CALCIUM AND PHOSPHORUS METABOLISM IN OSTEOMALACIA.
XI. THE PATHOGENETIC RÔLE OF PREGNANCY AND RELATIVE IMPORTANCE OF CALCIUM AND VITAMIN D SUPPLY

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Though osteomalacia is fundamentally a disease due to vitamin D deficiency and dietary calcium shortage, it is made manifest or aggravated by a host of predisposing factors among which the processes of reproduction deserve special attention. Pregnancy and lactation, albeit normal physiological phenomena, make additional demands upon the calcium and phosphorus supplies of the mother, so that diets adequate under ordinary circumstances become deficient during reproductive activity. Our previous reports (1, 2) on the metabolic data of eight Chinese lactating women, with or without osteomalacia, have demonstrated that the drain of lactation varies with the stage of lactation and the quantity of milk secretion. During late lactation when milk yield is small, positive balances in calcium and phosphorus can usually be secured with the addition of vitamin D, even when the intake of minerals is moderate or limited. However, in early lactation, especially if abundant, the loss of calcium in milk is so great that a high intake of calcium is essential in addition to adequate vitamin D supply to prevent depletion of skeletal store. Therefore, if nursing is maintained on dietaries deficient in vitamin D and calcium, as is often the case in China, skeletal demineralization will inevitably result.

A similar chain of events probably occurs in pregnancy. In this part of the reproductive cycle nutritional requirements are increased to provide building material for the fetus and its adnexa and for the development of maternal tissues such as the uterus, mammary glands and other organs, in order to meet the demands of labor and parturition and to prepare for milk secretion. The quantitative aspects of the question are not accurately known, but may be approached from the chemical analysis of fetuses at term and at various ages. Givens and Macy (3) and Macy and Hunscher (4) have shown the average calcium content of

the human fetus at birth to be about 21 to 23 grams; Coons et al. (5) give similar estimates, while McIlroy (6) puts the figure considerably higher, namely, at 30 grams. The average phosphorus content of the fetus at term is approximately 14 grams. The whole subject has been reviewed by Macy and Hunscher (4) and by Garry and Stiven (7). It is generally accepted that the mineral needs of the fetus are insignificant during the first four months, but from then on they increase rapidly so that about two-thirds of the total are deposited during the last three months. Therefore, a minimum of 200 mgm. of calcium and 100 mgm. of phosphorus per day should be retained by the mother during the last three months of pregnancy in order to satisfy the fetal requirement without drawing upon the maternal mineral store. These estimates, though they are from Western sources, may serve to indicate the magnitude of drain upon the maternal tissues during pregnancy if living conditions and dietaries are incapable of supporting such a degree of mineral retention, as they appear to be frequently in China.

The primary purposes of the work to be reported in the present communication are to observe the calcium, phosphorus and nitrogen metabolism of patients with osteomalacia during pregnancy, to compare it with that of individuals without skeletal decalcification and to assess the relative importance of vitamin D, calcium and phosphorus intake in securing adequate mineral balances for the added requirements of gestation.

PROCEDURE

All the patients were studied in the metabolism ward where diets were quantitatively prepared and served, and excreta completely collected. The diets were practically free from vitamin D except those containing small amounts of eggs. They were low in calcium but, when desired, the calcium intake was raised by administering

TABLE I

Composition of diets in grams per day

(Values for calcium, phosphorus and nitrogen are actually analyzed.)

Case	Diet number	Periods (4-day)	Protein	Carbohydrate	Fat	Calories	Calcium, mgm.	Phosphorus, mgm.	Nitrogen
1	1	1–2, 5–6, 9–10	54	242	42	1562	141	325	7.68
1	2	3–4, 7–8, 11–13	67	263	65	1866	150	674	8.92
2	1	1–2, 7–8, 13–14	60	287	62	1952	189	341	8.50
2	2	3–4, 9–10, 15–16	51	285	70	1899	192	565	7.84
2	3	5–6, 11–12, 17	72	323	42	1953	268	826	9.98
3	1	1–3, 7–9, 13–15, 19–21	89	457	78	2882	277	1296	14.67
3	2	4–6, 10–12, 16–18, 22–24	81	516	52	2858	314	837	12.34
4	1	1–3, 7–9, 14–18	71	380	55	2300	215	926	9.69
4	2	4–6, 10–13, 17–18	68	403	52	2353	275	692	8.69
5	1	1–3, 11–13	76	404	50	2371	260	1199	12.59
5	2	4–5, 6–7, 14–16	74	402	52	2374	196	782	12.10
6	1	1–3, 7–9, 13–15	91	406	70	2611	212	1078	14.19
6	2	4–6, 10–12, 16–18	76	494	76	2936	257	703	9.42
7	1	1–2, 7–8, 13–14, 19–20, 21	63	360	47	2116	160	1026	10.49
7	2	3–4, 9–10, 15–16, 21–22	63	330	41	1951	205	651	9.30
7	3	5–6, 11–12, 17–18, 23	60	287	62	1952	142	308	8.64
8	1	1–9	68	369	63	2315	273	724	10.39
8	2	11–14	48	272	46	1688	273	514	6.87
8	3	15–19	64	305	63	2042	271	694	9.10
9	1	1–10	71	368	63	2325	283	832	10.52
10	1	1–4	65	165	58	1442	304	974	10.40
10	2	5–7	43	232	45	1505	462	924	6.88
10	3	8–12	51	315	58	2004	118	634	8.16
10	4	13–16, 20–32	75	214	66	1750	126	1041	12.00
10	5	17–18	64	239	59	1743	148	366	10.24
10	6	36–31	76	199	68	1712	145	1108	12.16

a 7.7 per cent solution of calcium lactate. Distilled water was used for cooking and drinking. The diets were quantitatively consumed with the exception of a few instances. The refused food or vomitus, as the case may be, was then separately analyzed and subtracted from the day's intake. The ward routines and chemical methods for the analysis of food, excreta and serum were described previously (1, 2, 8). The metabolic periods were four days each.

