STUDIES IN PARATHYROID PHYSIOLOGY: *III. The Effect of Phosphate Ingestion in Clinical Hyperparathyroidism*

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STUDIES IN PARATHYROID PHYSIOLOGY

III. The Effect of Phosphate Ingestion in Clinical Hyperparathyroidism [1]

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In the second paper of this series (1) the disorders of calcium phosphate metabolism were divided into three fundamental groups. It was believed that under normal conditions body fluids contain all the calcium phosphate which that particular fluid system can hold at that particular time. The first and commonest group was that in which the body fluids contain less than this saturating amount of calcium phosphate. Because of this, calcium phosphate is not deposited into osteoid tissue with the resulting pathological picture of wide osteoid seams on the trabeculae (cf. rickets and osteomalacia). The second group was that in which the body fluids, because of certain extraordinary circumstances, contain more than the normal quota of calcium phosphate and deposition in tissues other than osteoid tissue results (e.g. ergosterol poisoning and cases of metastatic malignancy and myeloma). Finally, a third possibility presented itself. It is conceivable that the body fluids might contain a normal saturating amount of calcium phosphate, but that the proportion of the calcium ions to the phosphate ions might be abnormal. Such, it was believed, is the disorder in diseases of the parathyroid glands. To recapitulate then, we conceived of three possible variations from the normal saturation of body fluids with calcium phosphate: (*a*) subsaturation, (*b*) supersaturation, and (*c*) anomalous-saturation (i.e. quantitatively normally but qualitatively abnormally saturated).

In the first paper of this series (2), the hypothesis was advanced that this abnormality in the relation of the calcium ion to the phosphate ion in parathyroid disorders was dependent upon changes in phosphorus excretion in the urine brought about by the parathyroid hormone. Thus it was believed that on administration of the parathyroid hormone the first effect was an increased phosphorus excretion; that this resulted in a decreased serum inorganic phosphorus; that this tended to leave the serum's capacity to take up calcium phosphate unfulfilled; that calcium

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phosphate was mobilized from the bones to meet this tendency to a deficiency; that equilibrium was finally established with the blood phosphorus slightly lowered and the blood calcium slightly raised; and that, as a result of the raised blood calcium, the urinary calcium excretion was increased. No hypothesis was offered to explain the mechanism of this initial increased phosphorus excretion. The known facts would be explained if we hypothesized a sudden lowering of the threshold for phosphorus excretion in the urine on the administration of the parathyroid hormone. The cause for this apparent change in the kidney threshold for phosphorus might be clear if we knew what the cause for any kidney threshold was, and will probably not be found in the kidney but rather in some physical-chemical equilibrium in the body as a whole.

If one believes in this hypothesis of Albright and Ellsworth (2), which makes the calcium changes in parathyroid dysfunctions secondary to phosphate changes, it is of course logical to attempt to correct the calcium abnormalities in hyperparathyroidism by first attacking the phosphorus abnormalities. In their experiment III, Albright and Ellsworth (2) were able to influence only slightly the high blood phosphorus of a patient with hypoparathyroidism by first giving a high phosphorus diet and then abruptly changing to a low phosphorus diet. The present investigation is the exact antithesis to the above; it was undertaken to determine whether the low blood phosphorus in hyperparathyroidism can be altered by diet. Bauer, Albright, and Aub (3) pointed out that in clinical hyperparathyroidism "a high phosphorus diet might be more efficacious from a therapeutic standpoint than a high calcium diet."

Whereas it is our working hypothesis that the state of hyperparathyroidism with its high blood calcium and low blood phosphorus is reached because the parathyroid hormone lowers the threshold for phosphorus excretion in the urine, it must be emphasized that this state leads to skeletal decalcification and dephosphatization because of the increased calcinuria resulting from the high blood calcium. Because the blood calcium is not much increased by a high calcium diet, this increased calcinuria, dependent on the height of the blood calcium, is not appreciably increased by a high calcium diet, and the patient with clinical hyperparathyroidism studied by Bauer, Albright and Aub (3) was kept in calcium equilibrium by this means. Thus a high calcium diet merely combats a complication (increased calcinuria) of the state of hyperparathyroidism but does not alter the state. It was to be hoped that a high phosphorus diet would raise the blood phosphorus; as a result lower the blood calcium; and thus decrease the calcium excretion. Thus calcium balance might be obtained likewise, and furthermore, the state of hyperparathyroidism might be altered in the direction of normal.

EXPERIMENTAL

Three patients with conditions which metabolically correspond to hyperparathyroidism were studied in the Metabolism Ward for fore periods on weighed diets and then under exactly the same conditions except for the addition of large amounts of phosphate to the diet. The urine and feces were analyzed in three-day periods for calcium and phosphorus. The methods for the preparation of the diet and the collection of the excreta were those previously reported (4). Serum inorganic phosphorus and calcium determinations were done on venous blood obtained before breakfast. All calcium determinations were done by the Fiske method (5), and all phosphorus determinations by the Fiske and Subbarow method (6).

Experiment I

The subject of this investigation was the same sea captain on whom in 1926 the clinical diagnosis of hyperparathyroidism was made for the first time in this country by Dr. Eugene F. DuBois. It is not necessary to repeat the details of his history or previous metabolic findings as they have been reported elsewhere (7) (3) (8). The essential features are that he presented all the criteria of hyperparathyroidism,—osteitis fibrosa cystica generalisata, high blood calcium, low blood phosphorus, and increase of calcium and phosphorus in the urine; that at operation, no parathyroid tumor was found; that the situation was little if at all altered by the removal of two small parathyroid glands; that it was found that the decalcification could be combatted by a very high calcium diet; that as a result of a prolonged regime on a high calcium diet the patient was brought from a bedridden state to an economically self-supporting state; but that in spite of all he continued to present all the criteria of hyperparathyroidism.

The patient was studied for three three-day periods on a high calcium, moderately high phosphorus diet. He was then studied for one two-day period and for three three-day periods on the same regime plus large amounts of phosphate by mouth. Periods IV and V, the first two periods on the high phosphate diet, are of little value because of nausea and vomiting occasioned by the ingestion of secondary sodium phosphatel As a result acid sodium phosphate was resorted to. The more neutra. salt had been chosen because of the known action of acid salts in increasing the excretion of calcium in the urine. Any diminution in the calcium excretion obtained by the ingestion of the primary sodium phosphate salt may be considered to have occurred in spite of this factor. The CO_2 combining power of the serum as a matter of fact was little altered, being 47 and 44 volumes per cent during the last period at the height of the acid ingestion. The data are presented in Table I and Chart I.

