STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

VI. In Hypoparathyroidism and Chronic Steatorrhea with Tetany with Special Consideration of the Therapeutic Effect of Thyroid

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Following the observation by Aub, Bauer, Heath, and Ropes (1), that the thyroid hormone exerts a marked effect upon the excretion of calcium, it became of interest to determine the therapeutic effect of this internal secretion upon the calcium metabolism in tetany. In hyperthyroidism, although the blood calcium and phosphorus levels are essentially normal, the calcium and phosphorus excretions are abnormally high. Tetany of the low calcium variety, however, has been shown to have an abnormally low calcium excretion associated with the abnormally low blood calcium level. The primary purpose of these metabolic studies was to study the influence of thyroid medication on the level of calcium and phosphorus in the blood and excreta of patients suffering from tetany. Other observations, however, were made for comparison and this paper includes data illustrating the influence on inorganic salt metabolism of:

1. Hypoparathyroidism,
2. Chronic steatorrhea complicated by tetany,
3. The immediate and prolonged use of parathyroid and thyroid medication in the tetany of hypoparathyroidism, and
4. The production of acidosis in the above types of tetany.

The data reported in this paper were obtained from three cases of tetany which we observed over prolonged periods. K. L. (Case I) had severe, chronic parathyroid tetany which was precipitated by two radical thyroidectomies for very mild Graves' disease. The tetany eventually could not be controlled, and the patient died. B. W. (Case II) [1] apparently had idiopathic parathyroid tetany. DeLaB. (Case III),[1] a young woman with tetany produced by celiac disease or steatorrhea, was similar to patients reported by Blumgart (2), Thaysen (3), Holmes and Starr (4), Linder and Harris (5), and Hunter (6). The summaries of the case histories are attached to the end of this paper. These cases were studied in

[1] Cases II and III are further discussed in other papers (9, 10, 11).

the metabolism ward of the Massachusetts General Hospital with the same careful routine and methods already fully described in papers I and II of this series (7) (8). We were able to maintain a rigid regime with constant food intake in which a change of medication was often the only variant. The excellent cooperation of the patients allowed us to obtain repeated observations over many months. (The metabolic data are given in Tables I, II, and III.)

The metabolic characteristics of parathyroid tetany

These three patients grouped themselves into two types. K. L. and B. W. (Cases I and II) represented parathyroid deficiencies, while DeLaB. represented a metabolic abnormality which was probably primarily digestive. Each of the types had a low blood calcium level and the signs and symptoms of tetany (see Table IV). The difference in these two types was best seen in the blood inorganic phosphorus levels, a determination which is of prime importance in the differentiation of types of tetany. Thus, both K. L. and B. W. had elevated blood phosphorus levels, characteristic of parathyroid tetany, while DeLaB. had a lower level than normal.

Low blood calcium values in parathyroid tetany are now well established, and these cases showed a reduction which was more than 50 per cent below the normal value. Calcium chloride intravenously did not raise the blood calcium or affect blood phosphorus levels for any prolonged period. Within two hours after the injection these values had returned to their previous levels in Case I. Hourly blood calcium determinations, after B. W. (Case II) ingested 5 grams of calcium lactate, disclosed a maximum elevation at the end of two hours of less than 1 mgm.

The extraordinarily low calcium excretion in the urine, like the low serum calcium, was present in both types of tetany. In the three cases it averaged only 26 mgm. in three days while in our normal controls the average was 190 mgm. The fecal excretion on a low calcium diet was essentially normal in the two patients with hypoparathyroidism in contrast to the slight elevation in the patient with steatorrhea. This indicates that the excretion of calcium by bowel, inasmuch as it is not decreased by a low blood calcium, is probably not a threshold phenomenon. This supposition is strengthened by the finding of a decreased fecal calcium excretion in hyperparathyroidism.

The excretion of phosphorus in the two untreated cases of parathyroid tetany was lower than that in normal individuals. Just as with calcium, the urinary phosphorus excretion was reduced, but the fecal excretion was essentially normal. Thus, just as a high partition of phosphorus in the urine as compared with the feces is characteristic of hyperparathyroidism (12), the opposite is the case in parathyroid tetany.

TABLE I

Katherine L., aged 25, white, female. Admitted January 28, 1926
(Intake and output per 3-day period)

Date ending period	Period number	Calcium				Phosphorus				Nitrogen				Total caloric intake	Blood plasma				Basal metabolic rate	Treatment and remarks
		Excretion			Intake	Excretion			Intake	Excretion			Intake		Date	Ca	P	Serum Ca		
		Urine	Feces	Total		Urine	Feces	Total		Urine	Feces	Total								
		grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*		*per cent*	
																5.2			2/ 1	−11	
																			2/ 2	−12	
																			2/ 3	−18	
															2/ 9	4.4					
															2/11	4.6	4.8				2/11. Severe tetany. $CaCl_2$ 1 gram intravenously, plus parathormone 20 units
2/12	1	.04	.78	.82	.23	.56	.78	1.34	1.39	7.3	1.5	8.8	14.2	3925	2/12	4.3	5.6		2/12	−13	2/12 to 2/15. Parathormone 10 units daily
2/15	2	.01	.14	.15	.21	.59	.36	.95	1.34	7.5	1.9	9.4	13.3	4130	2/15	4.2	5.8				2/16. Severe tetany. $CaCl_2$ 1 gram intravenously, plus parathormone 30 units
															2/16	4.6	5.7				2/17. Parathormone 15 units daily until 4/7
															2/18	6.2	4.2				
2/21	3	.01	.29	.30	.33	.48	.21	.69	1.48	11.6	2.0	13.6	15.9	5745	2/20	6.0	4.3				
															2/22	5.9	4.2				
2/24	4	.04	.33	.37	.33	.98	.70	(1.68)	1.48	10.0	4.3	14.3	15.8	5745	2/24	5.6	4.2		2/24	−20	
															2/26	6.7	5.5				
2/27	5	.15	.34	.49	.33	.96	.12	1.08	1.63	17.1	2.1	19.2	20.1	6281							
															3/ 1	6.7	4.3				
3/ 2	6	.06	.26	.32	.33	1.13	.13	1.26	1.63	14.8	1.8	16.6	20.1	6333					3/ 2	−14	3/2. Thyroxin 10 mgm.
															3/ 4	7.8	6.0				
3/ 5	7	.06	.47	.53	.33	.74	.85	1.59	1.48	10.4	5.7	16.1	18.0	4810							
															3/ 6	7.5	5.9		3/ 6	− 2	3/8. Attacks of tetany until now. None hereafter
3/ 9	8	.07	.32	.39	.31	1.60	.88	2.48	1.52	21.4	2.5	23.9	19.3	5875	3/ 8	8.0	4.5		3/ 9	−10	3/9. Thyroxin 10 mgm.
															3/10	8.5	4.0				3/10. Thyroid 0.3 gram daily
3/12	9	.14	.40	.54	.33	1.60	.33	1.93	1.63	20.1	1.5	21.6	20.1	6333	3/12	9.2	(5.1)		3/12	− 2	3/12. Thyroxin 5 mgm.
3/14	10	.17	.34	.51	.33	2.10	.26	2.36	1.63	24.3	2.7	27.0	20.1	6333	3/15	10.1	4.4				
3/17	11	.35	.62	.97	.33	2.17	.43	2.60	1.63	26.7	3.4	30.1	20.1	6652	3/17	11.2	4.3		3/18	+22	3/17. Thyroid stopped
															3/19	11.9	4.4				
3/20	12	.75	.48	1.23	.33	1.61	.30	1.91	1.63	20.5	2.3	22.8	20.1	6333	3/22	9.5	3.5		3/20	+10	
3/23	13	.74	.52	1.26	.34	.98	.42	1.40	1.63	18.5	1.9	20.4	20.1	6333	3/24	11.4	5.3		3/23	+ 5	
3/26	14	.60	.47	1.07	.33	1.21	.40	1.61	1.63	13.2	2.8	16.0	20.1	6333	3/26	10.7	4.6		3/27	− 5	
3/29	15	.60	.54	1.14	.33	1.11	.43	1.54	1.63	13.1	2.3	15.3	20.1	6333	3/29	10.6	2.7		3/30	− 8	
															3/31	11.0	4.7				
4/ 1	16	.48	.87	1.35	.33	.84			1.63	19.1	3.9	23.0	20.1	6333	4/ 2	9.9	4.6		4/ 2	−16	

TABLE I (*continued*)