RESULTS

This study includes ten Chinese women admitted during various stages of pregnancy. For convenience in presentation, these subjects may be divided into 3 groups according to the condition of their skeletal system. Group I consists of three cases which may be considered, for our purpose, as normal controls, there being no tetany, nor roentgenologic evidence of osteomalacia. Group II contains four subjects, all of whom showed mild osteoporosis, and three of whom had active tetany prior to the metabolic studies. Group III is composed of three patients with advanced osteomalacia, with marked skeletal rarefaction, deformity and fractures. This classification is only approximate because slight depletion of the mineral contents of bones may be passed as normal and small differences in the density of bones from case to case are not detectable by x-ray examination. Moreover, the current state of vitamin D nutrition, as shown by the metabolic behavior at the moment, may not always correspond with the condition of the skeleton. However, there is a general parallelism between the skeletal condition and the state of vitamin D store as revealed by metabolic observation in those patients receiving no prior vitamin D medication.

Group I. Normal

Case 1, K. C. H. This was a 19-year-old primipara with normal serum calcium and inorganic phosphorus and without clinical or roentgenologic evidence of skeletal decalcification. She was observed for 13 four-day periods from the end of the eighth month of gestation to term. Two diets, one low in both calcium and phosphorus and the other low in calcium but moderate in phosphorus, alternated with each other every 2 periods. As seen from Figure 1 and Table II, an intake of 141 to 150 mgm. calcium (Periods 1 to 4) gave
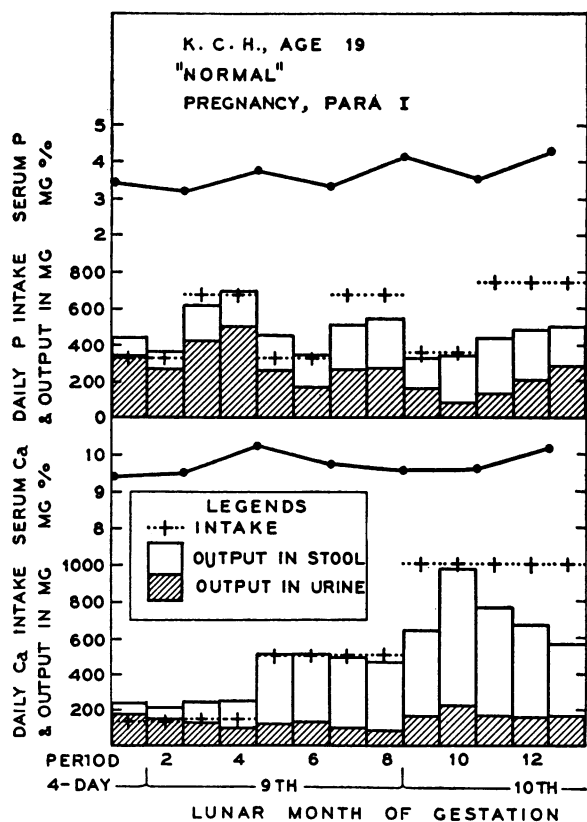
FIG. 1. CASE 1. CALCIUM AND PHOSPHORUS METABO-
LISM IN A PRESUMABLY NORMAL INDIVIDUAL DURING THE
LATTER PART OF PREGNANCY

rise to considerable negative balance, averaging 92
mgm. per day. Raising the intake to 500 mgm.
(Periods 5 to 8) elicited barely even balances.
On further augmenting the intake to 1000 mgm.
(Periods 9 to 13), one notices a considerable cal-
cium gain, namely, 284 mgm. per day. The cal-
cium balance at a given level of calcium intake
was not influenced by the different amounts of
phosphorus in the two diets.

However, phosphorus balances were naturally
dependent on the phosphorus intake. With an
intake of 325 to 358 mgm. per day (Periods 1 to
2, 5 to 6 and 9 to 10), the balances were in the
main negative, averaging 44 mgm. per day; while
an intake of 674 to 741 mgm. (Periods 3 to 4,
7 to 8 and 11 to 13) gave rise to considerable gain,
namely, about 160 mgm. per day. The extent of
phosphorus retention at a given level of intake
also depended upon the calcium intake. As the
latter was gradually raised from 150 to 1000
mgm., there was a progressive diminution of the

negative phosphorus balance on the low phos-
phorus intake and a similar increase of the posi-
tive phosphorus balance on the moderate phos-
phorus intake. This dependence of both calcium
and phosphorus balances upon the calcium intake
indicates that calcium is a more important limit-
ing factor in the metabolism of the two elements,
an observation which has already been described
in our previous studies (9, 10).

Nitrogen balances remained fairly satisfactory.
Serum calcium did not vary significantly through-
out the periods of observation, but there was a
tendency for serum inorganic phosphorus to fluc-
tuate with the phosphorus intake.

In a previous communication (11), it has been
shown that the earliest sign of vitamin D de-
ficiency is a diminution or disappearance of urinary
calcium. Increase of stool calcium, decrease of
calcium balance and changes in serum calcium and
phosphorus follow in that order as the deficiency
is allowed to go on. This patient was able to
maintain good amounts of calcium in the urine
throughout the 13 periods of study. This, to-
gether with the consistently normal serum calcium
and phosphorus, indicates that the patient had an
adequate store of vitamin D during the studies.
Most of that store probably had been acquired
prior to admission, as only one of the diets served
on the ward contained any vitamin D-containing
food, namely, egg, and that in small amounts only.

With vitamin D operative, one may perhaps
expect this patient to keep definitely positive bal-
ances on an intake of 500 mgm. calcium a day.
However, only even balances were obtained, and
this suggests that her usual intake had been at
that level because, as previously pointed out (1),
the calcium requirement depends upon, among
other factors, the customary dietary level. If 500
mgm. be the usual level of intake, considerably
more should be supplied during pregnancy to meet
the fetal needs. In this patient an intake of 1000
mgm. of calcium enabled her to retain a sufficient
amount for the added requirement.