TABLE I

Calcium and phosphorus data of experiment I

Period	Calcium (per 3-day period)					Phosphorus (per 3-day period)					Serum			Remarks
	Urine	Feces	Total excretion	Intake	Balance	Urine	Feces	Total excretion	Intake	Balance	Ca	P	Ca × P	
	grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*		
I.....	1.00	1.68	2.68	2.79	+0.11	2.52	0.36	2.88	1.98	−0.90	14.1(1)‡	2.80	40	Control period
II.....	1.51	2.06	3.57	2.79	−0.78	2.83	0.49	3.32	1.98	−1.34	14.6(1)	2.84	41	Control period
III....	1.42	2.61	4.03	2.79	−1.24	2.30	0.67	2.97	1.98	−0.99	13.9(1)	2.50	35	Control period
IV*...	1.32	2.19	3.51	†		3.63	0.95	4.58	†		14.5(1)	2.62	38	Phosphate ingestion
V.....	0.88	2.22	3.10	†		3.47	1.07	4.54	†		13.2(2)	3.10	41	Phosphate ingestion
VI....	0.73	1.36	2.09	2.79	+0.70	5.25	1.97	7.22	12.18	+4.96	12.2(2)	4.37	53	Phosphate ingestion
VII...	0.60	2.06	2.66	2.79	+0.13	6.90	2.30	9.20	12.18	+2.98	12.8(1) 12.9(2) 12.6(3)	5.90 4.37 5.87	76 56 79	Phosphate ingestion

* As period IV was a two- instead of a three-day period, values for this period in the chart have been multiplied by 3/2 in order to be comparable.

† The intakes in periods IV and V, though high in phosphorus, are not known because of nausea and vomiting occasioned by the secondary sodium phosphate ingestion (see text).

‡ The arabic numeral in the parenthesis indicates on which day of the period, first, second, or third, the blood specimen was collected.

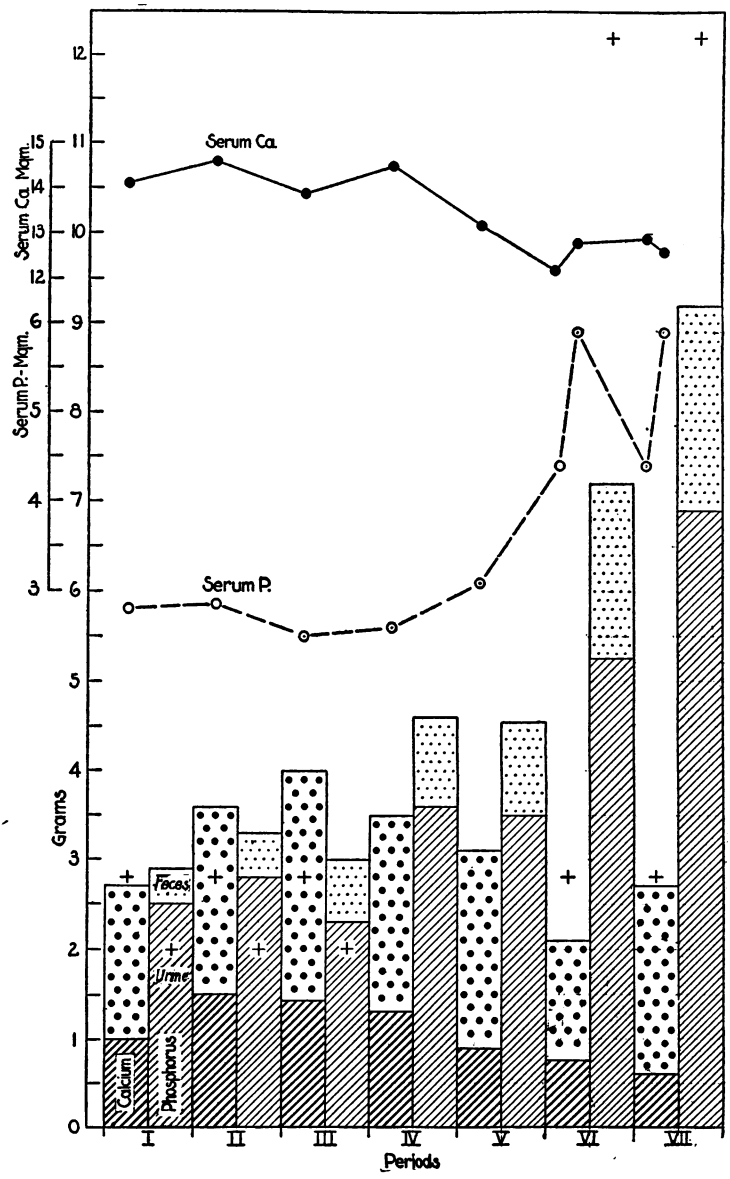

CHART I. CALCIUM AND PHOSPHORUS DATA FOR EXPERIMENT ONE

Heavily hatched and dotted columns indicate Ca excretion; lightly hatched and dotted columns indicate phosphorus excretion. Hatched area urinary excretion; dotted area fecal excretion. + indicates intake.

During the three control periods the expected findings were present. The serum calcium was very high (14.1 mgm. per 100 cc.); the serum phosphorus was correspondingly low (2.8 mgm. per 100 cc.); the calcium in the urine was markedly elevated (1.00 gram in 3 days); and the ratio of phosphorus in the urine to phosphorus in the feces was very high. The serum phosphorus was slightly higher than in 1926 when it averaged about 2.0 mgm. per 100 cc. The calcium excretion in the feces was much higher than one would have expected from the 1926 studies. At that time on a calcium intake of 3.22 grams per three-day period, the fecal calcium was 1.68 gram. The high calcium intake in the present investigation was obtained by adding calcium gluconate to the diet whereas in 1926 it was obtained by altering the diet itself.

Examining first the phosphorus changes, one notes that with the establishment of the high phosphorus intake most of the phosphorus was absorbed as judged from the fecal values, but that there was an immediate and marked increased excretion of phosphorus in the urine. The increased urinary phosphorus excretion did not, however, compensate for the increased phosphorous absorption and the serum phosphorus rose (2.5 mgm. to 5.9 mgm.). Judging from the rapidity with which the urinary phosphorus excretion rose one can infer, we believe, that the low serum phosphorus at the outset was not below the threshold for phosphorus excretion, but that the threshold itself was low. Comparing period VII with period I, one notes that about 4.0 grams more phosphorus were excreted in the urine in period VII than in period I. This means that 4.0 more grams of phosphorus went from the blood into the urine. However, if one assumes that the blood volume was 5 liters for rough calculations, there was only about 150 mgm. increase in phosphorus content in the entire blood in period VII over period I. It would appear that the kidney was making every effort to excrete the added absorbed phosphorus and was only about 150 mgm. behind at the end of the investigation. One gets the impression that any changes brought about by the high phosphorus ingestion are merely due to the slight lag in the ability of the kidney to establish equilibrium.

