but slightly thin with moist skin. Throat and tonsils were slightly red. There were no definite eye signs. Thyroid showed moderate, smooth, diffuse enlargement greater on the right with a marked bruit. Heart was enlarged. A diastolic murmur was heard by one examiner only. Blood pressure was 144/80.

Laboratory findings. Urine showed a few white cells, otherwise negative on five examinations. Blood: red count 4,300,000; white count 8,000; hemoglobin 70 per cent. Differential count showed polymorphonuclears 50 per cent, small lymphocytes 40 per cent and large lymphocytes 10 per cent. Wassermann was negative. Non-protein nitrogen was 29 mgm. per 100 cc. Basal metabolism on January 11, 1926, was plus 79 per cent.

Treatment and progress. Patient had complete rest in bed and Lugol's solution was started at the end of eleven days. During her stay in the hospital she had several attacks of severe pain in her joints accompanied by slight fever and a rise in her white blood count. Joints were all slightly swollen, warm, tender, but not red. She was relieved by salicylates. February 13, 1926, a subtotal thyroidectomy was done. Pathological report showed follicular hyperplasia.

Treatment and progress. She was greatly improved by the operation and left the hospital apparently well. Basal metabolism on February 23, 1926 was plus 7 per cent.

Impression. Moderately severe exophthalmic goiter—complicated by a mild attack of rheumatic fever.

Sophia J. K. No. 277495. Age 58 years, married, white, female. Admitted: July 15, 1926. Discharged: August 8, 1926.

History. Patient was in good health until three years ago when she first noticed a lump in the right side of her neck which had gradually increased in size. She then became nervous and "fidgety." This increased so that two years ago her hands began to tremble, enough to bother her in writing. She also has noticed some palpitation and shortness of breath on the slightest exertion. There has been no increased perspiration. For the past three years she has had occasional stabbing pains in the lumbar region. During the past seven months she has had a vaginal discharge which is watery, at times bloody, and at other times purulent and bloody, no odor. She had measles and whooping cough as a child and rheumatism twenty years ago. Thirty years ago she was treated for metritis. Eleven years ago she had two uterine tumors removed.

Physical examination. She was a nervous woman with marked coarse tremor of hands but no exophthalmos. There was a small round hard mass in the right lobe of the thyroid. There was a blowing systolic murmur at apex. Heart was normal in size. Blood pressure was 150/70. She had a moderate cystocele and a marked bloody discharge from the uterus.

Treatment and progress. Operation was performed with excision of adenoma. Dilatation and curettage was done; the curettings showing tuberculosis.

Impression. Toxic adenoma of thyroid; tuberculous endometritis.

Margaret D. No. 269527. Age 48 years, white, married, female. Admitted: April 8, 1926. Discharged: May, 13, 1926.

History. She has been married twice. First husband divorced. She has one child living and well. Menopause occurred at 44 years. Patient entered the hospital one year previous to present entry complaining of nervousness of 8 months duration, some dizziness and dyspnea, increased perspiration, dislike of warm places, slight palpitation for one month, with a tight feeling in her throat. She had noticed enlargement of the thyroid for some time. She refused operation at that time. Two treatments by x-ray were without benefit and she feels she has grown worse since her first entrance. Dyspnea and weakness are increased. She is emotionally unstable and she has noticed an increase in the size of her neck with some difficulty in swallowing.

Physical examination. She was a well developed and fairly well nourished woman with considerable brownish pigmented areas of the skin. There was moderate exophthalmos and some tremor of fingers. The right lobe of the

thyroid had a solid, nodular enlargement, approximately 5 by 5 cm. with a left lobe not appreciably enlarged. Heart showed no enlargement. There was a systolic murmur at the aortic area. Blood pressure was 124/80.

Laboratory findings. Urine was negative. Blood was negative. Wassermann was negative. May 10, 1926, non-protein nitrogen was 26 mgm. per 100 cc.

Treatment and progress. She had complete rest in bed and Lugol's solution was started after seven days. April 28, 1926 a lobectomy was performed. Pathological report: "Probably comes within limits of normal thyroid except for few miliary adenomata." She made an uneventful recovery. Patient was very quiet and calm when discharged. Basal metabolic rate on discharge was plus 5 per cent.

Impression. Adenoma of thyroid with mild toxicity.

John Francis W. No. 277489. Age 63 years, widower. Admitted: July 15, 1926. Discharged: August 14, 1926.

