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## STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

### XV. IN VARIOUS METABOLIC AND BONE DISEASES

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The bones may well be looked upon as a storehouse for calcium and phosphorus, readily available for the body needs for fixed base. The demands upon this supply can readily be determined if a carefully controlled diet inadequate in calcium is administered. Under such conditions the normal excretion of calcium remains fairly constant, and a comparison with disease states may readily be undertaken.

For several years this laboratory has systematically studied the calcium and phosphorus exchange in numerous pathological conditions. In the course of these studies various diseases have been investigated and are to be published (1, 2, 3).

We have also had the opportunity to investigate many interesting diseases in which a disturbance of bone metabolism might well be expected. Some of these isolated cases are here brought together and this paper, therefore, demonstrates the metabolic need of calcium and phosphorus in various bone abnormalities as well as in gout and chronic hepatitis with jaundice.

#### EXPERIMENTAL METHODS

The patients were, with one exception, studied in the metabolism ward at the Massachusetts General Hospital. The careful management and routine used there for the preparation of accurate diets and for the collections of urine and feces has already been fully described (4). The periods used here were of three days' duration, and the feces were divided by the appearance of carmine. The methods of analysis for calcium and phosphorus were those of Fiske (5) and the nitrogen determinations were made by Kjeldahl method. In order to determine the endogenous need for calcium the patients received our usual neutral diet, which is inadequate only in calcium. In nine normal control subjects on similar neutral diets, the excretion of calcium averaged 186 mgm. in the urine and 386 mgm. in the feces per period.

#### A. DISEASES AFFECTING THE SKELETON

##### *Secondary carcinoma involving bone*

In the course of studies on the effect of lead therapy upon cancer growth, observations were also made upon the calcium and phosphorus

metabolism of patients with secondary breast carcinoma involving the spine, pelvis, and other bones. The calcium excretion of most of these patients fell within the normal range. In one patient, however, whose lesion in the pelvis was progressing, there was a very high urinary calcium excretion.

Case I, Mrs. B., age 47, weighing 48 kilos, had the left breast removed in 1925, and the right in June, 1927, both breasts being infiltrated with carcinoma. For approximately six months before her admission to the hospital, she had suffered from stiffness and soreness in the back and right shoulder and, for some weeks immediately preceding admission, with more severe pain low in the back. She was fairly comfortable when lying still but was afraid to move. X-ray examinations revealed metastases in the spine, ribs, and pelvis, with pathological fracture of a vertebra, and some weeks later showed that the process in the pelvis had rapidly advanced. The values for calcium determinations are presented in Table I.

TABLE I  
*Secondary carcinoma involving bone  
(Intake and output in 3-day periods)*

Subject and diet	Period	Calcium				Phosphorus		Serum		
		Urine	Feces	In-take	Balance	Urine	In-take	Ca	P	Protein
Subject B. M.—Case I. Low Ca diet.	(3-day)	grams	grams	grams	grams	grams	grams	mgm. per 100 cc.	mgm. per 100 cc.	grams per 100 cc.
	1	.92	.58	.25	-1.25	1.02	1.50	10.7	5.1	6.8
	2	1.11	.66	.25	-1.52	1.31	1.50			
	3	1.33	.29	.26	-1.36	1.55	1.50			
	4*		.37	.26		1.62	1.50			
	5*	1.19	.25	.28	-1.16	1.59	1.50			
	6*	.92	.40	.35	-.97	1.61	1.47			
	7*	.48	.39	.32	-.55	1.09	1.39			
High Ca diet.	8	.62	.22	.38	-.46	.95	1.47			
	9*	.77	1.06	2.83	+1.00	1.43	3.43	10.5	3.9	7.3
	10*	.69	1.05	3.18	+1.44	1.38	3.43			
	11	.49	1.15	3.19	+1.55	1.59				
Subject L. N.—Case II. Low Ca diet.	1	.33	.27	.34	-.26		2.04	9.3	3.6	7.3
	2	.35	.36	.33	-.38					
	3*	.41	.29	.31	-.39					
	4*	.59	.26	.32	-.53					

\* 60 mgm. of lead injected intravenously in the form of colloidal lead phosphate.