Turning to the calcium data one notes that as the serum phosphorus rose the serum calcium fell. However, one notes that the Ca $\times$ P product rose very appreciatively. This is in striking contrast to the situation which one obtains when the calcium is lowered by decreasing the degree of hyperparathyroidism (1). This again suggests that the increased absorption of phosphorus was too rapid to allow equilibrium to be established. As was to be expected, with the lowering of the blood calcium there was a corresponding lowering of the urinary calcium excretion. The fecal calcium excretion was not affected. It would appear that fecal calcium excretion is not a threshold phenomenon (cf. normal fecal calcium excretion in hypoparathyroidism at a time when the

serum calcium is below the threshold for urinary calcium excretion). With the increase in the Ca × P products it is probable that the tendency to deposit calcium phosphate into the bones was increased and this is borne out by the tendency for the balances of Ca and P to become positive.

The conclusions suggested from experiment I are:

I. In clinical hyperparathyroidism the ingestion of large amounts of phosphate results in almost complete absorption of the phosphate into the blood stream.

II. The absorbed phosphates are rapidly excreted by the kidney suggesting that the depressed serum phosphorus level in hyperparathyroidism is not below the threshold for phosphorus excretion, but that the threshold itself is low.

III. In spite of the effort of the kidney to excrete the phosphate, the serum phosphate can be made to rise and the serum calcium to fall by ingestion of huge amounts of phosphate.

IV. However, the fall in calcium does not correspond to the rise in phosphorus and the Ca × P product rises. This rise promotes calcium deposition.

V. Finally, with the lowering of the serum calcium, the urinary calcium excretion is diminished.

VI. The net result of ingestion of phosphate in hyperparathyroidism is the tendency to produce a positive balance of calcium phosphate and the altering of the serum calcium and phosphorus values in the direction of normal.

Experiment II

The subject of this investigation is suffering from a malady which in every respect resembles that of the previous patient and which has run the same course. The history and x-ray findings are given in the appendix (q.v.). The essential facts for the present discussion are that she is a married woman of 41 who entered this hospital with marked osteitis fibrosa cystica generalisata and metabolic evidence of hyperparathyroidism; and that, following the investigation to be reported here, she was operated upon without the finding of a parathyroid tumor, but with the removal of two normal parathyroid glands. The operation was apparently without benefit.

The patient was studied for two control periods on a low calcium and normal phosphorus diet. In period III large amounts of tertiary sodium phosphate by mouth were added to the diet. This immediately caused nausea and vomiting so that again acid sodium phosphate was resorted to. This was well tolerated. No marked acidosis was occasioned by this therapy as the CO_2 combining power of the serum at the end of the investigation was 59 volumes per cent. The data are shown in Table II and Chart II.

TABLE II

Calcium and phosphorus data of experiment II

Period	Calcium (per 3-day period)					Phosphorus (per 3-day period)					Serum			Remarks
	Urine	Feces	Total excretion	Intake	Balance	Urine	Feces	Total excretion	Intake	Balance	Ca	P	Ca × P	
	grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*		
I.....	0.71	0.16	0.87	0.22	−0.65	1.09	0.20	1.29	1.67	+0.38	14.2(1)†	2.3	33	Control period
II.....	0.54	0.20	0.74	0.22	−0.52	1.33	0.44	1.77	1.63	−0.14	14.0(1)	2.4	34	Control period
III....	0.59	0.11	0.70	*		4.06	0.32	4.38	*		14.3(1)	2.3	33	Phosphate ingestion
IV....	0.26	0.10	0.36	0.22	−0.14	6.74	0.35	7.09	8.51	+1.42	12.3(1) 12.2(2)	3.2 3.1	39 38	Phosphate ingestion
V.....	0.31	0.11	0.42	0.22	−0.20	8.54	0.39	8.93	11.91	+2.98	12.3(1)	3.2	39	Phosphate ingestion
VI....											10.7(1)	3.1	33	

* Intakes could not be obtained in period III because of vomiting.

† The arabic numeral in the parenthesis indicates on which day of the period,—first, second, or third,—the blood specimen was collected.

During the two control periods the expected findings were present. The serum calcium was very high (14.2 mgm. per 100 cc.); the serum phosphorus was very low (2.32 mgm. per 100 cc.); the calcium in the urine was markedly elevated (706 mgm. in period I compared to a normal

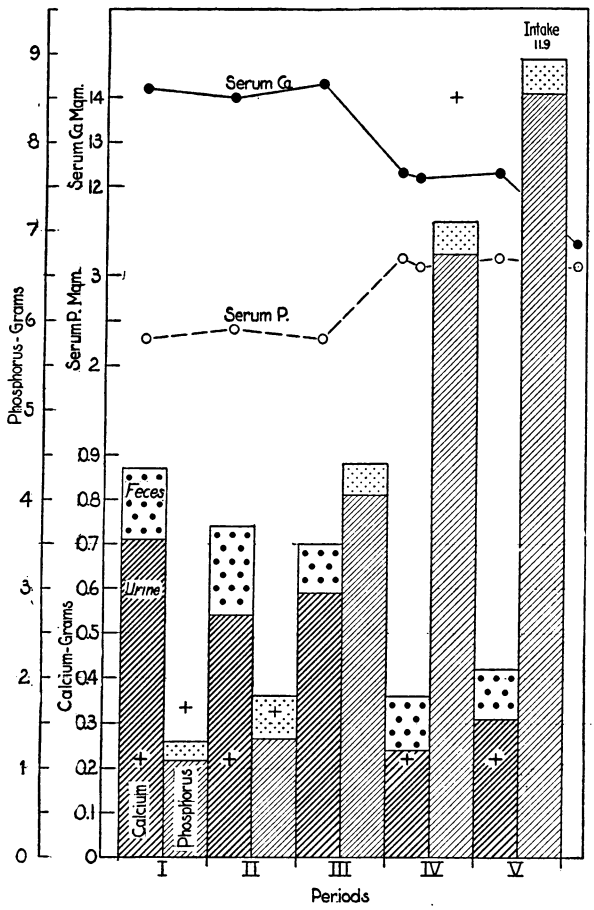

CHART II. CALCIUM AND PHOSPHORUS DATA FOR EXPERIMENT TWO

Heavily hatched and dotted columns indicate Ca excretion; lightly hatched and dotted columns indicate phosphorus excretion. Hatched area urinary excretion; dotted area fecal excretion. + indicates intake.