Case 2, W. T. Though this 17-year-old primi-
para had a normal skeleton, her serum calcium
and phosphorus were somewhat lower than nor-
mal. Metabolic studies extended for 17 periods
from the sixth to the eighth lunar month of gesta-
tion (Table II). This subject was given 3 diets,
all low in calcium, but progressively increased in

TABLE II

Group 1. Normal calcium, phosphorus and nitrogen metabolism

Case	Date		Period 4-day	Stage of gestation	Calcium, average daily				Phosphorus, average daily				Nitrogen, average daily			
					Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
				lunar months	mgm.	mgm.	mgm.	mgm.	mgm.	mgm.	mgm.	mgm.	grams	grams	grams	grams
1. K.C.H.	March	1937 29–April 5	1–2	8–9	141	164	60	− 83	325	306	96	− 77	7.68	6.74	0.62	+0.32
	April	6–13	3–4	9	150	116	134	−100	674	459	196	+ 19	8.92	7.88	0.65	+0.39
		14–21	5–6	9	500	128	376	− 4	325	216	182	− 73	7.68	5.92	0.70	+1.06
		22–29	7–8	9	500	97	385	+ 18	674	268	259	+147	8.92	6.52	0.64	+1.76
		30–May 7	9–10	10	1000	200	612	+188	358	122	218	+ 18	8.45	6.68	0.64	+1.13
	May	8–19	11–13	10	1015	165	502	+348	741	208	266	+267	9.81	7.68	0.65	+1.48
2. W.T.	December	1936–37 27–January 3	1–2	6	189	39	256	−106	341	327	240	−226	8.50	8.40	1.01	−0.91
	January	4–11	3–4	6–7	192	29	162	+ 1	565	445	171	− 51	7.84	7.29	0.74	−0.19
		12–19	5–6	7	268	20	220	+ 28	826	491	258	+ 77	9.98	8.57	0.87	+0.54
		20–27	7–8	7	500	57	380	+ 63	426	206	295	− 75	10.63	7.80	1.13	+1.74
		28–February 4	9–10	7	500	9	414	+ 77	706	363	247	+ 96	9.80	7.20	0.86	+1.74
	February	5–12	11–12	8	500	4	444	+ 52	1032	458	388	+186	12.48	8.21	1.16	+3.11
		13–20	13–14	8	1000	20	682	+298	426	378	350	−302	10.63	7.94	1.26	+1.43
		21–28	15–16	8	1000	4	809	+187	706	288	324	+ 94	9.80	8.04	0.94	+0.82
	March	1– 4	17	8	1000	12	698	+290	1032	329	333	+370	12.48	9.31	1.07	+2.10
3. L.C.P.	March	1940 11–22	1–3	7	277	3	138	+136	1296	544	463	+289	14.67	9.22	1.99	+3.46
		23–April 3	4–6	8	1314	6	939	+369	837	426	294	+117	12.34	9.66	1.15	+1.53
	April	4–15	7–9	8	277	5	507	−235	1296	581	566	+149	14.67	9.15	2.29	+3.23
		16–27	10–12	8–9	1314	7	820	+487	837	437	223	+177	12.34	8.54	0.99	+3.45 .
		28–May 9	13–15*	9	277	2	326	− 51	1296	614	500	+182	14.67	8.89	1.74	+4.04
	May	10–21	16–18*	9	1314	297	475	+542	837	281	242	+314	12.34	8.54	1.28	+2.52
		22–June 2	19–21	10	218	21	128	+ 69	1277	552	504	+221	14.48	8.44	2.05	+3.99
	June	3–14	22–24	10	1257	118	446	+693	708	189	261	+258	12.65	7.91	1.06	+3.68

* Vigantol during Periods 13–16.

phosphorus content. She showed similar metabolic behavior to Case 1 in that negative calcium balances (— 26 mgm. daily) prevailed on an intake of 189 to 268 mgm., slightly positive balances (64 mgm. daily) were obtained on an intake of 500 mgm. and substantial gain (253 mgm. daily) was secured on an intake of 1000 mgm. This is also true with phosphorus balances which varied directly not only with the level of phosphorus intake but also with that of calcium intake.

In comparison with the first case, although this individual exhibited the same degree of conservatism in handling calcium and phosphorus, her store of vitamin D was probably not as adequate, in that the levels of serum calcium and phosphorus were not strictly normal and urinary calcium tended to decrease and disappear even on high intake. Although small amounts of eggs were present in the diet, they were evidently not sufficient to prevent a gradual depletion of the scanty vitamin D store of the body. However, an intake of 1000 mgm. of calcium seemed adequate to fulfill the requirements of pregnancy even if the vitamin D store was somewhat inadequate.

Case 3, Mrs. L. C. P. This pregnant woman, para IV, was considered normal from the standpoint of her skeleton, and her serum calcium and

phosphorus on admission were essentially normal. The plan of observation in this case consisted of 3 periods of low calcium-high phosphorus intake followed by 3 periods of high calcium-moderate phosphorus intake; and this cycle was repeated 3 more times. Therefore, the study covered 24 periods from the seventh month to term. The data are set forth in Figure 2 and Table II. During the first 3 periods on low calcium diet (277 mgm.), the patient exhibited extraordinary ability in maintaining positive balance, averaging 136 mgm. per day. During the next 3 periods on high calcium intake (1296 mgm.), the average positive balance of 369 mgm. per day was likewise satisfactory. When the cycle of dietary regime was repeated, though the calcium balance was excellent on high intake (Periods 10 to 12), it was markedly negative on low intake (Periods 7 to 9), indicating poor conservation. This, together with a tendency for the serum calcium to fall during the low calcium periods, suggests the wearing out of whatever vitamin D store the patient might have had at the beginning of the studies.