Date ending period	Period number	Calcium				Phosphorus				Nitrogen				Total caloric intake	Blood plasma				Date	Basal metabolic rate	Treatment and remarks
		Excretion			Intake	Excretion			Intake	Excretion			Intake		Date	Ca	P	Serum Ca			
		Urine	Feces	Total		Urine	Feces	Total		Urine	Feces	Total									
		grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*		*per cent*	
4/ 4	17	.35	.37	.72	.33	.72	.37	1.09	1.63	12.8	2.3	15.1	20.1	6333	4/ 5	9.3	4.7		4/ 6	−18	
4/ 7	18	.40	.64	1.04	.33	1.24	.61	1.85	1.63	9.0	2.5	11.5	20.1	6333	4/ 7	9.4	3.8				4/7. Parathormone dosage changed,—given on alternate days only
4/10	19	.37	.54	.91	.34	.81	.48	1.29	1.83	12.8	2.2	15.0	23.3	6971	4/10	7.0	4.5		4/ 9	−18	
															4/12	7.8	6.4				
4/13	20	.21	.47	.68	.33	.45	.47	.92	1.92	16.3	4.3	20.6	24.9	7290	4/13	7.4	5.0		4/13	−21	4/13. Parathormone units 7 daily until 6/19
															4/14	7.1	5.4				
4/16	21	.14	.59	.73	.33	1.17	.60	1.77	1.92	17.4	2.8	20.2	24.9	7290	4/16	7.7	5.3		4/16	−27	
4/19	22	.13	.60	.73	.33	.85	.54	1.39	1.92	19.9	2.8	22.7	32.9	7290	4/18	6.7	6.5	7.0			4/19. Tetany. Thyroxin 10 mgm., Ca lactate 2 grams, milk 160 cc.
															4/20	6.5	6.7	7.9			
4/22	23	.12	.66	.78	.74	1.47	.48	1.95	1.95	25.2	4.0	29.2	24.9	6966	4/22		6.5	7.1	4/22	−14	
															4/24	7.7	5.8	8.2			
4/25	24	.13	.59	.72	.33	1.13	.49	1.62	1.92	24.7	2.9	27.6	20.8	7290	4/26	10.1	4.9	9.9	4/26	− 1	
4/28	25	.26	.50	.77	.23	2.20	.43	2.63	1.44	26.2	2.1	28.3	26.8	4525	4/28	8.4	5.4	8.9			4/27. Thyroxin 9.5 mgm.
5/ 1	26	.21	.46	.67	.31	1.25	1.00	2.25	1.79	16.9	2.3	19.2	28.3	6075	4/30	7.9	6.1	8.4	4/30	+ 5	5/1. Thyroxin 10 mgm.
															5/ 3	8.4	5.6				
5/ 4	27	.17	.50	.67	.33	1.12	.46	1.58	1.92	25.2	2.0	27.2	28.3	6537	5/ 5	9.2	4.3	9.7	5/ 4	+16	
5/ 7	28	.38	.59	.97	.33	1.59	.41	2.00	1.92	20.4	2.0	22.4		6537	5/ 7	8.7		9.8	5/ 6	+10	
5/10	29	.62	.68	1.30	.33	1.70	.64	2.34	2.02	24.2	3.3	27.5	24.5	6495	5/ 9	9.5	4.8				5/10. A little urine was lost
5/13	30	.52	.77	1.29	.33	1.60	.71	2.31	2.02	19.3	3.7	23.0	23.2	6474	5/12	8.7	5.2		5/13	− 1	
5/16	31	.62	.61	1.23	.33	1.61	.52	2.13	2.02	17.2	4.4	21.6	23.5	6474	5/14	9.2			5/17	− 4	
5/19	32	.62	.47	1.09	.33	1.44	.57	2.01	2.18	14.6	2.9	17.5	25.6	7032	5/19	7.8	4.8		5/19	−11	
5/22	33	.62	.48	1.10	.33	1.14	.55	1.69	2.49	17.1	2.4	19.5	29.7	6148	5/21	9.6	4.8				
															5/23	7.3	6.3				
5/26	34	.46	.58	1.04	.32	1.42	.45	1.87	2.48	16.3	3.3	19.2	29.1	7928	5/26	8.1	6.3		5/27	−16	
5/28	35				.32								28.8	7548	5/28	8.3	4.3				
															5/29	9.5	5.7				
5/31	36	.36	.58	.94	.32	1.34	.59	1.93	2.49	17.6	2.7	20.3	28.8	7413	5/31	8.8	5.8				
6/ 3	37	.32	.60	.92	.32	1.08	.64	1.72	2.49	21.0	2.2	23.2	28.8	7413	6/ 3	8.7	5.0				
6/ 6	38	.30	.66	.96	.32	1.62	.67	2.29	2.49	19.4	3.2	22.6	28.8	7413	6/ 5	7.7	4.7				
															6/ 7	10.1	4.5				6/8. Blood nonprotein nitrogen 29
6/10	39	.37	.70	1.07	.32	1.13	.63	1.76	2.49	16.9	5.3	22.1	28.8	7413	6/ 9	9.5	4.8				
6/12	40				.32								28.8	7413	6/12	8.8	5.2		6/11	−26	
6/15	41	.33	.75	1.08		1.95	.91	2.86		17.0	5.9	22.9			6/14	9.2					6/15. Unrestricted diet

TABLE I (*continued*)

Date ending period	Period number	Calcium				Phosphorus				Nitrogen				Total caloric intake	Blood plasma				Date	Basal metabolic rate	Treatment and remarks
		Excretion			Intake	Excretion			Intake	Excretion			Intake		Date	Ca	P	Serum Ca			
		Urine	Feces	Total		Urine	Feces	Total		Urine	Feces	Total									
		grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*		*per cent*	
6/18	42	.57	.76	1.33		2.09	1.11	3.20		20.4	9.1?	29.5			6/19	7.8	5.2				6/19. Thyroid started
6/21	43	.39	1.14	1.53		3.14	1.16	4.30			4.8				6/21	8.4	4.9				
6/24	44	.40	.92	1.32		4.35	.89	5.24			6.4				6/23	7.3	6.3		6/23	− 6	
6/27	45	.41	.93	1.34		2.46	1.01	3.47			8.6				6/26	8.7	5.3		6/26	−10	
															11/ 4	4.9	5.0				
															11/ 8	4.8	6.3		11/ 8	− 3	11/8. Parathormone 15 units daily
11/14	46	.07			2.24	1.54	1.14	2.68	2.15	22.2	2.8	25.0	31.5	6058	11/13	5.0	6.3				
11/17	47	.06			2.25	1.50	.93	2.43	2.15	22.2	2.9	25.1	32.2	6288	11/17	4.8	6.6				
															11/18	5.4					
11/20	48	.08			2.25	1.47	1.00	2.47	3.04	22.5	2.4	24.9	29.6	5830	11/19	5.2	6.1		11/19	−12	
															11/22	5.9	6.1				
11/23	49	.10			2.25	1.26	.93	2.19	2.98	23.4	3.8	27.2	28.3	5601							
11/26	50	.07			2.25	1.13	.76	1.89	2.99	21.7	2.6	24.3	28.3	5664	11/27	4.4	5.8		11/26	0	
11/29	51	.05			2.25	1.12	1.17	2.29	2.78	21.1	(2.6)	(23.7)	26.3	5413	11/29	5.0	6.4				11/29. HCl 25 cc. per day
12/ 2	52	.09			2.25	1.23	.87	2.10	2.98	20.7	2.9	23.6	28.3	5596	12/ 3	4.9	6.4		12/ 3	−16	12/3. Milk
12/ 5	53	.09			2.25	1.55	.98	2.53	2.99	24.2	2.0	26.2	28.3	5601	12/ 6	5.1	5.7				12/5. NH_4Cl 3 grams per day
12/ 8	54	.13			2.25	1.32	.68	2.00	2.99	23.2	3.9	27.1	28.3	5601							
12/11	55	.07			2.25	1.54	1.38	2.92	3.01	26.5	(2.9)	29.4	28.6	5713	12/11	5.5	4.1				12/11. HCl stopped. NH_4Cl 6 grams per day
12/14	56	.16			2.24	1.08	.49	1.57	3.89	23.0	3.9	26.9	26.4	5590	12/15	4.7					
12/17	57	.16	1.28	1.44	2.24	1.17	.46	1.63	2.98	25.0	2.6	27.6	27.8	5700							
12/20	58	.18	1.93	2.11	2.25	1.46	.58	2.04	3.04	27.5	1.1	28.6	29.3	5900	12/20	4.6	6.7		12/20	−13	
															12/21	4.9	6.2				12/21. Parathormone 50 units
12/23	59	.17	2.16	2.33	2.25	1.46	1.21	2.67	3.04	25.1	(3.0)	(28.1)	30.5	5801	12/23	5.2	6.5				
															12/27	5.4	7.1				1/3. Parathormone 30 units
1/10	60	.05	1.37	1.42	2.25	1.31	.87	2.18	3.04	20.9	(2.9)	(23.8)	29.3	5826	1/ 4	4.4	7.6		1/ 5	− 9	1/4. Parathormone 40 units
															1/ 7	4.8	7.3				1/5. Parathormone 80 units
															1/10	4.8	7.2				1/6. Parathormone 100 units. (This dose continued)
1/13	61	.06	1.70	1.76	2.25	1.10	1.14	2.24	3.04	21.4	(2.9)	(24.3)	29.3	5831	1/13	4.6	7.0				
1/16	62	.09	1.43	1.52	2.17	1.03	.93	1.96	3.01	19.5	(2.8)	(22.3)	28.3	6190							1/7. NH_4Cl stopped
1/19	63	.10	.99	1.09	2.24	1.10	.61	1.71	2.99	15.9	(2.7)	(18.6)	27.5	5967	1/19	5.0	7.8		1/18	−23	
1/22	64	.15	1.41	1.56	2.25	1.36	.76	2.12	3.07	23.4	(2.8)	(26.1)	28.8	6246	1/24	3.8	7.0		1/22	− 2	1/21. $CaCl_2$ intravenously
1/25	65	.16	.71	.87	2.11	1.59	.35	1.94	2.01				15.4	3743	1/26	5.0	7.6				