value of 190 mgm. for normal individuals under a similar regime (9)); and the phosphorus excretion was predominantly in the urine. The very low fecal calcium excretion alone demands special comment. It would appear that in hyperparathyroidism not only is there no increased excretion of calcium into the gut as a result of the high serum calcium, but there is an increased absorption of calcium from the gut. It is very

significant that in no one of the 46 three-day periods on 13 normal individuals reported by Bauer, Albright and Aub (9) was the fecal calcium excretion on a similar low calcium diet below 200 mgm. Apparently in hyperparathyroidism, calcium is withdrawn from the gastro-intestinal tract as well as from the bones. The low partition of fecal phosphorus compared with urinary phosphorus in this condition probably is dependent on the same principle. This particular finding in clinical hyperparathyroidism does not correspond with the observation made by Albright, Bauer, Ropes and Aub (10) that administration of parathyroid hormone to normal individuals is without effect on the fecal calcium and phosphorus excretions. The discrepancy may be due to the depletion of reserve supplies of calcium in the bones in the long standing cases. Such an explanation is supported by the fact that the fecal calcium continued low in a case of hyperparathyroidism recently studied even after removal of the parathyroid tumor, again suggesting that the decalcification rather than the degree of hyperparathyroidism is the deciding factor here.[2]

With the ingestion of phosphate in periods III, IV, and V, it is very remarkable that the fecal phosphorus excretion was not increased, showing that the additional ingested phosphate was completely absorbed. This again emphasizes the tendency in this condition to absorb calcium and phosphorus from the gastro-intestinal tract. The absorbed phosphorus immediately appeared in the urine. Again there was a rise in the serum phosphorus. One notes that during periods IV and V there was no further rise in serum phosphorus. This probably indicates that the serum phosphorus was now sufficiently above the threshold for phosphorus excretion so that as much phosphorus was leaving the blood through the urine and into the bones as was being absorbed from the gastro-intestinal tract. It is possible that some of the ingested phosphate of the last day of the investigation was still in the gastro-intestinal tract, thus explaining the otherwise unaccountably high balance of phosphorus in period V. As the serum phosphorus rose, the serum calcium fell but again not proportionately and there was a slight rise in the Ca $\times$ P product. The last serum values on the morning following the last day of the experiment are very instructive. We have previously explained the high Ca $\times$ P products with ingestion of phosphate on the ground that phosphorus was being so rapidly absorbed into the blood stream that equilibrium could not be established. Here in period V this absorbed phosphorus was being entirely excreted or deposited. It is not surprising, therefore, at the end of period V to find that the serum calcium had adjusted itself to the then stationary serum phosphorus level and that the Ca $\times$ P product was the same as at the beginning. Finally, with the

[2] To be published.

lowering of the serum calcium, the urinary calcium excretion was diminished.

Experiment II very much strengthens the observations made in experiment I, and suggests the following additional conclusions:

VII. In hyperparathyroidism there is either a decreased excretion into or more likely an increased absorption of calcium and phosphorus from the gastro-intestinal tract.

VII-A. It follows as a corollary that calcium excretion into the gastro-intestinal tract is not a threshold phenomenon in the sense that calcium excretion into the urine is.

VIII. The changing serum calcium and phosphorus values brought about by phosphate ingestion in hyperparathyroidism reach stationary levels at a new equilibrium when the serum phosphorus has risen sufficiently above the urinary threshold to cause the additional absorbed phosphorus to be excreted in the urine and when the serum calcium has adjusted itself to this new serum phosphorus level.

Experiment III

The subject of this investigation is extremely interesting in that she presents all the metabolic criteria of hyperparathyroidism, but in a milder degree than in any case yet reported. Most cases in the literature have had extreme degrees of this malady. The case history and clinical findings appear in the appendix.

The calcium and phosphorus data are given in Table III and Chart III.

During the control periods all the metabolic abnormalities of hyperparathyroidism were present: the high serum calcium (12.9 mgm. per 100 cc.), the low serum phosphorus (2.6 mgm. per 100 cc.), the high urinary calcium values, the very low fecal calcium values, and the high partition of phosphorus in the urine. With the ingestion of phosphate one notes again almost complete absorption. This time, however, the increase in the excreted phosphate plus the increase in what phosphate was apparently deposited in the bones was sufficient to account for all the increase in absorbed phosphate so that there was no increase in the serum phosphorus level. One would have expected, therefore, no lowering of the serum calcium and there was no lowering. Thus far everything fits previously discussed ideas.

But the unexpected finding is that the urinary calcium excretion is diminished to a normal level, in spite of no decrease in the serum calcium level. Obviously, some of the calcium which would have been excreted in the urine has been deviated into the bones together with the deposited phosphate. It is evident that one is confronted here with a high serum calcium and a normal urinary calcium excretion, an entirely unprecedented situation in our experience which weakens the conception of calcium as a threshold substance. We can merely point out this dis-

TABLE III

Calcium and phosphorus data of experiment III

Period	Calcium (per 3-day period)					Phosphorus (per 3-day period)					Serum			Remarks
	Urine	Feces	Total excretion	Intake	Balance	Urine	Feces	Total excretion	Intake	Balance	Ca	P	Ca × P	
	grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*		
I.....	0.63	0.12	0.75	0.22	−0.53	1.53	0.20	1.73	1.68	−0.05	12.9(2)†	2.6	34	Control period
II.....	0.61	0.17	0.78	0.22	−0.56	1.55	0.28	1.83	1.68	−0.15	13.3(3)	2.7	36	Control period
III....	0.62	0.18	0.80	0.22	−0.58	1.31	0.41	1.72	1.68	−0.04	12.1(1)	2.7	33	Control period
IV....	0.33	0.12	0.45	0.22		2.61	0.37	2.98	*		12.9(1)	2.8	36	Phosphate ingestion
V.....	0.22	0.13	0.35	0.22	−0.13	7.12	0.47	7.59	8.48	+0.89	13.3(1) 13.3(2)	2.6 2.8	35 37	Phosphate ingestion
VI....	0.17	0.09	0.26	0.22	−0.04	10.26	0.61	10.87	11.88	+1.01	13.1(1)	3.0	39	Phosphate ingestion

* Intakes could not be obtained in period IV because of vomiting.

† The arabic numeral in the parenthesis indicates on which day of the period,—first, second, or third,—the blood specimen was collected.