History. He dated his present pallor back twenty years. He said it came on following a "drinking bout" and had been present ever since. He thought his skin was more dry, coarse, and yellow than formerly. Several years later he noticed his body hair (eyebrows, chest, axillary and pubic) began to fall out. For the past three years he had noticed he could not stand cold weather. He had had increasing weakness and inability to endure exercise. He was drowsy most of the time and said his memory was very poor for recent events. He had noticed increased constipation for the past few years. Appetite was fair. He had had puffy eyes of late. He could not obtain work as a collector because of his appearance. There had been no increase in weight.

Physical examination. He was a very obese man of 63 with a marked pallor of his mucous membranes. Skin had a yellow tint, was coarse, dry and appeared edematous—did not pit on pressure. His eyebrows were almost absent, as was the hair of his axillae, chest and pubic region. His tongue was thick. Speech was slow and sluggish. There was a perforation of the nasal septum. Lungs showed chronic bronchitis. Heart was negative. Blood pressure was 160/74. Vessels showed moderate sclerosis.

Laboratory findings. Urine, blood and Wassermann were all negative. Non-protein nitrogen on July 15, 1926 was 30 mgm. per 100 cc.

Progress and treatment. Patient was studied for 14 days before therapy was started. On July 31, 1926 he was started on thyroid extract grains 6 per day. On thyroid therapy he was greatly improved. Basal metabolic rate on August 8, 1926 was minus 14 per cent.

Impression. Myxedema; arteriosclerosis; emphysema and chronic bronchitis.

Hazel B. W. No. 277422. Age 23 years, single, white, female. Admitted: July 12, 1926. Discharged: August 12, 1926.

History. For years patient had suffered from backache which was relieved by rest. For the past eight months she had had increasing general weakness often

accompanied by shortness of breath requiring rest after she had walked a few hundred yards. For the past six months she had been sensitive to cold, in fact she felt cold most of the time. She also had noticed she perspired very little and that her skin was dry and much coarser than previously. During this same period her memory had become poor. At times her tongue had felt swollen and tender. With the above symptoms she had increased gradually in weight so that at the time of entry she weighed 130 as compared with her best previous weight of 102. Appetite was poor. She had been constipated for years. Catamenia had been absent for the past 2½ years.

Physical examination. She was a young woman of 23, well developed and nourished. She appeared drowsy and apathetic. Face had a puffy appearance especially about the eyes. Skin was coarse and dry. Hair was coarse. She had a definite pallor. Blood pressure was 80/60.

Laboratory findings. X-rays showed an enlarged sella turcica and sacroiliac arthritis. Electrocardiogram showed the T₂ to be 1 mm. with small complexes and a rate of 85. Wassermann was negative. Blood—red count was 3,720,000, white count 7,500, hemoglobin 80 per cent. Non-protein nitrogen was 26 mgm. per 100 cc. Phthalein excretion was 5 per cent.

Follow-up notes. September 11, 1926. She did not mind the cold. Her strength seemed to have returned. Appetite was better. She talked much faster. Her skin was softer. She weighed 108 pounds. She was taking thyroid grains 6 daily. Basal metabolic rate was plus 35 per cent. Thyroid was cut down to grains 2 per day because of the high basal metabolic rate.

November 16, 1926. Menses returned last month, lasted seven days, required three to four napkins per day. It was non-painful. Her basal metabolic rate was plus 1 per cent but she had some symptoms of myxedema returning. Thyroid was increased to grains 4½ per day.

Impression. Myxedema.

Elizabeth M. D. No. 276291. Age 52 years, white, married, female. First admission: May 13, 1926. Discharged: May 20, 1926. Second admission: June 2, 1926. Discharged: July 2, 1926.

History. She had her menopause seven years ago. She felt well until one year ago. At that time numbness and a cold feeling in her hands began. She gained 28 pounds in one year. She had minded the cold especially during the past winter. Her skin always had been dry and she had not perspired much. Her hands had become broad and puffy in the past two years. She was not excitable and her memory had become poor. There had been very little loss of hair. Her appetite was good. She had no dyspnea and no palpitation. She had recently stumbled over curbstones and for six months she had had difficulty in climbing stairs because of stiffness of the legs.

Physical examination. She was a well developed and nourished, obese woman—dull and apathetic. Skin was coarse and dry. Hair was rather coarse. Heart

was not enlarged. The sounds were distant. There was a soft systolic murmur at the base. Abdomen was protuberant with diastasis recti. Extremities showed varicose veins and slight edema of both ankles.