TABLE II

Benjamin W. Aged 52, white, male. Admitted—July 10, 1926. Diagnosis—Idiopathic tetany
(Intake and output per 3-day period)

Date ending period	Period number	Body weight	Calcium				Phosphorus				Nitrogen				Total caloric intake	Date	Blood plasma		Basal metabolic rate	Treatment and remarks
			Excretion			Intake	Excretion			Intake	Excretion			Intake			Ca	P		
			Urine	Feces	Total		Urine	Feces	Total		Urine	Feces	Total							
		kilos	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*per cent*	
7/12		56.9																	− 1	7/10. Low calcium diet started 7/12. Calcium tolerance test. Ca lactate 10 grams
7/14	1	57.1	.02	.89	.91	.24	.82	.31	1.13	1.94	16.0	2.2	18.2	21.0	4505	7/12	5.1	6.1		
																7/14	5.1	5.9		
7/17	2	56.6	.03	.47	.50	.26	.81	.63	1.44	1.70	21.3	3.7	25.0	21.1	4376	7/17	4.3	7.3		7/17. Thyroxin 10 mgm.†
																7/19	4.3	7.8		
7/20	3	56.2	.03	.29	.32	.24	.88	.54	1.42	1.60	19.1	1.6	20.7	16.0	3609	7/21	4.2	7.9	−13	7/21. Thyroxin 10 mgm.
																			−23	
7/23	4	53.6	.03	.07	.10	.23	1.12	.16	1.28	1.04	14.3	1.4	15.7	10.4	2812	7/23	4.5	8.0		
																7/24	4.7	8.0	−21	7/24. Tetany
7/26	5	52.3	.01	.21	.22	.23	1.76	.39	2.15	1.23	22.1	3.0	25.1	19.0	3917	7/26	4.6	6.7	−15	
																7/28	4.6			7/29. Thyroxin 10 mgm.
7/29	6	52.8	.00	.23	.23	.24	.99	.39	1.38	1.46	19.4	2.7	22.1	18.0	3470	7/30	4.7		− 3	
8/ 1	7	52.0	.02	.30	.32	.21	.96	.52	1.48	1.26	23.5	4.0	27.5	18.4	3476	8/ 2	4.9	5.9		
																8/ 3	5.3	6.8	− 8	
8/ 4	8	50.4	.01	.32	.33	.30	1.28	.43	1.71	1.54	23.0	3.6	26.6	27.4	4908	8/ 4	5.2	6.5		
																8/ 5	5.8			
8/ 7	9	50.1	.05	.34	.39	.30	1.34	.57	1.91	1.69	23.5	4.2	27.7	23.3		8/ 6	5.7	4.9	− 7	
																8/ 7	5.5			
																8/9	6.0	5.4		
																8/10	6.1	5.7		
																8/12	6.7	4.4		
																8/14	6.7	3.0	−20	
																8/17	6.5			
																8/18	6.1	5.0		
																8/19	6.6	5.7		
																8/21	6.2	6.2		
																8/23	6.2	6.3		
																8/25	6.1	6.2		
																8/27	6.0	6.2		
																8/28	6.1	6.6		
																9/ 6	5.7	5.6		
																9/16	5.0			
																9/24	5.7	5.6		

TABLE II (*continued*)

Second admission—October 11, 1926

Date ending period	Period number	Body weight	Calcium				Phosphorus				Nitrogen				Total caloric intake	Date	Blood plasma		Basal metabolic rate	Treatment and remarks
			Excretion			Intake	Excretion			Intake	Excretion			Intake			Ca	P		
			Urine	Feces	Total		Urine	Feces	Total		Urine	Feces	Total							
		kilos	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*per cent*	
10/15		55.1														10/12	5.4	5.5		
																10/16			−22	
10/17	10	55.6	.05			5.96	1.85			6.42	30.4	2.1	32.5	50.2	7329	10/17	6.0			
																10/19	6.0	5.5		
10/21	11	56.2	.04			6.01	1.88			6.47	26.3	2.9	29.2	50.4	7404	10/20			−14	10/20. Thyroxin, 10 mgm.
																10/21	5.9	6.3		
10/23	12	57.2	.02			6.05	2.59			6.47	35.2	2.6	37.8	50.5	7396	10/23	5.9	5.8	− 9	
																10/25	5.7	5.3		10/24. Thyroxin, 10 mgm.
10/27	13	56.6	.04			5.81	2.06			6.31	33.1	3.4	36.5	50.1	7332	10/26			−18	
																10/27	5.8	5.4		
10/29	14	57.0	.04			5.92	2.32			6.41	33.3	5.6	38.3	50.4	7356	10/29	5.9	4.2	− 7	
11/ 1	15	57.3	.05			6.01	1.79			6.46	30.1	5.5	36.2	55.5	7937	11/ 1	5.6	6.5	−16	11/1. Thyroxin, 10 mgm.
																11/ 3	5.8	6.4	−12	
11/ 4	16	57.0	.03			5.07	2.24			5.36	30.1	2.6	33.1	45.7	6636	11/ 6	6.2	5.4		
11/ 7	17	56.8	.03			5.10	1.87			6.15	29.3	9.3	31.6	52.0	6917					
																11/ 8	5.6	5.8	−14	
11/10	18	57.4	.03			6.00	1.91			6.47	32.2	4.3	36.5	55.2	7548					11/10. Thyroxin, 10 mgm.
																11/12	5.7	6.5	+ 2	
11/13	19	57.1	.05			6.01	3.00			6.35	35.4	4.0	39.4	52.9	7451					11/14. Thyroxin, 10 mgm.
																11/15	6.2	6.2	+10	
11/16	20	57.0	.04			5.73	3.02			5.40	40.4	3.0	43.4	42.5	6215					
																11/17	6.2	5.9	+16	11/18. Thyroxin, 10 mgm.
11/19	21	56.6	.02			5.66	2.67			5.37	33.5	2.9	36.4	43.3	6587					
																11/20	5.4	6.1		
11/22	22	56.6	.03			5.08	2.73			4.76	46.4	2.7	49.1	36.9	6028	11/22	6.3	5.8	+21	
																11/24	6.1	5.3	+12	
11/25	23	55.0	.02			5.22	2.38			5.33	39.8	4.1	43.8	39.5	6285					
																11/27	7.1	5.1		
11/28	24	55.2	.04			5.79	2.35			5.88	40.8	5.1	45.9	43.0	6845					
																11/29	7.1	4.7		
12/ 1	25	55.0	.02			5.76	1.53			5.91	37.4	3.0	40.4	42.5	6814	12/ 1	7.3	5.2	+ 6	
																12/ 3	7.5	5.8		
12/ 4	26	55.2	.04			6.05	1.41			6.04	32.0	4.1	36.1	45.2	7168					
																12/ 6	6.4	6.1		

TABLE II (*continued*)

Date ending period	Period number	Body weight	Calcium				Phosphorus				Nitrogen				Total caloric intake	Date	Blood plasma		Basal metabolic rate	Treatment and remarks
			Excretion			Intake	Excretion			Intake	Excretion			Intake			Ca	P		
			Urine	Feces	Total		Urine	Feces	Total		Urine	Feces	Total							
		kilos	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*per cent*	
12/ 7	27	55.2	.04			6.03	1.47			5.53	28.0	4.5	32.5	44.5	7248	12/ 8	6.0	5.0	− 8	12/8. Parathormone, 10 units daily to 1/13/1927 inclusive
																12/10	7.2	4.3		
12/11	28	55.4	.05	3.21	3.26	5.44	1.90	2.42	4.32	6.00	25.3	3.8	29.1	38.4	6894					
12/13	29		.03	3.72	3.75	5.76	1.68	1.98	3.66	5.62	25.9	4.2	30.1	42.0	6871	12/13	7.6	4.6		
																12/15	7.8			
12/16	30	55.0	.01	3.73	3.74	5.53	1.38	2.32	3.70	5.33	24.6	3.8	28.4	39.2	6458					
																12/17	7.6	6.1		
12/19	31	55.6	.08	3.90	3.98	5.57	1.48	1.80	3.28	5.75	22.3	5.5	27.8	41.9	6969				−12	12/20. Thyroxin, 10 mgm.
																12/20	7.3	6.2	− 2	
12/22	32	55.2	.07	4.29	4.36	5.12	1.58	1.47	3.05	4.96	24.9	3.7	28.6	36.6	6195	12/23	7.8	7.0		
12/25	33	54.6	.05	3.87	3.92	4.36	2.25	1.45	3.70	3.19	31.3	3.3	34.6	33.1	5022	12/27	7.1		+ 7	12/27. Thyroxin, 10 mgm.
																12/30	8.3		+32	
1/ 1	34	53.0	.03	3.78	3.81	4.05	2.27	1.29	3.56	4.40	32.9	3.4	36.3	33.8	4890	12/31	8.1		+33	
																1/ 3	9.5			
1/ 5	35	52.6	.02	3.51	3.53	3.73	1.79	1.38	3.17	4.00	27.0	3.1	30.1	30.7	4592	1/ 5	9.3	4.7	+12	
1/ 7	36	52.0	.28	2.01	2.29	4.28	1.50	1.25	2.75	4.35	33.1	3.5	36.6	34.6	5429	1/ 7	9.3	3.7		
																				1/ 7 }
1/10	37	51.8	.11	2.12	2.23	2.94	.74	1.25	1.99	2.85	25.4	2.2	27.6	21.9	4356	1/10	9.4	5.0		1/10 } Teeth extracted
																				1/12 }
1/13	38	52.2	.02	3.92	3.94	4.68	1.01	1.43	2.44	4.76	18.5	3.6	22.1	35.8	7441	1/13	8.5	4.4		
																				Third admission—1927
11/ 8	39	55.3	.04	.61	.65	.45	.72	.80	1.52	1.84	18.7	*	21.1	23.8	5177	11/ 8	4.9	6.4		Moderately low calcium diet
11/11	40	55.1	.04	.34	.38	.44	.82	.34	1.16	1.50	15.3	*	16.4	11.4	4238	11/11	4.5	6.9		Same diet
11/14	41	55.0	.03	.50	.53	.85	.80	.56	1.36	1.67	12.6	*	13.9	12.5	4902	11/14	5.5	7.8		11/14. 10 cc. 5 per cent calcium chloride solution intravenously
11/17	42	54.8	.04	.22	.26	.89	.65	.22	.87	1.82	13.0	*	14.7	17.1	5521				−24	11/16. 10 cc. 5 per cent calcium chloride intravenously
																				11/18. 10 cc. 5 per cent calcium chloride intravenously