In the initial periods on a constant, potentially neutral diet low in calcium, the urinary excretion of calcium was very high, the calcium of the feces being within normal limits. There was a large negative calcium

balance. While she remained on the same diet the urinary calcium excretion fell to a level within the normal range. Then she was given a high calcium diet on which the calcium of the urine remained at the relatively low level while the fecal calcium increased greatly and there was a positive balance. The serum calcium did not change.

It seems reasonable to associate the excretion of large amounts of calcium in the urine with the abnormal liberation of calcium about the enlarging, destructive lesion in the pelvis. The periodicity of growth of malignant disease in bone is generally recognized. As the activity decreases temporarily the flow of calcium from the bone into the excretory channels would naturally diminish and the calcium of the urine fall toward normal amounts. It is interesting that in this case the subsequent ingestion of a diet fairly high in calcium, which gave rise to a large positive calcium balance, had little effect on the amount of calcium in the urine or on the serum calcium level. The same thing has been found in other cases.

We do not attribute the change in calcium excretion to the effect of injected colloidal lead, as we have had no evidence in other cases to indicate that lead given under the conditions of our work had any specific effect on the tumor growth or on calcium metabolism.

Case II, Mrs. L. N., age 33, weighing 62 kilos, suffered from extensive metastatic carcinoma involving the skull, spine, pelvis, and humerus. The data for calcium and phosphorus excretion in her case are also given in Table I. In spite of the extensive malignant disease the calcium excretion during the period of observation was within the normal range. A very marked clinical improvement after lead and x-ray therapy with recalcification of tumor masses is interesting though of doubtful significance.

### *Myeloma*

It was interesting to compare the calcium metabolism in a patient suffering from multiple myeloma with that of cases of breast carcinoma with metastases in the bones. Case III (Mrs. M), age 27, weighing 44 kilos, had suffered for approximately two years with darting pains in various bones, which followed sudden movements. She was comfortable when resting, but weak and pale. X-ray examinations demonstrated a diffuse and destructive process involving the spine, ribs, scapulae, humeri, pelvis, and heads of the femora. Some of the areas of destruction were quite large with sharply defined margins. The 9th dorsal vertebra was mushroomed. The appearance suggested to Dr. George Holmes either myeloma or metastatic carcinoma. Large amounts of Bence Jones protein were found in the urine. The pathological diagnosis of myeloma was made from sections of bone removed at biopsy. Results are given in Table II.

TABLE II  
*Cases III to V*  
*(Intake and output in 3-day periods)*

The excretion of calcium and phosphorus in both urine and feces was within the normal range for adult patients on a low calcium diet (6). It is notable that in spite of wide-spread involvement of bone there was no increased excretion of calcium. Due to a very low urinary calcium excretion, the negative balance was actually less than that of the average normal adult. From the clinical point of view also the disease appeared to be relatively stationary.

#### *Focal osteitis fibrosa*

Case IV<sup>1</sup> (Miss R.), aged 34, weight 53 kilos, had been well up to three years ago, when a fracture of the right femur occurred at the site of a large cyst. At open operation the cyst wall was curetted, following which firm bony union occurred. The report of histological examination of the curettings described "a cell rich fibrous tissue containing bone trabeculae with areas of hemorrhage and blood pigment. The histological appearances are those of osteitis fibrosa." In 1928 she began to suffer severe shooting pain in the right ankle. X-ray examination revealed a large cyst in the lower end of the right tibia and another in the right pubis; but the rest of the skeleton appeared to be normal. The cyst in the tibia was opened and its wall curetted. The pathological examination revealed a similar picture to that previously reported.

Before operation she was given a low calcium diet for nine days. In Table II are presented results of the calcium and phosphorus determinations.

The excretion of calcium and phosphorus was within normal limits and the blood serum values were normal. On a higher calcium intake part of this calcium was retained as in normal individuals. The normal calcium metabolism in this case of focal osteitis fibrosa is in striking contrast with that of cases of generalized "osteitis fibrosa cystica" (hyperparathyroidism) (1) in which the serum calcium is high and calcium excretion greatly increased. There is an equally great contrast in the clinical picture of the two conditions.