The supply of vitamin D as Vigantol 1 cc. per day (12,000 international units) for Periods 13 to 16 brought about striking changes. From Pe-

riod 13 to 15, the first 3 periods of Vigantol administration, when the effect of the therapy could hardly be maximal, the calcium balance on low intake began to show favorable influence. In the next 3 periods (Periods 16 to 18), while on high calcium intake, the stool calcium was much reduced, and the urinary calcium much increased. As the reduction of calcium in the stool was greater than the increase of urinary calcium, the

net balances exceeded those of previous periods on similar high intake. The last 6 periods showed even better calcium retention. During Periods 22 to 24, the average daily retention was 693 mgm., namely, 55 per cent of the intake.

Phosphorus balances remained positive throughout, more so after Vigantol administration. Periods of high phosphorus intake were not necessarily associated with greater phosphorus retention
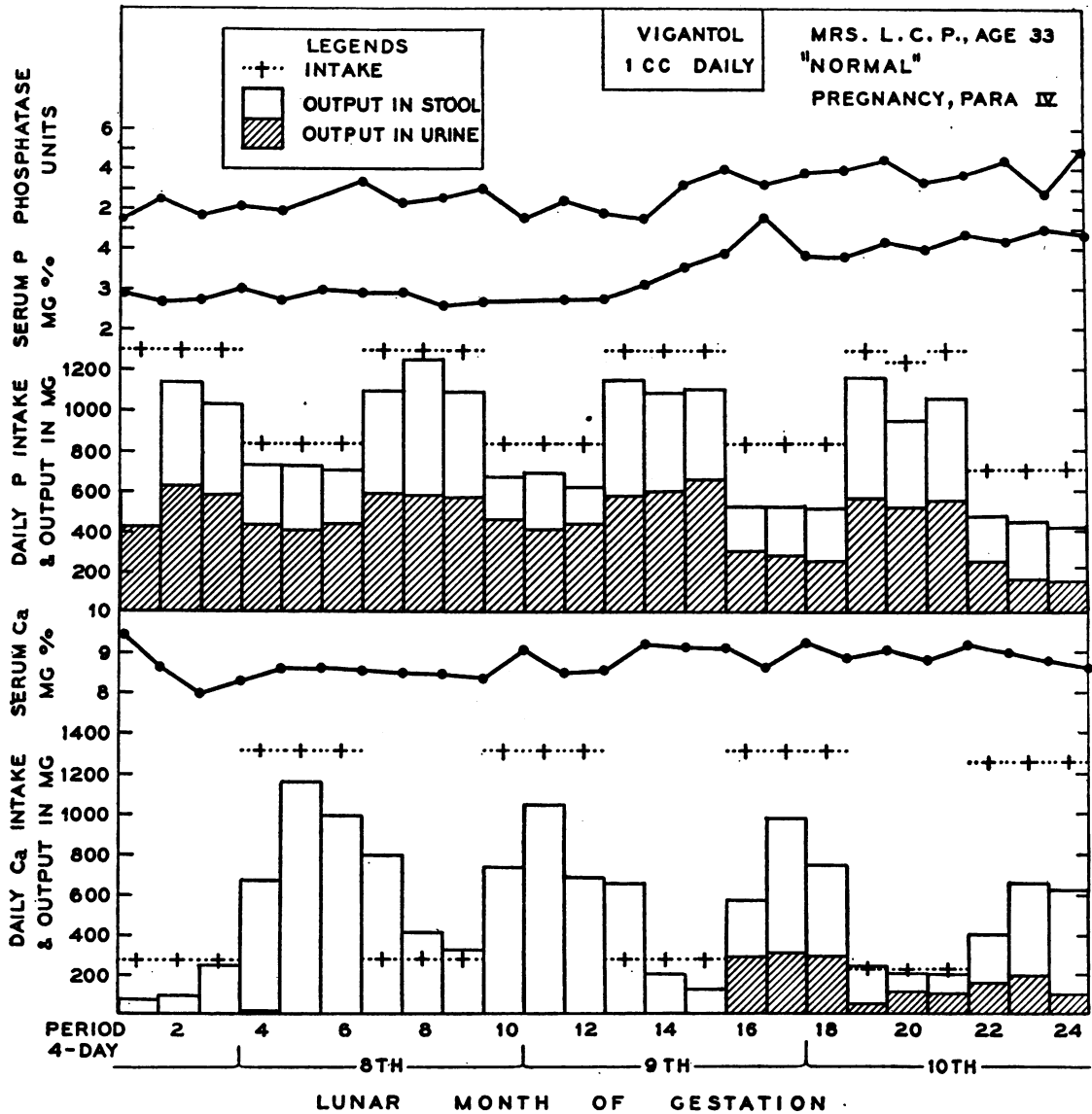

FIG. 2. CASE 3. CALCIUM AND PHOSPHORUS METABOLISM IN A WOMAN DURING THE LATTER PART OF PREGNANCY

Although there was no skeletal decalcification, metabolic behavior showed vitamin D deficiency and responded well to Vigantol therapy.

than periods of moderate phosphorus intake. In fact, the average daily retention during all the moderate phosphorus periods was slightly more than that during all the high phosphorus periods, undoubtedly because of the limiting effect of low calcium intake during the latter.

Serum calcium and phosphorus both showed a tendency to rise after vitamin D therapy. The rise of serum phosphorus was particularly striking. The nitrogen balance remained excellent throughout.

In comparison with the preceding case, this patient probably had even scantier vitamin D store, because the urinary calcium was absent from the beginning of the experiment. The unusual ability to maintain a positive calcium balance on a low intake during the first 3 periods is to be explained by her previous low calcium intake, which was quite likely the case. In agreement with this supposition is her inability to maintain a balance when the low calcium intake periods were repeated immediately after 3 periods of high intake. However, further depletion of the scanty vitamin D store probably played a contributory rôle in the difference in behavior between the first and second series of low calcium intake periods.