* Feces assumed to be 10 per cent of nitrogen intake.

† Thyroxin was given in all instances intramuscularly.

TABLE III

Mrs. DeLaB., aged 27, white, female

(Intake and output per 3-day period)

Date	Period	Treatment	Weight	Urine	Dried feces	Titratable acidity minus CO_2	Ammonia	NH_3+ titratable acidity	Total excess acid in diet	Acid or base added	Calcium					Phosphorus					Nitrogen				Total base					Serum values					
											Excretion			Intake	Balance	Excretion			Intake	Balance					Excretion			Intake	Balance	Day of period	Plasma CO_2 content	Calcium	Phosphorus	Protein	Non-protein nitrogen
											Urine	Feces	Total			Urine	Feces	Total			Urine	Total	Intake	Balance	Urine	Feces	Total								
			kilos	*cc.*	*grams*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*		*volumes per cent*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*grams per 100 cc.*	*mgm. per 100 cc.*
3/31 4/1 4/2	1	Neutral low calcium diet 79 mgm. Ca per day	43.6	3790	34						.015	.620	.635	.240	−.395	1.47	.51	1.98	1.37	−.61	16.57	18.20	16.3	−1.90	3610	775	4385	3795	−590	1		5.8	3.1	6.34	22.9
4/3 4/4 4/5	2		43.3	4420	8						.019	.210	.229	.243	−.014	1.43	.49	1.92	1.37	−.55	16.81	18.44	16.3	−2.14	3880	122	4002	3795	−207						
4/6 4/7 4/8	3		43.0	2840	54						.006	.855	.861	.240	−.621	.86	.75	1.61	1.37	−.24	9.34	10.97	16.3	5.33	1855	903	2758	3795	1037	1		5.1	2.4		
4/9 4/10 4/11	4		43.2	4380	58						.012	.820	.832	.249	−.583	1.51	.89	2.40	1.37	−1.03	16.39	18.02	16.3	−1.72	3465	1104	4569	3686	−883	3		5.2	2.8		
4/12 4/13 4/14	5		43.1	5120	47						.013	.755	.768	.242	−.526	2.02	.74	2.76	1.37	−1.39	19.15	20.78	16.3	−4.48	3880	962	4842	3686	−1156						
4/15 4/16 4/17	6		42.2	3740	73						.009	.985	.994	.261	−.733	1.38	.90	2.28	1.55	−.73	16.68	18.60	19.2	.60	2578	1230	3808	4221	413						
4/18 4/19 4/20	7	Higher calcium diet (About 500 mgm. Ca per day)	42.8	4040	90						.011	1.130	1.141	1.469	.328	1.45	.98	2.43	2.61	.18	17.05	19.87	28.2	8.33	2845	1604	4449	5959	1510	1		6.1	2.2		
4/21 4/22 4/23	8		43.1	4440	74						.008	.780	.788	1.448	.660	1.96	.36	2.32	2.44	.12	17.64	20.07	24.3	4.23	3088	971	4059	4853	794						
4/24 4/25 4/26	9		43.2	4360	87						.010	1.090	1.100	1.566	.466	1.96	.63	2.59	2.45	−.14	18.70	21 00	23.0	2.00	2740	1438	4178	4434	256						
4/27 4/28 4/29	10		43.3	4370	80	−55	677		−.10		.009	1.160	1.169	1.570	.401	1.75	.58	2.33	2.45	.12	17.91	20.21	23.0	2.79	2895	1310	4205	4434	229	1		6.0	2.7		
4/30 5/1 5/2	11		43.9	3660	144	52 −45 −32 −25	682 941 728 2351	2326	−.30		.008	2.010	2.018	1.563	−.455	2.08	.67	2.75	2.45	−.30	19.67	21.97	23.0	1.03	2635	2485	5120	4434	−686						
5/3 5/4 5/5	12	Same diet plus 4 grams NH_4Cl per day	44.3	4190	109	−18 54 138 174	867 1174 1356 3397	3571	−.30	1496	.011	1.820	1.831	1.563	−.268	2.45	.71	3.16	2.45	−.71	23.63	26.14	25.1	−1.04	3082	2372	5454	4434	−1020	2	58.9	5.8			
5/6 5/7 5/8	13		44.4	3910	85	97 127 230 454	1314 1156 1563 4033	4487	−.30	2244	.013	1.570	1.583	1.563	−.020	2.41	.38	2.79	2.45	−.34	22.95	25.56	26.1	.54	2765	1742	4507	4434	−73						
5/9 5/10 5/11	14		44.6	4220	117	121 46 177 344	1208 944 1305 3457	3801	37.7	2244	.022	2.020	2.042	1.553	−.489	2.38	.51	2.89	2.43	−.46	21.47	24.08	26.1	2.02	3558	2180	5738	4388	−1350						
5/12 5/13 5/14	15		44.6	3910	127	93 156 56 305	911 1393 1059 3363	3668	119.7	2244	.016	1.660	1.676	1.563	−.113	2.23	.52	2.75	2.45	−.30	20.64	23.25	26.1	2.85	3300	2340	5640	4434	−1206	3	61.3	6.2	3.0		
5/15 5/16 5/17	16	Same diet plus 6 grams NH_4Cl per day	44.2	3280	105	197 228 184 609	1312 1596 1562 4470	5079	119.7	3366	.014	2.090	2.104	1.568	−.536	2.32	.47	2.79	2.45	−.34	21.60	25.37	27.7	2.33	2382	2248	4630	4434	−196						
5/18 5/19 5/20	17		44.6	4480	125	227 182 153 562	1622 1480 1336 4438	5000	47.1	3366	.023	2.010	2.033	1.617	−.416	2.42	.47	2.89	2.35	−.54	21.59	24.24	26.5	2.26	3050	2340	5390	4810	−580						
5/21 5/22 5/23	18		44.4	4430	94	160 177 173 510	1398 1467 1443 4308	4818	10.8	3366	.014	1.830	1.844	1.644	−.200	2.08	.34	2.42	2.30	−.12	15.13	17.71	25.8	8.09	2755	1720	4475	4998	523	1	58.2	7.6	2.6		
5/24 5/25 5/26	19	Same diet. No medication	45.0	4140	118	34 −100 −48 −114	897 630 764 2291	2177	10.8		.011	1.930	1.941	1.644	−.297	1.81	.51	2.32	2.30	−.02	20.08	22.19	21.1	−1.09	2515	1910	4425	4998	573	1	56.5	7.6	3.4		
5/27 5/28 5/29	20		44.8	4470	90	−6 −123 −91 −220	572 625 577 1774	1554	10.8		.012	1.650	1.662	1.644	−.018	1.87	.39	2.26	2.30	.04	15.16	17.27	21.1	3.83	3185	1635	4820	4998	178						
5/30 5/31 6/1	21		44.2	4530	104	−56 −100 −2 −158	530 679 523 1732	1574	10.8			1.810		1.644		2.01	.46	2.47	2.30	−.17	15.63	17.74	21.1	3.36	3098	1860	4958	4998	40	2	61.4	7.0	2.9		
6/2 6/3 6/4	22		44.4	4560	106	−263 −112 −25 −400	577 583 476 1636	1236	3.1		.016	2.000	2.016	1.571	−.445	1.94	.44	2.38	2.24	−.14	14.56	16.66	21.0	4.34	3812	1845	5657	4911	−746	3		6.8	3.2	6.36	
6/5 6/6 6/7	23		44.4	3870	75	55 94 8 157	729 651 651 2031	2188	−38.0		.008	1.00	1.008	1.694	.686	2.02	.31	2.33	2.36	.03	15.93	18.07	21.4	3.33	2720	1320	4040	4809	769						
6/8 6/9 6/10	24		45.2	4070	156	−100 −123 90 −133	570 524 783 1877	1744	10.8		.012	2.150	2.162	1.644	−.518	1.85	.57	2.42	2.30	−.12	14.43	16.54	21.1	4.56	3862	2700	6562	4998	−1564						
6/11 6/12 6/13	25	Same diet plus 12 grams sodium bicarbonate daily. Sodium salicylate grams 2 on June 14, 15, 18, 19	45.4	3730	86	86 −75 −561 −550	738 646 333 1717	1167	10.8	−1469	.016			1.644		1.94			2.30		16.43	18.54	21.1	2.56	4140			6467		2		5.9	2.5	6.51	
6/14 6/15 6/16	26		44.9	5320	117	−1022 −936 −1008 −2966	262 199 385 846	−2120	3.3	−4532		1.700		1.591		2.15	.43	2.58	2.24	−.34	20.85	22.95	21.0	−1.95	8900	2920	11820	8468	−3360	2	61.0	5.9			
6/17 6/18 6/19	27		44.7	7300	149	−1297 −1278 −482 −3057	333 281 171 785	−2272	58.0	−4515	.028	2.100	2.128	1.595	−.533	2.01	.61	2.62	2.28	−.34	19.07	21.19	21.3	.01	7620	2430	10050	9502	−548						
6/20 6/21 6/22	28	Same diet. No medication	45.2	4340	140	79 −99 85 65	483 646 936 2065	2130	114.9		.009	2.20	2.209	1.635	−.574	2.17	.38	2.55	2.39	−.16	15.07	17.28	22.1	4.82	2740	2530	5270	5175	−95	3	54.6	5.8	3.1		
6/23 6/24 6/25	29	Same diet plus 9 grams of $CaCl_2$ per day	45.3	4500	201	104 109 115 328	1037 877 1137 3051	3379	114.9	2275*	.017	3.78	3.797	11.374	7.577	2.17	.61	2.78	2.39	−.39	16.39	18.60	22.1	3.50	2305	3270	5575	10040	4465						
6/26 6/27 6/28	30		45.3	3150	452	126 145 130 401	1128 1218 1197 3543	3944	114.6	2275*	.014	4.70	4.714	11.374	6.660	1.75	.71	2.46	2.39	−.07	16.49	18.70	22.1	3.40	1356	3980	5336	10040	4704						
6/29 6/30 7/1	31	Same diet. No medication	44.9	4400	138	137 13 24 174	1141 706 847 2694	2868	73.7		.021					1.58			1.72		14.66	16.67	20.2	5.43	2090			4825		1	57.7	7.2	2.4	6.66	

