STUDIES ON THE MODE OF ACTION OF IRRADIATED ERGOSTEROL

II. Its Effect on the Calcium and Phosphorus Metabolism of Individuals with Calcium Deficiency Diseases [1,2]

By WALTER BAUER and ALEXANDER MARBLE [3]

(From the Medical Clinic of the Massachusetts General Hospital, Boston)

(Received for publication June 6, 1931)

INTRODUCTION

In the first paper of this series (1), we reported that the administration of adequate doses of irradiated ergosterol to normal individuals resulted in definite alterations in the fecal and urinary excretion of calcium and phosphorus. These changes consisted in a gradual fall in the fecal excretion and a gradual rise in the urinary excretion of both elements with little effect on the total balances of either. These findings are best interpreted as signifying increased absorption from the gastro-intestinal tract without an accompanying increased body retention.

The fact that irradiated ergosterol acts as a curative agent in calcium deficiency diseases such as rickets and osteomalacia indicates that an increased retention of calcium and phosphorus must take place when it is administered to individuals with such diseases. In order to determine what changes occur in the calcium and phosphorus metabolism of individuals with calcium deficiency diseases when irradiated ergosterol is administered, two such patients were studied in an effort to ascertain whether the action of irradiated ergosterol was in any way different from that which we had observed in normal individuals.

METHODS OF STUDY

These two patients were studied under the same conditions as those previously reported (1). The diets employed were the same except for calcium content. The collection and preparation of the excreta and the methods of analysis used were identical with those described in the first paper of this series (1).

---

[1] This is publication No. 5 of the Robert W. Lovett Memorial for the study of crippling disease, Harvard Medical School, Boston, Massachusetts.

[2] Part of the expense of this investigation was paid by the William W. Wellington Memorial Research Fund.

[3] Medical Resident, Massachusetts General Hospital.

EXPERIMENTS

I. The effects of gradually increasing doses of irradiated ergosterol on a patient with osteoporosis

Experiment I

Mrs. M. B., a 54 year old American widow, was admitted to the hospital on April 9, 1929, because of disabling pain in the back of two months' duration. X-ray examination showed a compression fracture of the vertebrae and *generalized rarefaction* of all her bones. Interestingly, her diet for the preceding six years had been almost an exact duplicate of the low calcium diet used in our previous calcium studies (2) (approximately 0.1 gram of calcium per day). Its vitamin content was very low. Other laboratory and clinical observations revealed no noteworthy abnormalities. A gastric analysis showed a normal amount of free hydrochloric acid. The only treatment employed prior to her transfer to the Metabolism Ward was that of hyperextension on a suitable frame. She was kept on a low calcium diet for six days, then on a high calcium diet for eighteen days, and finally on a high calcium diet plus irradiated ergosterol for thirty-six days. Her average weight was about 59 kgm. The metabolism data are presented in Charts 1*A*, 1*B* and Table I.

One notes that the calcium excretion on a low calcium diet, in periods 1 and 2, was very similar to that observed in normal individuals (2). The presence of normal serum calcium and phosphorus values and the finding of a normal excretion of calcium and phosphorus on a low calcium diet proved that the osteoporosis was not due to increased parathyroid activity (3–11).

During periods 3 to 8 on a high calcium diet (see Table I), the average urinary and fecal calcium values were 0.67 gram and 2.56 grams, respectively, with a positive balance of 0.70 gram. Following the administration of 5 mgm. of irradiated ergosterol a day during periods 9 to 17, inclusive, the urinary calcium rose to 0.92 gram and the fecal calcium fell to 2.49 grams, thus leaving the calcium balance + 0.50 gram. (Unfortunately the fecal extracts during periods 16 and 17 were lost.) During period 18, 8 mgm. of ergosterol per day were given. The urinary excretion remained the same, but the fecal excretion fell to 1.48 gram and the balance rose to + 1.52 gram. (These values are not so reliable as those with which they are compared, since they represent only one three-day period.) In the last two periods, 19 and 20, during which 20 mgm. of irradiated ergosterol per day were given, the urinary calcium rose to + 1.08 gram, the fecal calcium to 1.69 gram and the total balance was + 1.15 gram. Hence irradiated ergosterol administration caused a consistent decrease in the fecal calcium and an increase of the urinary calcium to a smaller degree, with a resulting increase of the positive calcium balance.