#### *Fragilitas ossium*

Case V (May T.), age 14, weighing 25 kilos, had a typical history of fragilitas ossium. One femur had been broken at birth and x-ray examination the next day also showed healed fractures of both femora. There had been repeated fractures from the slightest trauma in early years. When she was 4 years old attention was drawn to the fact that her trunk was unusually short and this has become progressively more marked since that time. Her diet, as described, had been adequate in both calcium and vitamin D. On admission she presented a very unusual appearance

<sup>1</sup> After this article had gone to press, similar findings were reported by Donald Hunter, Hyperparathyroidism: Generalized Osteitis Fibrosa. *Brit. J. Surg.*, 1931-32, *xix*, 203.

with great deformity due to the shortness of the trunk, which exhibited a broad kyphotic curve and a gross scoliosis. The head was large and the upper extremities appeared normal, but there was extreme deformity of the lower limbs which had suffered repeated fractures. Apart from the skeletal changes no abnormalities were found.

On x-ray examination all the bones showed increased radiability with coarse irregular trabeculation and thin cortex. The findings, according to Dr. George Holmes, were those of osteomalacia.

The calcium excretion on a low calcium diet was within the limits of normal, although the urinary calcium was probably a little higher than in most children of her age. Serum calcium was normal and serum phosphorus slightly above the usual level for children. More than three years since this observation her bones remained unchanged, as judged by x-ray photographs, in spite of ample calcium and vitamines in her diet.

*Osteosclerosis (marble bone disease)*

Case VI (Mrs. H. B.), P. B. B. H. No. 67748, age 41, weighing 63.7 kilos, complained that for eight months she had dull pain in the back of the neck and shoulders with limitation of motion. Her previous history was interesting. A very severe diabetes started ten years ago with diabetic coma relieved by insulin eight years ago. The removal of an adenoma of the thyroid four years ago greatly improved the diabetes and also relieved attacks of cardiac palpitation. X-rays of nearly the whole skeleton disclosed a marked osteosclerosis which had not obviously increased in the past four years. All the bones except the ribs were unusually dense and rather structureless in appearance but with very thick cortices. There were no areas of decreased density as seen in Paget's disease. Four other members of the immediate family had similar findings by x-ray examination.

TABLE III  
*Osteosclerosis. Case VI. (Mrs. H. B.)*  
(Intake and output in 3-day periods)

Period (3 days)	Calcium			Intake grams	Balance grams		
	Excretion						
	Urine grams	Feces grams	Total grams				
2	.19	.06	.25	.20	-.05		
3	.20	.13	.33	.20	-.13		
4	.20	.19	.39	.20	-.19		
5	.15	.18	.33	.20	-.13		

*Blood serum values*

Calcium—8 mgm. per 100 cc., 10 mgm. per 100 cc.; Phosphorus—3.2 mgm. per 100 cc., 3.2 mgm. per 100 cc.; Total protein—8.0 grams per 100 cc.; Albumin—5.6 grams per 100 cc.; Globulin—2.4 grams per 100 cc.

Extensive laboratory studies disclosed no variation from the normal, except a slight elevation of sugar in the blood. A study of the calcium exchange is shown in Table III. The findings are not abnormal except possibly a diminution in fecal calcium excretion. This is of less significance considering her basal metabolic rate of - 19 per cent. Therefore, further studies of phosphorus and nitrogen balance were not made in this case.

*Osteochondritis deformans juvenilis (Legg's disease)*

Case VII (Robert W.<sup>2</sup>), M. G. H. No. 279602, age 10, weighing 25.5 kilos, was an adopted child. Birth was two months premature. His childhood had been characterized by a limping gait and an avoidance of such activity as walking upstairs. These signs had become progressively more marked. He had lived upon a vegetarian diet all his life. Physical examination disclosed a short, stocky, well nourished boy with nothing abnormal to be found except in his skeleton. There was normal, free movement of all his joints. The right leg was shorter and smaller than the left with slight atrophy of the muscles. The x-rays, taken at the Boston Children's Hospital, included all the bones in the body. They showed a wide-spread disturbance practically limited to the epiphyses. This disturbance was characterized by delayed development, mushrooming of the weight-bearing epiphyses, and increased density of the bone along the epiphyseal margins. In some areas, particularly the spine and pelvis, this had resulted in absence of parts of the bone. The diagnosis of generalized osteochondritis deformans was made by all the many physicians who saw him.

Prolonged metabolic studies were undertaken with both a low and a high calcium diet, with the addition of parathormone and cod liver oil. These results are difficult to interpret because there are practically no data of the normal excretion of calcium at this age period. When compared to other growing children the urinary calcium excretion is slightly elevated. This is particularly true, for his diet was essentially neutral throughout the whole observation. In spite of the abnormality of most of his epiphyses he had no difficulty in storing calcium at a rapid rate.

