STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

VIII. The Influence of the Thyroid Gland and the Parathyroid Hormone upon the Total Acid-Base Metabolism

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INTRODUCTION

The studies of Aub, Bauer, Heath, and Ropes (1) demonstrated that there is a marked increase in calcium excretion in hyperthyroidism and a decrease in calcium excretion in hypothyroidism. Moreover, these studies showed that the increased calcium in hyperthyroidism was partly in the feces, although predominantly in the urine. The present investigation was undertaken to determine if possible the wherefore of this increased calcium excretion. Three possible explanations had been suggested.

In the first place it seemed possible that there might be an associated hyperparathyroidism with hyperthyroidism and an associated hypoparathyroidism with hypothyroidism. That this is not the right explanation is suggested by the fact that in hyperthyroidism the serum calcium is only slightly elevated and there is an increased calcium excretion in the feces, whereas in hyperparathyroidism the serum calcium is much elevated and there is no increased excretion in the feces (see studies by Albright, Bauer, Ropes, and Aub (2)).

Secondly, the possibility occurred that the calcium of the bones in its capacity as a reserve supply of base might be excreted in hyperthyroidism to neutralize some acid. There are four known methods of neutralizing such acids:

I. Titratable acidity, used particularly for the excretion of phosphates.

II. Ammonia.
III. Fixed Base from extracellular fluids (Gamble, Blackfan, and Hamilton (3)).
IV. Calcium phosphate from the bones.

These various mechanisms are to a certain extent simultaneously called into play. The fourth is often the least affected by acid diets (4). It is, therefore, fair to assume that if the marked increased excretion found in hyperthyroidism is due to an acidosis, there must also be obvious stimulation of the other three mechanisms.

It is true that the increased calcium excretion in both hyperthyroidism and in acidosis is associated with an essentially normal blood calcium level. On the other hand studies from this laboratory (4) show that the increased calcium excretion found in the feces in hyperthyroidism is not present in the disordered metabolism of acidosis.[1] This discrepancy seemed important, but perhaps not fundamental, for the increased fecal excretion in hyperthyroidism may merely be an expression of increased intestinal rate and increased excretion of gastrointestinal juices. It was thought, too, that the negative nitrogen balance, which was present in most of the cases of hyperthyroidism studied (1), might point to one source of acid. A negative nitrogen balance means that energy is being derived from the patient's own flesh,—really a meat diet, which, of course, is an acid diet because of its high sulphate and phosphate contents. This thought appeared to be supported by the observation that the negative nitrogen balances during fasting experiments were associated with calcium excretions in the urine almost comparable with those in hyperthyroidism (5, 6, 7). Furthermore, Benedict's fasting man showed a distinct parallelism between his negative nitrogen balance and his urinary calcium excretion. Of course, the large fecal calcium found in hyperthyroidism was not found in the starving man.

Finally, as a third possibility, it was thought that the thyroid hormone might have a direct stimulating catabolic effect on the calcium deposits in the bones. This, we appreciate, is no explanation of how

[1] Givens (8) and Givens and Mendel (9) likewise found no increase in fecal calcium in dogs as a result of acidosis although Stehle (10) found a very definite increase.

this catabolic effect is exerted. It merely serves to differentiate it from other known methods of mobilizing bone salts.

PLAN OF STUDY

In order to investigate the second possibility, namely, that the calcium excretion in hyperthyroidism might be increased because of a demand to help in the excretion of some acid—it was decided to do total acid-base studies. By following the changes in acid and basic radicles from the hypothyroid state to the normal and from the hyperthyroid state to the normal we believed it would at once be apparent whether or not calcium was being called out to neutralize an excess of acid. Furthermore, it was decided to study in a similar manner a normal subject before and during parathormone medication in order to see whether there was any analogy between the effect of the thyroid and parathyroid hormones on total acid-base metabolism.

In order to balance the basic factors in the urine against the acid factors, one has to know on the basic side

(1) Fixed base excretion (= sum of Na, K, Ca, Mg).
(2) NH_4 excretion.
(3) Titratable acidity (= base necessary to bring urine to a pH of 7.35).

and on the acid side

(1) Chlorides.
(2) Sulphates.
(3) Base binding value of phosphates at pH 7.35.
(4) Undetermined acid (= mostly organic acids).
(5) Carbonates.

The sum of the acid factors expressed in cubic centimeters of N/10 should equal the sum of the basic factors expressed in cubic centimeters of N/10 (see Gamble (11)). Rather than undertake the necessarily difficult task of determining the carbonates, we have used a procedure described by Albright and Bauer (12). This consists in making both the cation and anion columns shorter by the carbonic acid value; i.e. on the cation side our third value is the "titratable acidity minus CO_2" instead of titratable acidity and on the anion side we have not

TAB

Lilly C.—

Period number	Weight	Caloric intake	Fluid intake	Urine	Dried feces	Basal metabolic rate	Calcium metabolism					Phosphorus metabolism (valence assumed at 1.8)					Nitrogen met			
							Urine	Total output	Intake	Balance	Phosphorus equivalent of calcium balance	Urine output	Total output	Intake	Balance	Theoretical balance	Urine	Total output	Intake	Balance
	kilos	*calories*	*cc.*	*cc.*	*grams*		*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*grams*	*grams*	*grams*	*grams*
I	76.0	4,096	7,092	6,590	67.2	−44	154	290	113	−177	−93	840	1,197	948	−249	−81	21.10	23.48	23.8	0.
II	75.5	4,095	7,092	6,290	41.5		98	172	113	−59	−31	530	715	948	233	19	21.23	23.63	24.0	0.
III	75.4	4,143	7,113	5,370	51.8	−35	110	244	116	−129	−67	500	697	989	292	−76	21.87	24.27	24.0	−0.
IV	74.3	3,945	6,257	5,495	5.8	−46	90	105	67	−39	−20	470	558	552	−006	−235	19.33	20.77	14.4	−6.
V	72.5	3,999	7,087	5,905	88.8	−41	139	361	110	−251	−131	430	715	948	233	−96	20.74	23.16	24.2	1.
VI	73.1	4,223	7,113	5,725	38.2	−42	224	303	116	−187	−98	1,110	1,389	989	−400	−115	23.39	25.93	25.4	−0.
VII	72.2	4,229	7,109	6,260	31.7	−22	217	297	115	−182	−95	1,230	1,465	982	−483	−490	34.25	36.76	25.1	−11.
VIII	71.4	4,064	7,047	5,995	57.5		248	407	110	−297	−155	1,180	1,553	948	−605	−1,003	47.23	49.69	24.6	−25.
IX	70.2	4,309	7,060	5,580	70.1	−13	255	422	117	−305	−159	2,160	2,418	948	−1,470	−1,037	48.45	50.95	25.0	−25.
X	69.0	4,281	7,113	7,545	40.7	−13	312	447	117	−331	−173	1,180	1,361	989	−372	−1,316	56.68	59.22	25.4	−33.
XI	67.2	3,596	6,937	6,455	31.8	−10	275	420	100	−320	−167	1,360	1,592	878	−714	−1,028	46.54	48.88	23.4	−25.
XII	65.4	4,247	7,105	5,665	44.9	−6	248	464	114	−350	−183	1,500	1,832	976	−856	−968	45.42	47.88	24.6	−23.
XIII	65.4	4,308	7,113	5,395	34.9	−1	320	494	119	−376	−196	1,340	1,570	989	−581	−859	42.45	44.98	25.3	−19.
XIV	64.4	4,039	7,111	5,340	35.5	+3	359	497	113	−385	−201	1,380	1,564	959	−605	−858	41.34	43.76	24.2	−19.
	63.5																			
	63.2																			
XV	62.4	4,223	7,113	5,120	53.4	+5	293	704	116	−588	−306	970	1,273	989	−284	−527	29.55	32.09	25.4	−6.
XVI	61.8	4,223	7,113	4,960	50.0	+5	319	597	116	−481	−250	1,030	1,377	989	−388	−459	29.12	31.66	25.4	−6.