This same effect is equally well shown in the case of phosphorus (see Table I). During the control periods the urinary phosphorus was 2.41 grams; during the subsequent periods in which irradiated ergosterol was given, it was 2.64 grams in periods 9 to 17, 2.54 grams in period 18, and 2.49 grams in periods 19 and 20. The fecal phosphorus was 1.71 gram

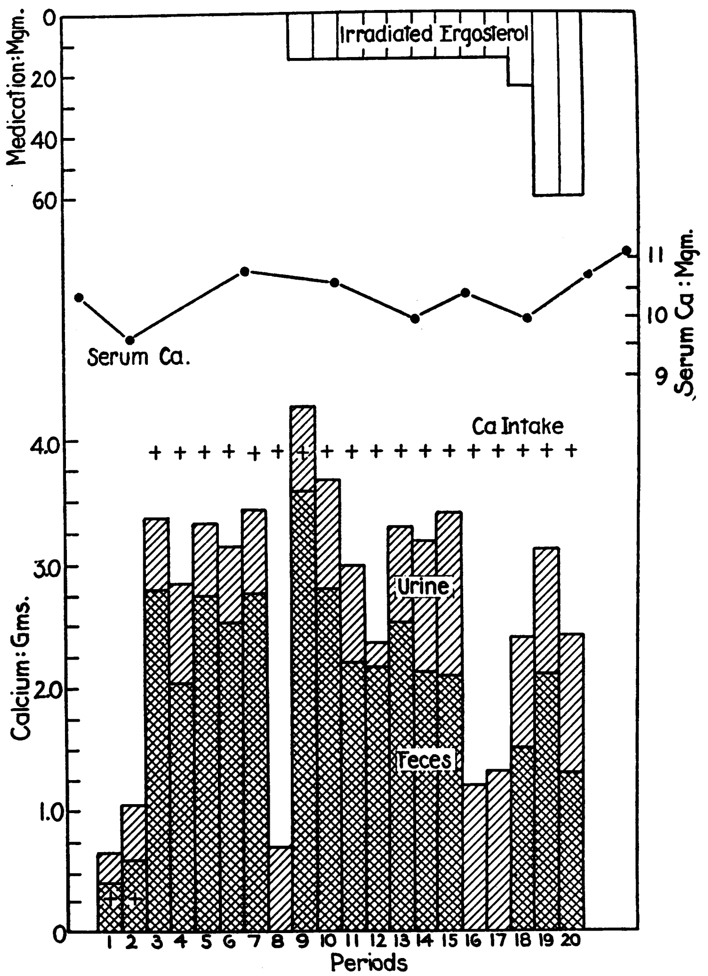

CHART 1*A*. CALCIUM METABOLISM IN EXPERIMENT I

during the control period; this fell steadily to 1.44 gram in periods 9 to 17, 1.29 gram in period 18 and 1.12 gram in periods 19 and 20. That most of this phosphorus was retained in the body is evidenced by the fact that the increases in the urinary values were much smaller than the decreases in the fecal values. This is further borne out by the fact that the total phosphorus balances gradually increased from + 0.50 gram in the control periods to + 0.54 gram in periods 9 to 17, + 0.79 gram in period 18 and + 1.01 gram in periods 19 and 20.

During the time of observation in the hospital, the serum calcium was always quite normal. One month after discharge a value of 11.1 mgm. per 100 cc. was obtained, which may possibly have been an ergosterol

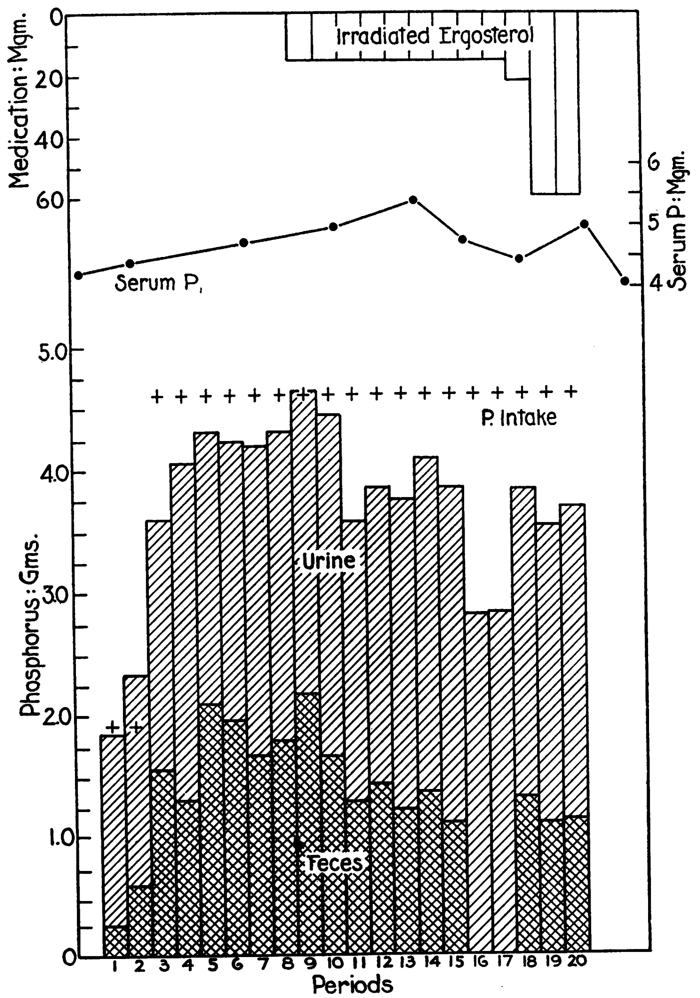

CHART 1*B*. PHOSPHORUS METABOLISM IN EXPERIMENT I

effect, since the patient remained on a high calcium diet and continued to take irradiated ergosterol. In the serum phosphorus there occurred changes which have not been seen in other patients. Under the influence of irradiated ergosterol, the control values of 4.42 and 4.79 mgm. per 100 cc. rose to a high point of 5.44 mgm. per 100 cc. two weeks after the drug was started.