The abnormality of this boy's metabolism was in the phosphorus excretion. This was distinctly above the theoretical value to be derived from the calcium and nitrogen balances (see Paper IV (7)) for the first nine periods. Thereafter, more phosphorus was retained than could be theoretically explained. This change appeared before cod liver oil was given and followed the distinct elevation in plasma calcium produced by parathormone.

The nitrogen excretion and the blood findings are not abnormal for a growing boy. The results of these studies are given in Table IV and Figures 1 and 2.

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<sup>2</sup> Referred by Dr. Robert Osgood.

TABLE IV  
*Osteochondritis deformans juvenilis. Case VII. (Robert W.)*  
*Intake and output in 3-day periods.*

Dates Period ending number	Calcium			Phosphorus			Nitrogen			Total caloric intake	Date	Blood plasma	Basal meta- bolic rate				
	Excretion		In- take	Excretion		In- take	Urine Excre- tion		In- take								
	Urine	Feces		Urine	Feces		Urine	Feces									
	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams				
10/29																	
11/1	1	0.29	0.22	0.51	0.24	1.35	0.47	1.62	1.56	11.6	20.6	4,434	10/29				
11/4	2	0.29	0.11	0.41	0.25	1.86	0.27	2.13	1.57	14.2	20.6	4,740					
11/7	3	0.31	0.12	0.43	0.24	1.84	0.34	2.19	1.54	13.8	19.7	4,526					
11/10	4	0.33	0.30	0.63	—	1.88	0.30	2.18	1.96	11.4	17.9	4,167	11/9				
11/13	5	0.46	1.05	1.51	2.25	2.13	0.83	2.96	3.05	14.2	24.4	6,066	10.5				
11/16	6	0.42	0.71	1.14	2.25	2.12	0.68	2.80	3.05	13.9	24.4	6,111	5.0				
11/19	7	0.56	0.92	1.47	2.25	2.56	0.82	3.38	3.05	14.6	24.4	6,066	11/17				
11/22	8	0.73	0.53	1.25	2.25	2.86	0.68	3.54	3.05	15.4	24.4	6,066	11/22				
11/25	9	—	0.90	—	2.25	—	0.78	—	3.05	—	24.4	6,066	5.7				
11/28	10	0.53	0.47	1.00	2.25	1.36	0.53	1.88	3.17	21.1	26.8	6,361					
12/1	11	0.49	0.67	1.16	2.25	1.25	0.74	1.99	3.05	16.5	24.4	6,066					
12/4	12	0.57	0.56	1.12	2.25	1.34	0.62	1.95	3.05	15.0	24.4	6,066					
12/7	13	0.54	0.57	1.11	2.25	1.24	0.75	1.99	3.05	14.4	24.4	6,066					
12/10	14	0.41	0.50	0.91	2.25	0.93	0.69	1.62	3.07	11.2	24.4	6,066					
12/13	15				2.25	1.39			3.07	15.6	24.4	6,066	12/13				
													10.9				
													4.7				

\* From Children's Hospital record.