ABLE 1
—Myxedema

etabolism			Total base metabolism					Sulphur		Chloride					Blood serum		Medication and treatment per period
	Phosphorus equivalent of nitrogen balance	Total base equivalent of nitrogen balance	Urine	Total output	Intake	Balance	Theoretical balance	Inorganic sulphur urine	Total sulphur intake	Urine	Intake	Ammonia	Titratable acidity — CO_2	Organic acid	Calcium	Phosphorus	
us	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*mg. per 100 cc.*	*mg. per 100 cc.*	
.32	11	13	3,487	4,337	4,098	−239	−164	519	1,185	2,160	1,971	793	433	1,194	9.6	3.5	
.37	12	15	3,144	3,779	4,098	319	−44	586	1,185	1,963	1,971	765	308	1,138			
.27	−9	−11	3,713	4,553	4,182	−371	−140	695	1,272	2,586	1,977	785	324	1,041			
.37	−215	−260	3,114	3,759	2,753	−1,006	−299	530	909	1,972	1,597	604	173	919	10.4	3.9	
.04	35	42	3,554	4,764	3,757	−1,007	−209	643	1,206	1,470	1,697	849	212	2,072			0.2 gm. thyroid extract
.53	−18	−22	3,039	3,743	4,182	439	−209	618	1,272	1,763	1,977	1,051	443	1,042			1.2 gm. thyroid extract
.66	−395	−476	2,980	3,719	4,153	434	−658	1,082	1,263	1,740	1,955	1,338	675	941			1.2 gm. thyroid extract
.09	−849	−1,024	3,000	4,390	4,023	−367	−1,321	1,569	1,254	1,457	1,964	1,411	976	1,181			1.2 gm. thyroid extract
.95	−878	−1,059	3,495	5,095	4,128	−967	−1,364	1,676	1,241	1,590	1,974	1,371	966	406			1.2 gm. thyroid extract
.82	−1,139	−1,380	4,644	5,664	4,186	−1,478	−1,711	1,906	1,272	2,762	1,977	1,161	962	919	10.6	5.5	1.5 gm. thyroid extract
.48	−861	−1,040	4,000	4,790	3,581	−1,209	−1,360	1,661	1,136	1,916	1,630	949	840	852			1.7 gm. thyroid extract
.28	−785	−950	3,530	4,605	4,154	−451	−1,300	1,559	1,243	1,455	1,974	1,041	964	1,021			1.9 gm. thyroid extract
.68	−663	−803	3,183	4,193	4,180	−13	−1,179	1,477	1,267	1,570	1,975	904	915	615			2.1 gm. thyroid extract
.56	−658	−798	2,999	3,869	3,886	17	−1,183	1,410	1,217	1,618	1,717	1,062	834	487			1.3 gm. thyroid extract
																	Sent home for two weeks on normal diet but continued thyroid therapy
.70	−221	−270	3,129	4,259	4,185	−74	−858	946	1,272	1,802	1,977	731	637	779	10.6	5.5	0.9 gm. thyroid extract
.30	−209	−255	3,456	4,446	4,185	−261	−736	893	1,272	2,020	1,977	734	670	917			0.9 gm. thyroid extract

determined the carbonic acid. One obtains the "titratable acidity minus CO_2" value by adding a known amount of mineral acid to the urine, blowing off the carbon dioxide, titrating with standard alkali back to a pH of 7.35, and then subtracting the acid added from the alkali used. The "undetermined acid" was not measured but taken as the difference between the sum of the basic radicles and the sum of the other acid radicles. During the remainder of the paper this value will be called "organic acid." It must be remembered that, derived as it is, the organic acid value contains all the errors of the experiment.

The three patients studied were carefully chosen. The cases of myxedema and exophthalmic goiter were classical examples of the severest types, and during our metabolic study both women essentially recovered. The patient to whom parathormone was given was a normal man except for a calcified hematoma in his thigh. The diets used were nearly neutral, low in calcium, and satisfied the desires of the patient although necessarily not the caloric requirement. The diet as well as the water intake was kept constant throughout each study. The variations which occurred in their metabolism, therefore, were dependent upon changes in the patients' conditions and not in their diets. The patients were, therefore, their own controls. The periods of study were three days each. The method of collecting urine and feces was that used in other studies (13). The chemical methods used were as follows: for calcium, McCrudden (25); for phosphate, Fiske and Subbarow (26); for ammonia, Folin (27); for titratable acidity, Folin (28); for total base, Fiske (29); for sulphur, Fiske (30); for chloride, Van Slyke (31); for nitrogen, the Kjeldahl method; and for serum calcium, Clark and Collip (32).

RESULTS

PART I

Effect of thyroid extract on patient with myxedema

(The data for Part I is given in table 1 and chart 1). Mrs. L. C. had severe myxedema. She was a very coöperative patient, who was maintained on a constant diet and fluid intake throughout this observation, although in several periods (IV, V, and XI) her dietary intake

was not quite so constant as in other periods. During the first five periods (i.e., 15 days) she received no thyroid medication, so that this period represents the metabolism of complete myxedema. Throughout the rest of the observation she received Armour's thyroid extract daily by mouth. Periods VI to IX inclusive represent the marked change of beginning of thyroid medication (0.4 gram per day), and the next five periods (X to XIV inclusive) represent thyroid medication after equilibrium has been more nearly established. In order to be sure that

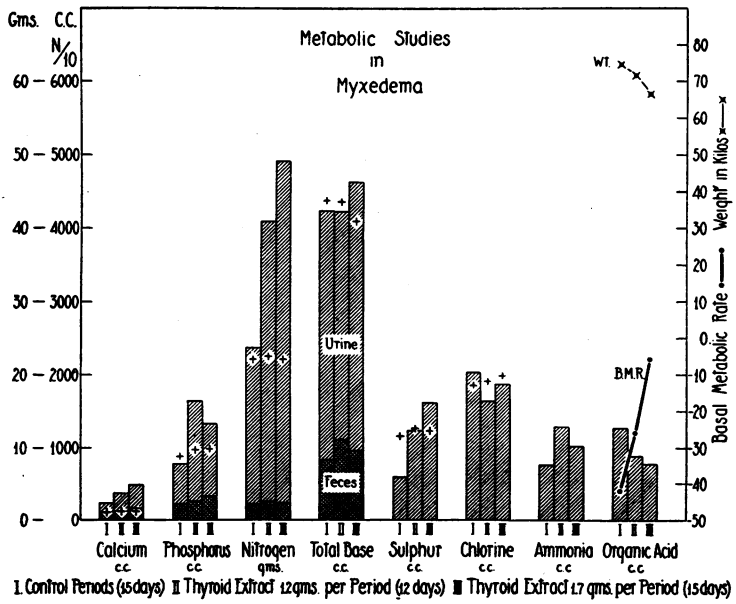

CHART 1

this represented the permanent stage metabolically, the patient was sent home for two weeks on constant thyroid medication but without dietary restrictions. She then returned to the metabolism ward on the previous regime and periods XV and XVI were obtained, which represent the steady state of her normal metabolism. Thus the entire investigative period can be divided into four main subdivisions:

(a) Periods I—V, control periods before thyroid medication.
(b) Periods VI–IX, showing marked changes at beginning of thyroid medication.

(c) Periods X–XIV, after equilibrium has been more nearly established, and
(d) Periods, XV–XVI, showing established thyroid medication.

Water balance

It is a striking fact that in spite of a constant fluid intake, but a marked loss in weight, the quantity of urine excreted per period was practically uninfluenced by thyroid feeding. Any increased fluid, therefore, was eliminated either through feces or through insensible perspiration,values which were not established in our observations.

Protein metabolism

Thyroid extract produced a marked effect upon the protein metabolism in this patient, for the nitrogen equilibrium, established during the control period, changed to a very marked negative nitrogen balance (equivalent to 24.4 grams N per period) during periods X–XIV. There was still an average negative nitrogen balance of 6.5 grams during periods XV and XVI after three weeks of continued thyroid medication.