TABLE I

The effect of irradiated ergosterol on the calcium, phosphorus and nitrogen metabolism of individuals with calcium deficiency diseases. Average values in grams per three-day period

Experiment	Periods	Average weight	Phosphorus				Calcium				Nitrogen				Irradiated ergosterol per period	HCl per period	Remarks
			Intake	Output		Balance	Intake	Output		Balance	Intake	Output		Balance			
				Urine	Feces			Urine	Feces			Urine	Feces				
		kgm.	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*mgm.*	*cc.*	
I. Mrs. M. B. . . .	3 to 8	58.6	4.62	2.41	1.71	+0.50	3.93	0.67	2.56	+0.70	41.6	37.5	4.2	−0.1	0		Low calcium diet during first two periods. High calcium diet in the succeeding periods. Average dietary formula per three-day period = C_{620} P_{280} F_{251}.
	9 to 17	59.1	4.62	2.64	1.44	+0.54	3.91	0.92	2.49	+0.50	44.6	38.1	4.5	+2.0	15		
	18		4.62	2.54	1.29	+0.79	3.92	0.92	1.48	+1.52	44.6	37.5	4.5	+2.6	24		
	19 to 20		4.62	2.49	1.12	+1.01	3.92	1.08	1.69	+1.15	44.6	34.4	4.5	+5.7	60		
II. Mrs. De la B. .	24	45.3	4.82	2.11	2.69	+0.02	3.39	0.02	3.74	−0.37	44.1	43.7	4.1	−3.7	0	0	High calcium diet. Average dietary formula per three-day period = C_{1095} P_{275} F_{110}.
	25 to 28	45.1	4.80	2.74	1.68	+0.38	3.39	0.03	2.77	+0.59	44.0	36.9	4.4	+2.7	0	54	
	29 to 39	45.6	4.76	2.77	0.46	+1.53	3.36	0.04	0.85	+2.47	43.9	33.3	4.4	+6.2	30	54	
	40 to 45	46.0	4.79	2.68	0.47	+1.64	3.39	0.03	0.93	+2.43	44.2	39.1	4.4	+0.7	30	0	

The blood plasma cholesterol showed no striking change, although too few determinations were made to warrant conclusions.

During this period of study, the nitrogen balances gradually increased, from a control value of -0.10 gram in periods 3 to 8 to $+2.0$ grams in periods 9 to 17 and $+5.7$ grams in periods 19 and 20. During this period of time, the patient gradually gained weight.

Clinically, marked improvement took place. The combination of prolonged treatment in hyperextension with a high calcium diet and irradiated ergosterol and subsequent braces relieved her symptoms entirely. She has been free from pain for over two years. She indulges in normal activity for a woman of her age.

From this study it is evident that a high calcium diet plus irradiated ergosterol produced an effect on the calcium and phosphorus metabolism similar to that which had been noted in normal individuals. In this case, however, the decreased fecal excretion was not accompanied by a comparable rise in the urinary excretion and as a consequence there occurred a marked increase in both the calcium and phosphorus positive balances. This might be interpreted as meaning that in an abnormal subject the extra calcium and phosphorus absorbed is retained for body needs; in the normal individual, because there is no need for calcium and phosphorus storage, the calcium and phosphorus is re-excreted in the urine. It is interesting that the positive balances increased as the dose of ergosterol was increased.

The retention of phosphorus in the body was more striking than was the retention of calcium. This may perhaps be explained on the assumption that the additional phosphorus was used by the body for the building of active tissues; this is suggested by the accompanying increase in the nitrogen balance and the slight gain in body weight.

II. *The effect of irradiated ergosterol administration on a patient with chronic diarrhea and associated tetany*

Experiment II

Mrs. de la B., a 27 year old, white, married secretary, had been previously studied in this clinic. A full case report will be published elsewhere. It is sufficient to state that for about four years she had suffered from almost constant diarrhea and tetany. No therapeutic measure had been of definite or lasting value.

Further study revealed that this patient had a persistently low serum calcium (4.5 mgm. per 100 cc.) and a serum phosphorus of 1.8 to 2.0 mgm. per 100 cc. Her bones showed decreased density on x-ray examination. The diarrhea was constant. A gastric analysis proved that she had a complete absence of free hydrochloric acid, uninfluenced by subcutaneous histamine injection. Analysis of her stools revealed an abnormally high fat content (at times 30 per cent of the wet stool). Examination of the pancreatic juice showed an abnormally low lipolytic enzyme activity. The features of this case which make it possible to group it as one of tetany of the infantile type are:

1. Low serum calcium.
2. Low serum phosphorus (in direct contradistinction to the parathyroid type of tetany, where the serum phosphorus is high).
3. Decreased bone density (in contradistinction to parathyroid tetany where the bone density is normal).
4. Absence of cataracts (so common in parathyroid tetany). The immediate cause of the tetany was thought to be calcium and phosphorus deficiency secondary to faulty absorption. Absence of free hydrochloric acid (12) (13), increased fat content of the stools (14) (15) (16) and diarrhea (14) (17) are three factors known to interfere with calcium absorption from the intestinal tract.