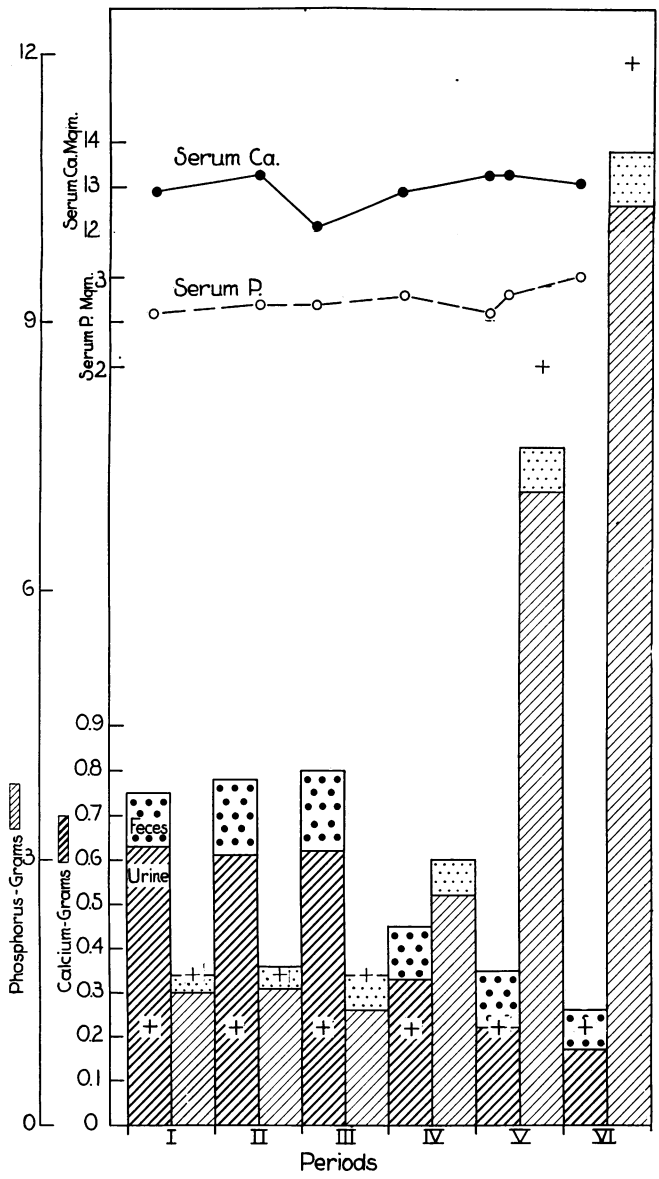

CHART III. CALCIUM AND PHOSPHORUS DATA FOR EXPERIMENT THREE

Heavily hatched and dotted columns indicate Ca excretion; lightly hatched and dotted columns indicate phosphorus excretion. Hatched area urinary excretion; dotted area fecal excretion. + indicates intake.

crepancy but cannot explain it. One might in this connection call attention to the hypercalcinuria with normal blood calcium seen in hyperthyroidism (11), and acidosis (10). These latter instances, although in certain respects the antitheses of the above, do not necessarily test the threshold theory. They merely illustrate that the kidneys can excrete large amounts of calcium without having a readily detectable increase in the serum calcium.

Experiment III, in addition to lending support to previous conclusions, suggests that:

IX. Unless the ingestion and absorption of phosphate is so great in hyperparathyroidism that the sum of the increased urinary phosphorus excretion and the increased deposition of phosphorus in the bones cannot keep pace with the increased absorption of phosphorus, there is no rise in serum phosphorus and consequently no fall in serum calcium.

X. It is possible that under certain conditions such as an excess of phosphate for deposit, there may be, in spite of a very high serum calcium, a normal calcium excretion in the urine.

DISCUSSION

A. Dangers of phosphate administration

By way of warning, we believe that phosphate ingestion in hyperparathyroidism is associated with two real dangers.

In the first place it has been shown by animal experimentation (12) that before death from parathyroid overdosage there is a shutdown of kidney function, presumably due to the increased viscosity of the blood, and a resulting rapid rise in serum nonprotein nitrogen and inorganic phosphorus. When this complication occurs there is present in the blood a high serum calcium and high serum phosphorus. One is then confronted with our second group of disorders of calcium phosphate metabolism, namely, a supersaturation of the blood with calcium phosphate and a tendency to precipitate calcium phosphate into tissues other than osteoid tissue. If parathormone administration is continued, the dogs die in uremia and show at autopsy calcium deposits in the alveolar walls of the lungs, the mucosa of the stomach, the kidney parenchyma, and the thyroid gland (13). Any administration of phosphates in the presence of this complication, this state of parathyroid poisoning as it were, would merely hasten death by increasing this supersaturation of the blood. On this ground we believe the administration of phosphate to a patient at a time when the serum calcium and phosphorus are both high is contraindicated. The patient with multiple myeloma reported by Bulger, Dixon, Barr, and Schregardus (14) may be a case in point. This patient had a blood calcium of 17.8 mgm. and a phosphorus of 5.3 mgm. when phosphate was administered and showed at autopsy calcium

deposits in the lungs, gastric mucosa, and kidneys. It is of interest that most of the cases of hyperparathyroidism reported are of a severity which would be considered near the danger level of parathyroid poisoning in animals. It is surprising that they do not surpass this level more often and reach the state of parathyroid poisoning and death. There are three such cases in the literature where death was probably due to parathyroid poisoning, Dawson and Struthers (41), Hoffheinz (15) and Penecke (16). These patients died in uremia and showed at autopsy, in addition to the osteitis fibrosa cystica generalisata and parathyroid tumors, calcium deposits in the lungs, thyroid, kidney parenchyma, and other organs. They were, therefore, pathologically analogous to dogs dying from parathormone overdosage (13).

The second danger of phosphate ingestion in these patients is more often encountered. Many of these patients have bilateral calcium phosphate stones in the kidney pelves. Thus, patient I gave the history of having passed gravel and patient II has bilateral kidney stones. The stones are without doubt due to the increased calcium and phosphorus in the urine. Phosphate ingestion increases tremendously the phosphaturia and hence the danger of stone formation. The decreased calcinuria is, of course, a favorable factor. It seems wise in administering phosphate to force fluids and to keep the urine acid. Mono-sodium phosphate is, therefore, perhaps preferable to the more alkaline salts.

B. Secondary hyperparathyroidism

In the introduction we have summarized our conception of the modus operandi of the parathyroid hormone in producing changes in Ca and P metabolism. We have suggested that the first step is an apparent change in the threshold for phosphorus excretion in the urine. The evidence for a high threshold in hypoparathyroidism is twofold: (*a*) The almost complete disappearance of phosphorus from the urine in a case of hypoparathyroidism on an extremely low phosphorus diet in spite of a continued high serum phosphorus (2), and (*b*) the promptness with which the phosphorus excretion in the urine dropped when a high phosphorus diet was suddenly changed to a low phosphorus diet in the same individual, showing that the high serum phosphorus did not represent a renal retention phenomenon.