In spite of inadequate vitamin D store, an intake of approximately 1300 mgm. of calcium resulted in adequate retention for the heightened requirements of pregnancy. However, the supply of vitamin D constitutes a more fundamental solution to the problem. Thus, after Vigantol administration in this case, not only did the urinary calcium appear, the calcium balances on high intake improve and the serum calcium and phosphorus rise to normal, but also positive balances were maintained on low intake. With adequate vitamin D supply the calcium intake necessary for the requirements of pregnancy could be considerably reduced from 1.3 grams.

Comment. These three patients are alike in possessing normal skeletal mineral store, but they differ in the state of vitamin D nutrition. The first subject apparently had an adequate store of vitamin D so that 13 four-day periods of a diet low in vitamin D failed to elicit any evidence of depletion. The average daily calcium retention on high intake was 284 mgm., namely 28 per cent of the intake. The vitamin D store of the second subject was not so adequate, in that signs of de-

pletion began to occur after a similar period of study. However, the extent of calcium retention was approximately the same, namely 263 mgm. on high intake, or 26 per cent. The third patient showed evidence of depletion even earlier in the course of observation than in Case 2. Still, the extent of calcium retention on high intake remained satisfactory (28 per cent during Periods 4 to 6 and 37 per cent during Periods 10 to 12). These observations indicate the frequency of the existence of early or subclinical vitamin D deficiency as in the second and third patients. Such deficiencies cannot be recognized unless detailed metabolic observations are made. In such cases, however, high calcium intake (1 to 1.3 grams) exerts an ameliorative influence and even promotes sufficient calcium retention for the augmented requirements of gestation. On the other hand, vitamin D is such an economizer of calcium that in the presence of a lower level of calcium, as is the rule here, an adequate supply of vitamin D is imperative, especially during periods of reproductive activity.

Group II. Early or mild osteomalacia

Case 4, Mrs. L. C. F. Though this 19-year-old primipara had no history or clinical evidence of osteomalacia or tetany, a roentgenologic survey of the skeleton showed slight but definite osteoporosis. Similar to Case 3, a low calcium-high phosphorus regimen alternated with a high calcium-moderate phosphorus regimen, covering a total of 18 four-day periods from the eighth month of gestation to term. The first series of 6 periods (Table III) witnessed a slightly positive calcium balance on an intake of 215 mgm. per day and a substantial gain (averaging 401 mgm. daily or 31 per cent) on an intake of 1275 mgm. per day. But, as the studies proceeded, a negative balance prevailed on a low intake, and retention on a high intake steadily diminished so that during the last 2 periods hardly any calcium was retained. This extraordinary behavior indicates the markedly defective intestinal absorption of calcium usually seen in advanced vitamin D deficiency.

Phosphorus balances were slightly positive throughout, but they tended to be less so with progress of time, corresponding to the behavior of calcium balances. Serum calcium remained constantly between 8 and 9 mgm., while inorganic

phosphorus, slightly above 3 mgm. at the beginning, went down to 2 mgm. per cent towards the latter part of the studies. Phosphatase was slightly above normal, mostly between 4 and 6, but on occasions above 7 Bodansky units.

The point worthy of note in this patient is that, in severe vitamin D depletion, even an intake as high as 1275 mgm. calcium may not enable the patient to maintain a positive balance. This fact may serve to support the contention that adequate vitamin D plays a more important rôle than high calcium intake in promoting calcium gain.

Case 5, Mrs. S. P. S. This subject, aged 29 years, para IV, may be characterized as a case of mild osteomalacia and latent tetany. Her studies during 7 four-day periods between the fifth and sixth months of gestation showed slightly negative calcium balances on an intake of 260 mgm. and an average daily retention of 363 mgm. on an intake of 1197 to 1266 mgm. (Table III). The same dietary regimen was repeated eleven days after spontaneous abortion of twin fetuses. Both the negative balances in calcium on low intake and the positive balances on high intake (averaging 302 mgm. daily) were essentially the same as those during pregnancy. Nor were there pronounced differences in phosphorus retention between the observations during pregnancy and those after delivery. However, there was an unquestionable tendency for both serum calcium and phosphorus to rise after parturition. Whereas before delivery serum calcium varied between 7.14 and 8.47 mgm., its range after delivery was between 7.24 and 8.96 mgm. per cent. Likewise, serum phosphorus, varying between 1.73 and 2.24 during pregnancy, was from 2.11 to 3.47 mgm. per cent after delivery.

In this patient moderate vitamin D deficiency was present, as evidenced by the low serum calcium and phosphorus, the absence of calcium in urine and the failure to retain larger amounts of calcium than she did in the face of mineral shortage in the skeleton.

This patient gave us the opportunity to compare the metabolic behavior of the same individual during pregnancy with her behavior postpartum and uncomplicated by lactation. The results revealed no essential difference between pregnancy at the fifth and sixth months and reproductive rest, as far as the mineral balances were concerned.

Of course, one is aware of the fact that during pregnancy a goodly portion of the retained mineral goes to supply the fetus and its adnexa, while during reproductive rest all remains in the maternal tissues. This is probably the explanation for the tendency of the serum calcium and phosphorus to rise after the termination of the pregnancy without any change in the dietary regimen and without any addition of vitamin D, as shown by this patient.

However, there was no extra demand over and above what was required by the products of conception for growth and development. This is in distinct contrast to the state of affairs in active and early lactation where, it has been demonstrated (1, 2), the metabolic processes are so greatly stimulated that calcium has to be supplied not only to cover what is secreted in the milk, but also to cope with this less well-defined factor of stimulation. This is true even in the presence of adequate vitamin D supply. From this we may infer that the drain of pregnancy, as a rule, is not as great as that of lactation.