In Charts 2*A* and Table I are presented the data concerning the calcium metabolism. During the sixty-six days of study, periods 24 to 45 inclusive, she received a high calcium diet, 3.39 grams per three-day period. Her fat intake remained constant throughout this period of study.

During period 24 the fecal calcium excretion was 3.74 grams, or 0.37 gram in excess of that ingested, 3.39 grams. The fact that she not only failed to retain any of the ingested calcium but actually excreted calcium from her body stores is further proof that the tetany was due to failure to absorb calcium. The urinary excretion was abnormally low and remained so throughout the period of observation. During periods 25 to 28 inclusive, she received 18 cc. of 10 per cent hydrochloric acid a day. This therapy caused a slight rise in the serum calcium and sufficient reduction in the fecal calcium excretion to enable her to remain in a slightly positive calcium balance, but was without effect on the diarrhea. With the institution of irradiated ergosterol therapy in period 29 in doses of 10 mgm. per day, there was a precipitous fall in the fecal calcium during the first period of its administration. The lowest fecal calcium value was observed in period 33. In this period it was 0.16 gram compared to 3.74 grams in the control period. This represents a decrease of 95.7 per cent.

Beginning with the first period of ergosterol therapy, the serum calcium gradually rose to 8.2 mgm. per 100 cc. (period 33). It remained about 8 mgm. per 100 cc. throughout her stay in the hospital, and not until 3½ months later did it increase to 9.0 and 9.5 mgm. per 100 cc. The fact that the serum calcium was slow to reach a normal value was interpreted as being due to an attempt to replenish the body calcium stores.

The dilute hydrochloric acid was discontinued in period 40 for the remainder of the study period without influencing the total calcium metabolism. From period 29 through period 45 the patient remained in marked positive calcium balance.

The changes which occurred in the phosphorus metabolism (see Chart 2B and Table I) were quite as striking as those in the calcium metabolism. During the one control period, the patient was just in balance (+ 0.02 gram) although the phosphorus intake was more than adequate for a

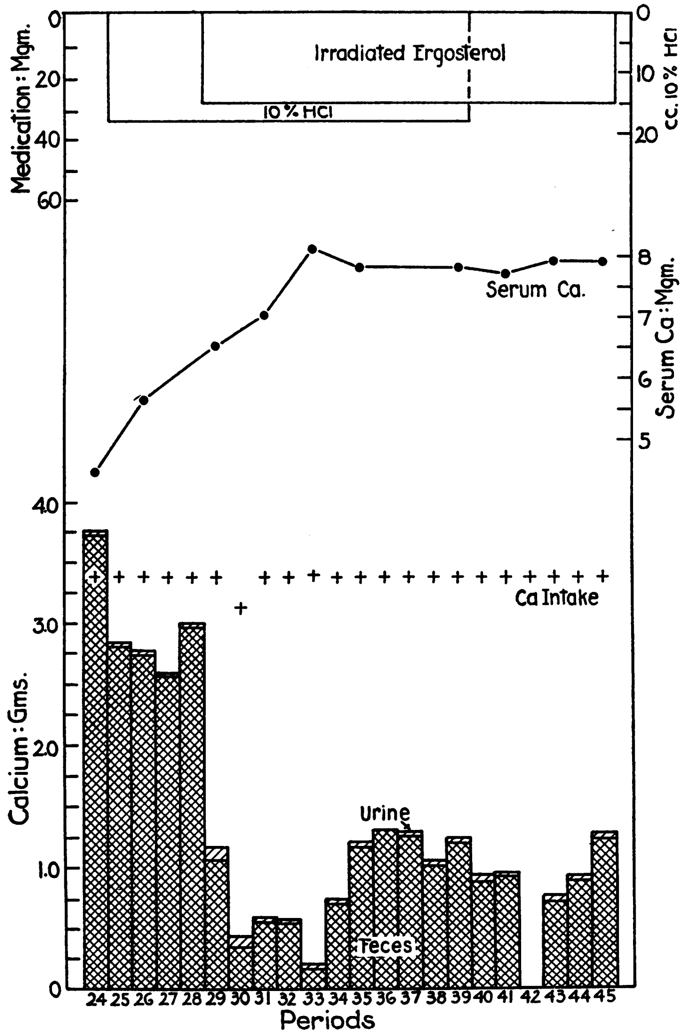

CHART 2A. CALCIUM METABOLISM IN EXPERIMENT II

normal person (4.82 grams). When hydrochloric acid was given (periods 25 to 28 inclusive), the average phosphorus balance was + 0.38 gram. With the institution of irradiated ergosterol therapy in period 29, the fecal phosphorus fell from 1.82 gram in period 28 to 0.41 gram in period 29 and the positive phosphorus balance was greatly increased. Except for minor variations, this beneficial effect was maintained throughout the period of study. The discontinuance of the hydrochloric acid in period 40 was without effect on the changes induced by irradiated ergosterol.