The evidence for a low threshold for phosphorus excretion in hyperparathyroidism is: (*a*) The promptness with which absorbed phosphate is excreted in the urine in the patients here discussed, and (*b*) the resistance which the low serum phosphorus exhibited to being raised by the large amounts of phosphate which passed through the blood in these experiments.

With these facts before us a previously unaccountable finding in a patient studied by Aub, Albright, Bauer, and Rossmeisl (17) perhaps now

becomes explainable and very instructive. This patient because of chronic steatorrhea and the consequent lack of absorption of calcium had reached a condition where the serum calcium was very much diminished. The serum phosphorus was likewise reduced. The disorder of the calcium phosphate metabolism was, therefore, of the "subsaturation" variety. The unexpected finding was that in spite of the low serum phosphorus this patient was excreting a normal or even increased amount of phosphorus in the urine. The supposition had to be made that, if such a thing as a kidney threshold for phosphorus exists, it must have been lowered in this patient. But, having used lowering of kidney threshold for phosphorus to explain the findings in hyperparathyroidism, one did not like to resort to this in an entirely different situation. But was the situation entirely different?

Is there any evidence that hyperparathyroidism may exist as a secondary phenomenon in the "subsaturation" group of disorders? In 1907 Erdheim (18), then a pupil of Weichselbaum, studied the parathyroid glands in seven cases of puerperal osteomalacia and one case of senile osteomalacia. In six of the eight cases the parathyroid glands were either enlarged or showed evidence of hyperplasia. In five of the six cases multiple parathyroid glands were involved. The histological evidence for hyperplasia rested on the presence of many circumscribed zones of young cells which were akin to the chief cells but which with fat stains showed very little intracellular fat. We can refer to these as proliferation zones (Wucherungsherde). In only one of nine control cases did Erdheim find the same degree of histological evidence of hyperplasia and this was a very old man whose skeleton was not examined. In 1914 Erdheim (19), by an ingenious projection method, made enlarged wax models of parathyroid tissue in rats and was able to show that hypertrophy of all parathyroid tissue including accessory parathyroid tissue occurs in rats suffering from rickets. The World War interrupted his measuring the parathyroids in cases of infantile rickets in the same way. He made the preliminary observation, however, that the parathyroids appear enlarged in this condition, although microscopically he was unable to note any constant changes. Bauer (20), also a pupil of Weichselbaum, reported in 1911 a case of osteomalacia in which the bone condition was noted only after attention had been directed to the skeleton by the finding of hypertrophy and hyperplasia in all the parathyroids. Weichselbaum (21) himself reported the finding of enlarged parathyroids in two cases of late rickets. The findings of this Viennese school have on the whole been substantiated.

Thus, in 1907 Schmorl (22) reported parathyroid hypertrophy in only one of four cases of osteomalacia and failed to find parathyroid changes in four cases of rickets and two cases of late rickets, but neglected to study the parathyroids with fat stains for proliferation zones; in 1909 Strada

(23) reported hyperplasia in one case of osteomalacia; in 1912 Todyo (24), a pupil of Schmorl, reported hyperplasia in six out of seven cases of osteomalacia and in eight out of eleven cases of senile osteoporosis, and in only four out of twenty-four control cases, two of these four being in pregnant patients, a condition which in itself brings about hyperplasia (25); in 1912 Hohlbaum (26) reported a case of osteomalacia with hypertrophy and hyperplasia of all parathyroid glands; in 1916 Maresch (27) reported hypertrophy and hyperplasia of the parathyroids in eight cases of senile osteomalacia and twenty-eight cases of senile osteoporosis; in 1920 Ritter (28) reported hyperplasia of the parathyroids in ten cases of rickets, three cases of osteomalacia and one case of osteoporosis; in 1921 Pappenheimer and Minor (29) found the parathyroid glands in fourteen cases of rickets much larger than those from eighteen non-rachitic controls; in 1922 Hartwich (30) found hypertrophy of the parathyroids in fifteen cases of rickets; in 1925 Kerl (31) found hypertrophy and hyperplasia of all parathyroids in a case of puerperal osteomalacia and a case of osteoporosis; in the same year Danisch (32) found proliferation zones of chief cells in the parathyroids in twenty-three out of forty-seven individuals over sixty years and out of these nineteen had senile osteomalacia; in 1925 Doyle (33) found the parathyroids of rachitic chickens enlarged; in 1926 Nonidez and Goodale (34) confirmed this; and in 1928 Higgins and Sheard (35) showed that ultraviolet light prevented the hypertrophy of chickens' parathyroids on a rachitic diet.

We have, therefore, pathological as well as metabolic evidence that the parathyroid glands are overactive in the "subsaturation" group of disorders. It should be emphasized that multiple parathyroids are involved in this condition and that as Erdheim first pointed out there is every reason to believe this a compensatory mechanism. The situation is in direct contrast to primary hyperparathyroidism, associated with osteitis fibrosa cystica generalisata, in which only one parathyroid is enlarged but this to a marked extent. It seems entirely probable that the stimulus for the parathyroid gland secretion is a low blood calcium; that a low blood calcium, when dependent on conditions outside of the parathyroid glands, produces a hyperplasia of the glands; that such conditions are, consequently, associated with a secondary hyperparathyroidism; and that, therefore, a low threshold for phosphorus excretion is to be expected. The presence of hyperparathyroidism with a low blood calcium is after all not so surprising as we are dealing with hyperparathyroidism complicating the "sub-" rather than the "normal-saturation" state. According to the theory outlined here the reason for the high blood calcium in hyperparathyroidism is to compensate for the low blood phosphorus in order to maintain normal saturation, but in the subsaturation group of disorders all possibility of compensation has been lost. Further evidence of the correctness of this view is given in un-

published data obtained by Bauer and Marble. They were unable to elevate the depressed serum calcium in this same patient with parathormone. This could have been and as a matter of fact was predicted. Furthermore, when this underlying difficulty, the failure to absorb calcium, was overcome by ergosterol medication, the serum calcium promptly rose, but the serum phosphorus lagged behind for many weeks and was the last abnormality to correct itself (36). One would expect the hyperplasia to disappear only gradually when the cause of the hyperplasia, the low serum calcium, had been removed.