Calcium metabolism

The conclusions in Paper III (1), in regard to calcium excretion in myxedema, are confirmed by this patient. The calcium elimination before treatment was very much below normal, but after thyroid was taken the calcium excretion more than doubled in the urine and it also rose in the feces. As pointed out in a previous publication (14), this increase in calcium excretion in the feces is a unique effect of thyroid, as other methods of increasing calcium excretion affect urinary excretion alone. This loss of calcium is quite out of keeping with the loss in body weight as in these 5 periods (X–XIV) the loss of body weight was only 2.6 kgm. more than in the control five periods. If one figured that the total loss of weight was due to body fluids and that these fluids contained 10 mgm. of calcium per 100 cc. as in serum, then the calcium excretion should have increased 260 mgm. The actual increased calcium output (2300 mgm.) would still be far in excess of this calculation. We are, therefore, again forced to the conclusion that the excess calcium was derived from the bones. It is clear that this

urinary calcium is markedly increased during the first three days of thyroid medication. This increase is also obvious in the phosphorus excretion, but the nitrogen elimination and the basal metabolic rate are not increased until the second period of thyroid feeding. It is thus evident that the response in the calcium metabolism to thyroid medication is partially independent of these other factors. This is confirmed in our studies of the treatment of parathyroid tetany with thyroid medication (Paper VI of this series (15)).

TABLE 2

The effect of thyroid administration on calcium excretion in the case of myxedema

Periods	Urine excretion	Total excretion	Balance	Remarks
	cc. N/10	*cc. N/10*	*cc. N/10*	
I–V	118*	234	−131	Before thyroid treatment
VI–IX	236	357	−243	First 4 periods of thyroid treatment
X–XIV	303	464	−352	5th–9th periods of thyroid treatment
XV–XVI	306	650	−534	Periods of established thyroid medication

* The average value per period is given in each case.

Phosphorus metabolism

In table 3 are given the data for the phosphorus balances. By "theortical balance" as described in an earlier paper (2) we mean that part of the phosphorus balance which is explainable by the calcium balance and by the nitrogen balance. This is based on the assumption that any balance of calcium represents $Ca_3(PO_4)_2$ in bones (Ca:P = 1.9)[2] and that any balance of nitrogen represents protein (N:P = 17.4). When the actual balance is less than the theoretical balance it should point to a loss of phosphorus from body fluids.

In table 3 one notes a tremendous increase in phosphorus excretion during thyroid medication. This was to be expected because of the large negative nitrogen balance. During the control periods (I–V) and

[2] Calcium has been thought to be deposited largely as tertiary calcium phosphate (Ca: P = 1.93) but is also partly deposited as calcium carbonate so that the ratio of calcium to phosphorus in bone is approximately 2.23: 1. For relatively rough calculations like the present it makes little difference whether one uses the factor 1.9 or 2.2. In this paper we have arbitrarily chosen 1.92.

the periods of established thyroid feeding (XV–XVI), one notes that not so much phosphorus was excreted as one would expect from the theoretical balance. This probably means that the phosphorus calculation from the diet was slightly too high. The interesting thing is that during the transition periods (VI–IX) more phosphorus was excreted than one should have expected, in contrast to these other periods. This occurred in spite of a rising blood phosphorus (see table 1). Again, even if the 4.1 kgm. loss of body weight during this period were entirely body fluids, which of course it was not as shown by the negative nitrogen balance, and if this body fluid were thought of as containing 4 mgm. of phosphorus per 100 cc., only 164 mgm. of phosphorus would be accounted for. It would appear that the imme-

TABLE 3

The effect of thyroid administration on phosphorus excretion in the case of myxedema

Period	Intake	Output	Actual balance	"Theoretical balance"	Excess of actual over "theoretical balance"
	*cc. N/10**	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*
I–V	877†	776	+101	−101	+202
VI–IX	967	1706	−739	−661	−78
X–XIV	958	1584	−626	−1006	+380
XV–XVI	989	1325	−336	−493	+157

* Phosphate figures are all reduced to cc. N/10 base which would be bound by phosphate at a pH of 7.35.

† The average value per period is given in each case.

diate effect of the thyroid hormone is to excrete phosphorus in excess of what can be explained by the increased nitrogen and calcium excretions. Furthermore, by comparing periods X–XIV with periods VI–IX, one gets the impression that the increased excretion of phosphorus at first is later compensated for. Thus if one averages periods VI–XIV together one obtains an average excess of actual over theoretical balance per period of +176, which is not far from that noted in the control periods. It would seem that the thyroid hormone had caused a breakdown of protein with an immediate excretion of the phosphorus and a later excretion of the nitrogen. Boothby, Sandiford, Sandiford and Slosse (16) found a temporary increase in the nonprotein nitrogen of the blood of two myxedema patients under thyroid treatment.

It should be further noted that the increased phosphorus excretion is entirely in the urine.

Acid radicles in urine

We have now to examine the acid elements which were excreted in the urine to see whether they increased appreciably under thyroid medication (see table 4). These factors are phosphates, sulphates, chlorides, and organic acid radicles.

The *phosphates* have been discussed above.

As was to be expected from the increased nitrogen excretion under thyroid medication, there was a corresponding increased *sulphur* excretion. The ratio of the increase in nitrogen excretion to the

TABLE 4

The effect of thyroid administration on acid excretion in the urine in the case of myxedema

Periods	Phosphates	Inorganic sulphates	Chlorides	Organic acid radicles	Total acids minus carbonates
	*cc. N/10**	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*
I–V	554†	595	2,030	1,273	4,452
VI–IX	1,420	1,236	1,638	892	5,186
X–XIV	1,352	1,603	1,864	779	5,598
XV–XVI	1,000	919	1,911	848	4,678

* Phosphate figures in terms of cc. N/10 base which would be bound by phosphates at a pH of 7.35.

† The average value per period is given in each case.

increase in inorganic sulphate excretion was during periods VI–IX, 17.3, during periods X–XIV, 15.8, and during periods XV–XVI, 17.3. This corresponds very closely with the ratio of 17.5 found by Gamble, Ross, and Tisdall (17) in fasting children. We may, therefore, assume that the increased sulphate excretion represents the oxidized sulphur from the increased protein catabolism.

It is interesting that during the whole observation of 48 days 416 cc. N/10 more *chloride* was eaten than was excreted in the urine. This is a variation of only 1.3 per cent of the intake. It is difficult to understand why more chloride was not excreted as a result of the large loss of weight. It is of special interest that least chloride was excreted during periods VI–IX and periods X–XIV when the loss of weight and

nitrogen were at their height. One wonders whether the chloride excretion in the urine was not diminished in these periods as a compensation to the increased sulphate and phosphate excretion. We did not examine the chloride excretion in the feces for it has not been considered a large factor. It is possible, however that the elimination of chloride here may have been appreciable and possibly more so at the time when other acids were increased in the urine.

Like the chloride excretion, the *organic acid* excretion was diminished during the periods of increased sulphate and phosphate excretion. This is in agreement with the observation made by Albright and Bauer (12) from a similar type of experiment that organic acid excretion is diminished in the urine during periods of increased excretion of acid radicles and increased during periods of increased excretion of basic radicles. It would appear that organic acid behaves somewhat like carbonic acid in this respect (see Gamble (11)).

In the last column of table 4 are given the figures for the *total acid excretion* in the urine. One notes that the net result is a gain of about 1000 cc. of N/10 per three-day periods during the first 27 days (periods VI–XIV) of thyroid medication. During the final periods (XV–XVI) the acid excretion has returned to approximately that found before thyroid medication. It would appear that the increased sulphate and phosphate excretions, resulting largely from the negative nitrogen balance, are not entirely compensated for by decreased chloride and organic acid excretion and that thyroid medication in this patient at least temporarily increased the sum total of acid electrolytes appearing for excretion in the urine.

Basic radicles in urine

We must now examine the basic radicles in the urine to see by what measures the increased acid excretion was met (see table 5). The basic factors are titratable acidity minus CO_2, NH_4 excretion, and total fixed base excretion.

The titratable acidity minus CO_2 showed the expected increase during the periods of increased acid excretion.

Likewise, the *ammonia* excretion was increased as a result of thyroid medication. Thus, two lines of defence against an acidosis had been partially mobilized.