* According to Gamble's calculations.

TABLE IV

Summary of metabolic data, with diet low in calcium. Untreated cases of tetany and normal individuals (Periods of three days' duration. Intake and output per 3 day period)

Subject	Diagnosis	Number of periods	Calcium			Phosphorus			Nitrogen			Fasting blood levels	
			Urine	Feces	Intake	Urine	Feces	Intake	Urine	Feces	Intake	Ca	P
			grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
B.W.....	Idiopathic tetany.....	(1–3)	0.03	0.55	0.25	0.84	0.49	1.75	18.8	2.5	19.4	4.6	7.0
K.L.*....	Parathyreopriva tetany	(1–3)	0.02	0.40	0.26	0.54	0.45	1.40	8.8	1.8	14.5	4.9	5.1
DeLaB...	Steatorrheic tetany on neutral diet..	(1–6)	0.01	0.71	0.25	1.44	0.71	1.40	15.8		15.9	5.4	2.8
Average of nine controls on neutral low calcium diets.....		29	0.19	0.38	0.32	1.17	0.61	2.00	24.2		28.1	9.5	3.8
Average of 13 controls on diets with uncontrolled potential acidity (8)		46	0.19	0.60	0.33								

* Some parathormone was given during these periods (see Table I).

Metabolic findings in patient with chronic steatorrhea

The metabolic abnormalities in the patient with chronic steatorrhea were so fundamentally dissimilar from those of the patients with parathyroid tetany that they must be considered separately (see Table III). The low serum calcium and the consequent low calcium excretion in the urine (cf. serum calcium below the kidney threshold) need no further comment. In periods 1–6 (Table III) the fecal calcium excretion while on a low calcium diet was perceptibly higher than that of normal individuals on a similar regime (Table IV). That this abnormality was due to lack of absorption of calcium from the gastro-intestinal tract rather than to increased excretion of calcium into the gastro-intestinal tract was well demonstrated in periods 7–11 (Table III). Here, on a higher intake of calcium, almost all of the ingested calcium appeared in the feces. This lack of absorption of calcium may apply, of course, to calcium excreted into the gastro-intestinal tract which ordinarily would be reabsorbed. In periods 29 and 30 (Table III) on a very high calcium intake there was considerable absorption of calcium and the serum calcium did rise. The abnormalities in the calcium metabolism in this case may thus be summarized as:

1. A long continued lack of absorption of calcium,
2. A resulting low serum calcium due to long continued calcium privation, and
3. A consequent low calcium excretion in the urine because of the low serum calcium (threshold phenomenon).

There were three possible factors to account for the decreased absorption of calcium from the gastro-intestinal tract. The formation of insoluble soaps was probably the most important factor. Increased intestinal rate may have been an added factor. Finally, an increased pH of the upper intestinal tract (cf. anacidity) may have played a part (9). The final proof that lack of calcium absorption was at the bottom of this disorder was shown in later studies by Bauer and Marble (9). By administering ergosterol they noted an immediate remarkable increase in calcium absorption and a later return of other abnormalities to normal.

It is now of interest to see how the phosphorus metabolism reacted to this disorder of calcium metabolism. It is apparent at once that the serum phosphorus was very low. Just as the total calcium excretion on a low calcium diet was within normal limits (periods 1–6), likewise the total phosphorus excretion was not abnormal. However, very unlike the situation in parathyroid deficiencies, there was a high partition of phosphorus in the urine as compared to the feces. Thus, in spite of the low serum phosphorus, there was a normal excretion of phosphorus in the urine. This makes one question whether phosphorus is a threshold substance at all in spite of the contention of Albright, Bauer, Claflin, and Cockrill (13) that the abnormalities in parathyroid disorders are de-

pendent on alterations in the threshold for phosphorus excretion. This point is discussed elsewhere (13). The findings in the phosphorus metabolism were, therefore:

1. A low serum phosphorus.
2. A normal excretion of phosphorus with a high partition in the urine as compared with the feces.

A study of the total acid-base balance throws further light on the metabolic abnormalities in this case. With the loss of large quantities of organic fatty acids, a large amount of base was also found in the feces, about half of which was available as alkali for the neutralization of organic acid (11). The fecal ash was markedly alkaline, probably because the ashing removed organic acids. When the fecal ash was ground with water and titrated to methyl red with normal HCL, an end point could only be approximated. During period 28, when no medication was given, it required 138 cc. normal HCl in this inaccurate titration, while 425 cc. normal HCl were required in period 30 when 9 grams of $CaCl_2$ were given daily. This large loss of base by feces naturally influenced the reaction of the absorbed part of the diet. The ingested diet was potentially neutral; the absorbed part was, in all probability, acid. This may well explain the high concentration of ammonia found in the urine (11). In agreement with such an explanation was the shrinking of urinary ammonia when sodium bicarbonate was added to the diet (periods 25–27), and the rise in ammonia excretion when ammonium chloride was ingested (periods 12–18). The fact that calcium chloride (periods 29 and 30) not only increased the fecal total base and fecal alkalinity but also the urinary ammonia was probably due to the greater absorption of the chlorine ions as was originally shown by Gamble (14).

The effect of parathormone medication in hypoparathyroidism

As a method of treating parathyroid tetany, parathormone is dramatic.[2] From the studies made on Cases I and II it is obvious that small doses of parathyroid extract exert a much greater effect in patients with parathyroid deficiency than in normal individuals. In our normal control cases, 100 units of parathormone daily resulted in a rise of the blood calcium level of about the same degree as 10 or 15 units did in these cases of tetany.

The effect of parathormone was more obvious on the blood calcium level than on the calcium excretion. There was only one control period in the observation upon K. L., so that the effect of parathormone on the calcium excretion was not certain, but it obviously was not marked, for even after the blood calcium had risen during parathormone administration from 4.2 to 6.9 mgm. per 100 cc. the total calcium excretion remained

[2] We wish to take this opportunity to thank Eli Lilly Co. for the generous supplies of parathormone which they gave to us for this investigation.

at the very low level of 0.37 gram in 3 days. Practically the same effect was seen in the case of B. W. He was on a high calcium diet when he was given daily injections of 10 units of parathormone. This was adequate to raise the blood calcium from 6 to 7.8 mgm., but there was no striking effect on either the fecal or urinary calcium excretion until the blood calcium had risen above 9 mgm. It is true that the high calcium intake would have hidden any minor effects upon the fecal calcium excretion, but no technical error ought to have obscured an effect on the low calcium excretion in the urine. The explanation suggested by Albright and Ellsworth (16) that the renal threshold for calcium excretion is about 8.5 mgm. probably explains these findings.