A lowering of the blood phosphorus without a raising of the blood calcium by the parathyroid hormone in the subsaturation group of disorders is not without example in the literature. Shohl, Wakeman, and Shorr (37), studying the effect of parathormone on infantile tetany, produced in one of two cases a fall in serum phosphorus from 9.3 to 3.1 with no corresponding rise in serum calcium. Our metabolic criteria of hyperparathyroidism, namely a high urinary P excretion in the presence of a low serum P, were present in the patient with osteomalacia studied by Gargill, Gilligan, and Blumgart (38) and in the four patients with osteomalacia studied by Miles and Feng (39).

The implication of such a theory, which states that disorders associated with subsaturation may be, in fact probably usually are, associated with secondary hyperparathyroidism is far reaching. It means that part of the disordered metabolism of rickets and osteomalacia is due to secondary hyperparathyroidism. It means that the blood calcium is no longer the measuring stick of the degree of hyperparathyroidism, rather the blood phosphorus. It means that, although in osteitis fibrosa cystica generalisata the bone condition is secondary to the parathyroid condition, in rickets and osteomalacia, and other allied conditions the parathyroid abnormality is secondary to the bone abnormality.

That the abnormalities in calcium metabolism in hyperparathyroidism are minimized by phosphate ingestion, and that these findings support the theory of parathyroid function which makes the calcium abnormalities secondary to the phosphorus abnormalities has been clearly demonstrated and amply discussed. We did not try phosphate ingestion on the one case of proven parathyroid tumor which we have had the opportunity to study in our clinic. That such patients, however, respond in a similar fashion is shown by the experiments of Bulger, Dixon, Barr and Schregardus (14). Their patient I belonged in this group and before operation phosphate ingestion produced changes similar to those reported in this paper. There is one very definite difference, however, between the sequence of events which follows the removal of a tumor in hyperparathyroidism and that which follows the ingestion of phosphates. In the former case, the phosphorus rise and the calcium fall in the serum are such that the product of Ca $\times$ P does not rise; in fact temporarily often

falls. In the latter case, we have observed that the product rises. Thus, whereas the calcium fall is obviously due to the phosphorus rise in the latter case, if the same is true in the former, there is left to be explained why in the former case the calcium fall is more delicately adjusted so as not to disturb the Ca × P product. Whereas this finding is against the theory we are supporting we believe it can be explained. The explanation will be reserved until a later paper which discusses the sequence of events in calcium and phosphorus metabolism following the removal of a parathyroid tumor.

SUMMARY AND CONCLUSIONS

1. Three cases of clinical hyperparathyroidism have been treated by ingestion of phosphates with beneficial results.

2. The metabolic sequelae of such treatment are: (*a*) almost complete absorption of phosphates into the blood stream; (*b*) rapid excretion of the absorbed phosphates by the kidneys; (*c*) a rise of the previously low serum phosphorus; (*d*) a fall of the previously elevated serum calcium; (*e*) a rise at first of the Ca × P product in the serum; and (*f*) a fall of the urinary calcium excretion.

3. The net result is an increase in the balances of calcium and phosphorus and a return of the serum levels of both in the direction of normal.

4. The rapidity with which the absorbed phosphorus is excreted in the urine and the resistance which the low serum phosphorus exhibits to being raised suggest that the threshold for phosphorus excretion into the urine is lowered in hyperparathyroidism, and we consider this the most fundamental change in the Ca and P metabolism in this condition.

5. It appears that in long standing hyperparathyroidism there is increased absorption of calcium and phosphorus from the gastro-intestinal tract and that excretion of calcium into the gastro-intestinal tract is not a threshold phenomenon dependent on the level of serum calcium.

6. There are two theoretical dangers of phosphate ingestion in hyperparathyroidism: (*a*) precipitation of the state of parathyroid hormone overdosage, called in this paper "parathyroid poisoning," with death from uremia and calcium deposits in the lungs, mucosa of the stomach, thyroid gland, and kidney parenchyma; (*b*) danger of producing bilateral phosphate stones in kidney pelves.

7. It is suggested that a low serum calcium is the stimulus for the parathyroid secretion and that a low serum calcium due to causes other than parathyroid hypofunction leads to secondary hyperparathyroidism.

8. Inasmuch as conditions other than hypoparathyroidism associated with a low serum calcium for the most part belong to the "subsaturation" group, and inasmuch as a rise in serum calcium in response to the parathyroid hormone would only be expected to occur under conditions of

normal saturation, secondary hyperparathyroidism is often not associated with hypercalcinemia.

9. It follows as a corollary that the serum calcium is not always a measuring stick of the degree of hyperparathyroidism,—rather the serum phosphorus.

10. A review of the literature adds both histological and metabolic evidence to support the existence of secondary hyperparathyroidism in the "subsaturation" group of disorders.

APPENDIX

Case 2. Mrs. N. B. (M. G. H. number 307624), a married white woman of 41 entered the Massachusetts General Hospital on July 11, 1930, complaining of rheumatism of 5 years' duration.

The *history* showed the following salient features: 5 years ago, following fifth pregnancy, onset with generalized weakness and pains in knees; 3 years ago exacerbation during eighth month of sixth pregnancy. Crutches then became necessary. She was treated for flat feet and teeth were removed without benefit. Two years ago she slipped and fractured right hip, requiring four months in plaster cast. The fracture united. Seven months ago, she slipped and fractured collar bone on right and shortly thereafter without adequate cause she fractured the upper end of her right humerus. Patient had had polydipsia for about two years. No abnormality of diet was elicited. Calcium and phosphorus intakes were not deficient.

The *past history* was entirely irrelevant. The catamenia was not remarkable.

Physical examination. A rather obese woman slightly bent over, mentally clear and very intelligent. Pupils reacted to light and in accommodation. Mucous membranes were slightly pale. Tonsils were small and buried. All teeth were out and no false teeth had been supplied. Neck showed no tumor. Left border of heart was 1 cm. beyond mid-clavicular line. A systolic murmur was present at the apex. Blood pressure was 185 systolic and 105 diastolic. Lungs not abnormal. Liver and spleen were not felt. Knee jerks present and sluggish. There was tenderness over ribs and long bones and left shin bone felt rough and nodular.

Laboratory findings. Blood—Red count 3,400,000. White count 4,800. Hemoglobin 60 per cent. Smear was not remarkable. Urine showed albumin and clumps of white cells in all specimens. Cultures showed no growth. Gastric analysis—Free hydrochloric acid was present after ergamine. Basal metabolism—+ 3. Wassermann—negative. Serum calcium, 14.2 mgm. per 100 cc. Serum phosphorus, 2.3 mgm. per 100 cc.

Cystoscopic report (Dr. C. S. Swan). "The pyelograms show bilateral hydronephrosis with injection. The functions and nonprotein nitrogen have not been materially affected to date. The stone in the left kidney is in the renal pelvis and acts probably as a ball-valve."