Case 6, Mrs. C. W. C. This woman of 31 years of age, with mild osteomalacia, cataract and tetany for many years, was studied during the eighth to tenth months of her fourth pregnancy. Prior to the commencement of metabolic observations, calcium gluconate and small amounts of vitamin D were given so that tetany was controlled. Metabolic behavior for the first 3 periods on a daily intake of 212 mgm. of calcium (Table III) was conservative in that positive balances were observed. With the intake raised to 1257 mgm. per day, the daily calcium retention averaged 416 mgm. (Periods 4 to 6). When the low calcium diet was repeated during Periods 7 to 9 and 13 to 15, negative balances prevailed, partly because of the preceding high calcium regimen and partly because of beginning depletion of the scanty store of vitamin D acquired prior to the studies. However, with high calcium intake during Periods 10 to 12 and 16 to 18, the patient had no difficulty in securing adequate positive balances which were, respectively, 324 and 474 mgm. per day.

Phosphorus balances were, on the whole, positive, the extent of retention varying with the level of phosphorus intake as well as with that of calcium intake. Serum calcium fluctuated irregu-

TABLE III

Group 2. Early or mild osteomalacia. Calcium, phosphorus and nitrogen metabolism

Case	Date	Period 4-day	Stage of gestation	Calcium, average daily				Phosphorus, average daily				Nitrogen, average daily			
				Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
			lunar months	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*grams*	*grams*	*grams*	*grams*
	1939–40														
	October 30–November 10	1–3	8	215	6	172	+ 37	926	369	426	+131	9.69	5.64	2.21	+1.84
4	November 11–22	4–6	8–9	1275	5	868	+402	692	282	249	+161	8.69	5.63	1.58	+1.48
L.C.F.	23–December 4	7–9	9	215	5	319	−109	926	505	419	+ 2	9.69	6.54	1.89	+1.26
	December 5–20	10–13	9–10	1275	4	1066	+205	692	288	308	+ 96	8.69	4.65	1.82	+2.22
	21–January 1	14–16	10	215	4	301	− 90	926	435	377	+114	9.69	5.14	1.59	+2.96
	January 2–9	17–18	10	1275	4	1252	+ 19	692	267	364	+ 61	8.69	4.57	1.67	+2.45
	1940														
	February 7–18	1–3	5	260	0	314	− 54	1199	500	576	+123	12.59	7.88	2.06	+2.65
5	19–26	4–5	5–6	1197	2	786	+409	782	324	436	+ 22	12.10	8.10	1.76	+2.24
S.P.S.	27–March 5*	6–7	6	1266	2	948	+316	753	238	374	+141	11.77	7.92	1.87	+1.98
	March 18–29	11–13		260	2	322	− 64	1199	660	494	+ 45	12.59	9.23	1.52	+1.84
	30–April 10	14–16		1266	4	960	+302	753	256	278	+219	11.77	7.58	1.27	+2.92
	1939–40														
	November 19–30	1–3	8	212	9	145	+ 58	1075	588	349	+138	14.19	7.8	1.93	+2.48
6	December 1–12	4–6	8	1257	21	821	+415	703	399	234	+ 70	9.42	7.29	1.37	+0.76
C.W.C.	13–24	7–9	8–9	212	2	342	−132	1075	458	413	+204	14.19	8.23	1.56	+4.40
	25–January 5	10–12	9	1257	2	931	+324	703	281	244	+178	9.42	5.90	1.25	+2.27
	January 6–17	13–15	9–10	222	5	398	−181	1123	509	452	+162	15.06	9.17	1.76	+4.13
	18–29	16–18	10	1257	3	780	+474	703	316	283	+104	9.42	7.12	1.19	+1.11
	1937														
	March 13–20	1–2	5	160	48	163	− 51	1026	402	470	+154	10.49	7.95	1.53	+1.01
	21–28	3–4	5	205	41	82	+ 82	651	388	328	− 65	9.30	6.93	1.27	+1.10
	29–April 5	5–6	5–6	142	48	62	+ 32	308	141	176	− 9	8.64	6.68	1.28	+0.68
	April 6–13	7–8	6	1000	70	640	+290	1026	128	630	+268	10.49	7.52	1.56	+1.41
	14–21	9–10	6	1000	44	872	+ 84	651	274	447	− 70	9.30	7.84	1.20	+0.26
7	22–29	11–12	6	1000	74	710	+216	308	84	242	− 18	8.64	6.85	0.95	−0.94
W.E.T.	30–May 7	13–14†	7	160	18	256	−114	1026	280	564	+182	10.49	7.05	1.46	+1.98
	May 8–15	15–16	7	205	33	60	+112	651	326	219	+106	9.30	6.34	1.34	+1.62
	16–23	17–18	7	142	58	46	+ 38	308	136	140	+ 32	8.64	5.87	1.31	+1.46
	24–31	19–20	7–8	1000	188	438	+374	1026	136	579	+311	10.49	6.68	1.74	+2.07
	June 1–8	21–22	8	1000	228	361	+411	651	176	310	+165	9.30	6.02	1.40	+1.88
	9–12	23	8	1000	272	370	+358	308	105	208	− 5	8.64	5.71	1.30	+1.63

* Abortion March 7.   † Vigantol during Periods 13–23.

larly between 8.12 and 9.73 mgm. per cent, while inorganic phosphorus ranged between 3.45 and 4.09 mgm. per cent. Thus, all the serum inorganic phosphorus values were normal, and most of the serum calcium values were within normal limits. Phosphatase was normal throughout.

Though this patient showed more marked anatomical evidence of previous vitamin D deficiency (osteomalacia, tetany and cataract) than the two preceding subjects, her metabolic behavior exemplified a greater degree of conservatism in that her serum calcium and phosphorus were maintained within normal limits, and her calcium balance on high intake was on the average somewhat higher. This more conservative behavior was most likely the result of the limited supply of vitamin D received prior to the studies. However, this supply was inadequate to enable her to maintain a balance on low calcium intake and to eliminate significant amounts of calcium in the urine. In other words, there was room for improvement in her metabolic behavior, as in Case 3,

if a more adequate supply of vitamin D had been available to her.