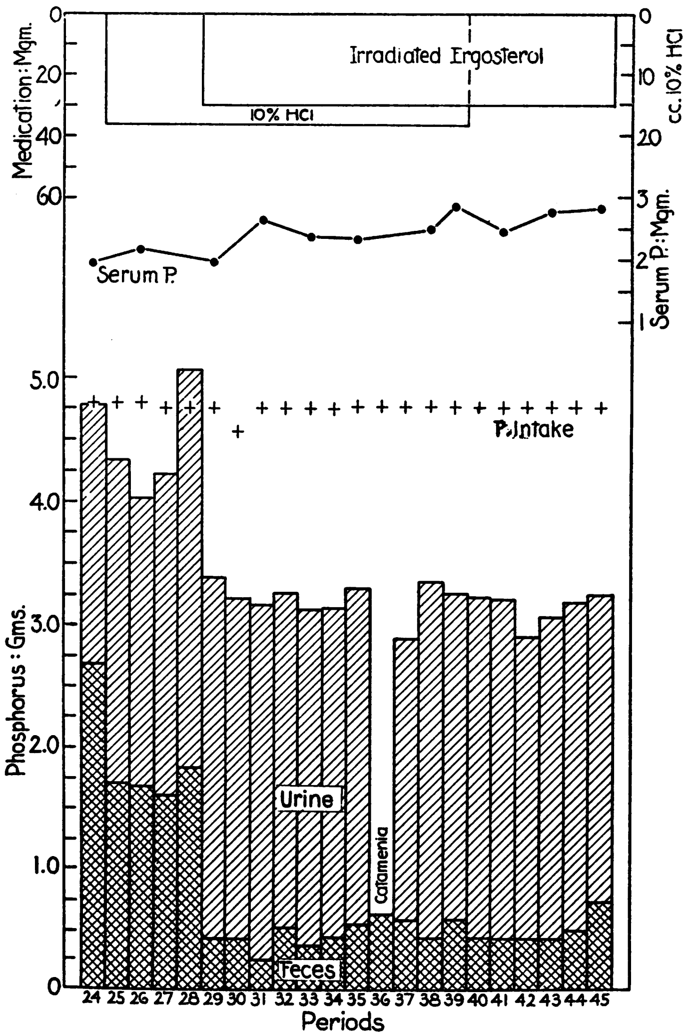

CHART 2*B*. PHOSPHORUS METABOLISM IN EXPERIMENT II

One notes that the urinary phosphorus was high during the control period (2.11 grams) and increased during the periods of hydrochloric acid administration. The finding of a high urinary phosphorus excretion at a time when the serum phosphorus is low (2 mgm. per 100 cc.) signifies that the often quoted phosphorus renal threshold of 2.8 mgm. (18) (19) is not confirmed. The high urinary phosphorus excretion implies that there was an adequate absorption from the gastro-intestinal tract of phosphorus, but, as this was not accompanied by calcium, it could not be used for bone deposition and therefore was re-excreted in the urine. The urinary phosphorus remained almost constant during the fifty-one days of ergosterol medication. Therefore, one might infer that the extra phosphorus absorbed was employed for bone deposition.

The serum phosphorus at the beginning of the experiment was 1.95 mgm. per 100 cc. This value was only slightly and temporarily raised by the giving of hydrochloric acid. With the beginning of irradiated ergosterol therapy, it began to rise, but did so very slowly and only after 7½ months had it reached a normal value of 4.30 mgm. per 100 cc.

In Table II, the ratios, calcium to phosphorus retained, are summarized.

TABLE II

Mrs. de la B. Calcium and phosphorus balances and their ratio per period

Period	Calcium balance	Phosphorus balance	Ratio Ca : P	Therapy
	grams	*grams*		
24......	−0.37	+0.02	—	Control period
25......	+0.56	+0.48	1.17 : 1	Hydrochloric acid
26......	+0.63	+0.79	0.80 : 1	Hydrochloric acid
27......	+0.79	+0.55	1.44 : 1	Hydrochloric acid
28......	+0.38	−0.51	—	Hydrochloric acid
29......	+2.23	+1.38	1.62 : 1	Irradiated ergosterol
30......	+2.72	+1.37	1.99 : 1	Irradiated ergosterol
31......	+2.81	+1.61	1.75 : 1	Irradiated ergosterol
32......	+2.82	+1.51	1.87 : 1	Irradiated ergosterol
33......	+3.21	+1.65	1.95 : 1	Irradiated ergosterol
34......	+2.66	+1.64	1.62 : 1	Irradiated ergosterol
35......	+2.19	+1.48	1.48 : 1	Irradiated ergosterol

During the administration of irradiated ergosterol, calcium and phosphorus were retained in proportions approaching very closely those found in calcium phosphate (Ca : P 1.93 : 1). Particularly was this true in periods 30 to 33 inclusive. In these periods the Ca : P ratio varied from 1.75 : 1 to 1.99 : 1 contrasted with values of 1.17 : 1 to 1.44 : 1 in the periods before ergosterol was given. These facts plus the knowledge that the nitrogen balance and the body weight were not affected signify that little of the retained phosphorus was used in the formation of active tissue.