When one examines the *total base* excretion (see table 1[3] as well as table 5), one is surprised to find that it is very little affected by thyroid medication. What little increased excretion there is, mostly in the feces, can be accounted for by the calcium lost from the bones rather than by base held in body fluids. As with the chloride excretion, one does not find even the increase which one would expect from the loss of weight and nitrogen (see calculation in footnote and table 1). Following the conception of Boothby, Sandiford, Sandiford and Slosse (16) we are led to believe that the loss of nitrogen represents deposit protein rather than true protoplasm and that this deposit protein does not hold water and salts to the same extent as structural protoplasm.

TABLE 5

The effect of thyroid administration on excretion of basic radicles in the urine in the case of myxedema

Periods	Titratable acidity minus CO_2*	NH_4	Fixed base	Sum of basic factors
	cc. N/10	*cc. N/10*	*cc. N/10*	*cc. N/10*
I–V	290	759	3,403	4,452
VI–IX	765	1,293	3,128	5,186
X–XIV	903	1,024	3,671	5,598
XV–XVI	653	732	3,293	4,678

* The meaning of "titratable acidity minus CO_2" has been discussed in the text.

Finally, when we examine the basic factors as a whole in the urine we find that the increased acid excretion is adequately taken care of

[3] By "theoretical total base balance" in table 1 is meant the total base balance which one would expect from the calcium balance and the nitrogen balance. Thus, if 100 cc. of N/10 calcium were lost from the bones one would expect the total base balance to be minus 100, other things being equal. Likewise, if nitrogen were lost from the body, one would expect the base held by the muscle water thus liberated to be excreted. In calculating the amount of muscle water liberated from the nitrogen balance, the following formula taken from Gamble, Ross, and Tisdall (17) has been used

$$N \times 29.5 \times 0.76 = \text{muscle water}$$

The first factor provides an estimate of the protoplasm destroyed and the second indicates the corresponding water content. The total base content of muscle water has been taken to be 180 cc. of N/10 per 100 cc. (17).

by an increase in the acidity of the urine and by an increase in ammonia excretion from body fluids; and that, consequently, the increased calcium excretion, the "fourth line of defence," is probably not acting in its capacity as a reserve supply of base but is caused by some other factor. This reasoning gains support by a comparison of the figures in this case with those obtained by administration of ammonium chloride to a patient with nephrosis studied by Albright and Bauer (12), and by the administration of phosphates and chlorides studied by Farquharson, Salter, Tibbetts, and Aub (4). These patients responded to acid ingestion by marked increase in total base excretion.

SUMMARY

The feeding of thyroid in this case of myxedema produced the following effects. The basal metabolism rose from minus 42 per cent to plus 5 per cent during the observation. With this change in the metabolic rate there was a loss of weight with a marked negative nitrogen balance. As a result of the negative nitrogen balance there was a large increase in the excretion of sulphates and phosphates in the urine. This increased acid value of the urine was somewhat diminished by a decreased excretion (? compensatory) of chlorides and organic acid radicles in the urine. The net increased acid value of the urine was entirely met on the basic side by an increase in titratable acidity and NH_4 excretion, so that there was no increased excretion of total base in the urine, other than the slight increase that could be accounted for by the increased calcium excretion. It is, therefore, thought unlikely that the increased calcium excretion which occurred in both urine and feces was due to a demand for base to help in the excretion of acid.

The figures also showed that the increased phosphorus excretion was at first more than could be explained by the increased calcium and nitrogen excretion, but that there was apparently later a compensatory retention of phosphorus.

From the fact that the increased nitrogen excretion was not associated with an increased excretion of total base and chloride it is believed that this nitrogen might represent destruction of deposit protein rather than of structural protoplasm and that deposit protein has a different relation to intra-cellular water and salts than has structural protein.

PART II

Effect of Lugol's solution and subtotal thyroidectomy on a patient with exophthalmic goiter

(The data for Part II is given in chart 2 and table 6.) The patient, Emma F., was a young woman who was suffering from a very acute and severe exophthalmic goiter. The six weeks' study includes the

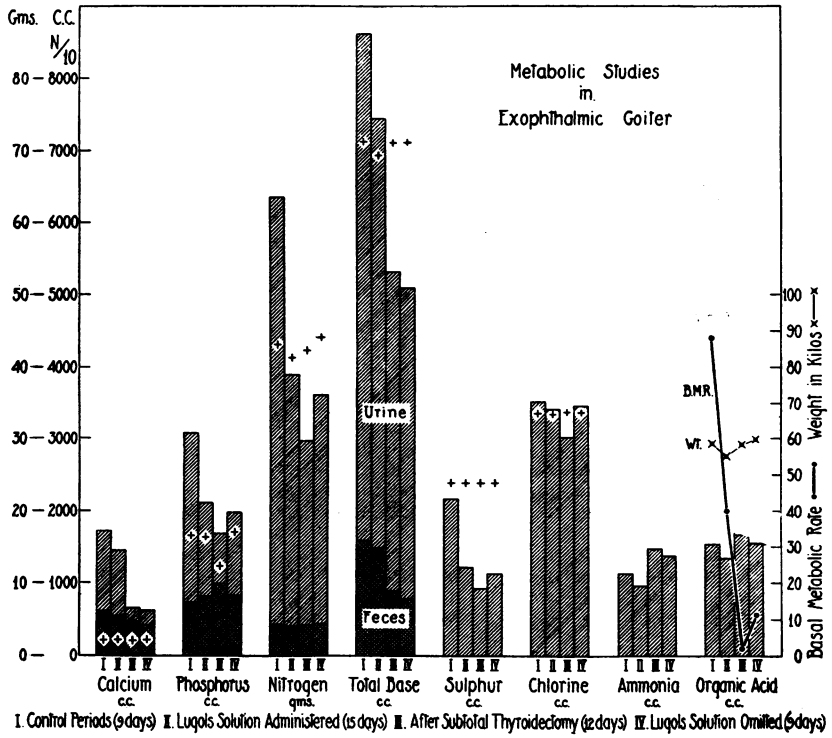

CHART 2

whole period of dramatic change from the severest type of the disease back to normal. Her basal metabolism changed from plus 99 per cent to a normal figure. The entire study of 16 three-day periods may be divided into:

(a) Control periods before treatment (periods I–III).
(b) Periods with Lugol's medication (periods IV–VIII).

TA

Emma F., aged 28. Admitted: April 14, 1927. Discharged: June 5, 1927. Diagnosis: Exophthalmic goite

Period number	Weight	Caloric intake	Fluid intake	Urine	Dried feces	Basal metabolic rate	Calcium metabolism					Phosphorus metabolism (valence assumed at 1.8)					Nitrogen m			
							Urine	Total output	Intake	Balance	Phosphorus equivalent of calcium balance	Urine	Total output	Intake	Balance	Theoretical balance	Urine	Total output	Intake	
	kilos	*calories*	*cc.*	*cc.*	*grams*		*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*grams*	*grams*	*grams*	*g*
I	59.2	8,997	11,802	5,460	93.4	+99	700	1,368	216	−1,152	−602	2,182	2,915	1,700	−1,215	−1,220	58.19	62.60	44.1	−
II	58.6	8,938	11,787	4,605	89.1	+95	1,176	1,738	215	−1,528	−797	2,498	3,230	1,674	−1,560	−1,648	64.21	68.51	43.0	−
III	57.8	8,934	11,760	6,320	71.5	+69	1,425	2,016	214	−1,801	−940	2,327	3,055	1,577	−1,478	−1,673	54.91	59.13	42.2	−
IV	57.0		13,600	5,745	73.9		1,161	1,685	207	−1,478	−771	1,826	2,428	1,373	−1,055		38.48			
V		9,033	13,600	7,550	69.6	+47	1,276	1,943	216	−1,727	−900	1,162	1,965	1,700	−265	−816	37.19	41.60	44.1	
VI	58.0	9,028	13,600	8,275	78 4		887	1,320	216	−1,104	−576	1,092	1,758	1,699	−59	−263	30.33	34.74	44.1	
VII	57.7	9,157	13,600	6,770	70.7	+34	663	1,284	216	−1,068	−557	1,144	1,952	1,700	−252	−304	32.11	36.52	44.1	
VIII	57.2	6,102	13,600	5,510	71.1		772	1,495	216	−1,279	−666	1,206	2,425	1,700	−725	−367	36.15	40.56	44.1	
IX		3,006	11,760	5,365			662		193			1,256		339			36.72	38.56	18.4	−
X	57 0	7,560	13,005	8,180	41.5		209	673	192	−482	−252	522	1,299	1,170	−129	27	25.03	28.74	37.1	
XI	57.6	9,033	13,600	9,185	59.4	+11	116	650	216	−434	−226	389	1,358	1,701	343	279	24.56	28.97	44.1	
XII	58.5	9.033	13,600	9,020	76.8	−7	156	713	216	−497	−259	598	2,389	1,700	−689	215	25.49	29.90	44.1	
XIII	59.4	9,147	13,600	9,140	72.0		210	561	216	−345	−180	681	1,220	1,700	480	262	26.40	30.80	44.0	
XIV	59.4	9,153	13,600	9,505	66.5		190	555	216	−339	−177	1,276	2,125	1,699	−426	227	27.60	32.00	44.1	
XV	59.5	9,153	13,600	10,310		+5	210	643	216	−427	−222	1,496	2,430	1,700	−730	−12	33.40	37.80	44.1	
XVI	60.2	9,153	13,600	9,085	72.5	+16	195	652	216	−436	−227	1,206	2,178	1,700	−478	−366	34.00	38.40	44.1	