In the course of our observations it has become obvious that parathormone has its most marked effects in the first few weeks of administration and that then its influence on calcium metabolism is sometimes gradually lost. Thus, its beneficial effects were strikingly observed in K. L. who lost all symptoms and signs of tetany on only 15 units (later 7 1/2 units) a day. This very satisfactory result lasted while the patient was in the hospital and on a low calcium intake. Then she was given a diet high in calcium and discharged from the hospital, but in spite of continued parathormone injections, her blood calcium gradually fell. On her re-admission to the hospital some months later, daily injections of over 100 units of parathormone would not change her low blood calcium or her total calcium excretion even though she was on an adequate calcium intake. This was not ascribable to poor parathormone because the same preparation had a marked physiological effect on other patients. We have observed such an immunity in other patients as well (17). This has also been reported by Lisser and Shepardson (18) in a striking case of tetany. In Boothby's recent studies (19) such an immunity was not observed.

The effect of thyroid medication in hypoparathyroidism

In paper III of this series (1) it was shown that the effect of thyroid on *blood* calcium was negligible, but that its stimulating effect on calcium excretion was of great magnitude. It was, therefore, natural to try the effect of thyroid therapy on these cases of parathyroid tetany. The resulting effect was very striking. This can best be demonstrated in the first observation on K. L. (See Table I and Figure 1.)

Prior to the administration of thyroid she had received daily intramuscular injections of 15 units of parathormone. This had raised her blood calcium from 4.2 to 6.7 mgm. per 100 cc.during a period of 18 days. Without altering the parathormone dosage, thyroxin (25.0 mgm.) and thyroid (2.4 grams) were administered to her during a period of two weeks. Her metabolic rate rose from minus 14 per cent to plus 22 per cent and her *blood calcium* rose from 6.7 mgm. to 11.9 mgm. per 100 cc. It was only then that the calcium excretion was influenced, increasing three-fold over

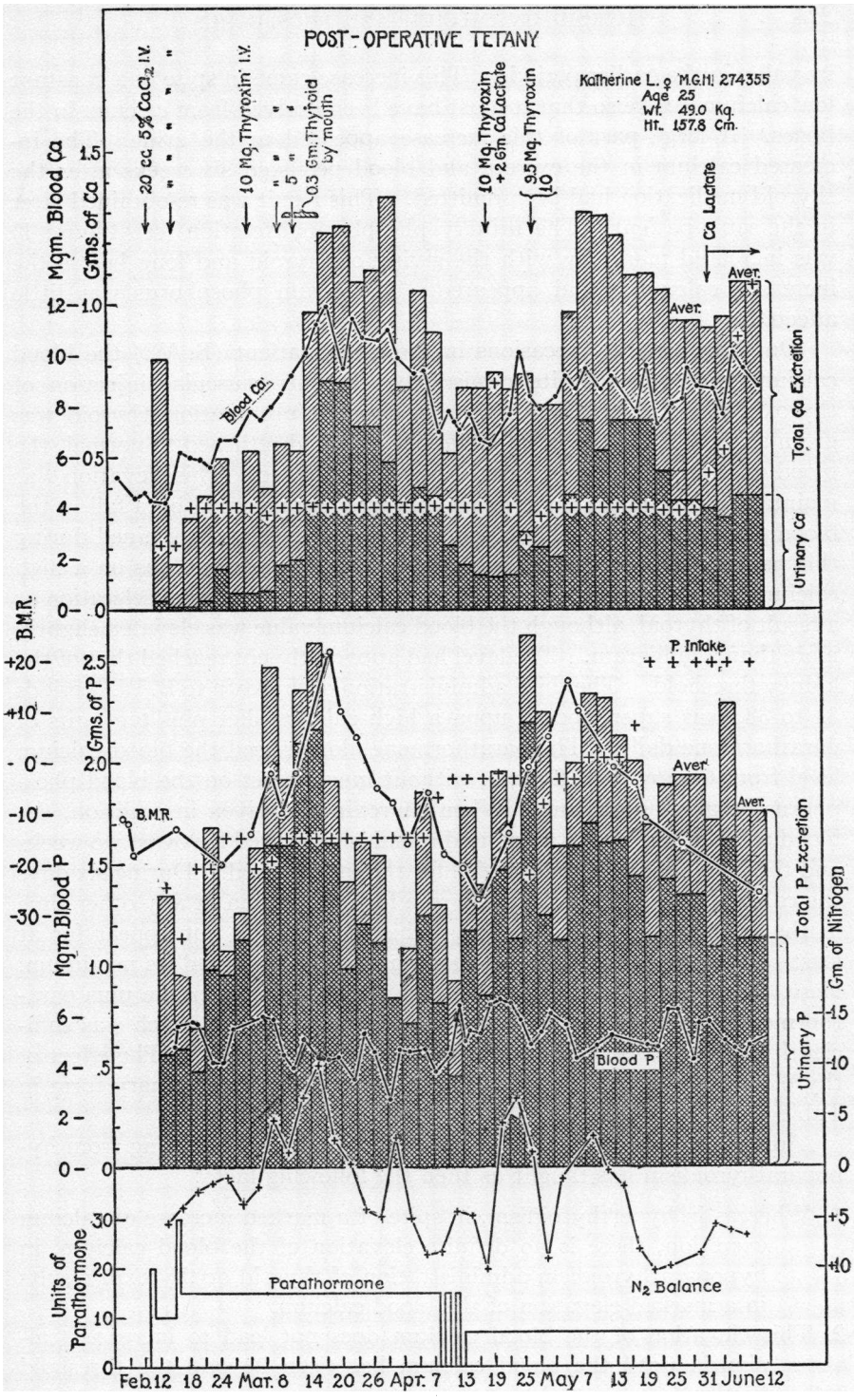
POST-OPERATIVE TETANY
Katherine L. ♀ M.G.H. 274355
Age 25
Wt. 49.0 Kg.
Ht. 157.8 Cm.
20 cc. 5% CaCl2 I.V.
10 Mg. Thyroxin I.V.
0.3 Gm. Thyfoid by mouth
10 Mg. Thyroxin + 2.6 Gm. Ca Lactate
9.5 Mg. Thyroxin
Ca Lactate
Aver.
Blood Ca
Total Ca Excretion
Urinary Ca
Mgm. Blood Ca
Gms. of Ca
B.M.R.
P. Intake
Gms. of P
Mgm. Blood P
Total P Excretion
Urinary P
Blood P
Gm. of Nitrogen
Parathormone
N2 Balance
Units of Parathormone
Feb. 12 18 24 Mar. 6 14 20 26 Apr. 7 13 19 25 May 7 13 19 25 31 June 12

FIG. 1

its value in the earlier periods. This increase came in spite of a constant low calcium intake so that it must have been derived from calcium in the bones. A large part of this increase appeared in the urine. The increased calcium in the excreta and blood persisted six weeks after the thyroid medication had been omitted. This result was re-obtained later in the same patient. The urinary phosphorus excretion (see Figure 1) was increased markedly with the giving of thyroid and long before the increased calcinuria had appeared. The serum phosphorus was little affected.

On three separate occasions in the other patient (B. W.) the blood calcium level was definitely raised by the intramuscular injection of thyroxin (see Tables, II and V). In the first observation, thyroid was given alone. After the basal metabolic rate had returned to normal, the blood calcium rose from 4.5 to 6.4 mgm. per 100 cc. This elevation was maintained for almost three weeks and was accompanied by a fall in the blood phosphate level. The calcium excretion was not determined during this period. During the second observation, the patient was on a high calcium diet. The low urinary calcium output showed no acceleration as a result of thyroid, although the blood calcium value was elevated slightly more than a milligram. The level had apparently not reached that of the kidney threshold. The third administration of thyroxin to B. W. (periods 31 to 38) was superimposed upon a high calcium diet plus ten units of parathormone daily. The parathormone alone raised the blood calcium level from 6 mgm. to 7.8 mgm. without much effect on the blood phosphorus or urinary calcium. When thyroxin was given in addition, the blood calcium rose to 9.4 mgm. and remained elevated for over two weeks and the blood phosphorus level fell for the same period. During six days the calcium excretion in the urine rose far higher than at any other time in the whole observation, although this increase did not appear for at least three days after the blood calcium level had reached its maximum. Here, then, thyroxin, superimposed on a high calcium intake plus parathormone, increased the calcium in the blood to a level which was sufficiently high to cause an increase in the urinary excretion. The effect of thyroid medication in parathyroid tetany is shown in summary form in Table V.

Administration of thyroid or thyroxin to patients suffering from hypoparathyroidism has taught us then the following facts:

1. Whereas in hyperthyroidism, in spite of a marked increase of calcium excretion, there is no definite elevation of the blood calcium, in hypoparathyroidism administration of thyroid or thyroxin results in a marked elevation of the blood calcium.
2. This elevation of the blood calcium does not lead to increased calcinuria until the blood calcium has risen beyond the threshold level.