Case 7, Mrs. W. E. T. Similar to the foregoing case, this was one of mild osteomalacia, cataract and tetany of many years' duration. Likewise, this patient received calcium and cod liver oil prior to the metabolic observation for the treatment of her tetany, so that her serum calcium and phosphorus were within normal limits and her metabolic behavior was conservative by the time the studies were begun (Table III). She was given for the first 2 periods a low calcium-high phosphorus diet, and successively for 2 periods each, two diets similarly low in calcium but progressively lower in phosphorus. On the low calcium intake (142 to 205 mgm. per day) the average balance was slightly positive and a considerable proportion of the calcium output was in the urine, showing that vitamin D action was operative. When this series of diets was repeated, but with the calcium intake raised to 1000 mgm. a day (Periods 7 to 12), the average daily bal-

ance was 195 mgm., and the urinary calcium, though smaller in relation to the total output, was still considerable, showing that her response to high intake was fairly satisfactory by reason of the prior vitamin D store. However, that this was not the best performance of which the patient was capable was demonstrated by the observations during the subsequent 11 periods in which vitamin D in daily doses of 1 cc. of Vigantol, or 12,000 international units, was given. The first 6 periods on vitamin D therapy were on low calcium regimen (Periods 13 to 18), and no obvious difference was noted in the calcium balance, but, subsequently, during Periods 19 to 23, while on high calcium diet, definite changes took place. Not only did the average daily retention improve to 386 mgm., but also the urinary calcium increased greatly. The urinary calcium averaged 221 mgm. per day, amounting to 36 per cent of the total output, signifying that intestinal absorption of calcium had improved so that much more calcium was absorbed than could be retained.

Phosphorus balances varied not only with the levels of phosphorus and calcium intake, but also with the state of vitamin D nutrition. All the high phosphorus periods (1 to 2, 7 to 8, 13 to 14 and 19 to 20) were associated with considerable positive balance, especially in periods of high calcium intake and after Vigantol therapy. In periods of moderate phosphorus intake (Periods 3 to 4, 9 to 10, 15 to 16 and 21 to 22), the balances, which were negative prior to vitamin D therapy, became positive afterwards. Low phosphorus periods showed slightly negative balances, the degree of phosphorus loss remaining uninfluenced by the high level of calcium intake or by the vitamin D therapy.

Serum calcium, fairly normal to start with, tended to fall as studies progressed until vitamin D was given. After this it slowly returned to the initial value. A more definite rise occurred in the level of serum inorganic phosphorus after Vigantol administration.

This patient, though clinically similar to the preceding patient, was somewhat different in metabolic behavior, in that urinary calcium persisted in significant amounts, indicating the presence of a greater store of vitamin D. However, that this store was not the optimum was shown by the improvement in calcium balance, the increase in

urinary calcium and the rise in serum phosphorus subsequent to Vigantol administration.

Comment. The four patients in this group are united by the presence of a mild degree of skeletal osteoporosis, but they vary in their metabolic behavior by reason of the varying store of vitamin D. Cases 4 and 5, though presenting less anatomical evidence of vitamin D deficiency than Cases 6 and 7, were nevertheless more deficient in vitamin D, as shown by the metabolic behavior at the time of observation. Obviously, anatomical evidence and metabolic behavior may not necessarily correspond with each other at a given moment. The former is the result of the extent and duration of previous vitamin D deficiency, and once the skeleton is decalcified to an extent to be appreciable by roentgenologic examination, a long period of replenishment is required to eradicate the physical evidence of disease. Some of the evidence, such as cataract, may remain permanently, even if the skeletal lesion is all repaired. On the other hand, metabolic behavior is dynamic, readily influenced by such small amounts of vitamin D as may be introduced by involuntary exposure to sunlight, inclusion in the diet of such items as eggs (11), or the use of limited amounts of cod liver oil for medication, as in Cases 6 and 7. Such factors, often neglected or unrecognized, may make no difference to an individual with an abundant store, but they exert a corrective influence on the metabolic behavior of a patient with vitamin D deficiency, and therefore must be taken into account in interpreting the metabolic data obtained. Furthermore, such vitamin D supply is usually small and, if not continued, can easily be depleted so that metabolic evidence of vitamin D deficiency appears after a varying number of periods of conservative behavior. This was true of Cases 4 and 6 and would have been true of Case 7, had vitamin D been withheld from her. Case 5 was probably deficient in vitamin D from the beginning of the metabolic observations.

Therefore, as a group, these patients all showed mild but definite osseous evidence of previous vitamin D deficiency, but at the time of observation the metabolic behavior indicated a greater current deficiency of the vitamin in Cases 4 and 5 than in Cases 6 and 7, in which some cod liver oil had been given prior to the observations. In severe deficiency (Case 4), high calcium may be of no

avail in promoting sufficient calcium gain for the fetal needs, although in moderate deficiency (Case 6), it is capable of doing so. With adequate vitamin D supply, high calcium intake will enable the patient not only to take care of the demands of pregnancy, but also to store enough calcium for the reparation of her depleted skeleton. Thus, in the treatment of this group of patients, adequate vitamin D therapy, as well as high calcium intake, is necessary.