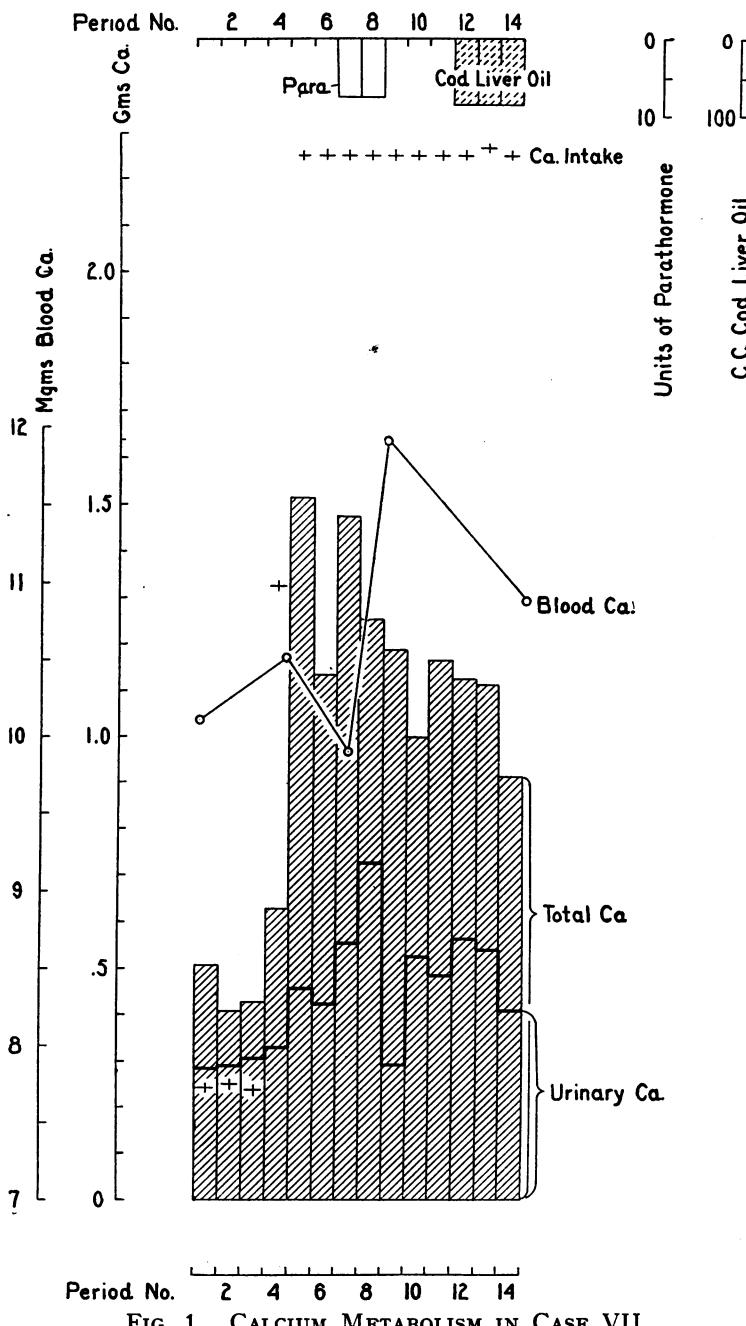


FIG. 1. CALCIUM METABOLISM IN CASE VII

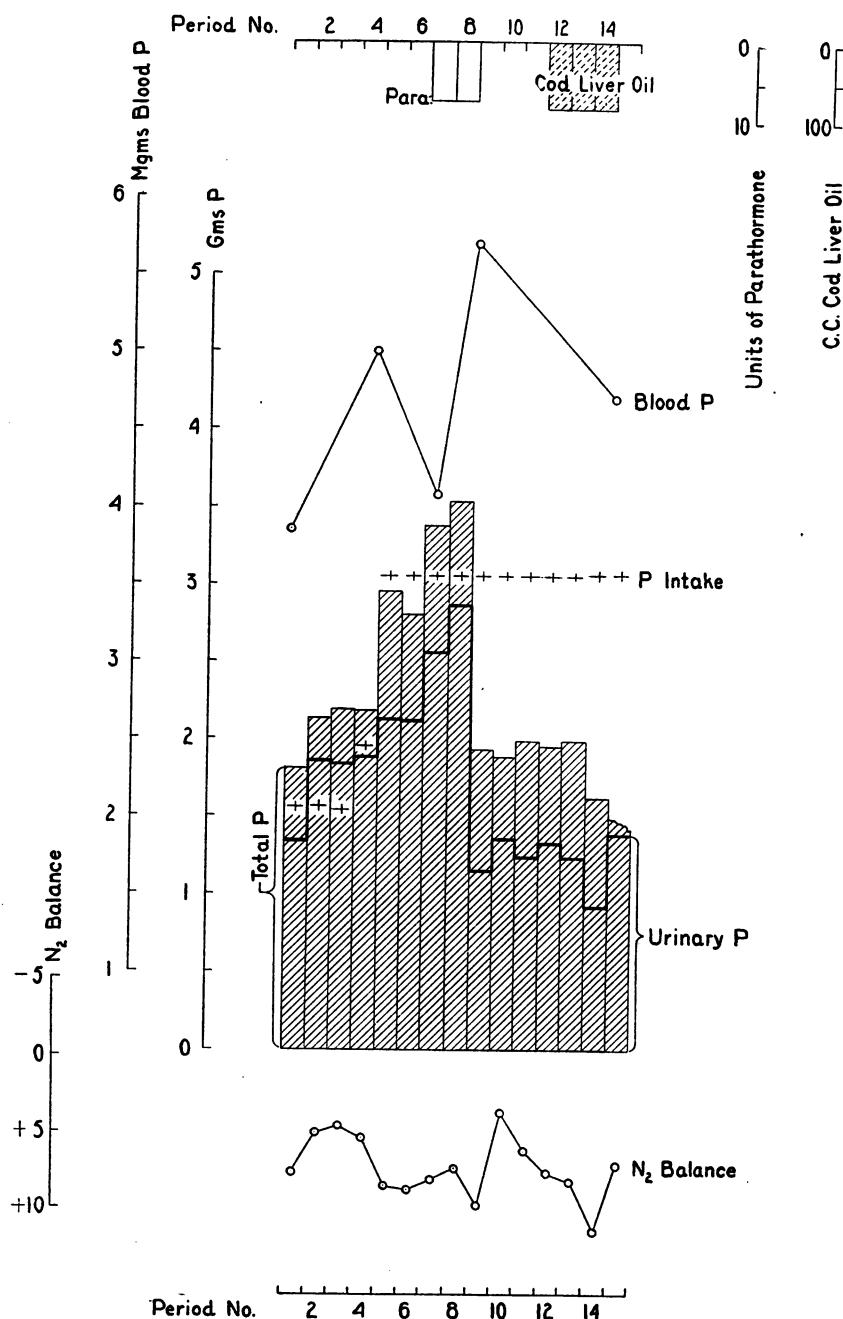


FIG. 2. PHOSPHORUS METABOLISM IN CASE VII

## B. OTHER METABOLIC DISEASES

*Gout*

Case VIII (H. H.), age 22, weighing 49 kilos, had suffered from recurring attacks of gout for five years. Many joints were involved and finally he became a complete invalid. There were numerous tophi in ears, fingers, and toes. Both olecranon bursae were involved. The metacarpophalangeal and interphalangeal joints of both hands were swollen and the interossei muscles were atrophic. There was great thickening of the common tendon sheath of the right palm. The prepatellar bursa was similarly affected. There was very marked swelling of the joints of the ankles and feet on both sides with preternatural mobility of the great toes. From an open sinus on the right great toe a chalky material made up of crystals of sodium biurate could be easily expressed. X-ray plates showed complete destruction of the articular surfaces of both first metatarsophalangeal joints with extensive destruction of the adjoining bones. There was a varying degree of destruction of the joints of the hands. The blood uric acid was 10.3 mgm. on one occasion and 12.4 mgm. on another. Results of studies of calcium and phosphorus metabolism are given in Table V.