TABLE V

Effect of thyroxin on average metabolic levels in cases of tetany (Intake and output per 3 day period)

Subject	Diagnosis	Regime	Before thyroxin					After thyroxin				
			Date	Average urinary calcium	Average blood plasma values		Average basal metabolic rates. Variation from normal*	Date	Average urinary calcium	Average blood plasma values		Average basal metabolic rates. Variation from normal*
					Calcium	Phosphorus				Calcium	Phosphorus	
				grams	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*per cent*		*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*per cent*
K. L.	Parathyreopriva tetany	Low Ca diet	February 18 to March 1	.06	6.2	4.5	−17	March 17 to 31	.61	10.9	4.2	+5
		Low Ca diet	April 13 to 25	.13	7.2	5.9	−25	May 3 to 14	.54	9.0	5.0	+8
B. W.	Idiopathic tetany	Low Ca diet	July 17 to 30	.02	4.47	7.61	−18	August 10 to 25		6.36	5.32	−7
		High Ca diet	October 12 to November 3	.04	5.81	5.66	−14	November 22 to December 6	.03	6.83	5.43	+15
		High Ca diet plus 10 units parathormone daily	December 10 to 23	.04	7.53	5.63	−10	January 3 to 13	.20†	9.20	4.44	+33

* Aub and DuBois standards.

† Two periods only.

3. There is an increased urinary phosphorus excretion, which begins almost immediately. The serum phosphorus is little affected.
4. Thyroid extract is a helpful adjunct in the symptomatic treatment of parathyroid tetany.

In paper VIII (20) of this series, a further discussion of the mode of action of thyroid on calcium metabolism is given.

The effect of potentially acid salts on tetany

Ammonium chloride or other potentially acid salts have been utilized by several investigators for the treatment of tetany. Just as alkalosis tends to bring on tetany, acidosis tends to dispel it. Because of the paucity of metabolic studies, however, we are briefly reporting the results on these patients. The clinical signs of tetany disappeared and the neurological electrical reactions improved in the patient K. L. when she was given hydrochloric acid and ammonium chloride (periods 52 to 59). But this improvement was accompanied by only small changes in her calcium and phosphorus metabolism. The blood calcium and phosphorus levels fluctuated back and forth without showing any decided change. The urinary calcium excretion was approximately doubled, but, because of the initial small value, this represented only a small, actual increase. The effect was slight in comparison with that of thyroid extract. A similar amount of ammonium chloride in normal individuals on a low calcium diet (10) produced on the average a four-fold increase in urinary calcium, but no effect on fecal calcium (see Table VI).

In patient DeLaB., who had steatorrhea, the effect of ammonium chloride was more carefully controlled. Metabolic studies of this patient showed that on a neutral low calcium test diet, she excreted approximately a normal amount of calcium but that this was almost entirely in the feces. When more calcium was added to the diet (periods 7 to 11) the blood calcium rose slightly, but the urinary calcium did not rise in spite of a positive calcium balance. The giving of ammonium chloride (4 grams daily in periods 12 to 15, and 6 grams daily in periods 16 to 18) then increased the fecal excretion of calcium enough to produce a negative calcium balance again, and there was a definite rise in her blood calcium from 6.0 to 7.6 mgm. This elevation of blood serum calcium was associated with a marked clinical improvement. All symptoms of tetany and the Chvostek and Trousseau signs disappeared only to return two days after ammonium chloride was discontinued. Corresponding to the increased fecal calcium excretion there was a definite increase in the urinary phosphorus excretion. Thus, whereas normally ammonium chloride causes an increased urinary excretion of calcium and phosphorus; in this case, presumably because of the low serum calcium, the increased calcium excretion was in the feces, while the increased phosphorus excretion, in spite of the low serum phosphorus level, remained in the urine.

TABLE VI

The effect of ammonium chloride on the calcium excretion. Average values of three-day periods, expressed in grams (Intake and output per 3 day period)

Subject	Diagnosis	Number of periods	Calcium			Fasting blood levels		Medication
			Urine	Feces	Intake	Ca	P	
			grams	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	
K. L.	Parathyreopriva tetany	46–51	0.07		2.25	4.9	6.1	15 units parathormone given daily throughout all periods
		54–55	0.10		2.25	5.2	5.4	Hydrochloric acid plus ammonium chloride—equivalent to chloride in 6.5 grams NH_4Cl daily
		56–59	0.17		2.24	4.7	6.5	NH_4Cl 6 grams daily
DeLaB.	Steatorrheic tetany	7–11	0.01	1.23	1.52	6.1	2.5	Control diet. No medication
		12–15	0.02	1.77	1.56	6.0	3.0	Same diet plus 4 grams NH_4Cl daily
		16–18	0.02	1.98	1.61	7.6	3.0	Same diet plus 6 grams NH_4Cl daily
Control B. E. (10)	Sciatica	20–21	0.31	1.08	2.12			No medication but moderate calcium diet
		15–17	1.00	1.02	2.13			NH_4Cl 6 grams daily with same moderate calcium diet
		1–5	0.12	0.32	.27			On low calcium diet
		12–14	0.60	0.26	.27			NH_4Cl 6 grams daily

Large doses of sodium bicarbonate added to her diet for three periods had no demonstrable effect on the calcium, phosphorus, or nitrogen excretions, nor on the blood serum levels of calcium or phosphorus.

The intravenous administration of calcium

In early periods of study both K. L. and B. W. received occasional intravenous injections of calcium chloride. These relieved their signs of tetany temporarily, but the calcium apparently was not subsequently found in the excreta. We, therefore, studied this more carefully in B. W. by maintaining him on a constant, moderately low, calcium diet. After control periods were obtained, he was given repeated intravenous injections of calcium chloride in such quantities that his calcium intake was twice that of the control periods. Table II demonstrates that in this short observation all of this extra calcium was stored (as in an observation by Salvesen, Hastings and McIntosh (21)) with a reduction in phosphorus excretion in the second period approximately equivalent to the amount needed for bone deposit (Ca : P = 2.2 : 1). This demonstrates a striking characteristic of parathyroid tetany, namely, the great avidity for storage of calcium and the resistance to its elimination. This retention could not be ascribed to a previous lack of calcium.

DISCUSSION

From the above rather miscellaneous assortment of data, one striking fact needs special discussion. The thyroid hormone, which raises only very slightly the serum calcium and phosphorus of otherwise normal individuals, elevates very appreciably the low serum calcium of patients with parathyroid tetany. A clarification of this phenomenon is suggested by an analysis of threshold values for excretion of calcium and phosphorus.

Albright and Ellsworth (16) point out that there is a threshold value for urinary calcium excretion, below which the calcium in the urine remains negligible. The extraordinary thing about this threshold is that it is surpassed by the normal value for serum calcium. Calcium privation, unless long continued, will not lower the serum calcium to the threshold value. There is no counterpart to this in physiology as far as we are aware. The implication is that there is another mechanism which keeps the serum calcium above this threshold, otherwise the calcium excretion in the urine would soon lower the serum calcium to the threshold value. This other mechanism may well be the parathyroid hormone.

Phosphorus is thought by Albright, Bauer, Claflin and Cockrill (13) to be a threshold substance. The normal value for serum phosphorus is thought by them to represent approximately the threshold value. The high serum phosphorus level of hypoparathyroidism and the low serum phosphorus level of hyperparathyroidism are thought by them to represent not levels above and below the threshold respectively, but changes in the threshold values.

Now the thyroid hormone, regardless of the exact mechanism, mobilizes large amounts of calcium and phosphorus from the bones into the blood stream and hence into the excretory channels. Thus, one would expect it in the normal state to cause a slight rise of the blood levels of both calcium and phosphorus and, because both thresholds would then be exceeded, to produce an immediate excretion of both. This is just what occurs. In hypoparathyroidism, however, the calcium on arriving in the blood stream still is below the threshold value and would not be immediately excreted. This is not true of the phosphorus. There would, therefore, be a tendency for the serum calcium to rise without any appreciable alteration in the serum phosphorus. This is just what occurs.

CONCLUSIONS

I. Previously noted alterations in the calcium and phosphorus metabolism in parathyroid tetany are confirmed, viz.,
   a. A low serum calcium level.
   b. A high serum phosphorus level.
   c. A low urinary calcium excretion with an unaltered fecal calcium excretion.
   d. A low urinary phosphorus excretion with an unaltered fecal phosphorus excretion,—hence a low partition of phosphorus in the urine as compared with the feces.

II. The alterations in the calcium and phosphorus metabolism in the tetany associated with chronic steatorrhea have the following points of similarity with parathyroid tetany:
   a. A low serum calcium level, and
   b. A low urinary calcium excretion,
   but the following points of dissimilarity:
   a. A low serum phosphorus level,
   b. A high fecal calcium excretion, and
   c. A high urinary phosphorus excretion,—hence a high partition of phosphorus in the urine as compared with the feces.