Laboratory findings. Urine was negative except for occasional white blood cells and epithelial cells on four examinations. Blood—red count was 4,300,000. White count was 6,400. Hemoglobin was 60 per cent. Differential count showed polymorphonuclears 64 per cent, small lymphocytes 30 per cent and large lymphocytes 6 per cent. Non-protein nitrogen was 38 mgm. per 100 cc. Wassermann was negative. Basal metabolic rate was minus 34 per cent. Weight was 73.5 kgm.

Treatment and progress. She had complete rest in bed and during this time metabolic studies were made. She was discharged on May 20th because of death in her family. No treatment was started.

She returned, June 2, 1926. She was put on a low calcium diet and calcium metabolism studies were made before and during thyroid therapy.

Impression. Myxedema.

Mable H. M. No. 274766. Age 34 years, white, married, female. First admission: February 19, 1926. Discharged: February 25, 1926. Second admission: April 6, 1926. Discharged: April 28, 1926.

History. She had been married eight years. She had one child. She had had no miscarriages. For ten years she had been troubled with a dull ache in her lower back on bending forward and had felt tired. For five years this weakness and fatigue had become increasingly more severe. She noticed slowing of her mental reaction and a feeling of coldness. Catamenia was always irregular and painful. She was nervous, irritable, and slept poorly. Three and a half years ago her basal metabolic rate at the Homeopathic Hospital was minus 15 per cent and minus 18 per cent. For two years she had noticed thickness of her tongue and lips with difficulty in her speech. "Thyroid extract" at first resulted in headaches and palpitation but gave her relief.

Physical examination. She was well developed and nourished, with thick lips and tongue. The skin of her face was slightly yellowish. Expression was slightly apathetic. She had external hemorrhoids.

Laboratory findings. Urine was negative. Red blood count was 4,384,000; white count 8,600, hemoglobin 80 per cent. Differential count was normal. Non-protein nitrogen was 35 mgm. per 100 cc. Wassermann was negative. Basal metabolic rate on February 20, 1926, was minus 17 per cent. Basal metabolic rate on April 8, 1926, was minus 29 per cent. Fundi were negative. X-ray showed a large deep sella turcica.

Progress. This patient was very much improved by thyroid therapy but was still nervous and easily upset emotionally. She tired very easily and had frequent frontal headaches.

Impression. Mild myxedema; question of pituitary tumor; sacro-iliac arthritis.

Jennie W. No. 270359. Age 46 years, white, single, female. History of previous entry—June, 1925.

History. Two years ago she came to the Out Patient Department complaining of weakness, lack of ambition, loss of appetite and coldness of extremities. These symptoms had come on gradually over two years. Her speech was dull and listless and she looked pale with pouches under her eyes. Menopause occurred six years ago. Basal metabolic rate on July 3, 1924, was minus 26 per cent. Basal metabolic rate on July 22, 1924, was minus 32 per cent. She was given thyroid extract—grains $1\frac{1}{2}$ three times a day. Basal metabolic rate on August 11, 1924 was minus 13 per cent. Thyroid was increased to $7\frac{1}{2}$ grains a day. Basal metabolic rate on September 5, 1924, was minus 1 per cent and patient felt better. Basal metabolic rate on January 26, 1925, was minus 24 per cent. Thyroid was reduced. Basal metabolic rate on April 10, 1925, was minus 13 per cent. She then entered the Hospital (June, 1925) and her condition was studied. Discharged: July 4, 1925.

Second admission was on April 30, 1926. She returned because of recurrence of symptoms. After discharge she was taking $7\frac{1}{2}$ grains of thyroid daily but her supply gave out about one month ago and symptoms slowly recurred. Basal metabolic rate on April 27, 1926, was minus 33 per cent.

Physical examination. She was well developed and nourished with slight puffiness under her eyes. There was moderate pallor of her skin with very slight dryness.

Laboratory findings. Urine was negative. Blood showed a red count of 4,216,000; white count 5,700, and a hemoglobin of 65 per cent. Differential count showed polymorphonuclears 38 per cent, small lymphocytes 47 per cent, large lymphocytes 4 per cent, mast cells 9 per cent and eosinophiles 2 per cent. Non-protein nitrogen was 23 mgm. per 100 cc. Basal metabolic rate was minus 34 per cent. Wassermann was negative.