* Constant low calcium diet. Protein 1.5 gram per kilogram per day. Calories 45 grams per kilogram per day. Fluid 3000 cc. per day

ABLE 6
er.

metabolism			Total base metabolism					Sulphur		Chloride					Blood serum		Medication and treatment per period
Balance	Phosphorus equivalent of nitrogen balance	Total base equivalent of nitrogen balance	Urine	Total output	Intake	Balance	Theoretical balance	Inorganic sulphur urine	Total sulphur intake	Urine	Intake	Ammonia	Titratable acidity — CO_2	Organic acid	Calcium	Phosphorus	
rams	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	
·18.50	−618	−748	6,307	7,927	7,104	−823	−1,900	2,100	2,505	2,974	3,388	1,258	1,264	1,573			See footnote*
·25.51	−853	−1,032	7,010	8,570	7,104	−1,466	−2,560	2,378	2,523	3,427	3,255	1,170	1,616	1,493	11.5	5.5	
·16.93	−570	−684	7,730		7,104		−2,485	2,010	2,465	4,168	3,377	975	1,339	1,544			
			6,045	7,343	6,279	−1,064		1,463		2,790		935	884	1,791	11.8	3.5	Lugol's solution 45
2.50	83	101	6,200	8,041	7,100	−941	−1,626	1,313	2,474	4,110	3,388	1,119	620	1,355	11.8	4.1	drops per day.
9.36	312	378	6,690	7,806	7,100	−706	−726	1,131	2,560	4,435	3,384	1,040	496	1,571	11.1	4.3	Fluid intake in-
7.58	253	306	5,620	7,311	7,100	−211	−762	1,210	2,560	3,472	3,388	1,061	656	1,510			creased to 3600 cc.
3.54	119	143	5,200	7,420	7,100	−320	−1,136	1,407	2,560	3,357	3,345	958	449	637	10.7	3.9	daily
·17.16	−573	−693	4,023					1,509	1,219	3,066	1,266	2,453	717				Subtotal thyroid-
·8.36	279	337	3,050	3,473	7,100	3,627	−145	1,066	1,861	2,552	3,222	1,904	190	996			ectomy
15.13	506	611	4,560	5,784	7,100	1,316	177	805	2,538	3,446	3,388	1,482	165	1,567			
14.20	475	574	5,200	6,016	7,100	1,084	67	986	2,538	2,784	3,388	1,188	238	2,258	9.2	5.9	
13.20	443	534	4,870	5,989	7,100	1,111	189	824	2,538	3,294	3,388	1,322	456	1,846	9.6	4.1	Lugol's solution dis-
12.10	404	489	5,600	6,383	7,100	717	150	922	2,538	3,730	3,388	1,308	804	1,777			continued
6.30	211	254	5,200		7,100		−173	1,264	2,538	3,003	3,388	1,426	859	1,722			
5.70	191	230	4,460		7,100		−206	1,216	2,538	3,642	3,388	1,392	1,015	800	10.2	4.0	

(c) Periods directly following subtotal thyroidectomy in which Lugol's medication was continued (periods IX–XII).
(d) Periods following cessation of Lugol's medication (periods XIII–XVI).

During the entire study she had almost the same food, water, and salt intake daily except for the period which included her operation.

Water balance

With the decreasing metabolism resulting from treatment there was an increased urinary excretion of water, in spite of a gain in weight. This diuresis, furthermore, was associated with a diminished excretion of urinary constituents. It is probable that this increase in urine was due to the decrease in the insensible perspiration associated with the decrease in basal metabolism.

Nitrogen metabolism

The urinary nitrogen excretion was very high at first, resulting in a considerable negative nitrogen balance during the first three control periods, but fell very rapidly under treatment so that a positive nitrogen balance was obtained during period V and thereafter with the exception of the time of the operation. The assumption is made that the fecal nitrogen is 10 per cent of the intake.

Calcium metabolism

In this patient, a marked increased calcium excretion in the urine and feces was found as in the cases of exophthalmic goiter which have already been reported. The urinary calcium excretion during the three control periods was 6.5 times normal and the fecal calcium excretion 2 times normal. By "normal"' we mean the calcium excretions of a series of normal men under a similar régime (18). It is most significant that this increased calcium excretion, although eventually brought almost to normal by treatment, remained nevertheless excessive after nitrogen equilibrium had been established (see table 7). This in itself is strong evidence that if the increased calcium excretion in hyperthyroidism is due to an acidosis, it is not simply due to the acidosis resulting from burning protein. Further evidence for this

will be found in Paper XIII (4) of this series: a normal man (R. F. F.) on a high protein diet excreted 83 grams of urinary nitrogen in three days. While this indicates a far higher protein catabolism, his calcium excretion remained less than one-fourth that found at first in this case of exophthalmic goiter.

TABLE 7

The effect of treatment on calcium excretion in the case of exophthalmic goiter

Periods	Urine excretion	Total excretion	Balance	Remarks
	cc. N/10	*cc. N/10*	*cc. N/10*	
I–III	1,100*	1,707	−1,494	Before treatment
IV–VIII	952	1,545	−1,331	Lugol's medication
IX–XII†	286	679	−471	Following subtotal thyroidectomy with continuation of Lugol's solution
XIII–XVI	201	603	−387	Following omission of Lugol's solution

* The average value per period is given in each case.

† In obtaining the averages the operative period (period IX) is omitted.

TABLE 8

The effect of treatment on phosphorus metabolism in the case of exophthalmic goiter

Periods	Intake	Output	Actual balance	"Theoretical balance"	Excess of actual over "theoretical balance"
	*cc. N/10**	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*
I–III	1,650†	3,067	−1,417	−1,514	+97
IV–VIII	1,634	2,105	−472	−438	−34
IX–XII‡	1,524	1,682	−158	+174	−332
XIII–XVI	1,700	1,988	−288	+28	−316

* Phosphate figures are all reduced to cc. N/10 base which would be bound by phosphate at a pH of 7.35.

† The average value per period is given in each case.

‡ In obtaining the averages, the operative period (period IX) is omitted.

Phosphorus metabolism

Table 8 shows an analysis of the phosphorus data. With the decrease in the negative nitrogen balance with treatment there was a marked reduction in the phosphorus excretion. Later there was a further reduction corresponding to the decreased calcium excretion. By a comparison of the actual and theoretical phosphorus balances it

will be seen that there was very close agreement at first. This supports the observation that the phosphorus lost from the body in hyperthyroidism is only what would be expected from the calcium and nitrogen losses (1). During recovery a little more phosphorus was excreted than could be accounted for by the calcium and nitrogen balances. As in the case of myxedema under treatment the phosphorus changes were almost entirely in the urine.