X-rays. These have been reported in detail by Dresser and Hampton (40). "All the bones examined are abnormal; they appear coarse in texture and of increased radiability. The bone trabeculae are widely separated, interrupted, and disorganized. There are multiple cyst-like areas of bone destruction most numerous in the pelvis and upper ends of the femora where they vary from 1 to 3 cm. in diameter. These cysts are sharply defined and are seen in the pelvis, left radius, ribs, both bones of both lower legs, skull and scapulae. In the ribs, radius, and fibulae, there is expansion and thinning of the cortex of the bone simulating a giant cell tumor. There is evidence of pathological fracture in the right fibula and crest of the left ilium. These fractures have united with an overgrowth of bone. The skull and vertebrae present a peculiar moth-eaten appearance, characterized by punched out areas of bone absorption intermingled with dense round bone deposits. These small bone deposits are about 2 mm. in diameter and the areas of bone destruction vary from 1 cm. down to 1 mm." In addition the x-rays showed bilateral renal calculi.

Operation (Dr. Richard C. Miller). The thyroid was completely exposed, but no parathyroid tumor could be found. The two lower parathyroids were identified and removed. They were each about the size of a split pea. The upper parathyroids were not seen. Some tissue was removed in addition which later turned out to be thymus.

Microscopic examination of parathyroids revealed "structure of normal parathyroid glands."

Result of operation was without benefit to patient.

Case 3, Mrs. M. D. (M. G. H. number 276450), a married colored woman of 22, first entered the hospital on May 21, 1926, because of pain in the right hip of two years' duration.

Present illness. Patient had been married $2\frac{1}{2}$ years. During this time she had had four pregnancies, the first two resulting in miscarriages, the third resulting in the birth of a child which lived four weeks, and the fourth terminating three weeks before entry with the birth of a healthy son.

For over two years patient had had pain in her right hip which was aggravated by pregnancies. During past five months patient had been unable to flex thigh or abdomen because of pain. There had been recently pains in ribs as well, made worse by deep breathing.

Past history. Mumps, measles, and pertussis in childhood. Scarlet fever at 4 years, typhoid at 8 years. "Pneumonia" three times, the last at 9 years of age. Catamenia had always been irregular and she often

skipped periods. She had lost from 105 pounds her best weight to 87 pounds during the past 4 years.

Physical examination. A very small colored girl in fair state of nutrition. Breasts were distended with milk. Teeth showed pyorrhea but otherwise appeared strong. Tonsils enlarged. Lungs negative. Ribs were painful to pressure. Tenderness of sacrum by rectal. Right hip motion (rotation) limited. There was transmitted tenderness to either

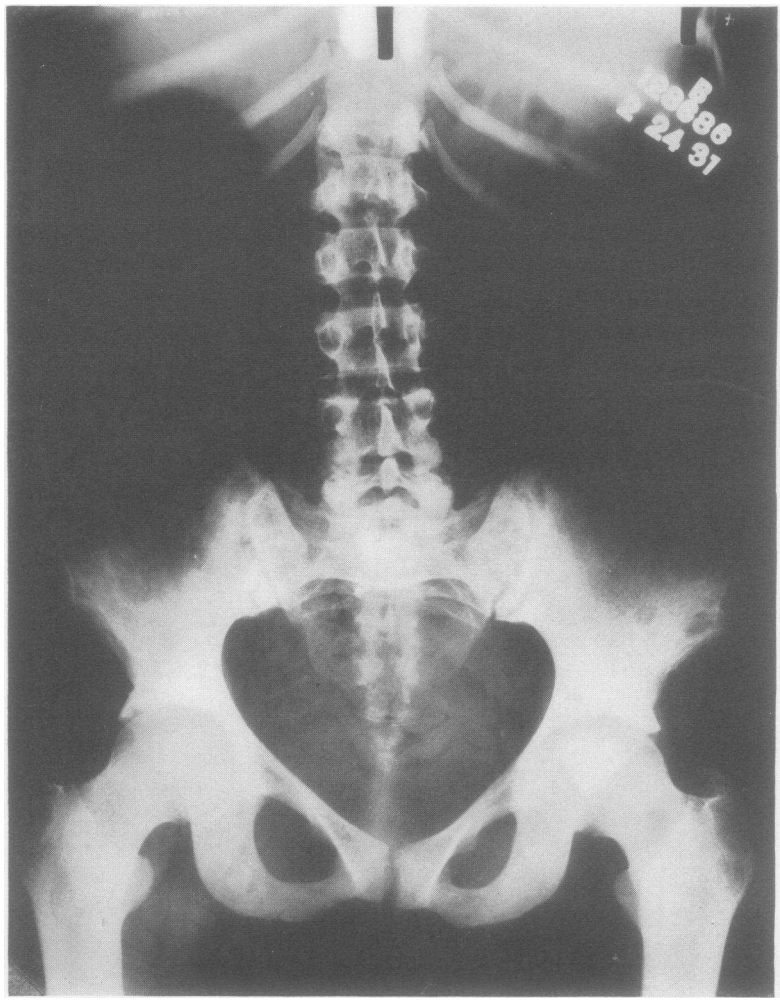

FIG. 1. X-RAY OF PELVIS IN MRS. M. D., PATIENT THREE

hip on percussion of opposite hip. She held right leg flexed and everted. Blood pressure was 90 systolic and 35 diastolic.

Laboratory findings. Urine not remarkable. No Bence-Jones protein. Red count 3,600,000. Hemoglobin 60 per cent. White count 6,800. Wassermann negative.

X-rays (Interpreted by Dr. George W. Holmes). Chest showed increase in hilus shadows. "Plate taken of the lumbar spine and pelvis shows multiple areas of diminished density in the bones of the pelvis, spine, ribs, and the upper end of the femur. These areas are ring-shaped and probably represent areas of destruction in the bone. There is very little if any evidence of reaction around them. All bones are less dense than normal. Skull shows characteristic appearance of osteomalacia." Teeth x-rays showed apical abscesses.

Diagnosis. Osteomalacia.

Treatment. X-ray sterilization and high calcium diet and cod liver oil.

Subsequent history. Patient again entered the hospital on June 16, 1930, for check-up. The symptoms related to her skeleton had disappeared. Her only complaint was hot flashes and amenorrhea of 4 months' duration, both attributable to x-ray sterilization. Serum calcium was 13.0 mgm. per 100 cc. and serum phosphorus 2.4 mgm. per 100 cc. X-rays of the bones at this time showed undoubted improvement although the previous x-rays were not available for comparison. The scattered areas of diminished density were still apparent in the pelvis (see Figure 1). At this time studies here reported were performed.

Final diagnosis. Mild hyperparathyroidism.

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