A slight lowering of the blood cholesterol was noted.

Thus it would appear that the tetany in this individual was due to long standing calcium and phosphorus deficiency because of faulty absorption. This difficulty of absorption was much greater in the case of calcium than of phosphorus. The interference with absorption may have been due to the excess of fat in the stools, the achlorhydria, the diarrhea, or to vitamin D deficiency.

Certain workers have attributed the calcium deficiency occurring in patients with fatty diarrhea and associated tetany to the excess of lipoids in the stool (14) (15) (16). Telfer (16) inferred that because of the excess fat excretion, calcium was bound as an insoluble soap and was therefore excreted. He contended that phosphorus was absorbed in the normal manner but could not be retained for calcium deposition without calcium and therefore was re-excreted in the urine. However, other investigators (18) (20) have shown that the formation of an insoluble soap is not the sole explanation for the inability to absorb calcium.

The restriction of fat seemed indicated in our case because of the low lipolytic ferment activity in the duodenal juice. However, restriction of the fat intake alone did not affect the absorption of either calcium or phosphorus. This is well shown in Table III, which represents periods of

TABLE III

Mrs. de la B. Additional data on phosphorus and calcium balance and fat intake

Period	Phosphorus					Calcium					Dried feces	Fat intake
	Output			Intake	Balance	Output			Intake	Balance		
	Urine	Feces	Total			Urine	Feces	Total				
	grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
7.......	1.19	1.25	2.44	3.31	+0.87	0.01	1.15	1.16	2.26	+1.10	198	328
8.......	1.26	0.84	2.10	3.48	+1.38	0.01	0.51	0.52	2.26	+1.74	181	208
9.......	0.66	1.76	2.42	3.48	+1.06	0.01	2.22	2.23	2.26	+0.03	39	165
10......	1.20	0.88	2.08	3.37	+1.29	0.03	1.04	1.07	2.26	+1.19	104	187
11......	1.42	2.13	3.55	3.31	−0.24	0.02	2.80	2.82	2.26	−0.56	93	198
24......	2.11	2.69	4.80	4.82	+0.02	0.02	3.74	3.76	3.39	−0.37	—	123

study not presented in Charts 2*A*, 2*B* or Table I. It is obvious that the absorption of neither calcium nor phosphorus seemed to bear any relation to the fat intake. These findings, plus the fact that Linder and Harris (18) obtained striking improvement in two out of three similar cases before any dietary restrictions were employed, would allow one to question the statement that the restriction of fat is of prime importance in the treatment of this syndrome (18).

The administration of dilute hydrochloric acid while on a low fat intake caused only a very slight positive calcium and phosphorus balance and was without effect on the diarrhea.

However, the administration of small doses of irradiated ergosterol acted as a specific, produced a marked fall in the fecal calcium and phosphorus with a marked increase of the calcium and phosphorus balances. The urinary calcium remained unchanged. The failure to obtain an increase in the urinary calcium was due to the fact that the serum calcium never approached the renal threshold level for calcium (19).

The serum phosphorus rose much later than the serum calcium, requiring 7½ months to reach the normal value. Linder and Harris (18) concluded that their cases were due to vitamin D deficiency and accepted Bergeim's theory (21) as to the mode of action of irradiated ergosterol. Bergeim stated that vitamin D, promoting the breakdown of organic tissue phosphorus, causes the serum phosphorus to rise, the increased absorption and deposition of calcium being secondary to this process. Such an explanation is not in agreement with the findings in this case, because the serum phosphorus did not rise above 2.8 mgm. during the fifty-one days of study. Furthermore, there was no such increase in the nitrogen excretion as might be expected from the breakdown of organic tissue.

The findings in our case show that the calcium and phosphorus deficiency resulted from faulty absorption due to vitamin D deficiency. We are unable to state definitely that the vitamin D deficiency was secondary to the fatty diarrhea. It is conceivable that most of the vitamin D-containing sterols were excreted with the excess fat. Such an hypothesis was put forth by Linder and Harris (18). It was thought that the fatty diarrhea in this case was probably due to decreased external pancreatic secretion, as evidenced by the low lipolytic ferment activity in the duodenal juice.