Acid radicles in urine

Table 9 has been constructed similar to table 4 to show the effect of treatment on the acid radicles in the urine.

TABLE 9

The effect of treatment on excretion of acid radicles in urine in the case of exophthalmic goiter

Periods	Phosphates	Sulphates	Chlorides	Organic acid radicles	Total acids minus carbonates
	*cc. N/10**	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*
I–III	2,336†	2,163	3,523	1,538	9,560
IV–VIII	1,286	1,305	3,633	1,373	7,597
IX-XII‡	503	952	2,928	1,607	5,990
XIII–XVI	1,165	1,056	3,417	1,536	7,174

* Phosphate figures in terms of cc. N/10 base which would be bound by phosphate at pH of 7.35.

† Average value per period is given in each case.

‡ In obtaining the averages, the operative period (period IX) is omitted.

The *phosphate* excretion has been discussed above and shows the marked fall under treatment with the terminal rise on the omission of Lugol's solution, thus paralleling the basal metabolic rate and the nitrogen excretion.

The *sulphate* excretion likewise parallels the nitrogen excretion. The ratio of urinary nitrogen excretion to the urinary inorganic sulphate excretion remains at about the level of 17.5 which Gamble, Ross, and Tisdall (17) found in children during fasting: 16.9 in periods I–III, 16.7 during periods IV–VIII, 17.2 during periods X–XII, and 17.4 during periods XIII–XVI.

The intake and output of *chlorides* over the whole period of observation are remarkably close. During this study of 48 days she consumed

550 cc. more N/10 chloride than were found in the urine. This is approximately one per cent of the total intake and is a very close approximation of the theoretical amount she should have retained considering the total gain of 1 kgm. in weight. Of course, during the period when she was losing weight her chloride excretion was higher than when she was depositing tissue. Thus, the low excretion of chlorides during periods IX–XII can be accounted for by the rapid gain in weight here. It appears, therefore, that the tissue losses and gains in exophthalmic goiter have essentially a normal chloride content in contradistinction to that found in myxedema.

The excretion of *organic acid* radicles remains on the whole quite constant although here again it tends to be highest when the other acids are lowest. Considering the large metabolic changes which occurred during this observation, the organic acid figures are remarkably constant.

When the figures giving the *total acid* excretion are compared it will be noted that there was a marked decrease in acid excretion as a result of treatment and that the total acid excretion followed the basal metabolism in a quite parallel curve. Except for the difference in the behavior of the chlorides it may be said that the acid radicle individually and collectively behaved oppositely to what they did in the case of myxedema under treatment.

Basic radicles in urine

Table 10 shows how the fluctuations in the acid excretion were met. The figures for the "*titratable acidity minus* CO_2" show the expected parallelism with the total acid excretion. Since the titratable acidity value of the urine is largely dependent on the buffer action of the phosphates one would expect it to be increased when a large amount of phosphate was being excreted.

The *ammonia excretion* is very surprising. It shows no parallelism with the acid excretion and is actually highest when least acid is present for excretion. This is all the more surprising when one realizes that the total nitrogen elimination was lowest when the ammonia excretion was highest. The ammonia mechanism is not called into use in this case of hyperthyroidism and the increased acid excretion is apparently completely taken care of by other factors. In other ex-

periments Farquharson, Salter, Tibbetts, and Aub (4) found that calcium and ammonia excretion increased together in response to chloride ingestion and neither responded much to increased phosphate ingestion. Here, however, there is no such parallelism.

The *total base* excretion, high at first, showed a tremendous decrease in the urinary excretion with treatment and a slight decrease in the fecal excretion. Thus, whereas the average urinary excretion per three-day period before treatment was 7018 cc. of N/10, after operation and before withdrawal of Lugol's solution it was 4269 cc. of N/10. When in table 6 the "theoretical total base balance" (= that derivable from calcium and nitrogen balances is compared with the actual total base balance it is seen that there is a discrepancy of about

TABLE 10

The effect of treatment on excretion of basic radicles in the urine in the case of exophthalmic goiter

Periods	Titratable acidity minus CO_2	NH_4	Fixed base	Sum of basic factors
I–III	1,407*	1,135	7,018	9,560
IV–VIII	622	1,024	5,951	7,597
IX–XII†	198	1,523	4,269	5,990
XIII–XVI	782	1,361	5,031	7,174

* Average value per period is given in each case.

† In obtaining the averages, the operative period (period IX) is omitted.

1000 cc. N/10 per three-day period throughout. This discrepancy, except in period X right after the operative period, remains reasonably constant and suggests that the figure for the base in the diet is constantly too large, although it was derived by actual analyses. The important thing is that the changes in the total base excretion are explainable by the changes in calcium and nitrogen excretions. This is in marked contrast again to the case of myxedema where the nitrogen balance seemed to have little influence on the total base balance. This is the exact counterpart of what occurred in the chloride excretion (v. supra).

Thus, in examining the basic factors as a whole (table 10) we see that the large fluctuations in the acid excretion were easily met by fluctuations in the acidity of the urine and in the total base excretion

and that the ammonia mechanism was never needed to help in the excretion of acid. Furthermore, the increased total base excretion during the hyperthyroid state was probably to be explained by the increased calcium excretion and the increase of base from intracellular fluid resulting from destruction of protoplasm, so that there was really no evidence of the "third line of defence" acting, namely, the excretion of base from extracellular fluid supplies.

SUMMARY

A patient with severe exophthalmic goiter (basal metabolic rate = plus 97 per cent) was brought to a normal state of metabolism (basal metabolic rate = minus 7 per cent) by Lugol's solution, followed by subtotal thyroidectomy. She later showed a slight secondary rise of metabolism (basal metabolic rate = plus 16 per cent) with omission of Lugol's solution. The marked negative nitrogen balance, present at first, disappeared with treatment. Associated with the negative nitrogen balance there was a large excretion of acid in the urine due to the sulphates and phosphates liberated from the metabolized protein and due to the chloride excretion from the intracellular water of metabolized protein. The fluctuations in the organic acid excretion were insignificant. This marked excretion of acid was met on the basic side by a large titratable acidity value in the urine and by a large total base excretion. These two factors apparently were sufficient so that the ammonia mechanism was not necessary and there was no excess of ammonia excretion. The total base excreted could probably be accounted for by the total base derived from the intracellular water of the metabolized protein plus the calcium excretion from the bones. There was apparently no increase in base derived from extracellular fluids. One is forced to the belief that the marked mobilization of calcium from the bones before treatment helped take care of the large acid excretion, but that the need for base to excrete acid was not the cause of the mobilization, in which case the ammonia mechanism and the excretion of base from extracellular fluid should also have been present. The fact that an increased titratable acidity of the urine was present before operation is probably merely a by-result of the increased phosphorus excretion and not evidence of an acidosis.

TABI

William S., aged 45. Admitted: January 21, 1927. Discharged: March 8, 1927. Diagnosis: Myositis ossifi