TABLE V  
*Gout. Case VIII. (H. H.)*  
*(Intake and output in 3-day periods)*

Period	Calcium				Phosphorus				Nitrogen		Serum	
	Urine	Feces	Intake	Balance	Urine	Feces	Intake	Balance	Urine	Intake	Ca	Protein
	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams	mgm. per 100 cc.	grams per 100 cc.
1	.09	.34	.29	-.14	1.21	.52	1.31	-.42	22.4	25.0	9.7	7.43
2	.16	.56	.29	-.43	1.23	.71	1.82	-.12	19.6	25.0		
3	.06	.37	.17	-.26	1.10	.44	.97	-.57	16.0	12.6		
4	.10	1.03	1.54	+.41	.98	1.14	2.03	-.09	17.8	18.9		
5	.05	1.15	1.63	+.43	.98	1.43	2.68	+.27	13.3	29.6		
6	.09	.85	1.66	+.73	1.10	1.07	2.45	.28	19.0	29.8		

On a low calcium diet the calcium metabolism was essentially normal. When the calcium intake was increased five-fold there was, as in Cases I and IX, no increase in the urinary calcium, although the fecal output increased considerably. On this diet, calcium was retained in the body.

*Chronic hepatitis with jaundice*

It has been shown that in experimental obstructive jaundice the serum calcium may be low (8). In animals with a bile fistula Whipple (9) noted that the bones became thin and spontaneous fractures occurred. It

seemed worth while to study the calcium and phosphorus metabolism of a case of chronic hepatitis with jaundice.