COMMENT

Comparison of these data with those obtained in the study of normal individuals reveals that in all instances the administration of irradiated ergosterol caused an increased absorption of calcium and phosphorus from the gastro-intestinal tract. However, in the case of individuals with calcium and phosphorus deficiency diseases the absorption of calcium and phosphorus was greater, the accompanying rise in the urinary calcium and phosphorus excretions was less and, consequently, the retention of calcium and phosphorus was definitely increased.

The observed differences in the calcium and phosphorus metabolism of normal individuals and individuals with calcium and phosphorus deficiency diseases following the administration of irradiated ergosterol are easily explained if one accepts the division of disorders of calcium and phosphorus metabolism recently proposed by Albright, Bauer, Cockrill and Ellsworth (22). These authors assumed that normally the circulating fluid contains all the calcium phosphate it can hold at that particular time and that calcification is somewhat analogous to the precipitation of a calcium salt due to some local change in the environment which favors precipitation. They divided all disorders of calcium and phosphorus metabolism into three fundamental groups, viz.:

1. Conditions in which the body fluids are deficient compared with normals in respect to calcium phosphate and as a result there is a failure of deposition of calcium phosphate in the osteoid matrix of bone, as in the case of rickets or osteomalacia.

2. Conditions in which the body fluids contain more than the normal amount of calcium phosphate. In such conditions calcium phosphate is deposited in tissues other than bone, osteoclastic tumors and irradiated ergosterol poisoning being examples of this group.

3. Conditions in which the body fluids contain the normal amount of calcium phosphate, but the relation of calcium to phosphorus is abnormal, as in hypo- and hyperparathyroidism.

With these facts in mind it is easy to understand why non-toxic doses of irradiated ergosterol when administered to normal individuals do not produce greater changes in the calcium or phosphorus metabolism. In normal individuals the body stores of calcium and phosphorus, the bones, are adequate and the circulating fluid already contains all the calcium phosphate it can hold at that particular time. Therefore, the additional calcium and phosphorus absorbed from the gastro-intestinal tract is rapidly excreted in an attempt to maintain the normal relation of calcium to phosphorus in the serum.

The patient with osteoporosis was similar to the normals in respect to the relation of calcium to phosphorus in the serum, but the body stores of calcium and phosphorus were greatly depleted. Evidently the lack of calcium phosphate in the bones was sufficiently great to allow more deposition of calcium phosphate than would normally take place, and in consequence, the amount of calcium and phosphorus which had to be excreted in the urine in order to maintain a normal serum calcium phosphate concentration was less than that observed in normal individuals. Therefore, the additional calcium and phosphorus absorbed because of the administration of irradiated ergosterol had only a slight effect on the serum calcium and phosphorus.

In patients such as the one studied in experiment II, the body fluids were deficient in respect to calcium phosphate and therefore deposition of calcium phosphate in the bones did not take place. In this patient the additional calcium and phosphorus absorbed following the administration of ergosterol was employed in restoring the normal relation of calcium to phosphorus in the serum, thus allowing calcium phosphate deposition in the bones to occur. The existing calcium phosphate deficiency in the body fluids and bones was so great that there was no need of increased urinary calcium and phosphorus excretion in order to maintain the normal relations as in the case of normal individuals or the patient with osteoporosis.

These findings make it clear why irradiated ergosterol therapy produces such beneficial results in calcium deficiency diseases such as rickets and osteomalacia. These are diseases in which the calcium deficiency is due to failure to absorb sufficient calcium and phosphorus from the gastro-intestinal tract.

CONCLUSIONS

1. A case of osteoporosis was greatly improved by the administration of irradiated ergosterol in conjunction with a high calcium diet.

2. A case of osteomalacia with tetany secondary to faulty absorption showed immediate and lasting benefit from irradiated ergosterol. Irradiated ergosterol acts as a specific drug in this type of calcium phosphate disorder.

3. No untoward symptoms were observed in either case as the result of such therapy.

4. The action of irradiated ergosterol is the same in normal individuals as in individuals with calcium deficiency diseases, namely: to increase absorption of calcium and phosphorus from the gastro-intestinal tract. If there exists a calcium phosphate deficiency of the serum as well as the bones, the additional calcium and phosphorus absorbed is retained in order to establish a normal relationship of calcium and phosphorus in the serum and thus allow the deposition of calcium phosphate in the bones. In calcium deficiency diseases where there is a calcium phosphate deficiency of the bones only, the consequent retention is not so marked, whereas in normal individuals little or no retention takes place because the serum and bones are both normal in respect to calcium phosphate.

5. The dose of irradiated ergosterol necessary to produce such changes in the calcium and phosphorus metabolism of individuals with calcium deficiency diseases is much smaller than the amount required to produce changes in the calcium and phosphorus metabolism of normal individuals.