Period number	Weight	Caloric intake	Fluid intake	Urine	Dried feces	Basal metabolic rate	Calcium metabolism					Phosphorus metabolism (valence assumed at 1.8)					Nitrogen metaboli			
							Urine	Total output	Intake	Balance	Phosphorus equivalent of calcium balance	Urine	Total output	Intake	Balance	Theoretical balance	Urine	Total output	Intake	Balance
	kilos	*calories*	*cc.*	*cc.*	*grams*		*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*grams*	*grams*	*grams*	*grams*
I	85.7	7,019	8,523	4,385	96	+15	125	417	169	−248	−129	1,150	1,570	1,360	−210	−283	32.7	35.8	31.2	−4.6
II	85.6	7,028	8,523	4,220	59		126	338	169	−168	−88	830	988	1,360	373	−51	27.0	30.1	31.2	1.1
III	84.7	7,035	8,523	4,175	100	−6	143	454	169	−284	−148	880	1,314	1,360	46	−138	27.8	30.9	31.2	.3
IV	84.6	7,035	8,523	5,180	60		226	452	173	−278	−145	1,640	1,920	1,360	−560	−419	36.3	39.4	31.2	−8.2
V	84.1	7,046	8,523	4,915	35		545	667	173	−494	−258	1,750	1,946	1,360	−586	−379	31.7	34.8	31.2	−3.6
VI	83.7	7,035	8,523	5,070	56		646	906	173	−730	−382	1,430	1,656	1,360	−296	−689	37.3	40.4	31.2	−9.2
VII	83.1	7,035	8,523	4,835	72		635	920	173	−746	−390	1,470	1,866	1,360	−506	−579	33.8	36.9	31.2	−5.7
VIII	82.9	7,035	8,523	5,110	29		735	880	169	−710	−370	1,242	1,410	1,360	−50	−484	31.5	34.6	31.2	−3.4
IX	82.8	7,035	8,523	5,325	74		647	859	173	−686	−360	1,420	1,630	1,360	−270	−408	29.6	32.7	31.2	−1.5
X	82.3	7,035	8,523	5,525	102		656	913	177	−736	−384	1,540	1,785	1,360	−425	−448	30.0	33 1	31.2	−1.9
XI	82.4	7,035	8,523	4,640	124		251	492	177	−315	−164	1,200	1,570	1,360	−210	−191	28.9	32.0	31.2	−0.8
XII	82.0	7,035	8,523	5,625	109		153	363	180	−182	−95	730	1,047	1,360	313	−90	28.0	31.1	31.2	0.1
XIII	82.0	7,035	8,523	5,090	95		89	336	177	−159	−91	640	1,012	1,360	348	16	24.9	28.0	31.2	3.2
XIV	82.0	7,035	8,523	4.860	89		52	285	184	−101	−53	635	1,012	1,360	348	151	22.0	25.1	31.2	6.1

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m		Total base metabolism					Sulphur		Chloride					Blood serum		Medication
Phosphorus equivalent of nitrogen balance	Total base equivalent of nitrogen balance	Urine	Total output	Intake	Balance	Theoretical balance	Inorganic sulphur urine	Total sulphur intake	Urine	Intake	Ammonia	Titratable acidity $-CO_2$	Calculated organic acid	Calcium	Phosphorus	
cc. N/10	cc. N/10	cc. N/10	cc. N/10	cc. N/10	cc. N/10	cc. N/10	cc. N/10	cc. N/10	cc. N/10	cc. N/10	cc. N/10	cc. N/10	cc. N/10	mgm. per 100 cc.	mgm. per 100 cc.	
−154	−186	4,720	5,961	6,135	174	−434	965	1,671	3,245	3,852	507	862	729			
37	44	5,000	5,861	6,135	274	−124	830	1,671	3,780	3,852	559	621	740	10.9	3.3	
10	12	5,330	6,622	6,135	−487	−272	822	1,671	3,668	3,852	488	659	1,117			
−274	−331	6,240	7,263	6,135	−1,128	−609	847	1,671	3,780	3,852	610	498	1,081	9.7 10.6 11.3	3.7 3.5	150 units parathormone
−120	−145	6,590	7,014	6,135	−879	−639	958	1,671	3,850	3,852	898	502	1,432	12.2 11.5	3.2 2.4	160 units parathormone
−307	−371	5,430	6,162	6,135	−27	−1,103	1,072	1,671	2,910	3,852	740	400	1,158	11.7 12.9	2.6	300 units parathormone
−190	−230	5,380	6,446	6,135	−311	−976	1,080	1,671	3,055	3,852	767	244	786	12.4	3.0	300 units parathormone
−113	−137	5,940	6,503	6,135	−368	−847	920	1,671	3,910	3,852	813	382	1,065	12.4	3.0	300 units parathormone
50	−61	6,040	6,894	6,135	−759	−747	765	1,671	3,780	3,852	473	300	848	11.3	3.3	300 units parathormone
63	−77	6,970	8,010	6,135	−1,875	−813	845	1,671	4,231	3,852	551	155	1,060	12.7	2.8	300 units parathormone
27	−33	3,450	4,848	6,135	1,287	−348	857	1,671	2,428	3,852	748	339	52			
4	4	6,000	7,101	6,135	−966	−178	718	1,671	4,118	3,852	819	242	1,495	10.7	4.0	
107	129	6,265	7,612	7,335	−275	−30	650	1,671	3,105	3,852	503	−458	1,915			120 cc. M. sol. $NaHCO_3$
204	246	6,680	7,986	7,935	−51	145	634	1,671	3,392	3,852	320	−874	1,460			150 cc. M. sol. $NaHCO_3$

PART III

The effect of parathyroid extract administration on the total acid-base metabolism of an essentially normal individual

This study has been discussed in a previous publication (2). As the data was never published, however, it is included here in table 11 and chart 3. It furnishes an opportunity to compare the effects of the parathyroid hormone with that of the thyroid hormone.

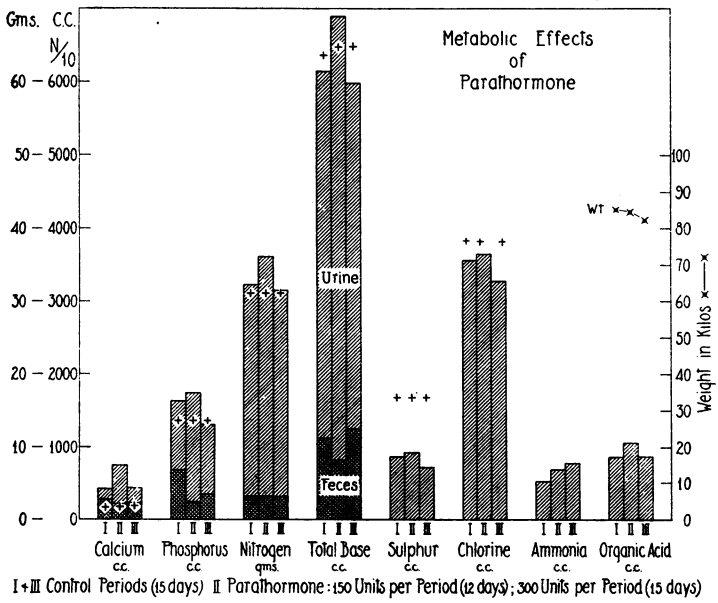

CHART 3

The patient was a laborer of 45 who received parathormone injections in the hope (which was unfulfilled) that an ossified hematoma of the thigh might be decalcified. He had a constant food and fluid intake throughout the duration of the investigation—14 three-day periods. During periods IV–X he received parathormone injections. During the final periods (XIII and XIV) he received sodium bicarbonate.

A detailed discussion of the results will not be repeated here. The outstanding effect of parathormone was on the calcium and phos-

phorus excretions and none of the other fluctuations were sufficient to seem fundamental. There was a tendency for the water, chloride, and total base excretion to increase during the periods of parathyroid administration. This was so slight that it would not deserve comment had there not been a marked reduction of these elements in the first period following cessation of the drug, suggesting that the previous rises were not coincidental. The slight increase in the protein metabolism as shown by the increased nitrogen and sulphur excretions was probably coincidental for it did not occur in the other normal individuals to whom we have given parathormone. Brehme and Gyorgy (19) stress the increased ammonia excretion after parathormone administration but the increase in this observation is certainly of small magnitude. The decrease in titratable acidity in the urine is very surprising, occurring at a time when the phosphates are much increased in the urine. The effect of sodium bicarbonate was what would be expected and needs no analysis here.

In summary it can be said that the parathyroid hormone had very little effect on the electrolytes of the urine except its well known effect on calcium and phosphate; that it did appear to increase slightly the excretion of body fluids with their salts as shown by an increased water, base, and chloride excretion; but that there was no evidence that it upset in any quantitative manner the acid-base balance of the body. In spite of an increased phosphate excretion in the urine there was a decreased titratable acidity under parathormone administration.