Case IX (P. N.), a patient of Dr. Chester Jones, age 35, weighing 51 kilos, had suffered from chronic hepatitis with jaundice (biliary cirrhosis) for 1 1/2 years. The jaundice ran an undulant course, gradually becoming worse. She was moderately jaundiced, thin, and looked weak and ill. The liver was grossly enlarged, extending as far as the umbilicus, and the spleen was readily palpable. There was no ascites or edema. Serum bilirubin was 7 to 8 mgm. per 100 cc., bile pigments were present in the urine, and serum protein and blood nonprotein nitrogen were normal. Results are presented in Table VI.

TABLE VI  
*Chronic hepatitis with jaundice. Case IX. (P. N.)*  
(Intake and output in 3-day periods)

Period	Calcium				Phosphorus				Serum	
	Urine	Feces	Intake	Balance	Urine	Feces	Intake	Balance	Ca	P
(3 days)	grams	grams	grams	grams	grams	grams	grams	grams	mgm. per 100 cc.	mgm. per 100 cc.
1	.17	.51	.39	-.29	1.07	.57	1.79	.15	8.5	3.3
2	.10	.66	.37	-.39	1.20	.54	1.88	.14	9.8	3.5
3	.12	3.95	3.41	-.66	1.19	1.01	2.93	.73		
4	.14	2.42	3.15	+.59	1.52	1.17	3.07	.38	8.9	3.6

The serum calcium on two of three occasions was slightly below normal. Excretion in stool and urine was within normal limits. The change to a high calcium diet, as in Case I, had no appreciable effect on the urine calcium but was associated with an increase in the fecal calcium and phosphorus.

#### *Osteomalacia*

Since this paper was written, a further type of bone abnormality has been studied—osteomalacia due to a dietary deficiency in calcium.

Mrs. L. H., P.B.B.H. No. 39821 (Medical), aged 64, weighing 63.5 kilos, had largely avoided milk and green vegetables in her diet. Six years ago she had symptoms suggesting arthritis of the spine. Five years ago she had a slight fall and fractured two thoracic vertebrae. Convalescence has been very slow and she is still wearing a supporting cast. Except for her bones, her physical examination was not abnormal for a woman of her age. X-rays of her whole skeleton disclosed marked generalized decalcification. The thoracic and lumbar spine also showed collapse of the central portions of the bodies and apparent marked expansion of the intervertebral discs. Several of the vertebrae in the mid-thoracic region showed marked collapse suggesting spontaneous fractures.

Laboratory data: The Wassermann was negative and the urine, feces, basal metabolic rate, blood urea nitrogen, blood sugar, and blood morphology were all within normal limits. There was no excess of fat or fatty acids in the feces. The blood serum calcium level was 9.8 mgm. and 10.6 mgm. per 100 cc. The serum phosphorus was found to be 4.0 and 4.8 mgm. per 100 cc.

*Mrs. L. H., aged 64, white, female.  
(Intake and output per 3-day period)*

Period	Calcium			Intake	Balance		
	Excretion						
	Urine	Feces	Total				
1	grams .29	grams .50	grams .79	grams .26	grams — .53		
2	grams .40	grams .40	grams .80	grams .28	grams — .52		
3	1.11	2.16	3.27	5.56	2.29		
4	1.03	2.55	3.58	6.00	2.42		

These data disclose normal blood values and a normal calcium excretion. When a diet with a moderate amount of calcium was given to her, a large proportion of this added calcium was retained. It is interesting that the organism can maintain normal blood levels and normal calcium excretion even with such marked decalcification of the bones.

#### DISCUSSION

The changes in deposition or removal of bone salts probably occur so slowly that the variation from normal cannot be observed by our methods in relatively short observations. The observations here reported do show, however, that there is nothing grossly abnormal in the blood level or in the excretion of calcium or phosphorus. The reason for this may well lie in the large amount of calcium readily available for utilization in times of need, such as occurs on our diet inadequate in calcium. This storehouse in the trabeculae, described by Bauer, Aub and Albright (10), apparently exists in all the diseases here studied, and is available for the liberation or storage of calcium. The method determining calcium exchange, therefore, does not necessarily disclose abnormalities which might be occurring in one part of the skeleton, as there is this compensatory mechanism still present in other bones. Calcium and phosphorus may well be liberated from one part and deposited in another portion of bone. It is, therefore, not surprising that in this series of patients suffering from various types of bone diseases or chronic jaundice the variations from normal in calcium and phosphorus excretions are relatively slight.

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