BIBLIOGRAPHY

1. Bauer, W., Marble, A., and Claflin, D., J. Clin. Invest., 1932, xi, 1. Studies on the Mode of Action of Irradiated Ergosterol. I. Its Effect on the Calcium, Phosphorus and Nitrogen Metabolism of Normal Individuals.
2. Bauer, W., Albright, F., and Aub, J. C., J. Clin. Invest., 1929, vii, 75. Studies of Calcium and Phosphorus Metabolism. II. The Calcium Excretion of Normal Individuals on a Low Calcium Diet, also Data on a Case of Pregnancy.
3. Mandl, F., Zentralbl. f. Chir., 1926, liii, 260. Therapeutischer Versuch bei einem Falle von Ostitis fibrosa generalisata mittels Extirpation eines Epithelkörperchentumors.
4. Mandl, F., Arch. f. klin. Chir., 1926, cxliii, 1. Klinisches und Experimentelles zur Frage der lokalisierten und generalisierten Ostitis fibrosa.
5. Hannon, R. R., Shorr, E., McClellan, W. S., and DuBois, E. F., J. Clin. Invest., 1930, viii, 215. A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies. Metabolic Study I.

   Bauer, W., Albright, F., and Aub, J. C., J. Clin. Invest., 1930, viii, 229. A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies. Metabolic Study II.

McClellan, W. S., and Hannon, R. R., J. Clin. Invest., 1930, viii, 249. A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies. Metabolic Study III.

6. Barr, D. P., Bulger, H. A., and Dixon, H. H., J. Am. Med. Assoc., 1929, xcii, 951. Hyperparathyroidism.
7. Wilder, R. M., Endocrinology, 1929, xiii, 231. Hyperparathyroidism: Tumor of the Parathyroid Glands Associated with Osteitis Fibrosa.
8. Boyd, J. D., Milgram, J. E., and Stearns, G., J. Am. Med. Assoc., 1929, xciii, 684. Clinical Hyperparathyroidism.
9. Snapper, I., Nederl. tijdschr. v. geneesk., 1929, ii, 4758. Gezwel Van Een Bijschildklier en Skeletafwijkingen.
10. Mandl, F., Zentralbl. f. Chir., 1929, lvi, 1739. Zur Frage der Exstirpation eines Epithelkörpertumors bei der allgemeinen Ostitis Fibrosa.
11. Hunter, D., Proc. Roy. Soc. Med., 1929, xxiii, 27. Hyperparathyroidism. (Hyperfunction of a Parathyroid Tumor in a Case of Generalized Osteitis Fibrosa.)
12. Irving, L., and Ferguson, J., Proc. Soc. Exp. Biol. and Med., 1925, xxii, 527. The Influence of Acidity in the Intestine upon the Absorption of Calcium Salts by the Blood.
13. Abrahamson, E. M., and Miller, E. G., Jr., Proc. Soc. Exp. Biol. and Med., 1925, xxii, 438. Hydrogen-ion Concentration in the Gastro-intestinal Tract of the Albino Rat.
14. Barach, A. L., and Murray, H. A., Jr., J. Am. Med. Assoc., 1920, lxxiv, 786. Tetany in a Case of Sprue.
15. Ryle, J. A., Guy's Hosp. Rep., 1924, lxxiv, 1. Fatty Stools from Obstruction of the Lacteals; with a Note on the Coeliac Affection.
16. Telfer, S. V., Quart. J. Med., 1922, xvi, 45. Studies on Calcium and Phosphorus Metabolism. I. The Excretion of Calcium and Phosphorus.
    Ibid., 1922, xvi, 63. Studies on Calcium and Phosphorus Metabolism. II. The Metabolism of Calcium and Phosphorus in Rickets.
    Ibid., 1924, xvii, 245. Studies on Calcium and Phosphorus Metabolism. III. The Absorption of Calcium and Phosphorus and their Fixation in the Skeleton.
17. Luckhardt, A. B., and Compere, E. L., Proc. Soc. Exp. Biol. and Med., 1923–24, xxi, 523. Increased Gastro-intestinal Permeability as a Possible Factor in Parathyroid Tetany.
18. Linder, G. C., and Harris, C. F., Quart. J. Med., 1930, xxiii, 195. Calcium and Phosphorus Metabolism in Chronic Diarrhea with Tetany.
19. Albright, F., and Ellsworth, R., J. Clin. Invest., 1929, vii, 183. Studies on the Physiology of the Parathyroid Glands. I. Calcium and Phosphorus Studies on a Case of Idiopathic Hypoparathyroidism.
20. Holt, L. E., Courtney, A. M., and Fales, H. L., Am. J. Dis. Child., 1920, xix, 97 and 201. Calcium Metabolism of Infants and Young Children, and the Relation of Calcium to Fat Excretion in the Stools. Part I. Infants Taking Modifications of Cow's Milk. Part II. Children Taking a Mixed Diet.
21. Bergeim, O., J. Biol. Chem., 1926, lxx, 51. Intestinal Chemistry. VII. The Absorption of Calcium and Phosphorus in the Small and Large Intestines.
22. Albright, F., Bauer, W., Cockrill, J. R., and Ellsworth, Read, J. Clin. Invest., 1931, ix, 659. Studies on the Physiology of the Parathyroid Glands. II. The Relation of the Serum Calcium to the Serum Phosphorus at Different Levels of Parathyroid Activity.