Treatment and progress. She had complete rest in bed. On May 14, 1926, she developed a definite psychosis with delusions of persecution. She wanted to leave the hospital. She was given thyroxin, 10 mgm. intramuscularly. On May 16, 1926, her psychosis was much improved, 48 hours after 10 mgm. of thyroxin intramuscularly, yet she retained certain ideas of persecution. The basal metabolic rate rose to plus 13 per cent on thyroid extract.

Impression. Myxedema complicated by mild psychosis.

Susan B. F. No. 265471. Age 48 years, white, married, female. Admitted: June 1, 1926. Discharged: July 15, 1926.

In 1924 she was in the Massachusetts General Hospital with the diagnosis of: (1) strangulated internal hernia, (2) myxedema, (3) chronic cystitis. A laparotomy for intestinal obstruction was done.

History. She was born and had lived in Halifax, N.S., until 7 years ago. She had nine children and no miscarriages. Her periods stopped when her last child

was born 17 years ago. She had not felt well since then. At that time she suffered from weakness and shortness of breath and often had to rest. She noticed some paleness and bloating of her skin with considerable drowsiness. After two years of these symptoms treatment with "pills and medicine" relieved her and she remained fairly well until 1918 when she had influenza, after which she became weaker and more short of breath on exertion. No other symptoms occurred until two or three years ago when a new group appeared. Her face became more bloated, lid fissures narrowed, at times her eyes almost closed and she had swelling of her hands and ankles. Her skin was rough, pale, dry and flaked readily and increased thickness was especially noticeable over the extremities. Her hair fell out, was coarser and more brittle. Her feet have been cold during the past three or four years. At times she had tingling and numbness of her fingers and toes. Her speech was more indistinct, slower and her tongue felt thick. Her memory was bad; she remembered past events better than present. She had frequent dizzy spells. Her appetite was poor. She had been constipated for years. Occasionally she had short transient pains over precordium accompanied by smothering and choking spells. All symptoms had grown progressively worse so that she needed a three to four day rest in bed every week. Apparently she had not taken the thyroid extract which had been prescribed for her.

Physical examination. She was a pale, sluggish woman with well marked edema about the eyes. Her skin was dry. Her hair was coarse and brittle. Tongue was large. Mucosae were pale. Heart was slightly enlarged to the left. Sounds were feeble and distant. There was a moderate amount of pitting edema over the vertebral column from first lumbar vertebra down. Knee jerks were extremely sluggish. There was a reddish brown scar of an old varicose ulcer, over the middle anterior surface of the left tibia.

Laboratory findings. Urine was negative except for occasional white blood cells and hyaline casts on three examinations. Blood showed a red count of 3,088,000; white count 3,160; hemoglobin 45 per cent. Differential count showed polymorphonuclears 44 per cent, small lymphocytes 46 per cent, large lymphocytes 1 per cent, mast cells 4 per cent, basophiles 2 per cent, and eosinophiles 3 per cent. Platelets were increased. Non-protein nitrogen was 38 mgm. per 100 cc. Basal metabolic rate was minus 35 per cent, weight 60.4 kgm.

Treatment and progress. She had complete rest in bed.

June 7, 1926. Patient was very weak. She complained of weakness, pains in elbows and knees. She seemed semi-stuporous at times. She had nausea and vomiting. Patient was given 10 mgm. thyroxin at 10:15 p.m.

June 10, 1926. Patient had sore throat with fever. Thyroxin 10 mgm. given.

June 13, 1926. Patient had very low caloric intake and continued fever. She complained of pain in the muscles of arms and legs. Thyroxin 10 mgm. again given.

June 22, 1926. She was weaker and very nauseated. She ate nothing and refused to cooperate.

June 26, 1926. She seemed disoriented and irrational at times. Non-protein nitrogen 80 mgm. per 100 cc. Serum phosphorus 8.8 mgm. per 100 cc. White blood count was 4100. She was given 20 cc. of CaCl_2 intravenously.

June 28, 1926. She was given 20 cc. CaCl_2 again and 500 cc. 5 per cent dextrose intravenously. Non-protein nitrogen today was 110 mgm. per 100 cc. At times she was irrational, at other times semi-comatose.

July 14, 1926. She was much improved, was eating again, and did not vomit her food. She looked thin. The signs of myxedema had disappeared.

Impression. The most marked type of myxedema.

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