III. In our patient with steatorrhea all the disordered calcium and phosphorus metabolism was dependent on a decreased calcium absorption from the gastro-intestinal tract. This was probably due to three factors:
   a. The formation of calcium soaps,
   b. The increased intestinal rate, and
   c. The decreased acidity of the gastric contents.

IV. *a.* A given dose of parathyroid extract is more efficacious the greater the degree of hypoparathyroidism.
   b. Some patients with long continued injections of the present preparation of parathyroid extract become refractive to the drug.

V. Thyroid medication has the following effects in hypoparathyroidism:
   a. To raise the serum calcium markedly.
   b. To increase the calcium excretion in the urine, but only after the serum calcium has surpassed the threshold value.
   c. To increase the phosphorus excretion in the urine, without any decided change in the serum phosphorus level.
   d. To alleviate the symptoms of tetany.

VI. The presence of a threshold for calcium excretion in the urine is confirmed. This threshold is below the normal level of serum calcium. In tetany any agent such as thyroid or parathormone which increases the level of serum calcium will not increase the urinary calcium excretion until the threshold has been passed. The excretion of calcium into the gastro-intestinal tract, inasmuch as it is not decreased with the low serum calcium of parathyroid tetany, is probably not a threshold phenomenon.

VII. The question of a threshold level for phosphorus excretion in the urine cannot be decided on the data presented. Two pertinent facts appear:
   a. In hypoparathyroidism with a high blood phosphorus the urinary phosphorus excretion is reduced.
   b. In the tetany of chronic steatorrhea with a very low blood phosphorus the urinary phosphorus excretion is normal.

VIII. In explanation of the phenomenon that thyroid medication raises the serum calcium of patients with hypoparathyroidism appreciably while its effect on the serum of normal patients is almost negligible, the following hypothesis is suggested: in hypoparathyroidism the calcium on being taken from the bones by the thyroid hormone finds itself in the blood below rather than above the threshold for excretion and hence is not immediately excreted.

APPENDIX

CASE HISTORIES

Case I. Miss K. L., M. G. H. no. 274355, a white, unmarried woman, twenty-five years of age, was admitted to the Hospital, January 28, 1926, and was discharged January 27, 1927. The discharge diagnosis was: Postoperative parathyroid and thyroid deficiency.

History of present illness: Miss K. L. was first a patient in this Hospital in 1917. At that time she was suffering from mild hyperthyroidism for which x-ray treatment was advised. She refused treatment and consulted another physician. He performed a subtotal thyroidectomy. Six months later, because of the return of symptoms of hyperthyroidism, another subtotal thyroidectomy was performed. She stated she had been hoarse since this last operation. Two months later she first noticed difficulty in breathing. Wheezing was always present but was made worse by cold and exertion. Besides this asthmatic-like breathing, she had frequent attacks of carpopedal spasms

during which times she was unable to talk. Prior to admission to the Hospital these attacks of tetany (laryngeal spasm) were so severe that she was unable to breathe for several minutes at a time. Following her second operation, she first noticed dimness of vision. This rapidly increased, finally necessitating the removal of bilateral cataracts.

Physical examination: She was a well developed, well nourished young woman with slightly labored breathing and a hoarse voice. Her skin was somewhat dry and coarse with scaling over the shins. Her hair was dry and coarse. The eyes, ears, nose, and throat showed no abnormalities. The heart was not enlarged. No murmurs were heard. Blood pressure was 100/70. Examination of the chest revealed slight dullness over either back. The breath sounds were prolonged accompanied by expiratory wheezes. Occasional sibilant râles were heard throughout the chest. The abdominal examination was negative except for voluntary muscle spasm. There was slight brawny edema of the ankles. The nails were coarse and very brittle. The Chvostek and Trousseau signs were positive. The reflexes were all hyperactive.

Laboratory findings: Five urine examinations revealed no abnormality. Blood examination showed a hemoglobin of 75 per cent, erythrocytes 5,656,000, leucocytes 7,900. The differential leucocyte count was normal and the smear was negative except for marked achromia. The phenolsulphonephthalein test was 60 per cent. The Wassermann test was negative. The nonprotein nitrogen was 28 mgm. per 100 cc. The serum calcium was 5.2 mgm. per 100 cc. and the serum phosphorus was 5.4 mgm. per 100 cc. Basal metabolism was − 11 per cent. X-ray examination of the skeletal system showed no deviation from the normal.

Progress notes: During her stay in the Hospital, she had frequent attacks of severe tetany with marked laryngismus. These gradually disappeared when parathormone and thyroid medication was given. However, she eventually became so refractory to parathyroid extract that 100 units a day did not keep her free from the signs and symptoms of tetany.

On January 23, 1927, she complained of toothache, accompanied by a temperature of 101 to 102° F. X-ray examination of her teeth showed several apical abscesses. Extraction of these teeth was advised, hoping that the elimination of these foci of infection might possibly benefit her. During the administration of ethylene anesthesia she developed severe laryngismus. This was not relieved by small amounts of ether, adrenalin, or 5 per cent calcium chloride intravenously. Finally a tracheotomy was performed. This procedure relieved her laryngismus but she was then in a shock-like condition with a low blood pressure. All subsequent treatment was without effect and she died in the surgical amphitheatre.

Autopsy: No. 5119, January 27, 1927, by Dr. Tracy Mallory. Anatomical diagnoses: Parathyroid and thyroid deficiency, persistent thymus and focal necrosis of the liver. Only a small remnant of thyroid tissue, measuring 22 × 9 × 9 mm. remained. This was firmly adherent to the cricoid cartilage. It contained considerable fibrous tissue in bands which separated the islands of parenchyma. The thymus was large, having roughly the shape of the numeral 8, with an isthmus, small upper and large lower poles. From top to bottom it measured 11 cm. and from side to side 6.5 cm., but it was not more than 3.5 mm. in thickness. It weighed 21 grams. In the fibrous tissue overlying the trachea several small, pinkish masses averaging 2 mm. in diameter were found. Microscopic examinations were not remarkable except as follows: Thymus—Infantile type, well differentiated cortex and medulla. Thyroid—

The remnant of the thyroid showed a marked increase in fibrous tissue, irregular in distribution. A few acini were greatly dilated; however, the majority were small, with a tendency to hyperplasia of the epithelium. No remnants of parathyroid tissue were found in the surrounding fibrous tissue. Neck tissue —Examination of the eight small glands removed from the neck showed no parathyroid tissue. The liver showed small areas of focal necrosis and invasion with polymorphonuclear cells.

Case II. Mr. B. W., M. G. H. no. 277407, a white, married Jewish tailor, 52 years old, was first admitted to the Hospital on July 10, 1926, and discharged August 30, 1926. He was re-admitted October 11, 1926, and discharged January 20, 1927. The patient had felt well until ten weeks before entrance to the Hospital. At this time he first noticed a general feeling of uneasiness with mild, irregular muscle spasms in his hands, forearms, and legs. A week later he fell in the street because of marked contractions of arms and legs. He did not lose consciousness; felt no pain; but his extremities seemed anesthetic. The attack lasted three or four hours, and was followed by repeated attacks of a shaking sensation of his muscles but without evidence of muscle contractions. He had a second severe attack three weeks prior to his first entrance. Otherwise he had only local muscle spasms of the arms and legs which recurred every few minutes. Five weeks before entrance to this Hospital he noticed his eyesight was failing, necessitating his giving up his position as a tailor. Seven days prior to his hospital entrance, he developed severe pain in both shoulders on motion.

Physical examination: The physical examination disclosed nothing abnormal save a few very carious and infected teeth, evidence of a bilateral subdeltoid bursitis, and very markedly positive Chvostek and Trousseau signs.

Laboratory findings: The routine urine and blood examinations were normal. The Wassermann test was negative. The serum calcium was 5.1 mgm. per 100 cc. and the serum phosphorus was 7.3 mgm. per 100 cc. The blood CO_2 combining power was 71.8 volumes per cent. The basal metabolism tests were -15 to -20 per cent. The nonprotein nitrogen was 38 mgm. per 100 cc. Gastric analysis showed acid values within normal limits. The electrical reactions were typical of those found in parathyroid tetany.

Case III. Mrs. DeLaB., M. G. H. no. 290165, was a white, married stenographer, 27 years of age. She considered herself well until five years prior to her entrance into the Hospital. At that time she weighed 123 pounds. She gradually lost in strength and energy. At the time she entered the Hospital she weighed 93 pounds. Four years previous she had developed "mild indigestion" associated with epigastric distress coming on about an hour after meals and lasting several hours. This was sometimes accompanied by nausea and rarely by vomiting. Large meals accentuated all of the above symptoms. She had suffered from alternating diarrhea and constipation all her life. For the past four years she had noticed twitchings of the face, areas of paresthesia over scalp and back, and frequent attacks of carpopedal spasm.

Physical examination: Physical examination was completely negative except for areas of paresthesia and markedly positive Trousseau and Chvostek signs.

Laboratory examination: Routine blood and urine examinations were negative. Phenolsulphonephthalein test was 60 per cent. Basal metabolism test was minus 4 per cent. The electrical reactions were characteristic of tetany. X-ray examination of the bones were negative except for slight decalcification. Gastric analysis revealed an anacidity. The feces contained much excess fat.

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