GENERAL SUMMARY AND CONCLUSIONS

The object of this study has been only partially fulfilled. We had hoped to determine the cause of the stimulating action of the thyroid hormone on calcium phosphate excretion but have merely ruled out certain possibilities. That the thyroid hormone does not act by stimulating the parathyroid glands seems evident from the lack of any marked effect of the thyroid hormone on serum calcium and serum phosphorus. That the thyroid hormone brings about mobilization of calcium phosphate to assist in the excretion of acid metabolites, a possibility which seemed a priori very probable, we believe we have likewise disproved. The evidence against this latter supposition is twofold. The marked increased excretion of acid resulting from thy-

roid administration in a case of myxedema was not sufficient to cause the excretion of base dissolved in extracellular body fluids even to a limited extent and the increased acid excretion in the case of hyperthyroidism was not sufficient to cause an increase in ammonia excretion or an increase in excretion of base dissolved in extracellular body fluids. One is forced to the supposition that the thyroid hormone exerts some specific action on the calcium-phosphate metabolism, which is the same as saying we have not found how it acts.

Certain speculations occur to one as possibly pertinent in the explanation of the action of the thyroid hormone on calcium phosphate mobilization from the bones. It seems not impossible that there may be a tissue acidosis resulting from increased cellular activity which is not reflected in the blood stream but which may increase the absorption of calcium from the bones. This is pure speculation. A second explanation is the possibility that the increased blood flow in hyperthyroidism is a factor in the increased calcium excretion. Investigators agree that the total blood flow is increased in hyperthyroidism and decreased in hypothyroidism, roughly proportionately to the metabolism (20, 21, 22). Since calcium is normally present in the blood stream well above its threshold for excretion (23), it would follow that the amount excreted by the kidney (and possibly by the gut) would be proportionate to the blood flow to these parts. Thus with a doubling of the metabolism one might expect an increase of the calcium excretion, provided that the increase in blood flow to the kidney is proportionate to increase in total blood flow. That increase in blood flow is not the entire explanation is shown by the over sixfold increase in calcium excretion in the urine in the case of exophthalmic goiter here reported. Such an explanation, furthermore, would not explain the rises, slight but definite, produced by the thyroid hormone on serum calcium and phosphorus. A third possibility is that the phenomenon may be associated with an increase in permeability of the tissues. Petersen and Levinson (24) in a recent review of this subject found "a striking increase in capillary permeability in exophthalmic goiter" and suggest this as the cause of the increase in calcium excretion. Since calcium diffuses with difficulty, any marked change in permeability of tissues might bring about a marked change in calcium excretion. This explanation, again, fails to account for the

changes in blood values. Finally, there may be a combination of several factors at work.

As an interesting by-result of the investigation, it appeared that the protein lost as a result of administration of thyroid to a patient with myxedema was dissimilar from protein lost during starvation or during thyrotoxicosis. Whereas hyperthyroidism is associated with the excretion of intracellular fluid with electrolytes in amounts depending on the destroyed protoplasm, these electrolytes seemed to be largely absent in myxedema. If as Boothby, Sandiford, Sandiford, and Slosse (16) suggest, administration of thyroid decreases deposit protein, it would appear that deposit protein does not have the same relationship to intracellular water as ordinary structural protein.

CLINICAL DATA

Case I. Mrs. L. C., Massachusetts General Hospital No. 281823. Clinical diagnosis: Myxedema. The patient's hospital entries were from February 18 to April 5, 1927, and from April 18 to April 27, 1927. She was a white, married woman of 63 who entered complaining of swelling of her extremities of 10 months' duration, orthopnea, and dyspnea. She had become mentally and physically sluggish.

Physical examination. Showed the following abnormalities: Appearance was typical of myxedema. The face and eyes were puffy and the skin coarse and dry. The edema did not pit much on pressure. Her sparse hair was fine and dry. Her tongue was large and her speech thick and deliberate. The heart was enlarged to the left.

Laboratory data (before giving thyroid). Red blood cells averaged 3,700,000 per cubic millimeter. Nonprotein nitrogen on whole blood: 60 mgm. per 100 cc., 30 mgm. per 100 cc. Wassermann reaction negative. Determinations by Dr. Arlie V. Bock: Oxygen capacity of whole blood: 16.0 volumes per cent CO_2 content of whole blood at 40 mm. pressure: 51.5 volumes per cent. Estimated pH of arterial blood: 7.50. Blood flow: 2.2 liters per minute. Urine: negative.

Electrocardiogram. Normal rhythm. Small complexes. T_2 inverted (minus 1 mm.). On her second admission to the hospital the electrocardiogram was normal with T_2 plus 2.5 mm.

X-ray. Heart increased in size to both right and left. Total width 14.1 cm. Internal diameter of chest 25.5 cm.

Diet. The daily diet consisted of: Total calories, 1420; calories per kilogram, 19; protein per kilogram, 0.81 gram. Diet averaged 100 cc. N/10 of excess acid over base in the ash.

Case II. Miss Emma F., Massachusetts General Hospital No. 282948. Clinical diagnosis: exophthalmic goiter. She remained in the hospital from April

14 to June 5, 1927. The patient was a white, unmarried, American governess of 28. During the previous nine months she had become progressively more nervous and had lost 17 lbs. For two months, after an attack of laryngitis, she had noticed a large appetite, marked tremor, perspiration, palpitation, and a progressively enlarging goiter. For one month she had noticed easy fatigability and a huskiness of her voice with slight dysphagia. For two days, stopping five days before entrance, she had taken 15 drops of a colorless solution of iodine daily.

Physical examination. Showed the following abnormalities: A large, hard, smooth symmetrical enlargement of the thyroid over which a systolic thrill and a systolic and diastolic bruit could be noted. There was a definite lid lag. The heart was large with a rapid rate and a loud systolic murmur, without a thrill, at both apex and base. The pulse rate remained above 120 before operation. Blood pressure was 140/70.

Labortory data. Urine: Normal except for traces of sugar in three tests. Blood morphology normal except for a relative lymphocytosis. Nonprotein nitrogen on whole blood: 35 mgm. per 100 cc. Blood sugar: 104 mgm. per 100 cc. Wassermann: negative.

X-ray examination showed a normal chest except for a heart increased in size both to the right and left. Transverse diameter 13.5 cm. Chest diameter 24.5 cm.

Operation. (By Dr. Edward Richardson.) A very large, horseshoe-shaped, symmetrical gland was found. About two grams of the right lobe and five grams of the left lobe were left behind. A small pyramidal lobe was removed.

Pathological report. (By Dr. H. F. Hartwell.) The removed tissue weighed 180 grams. No parathyroids were found after careful search. Microscopic examination showed proliferation of follicles and extensive hyperplasia of epithelium. There was little colloid. The stroma contained an increased amount of fibrous tissue and was infiltrated with mononuclear wandering cells.

Course in Hospital. During her stay in the hospital she had a temperature of 102° on the twelfth day after entrance (fourth period), due to a throat infection. For seven days after her operation she had a fever up to 102°—higher for the first five days.

Her basal metabolism and clinical condition, more than a year and a half after this operation, were normal. She appeared completely recovered.

Diet. Her diet consisted daily of the following: Total calories, 3000; calories per kilogram 45; protein per kilogram, 1.5 gram. Diet averaged 81 cc. N/10 of excess acid over base in the ash. Water intake was 3000 cc. per day.

Case III. Mr. William S., Massachusetts General Hospital No. 281245. Clinical diagnosis: Myositis ossificans. The patient stayed in the hospital from January 21 to March 8, 1927. He was a white, married laborer of 45 years. Three months before entrance he had been hit in the left thigh. The leg had become swollen, but he had been able to walk comfortably. X-ray examination showed a marked deposit of calcium in the muscle.

Physical examination. Showed the following abnormalities: On the lower third of the left upper leg there was a hard, irregular lump apparently attached to the soft parts.

Laboratory data. Blood morphology: normal. Wassermann reaction: negative. Basal metabolism: January 25, plus 15 per cent; February 1, minus 6 per cent; February 28, minus 7 per cent. Urine: negative.

Progress. The myositis ossificans was unaffected by the treatment.

Diet. His diet consisted daily of the following: Total calories, 2275; calories per kilogram., 27; protein per kilogram, 0.765 gram. Diet averaged 84 cc. N/10 excess base in the ash. Water intake was 2600 cc. per day.

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