Comparison of this group of patients with mild skeletal decalcification with the previous group without bone lesions shows no essential differences in metabolic behavior except insofar as they are related to the state of vitamin D nutrition. In the first group, absence of bone lesions is associated with an early or a mild grade of vitamin D deficiency, if it is present at all. On the other hand, in the second group where bony decalcification is already recognizable, usually severer grades of vitamin D deficiency are present if not previously treated. Whatever metabolic differences may exist between the two groups are to be accounted for by the differences in vitamin D store
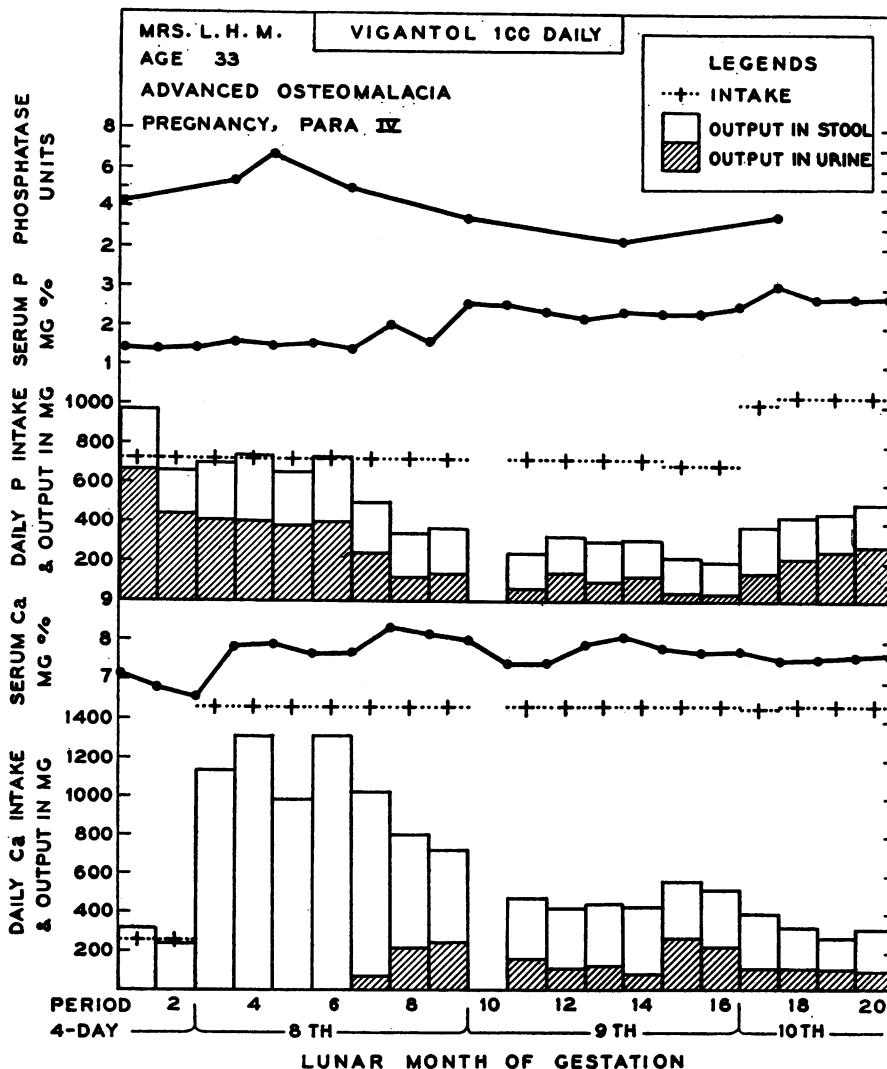

FIG. 3. CASE 8. CALCIUM AND PHOSPHORUS METABOLISM IN ADVANCED OSTEO-MALACIA SHOWING REMARKABLE MINERAL RETENTION AFTER VITAMIN D ADMINISTERED DURING THE LATTER PART OF PREGNANCY

TABLE IV

Group 3. Advanced osteomalacia. Calcium, phosphorus and nitrogen metabolism

Case	Date	Period 4-day	Stage of gesta-tion	Calcium, average daily				Phosphorus, average daily				Nitrogen, average daily			
				Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
			lunar months	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*grams*	*grams*	*grams*	*grams*
	1938–39														
	November 20–27	1–2	7	273	5	274	− 6	724	556	265	− 97	10.39	8.86	2.00	−0.47
8	28–December 9	3–5	8	1473	3	1147	+ 323	724	406	296	+ 22	10.39	7.05	1.55	+1.79
L.H.M.	December 10–25	6–9*	8	1473	140	835	+ 498	724	231	257	+236	10.39	6.42	1.63	+2.34
	30–January 14	11–14	9	1473	125	327	+1021	725	114	188	+423	6.87	4.57	1.24	+1.06
	January 15–22	15–16	9	1471	256	294	+ 921	694	42	178	+474	9.10	5.11	1.34	+2.65
	23–February 7	17–20	10	1468	110	225	+1133	1030	231	214	+585	9.10	5.87	1.54	+1.69
	1938–39														
9	December 26–January 10	1–4	9	1483	60	1268	+ 155	832	405	379	+ 48	10.52	7.47	1.58	+1.47
W.H.S.	January 11–14	5†	10	1438	123	1360	− 45	914	371	381	+162	10.80	7.45	1.77	+1.58
	15–February 3	6–10	10	1398	181	893	+ 324	878	337	282	+259	10.33	6.68	1.70	+1.95
	1934–35														
	September 18–October 3	1–4	3–4	304	6	124	+ 174	974	436	285	+253	10.40	8.12	0.94	+1.34
	October 4–15	5–7	4	458	0	179	+ 279	919	364	324	+231	6.88	5.91	0.93	+0.04
	16–23	8–9	4	118	4	211	− 97	634	281	404	− 51	8.16	5.13	1.35	+1.68
	24–November 4	10–12	5	88	1	65	+ 22	476	240	264	− 28	6.08	3.65	1.19	+1.24
	November 5–20	13–16	5	126	0	97	+ 29	1041	466	414	+161	12.00	8.31	1.28	+2.41
	21–28	17–18	6	1948	233	808	+ 907	323	22	194	+107	9.54	5.98	1.05	+2.51
10	December 3–10	20–21	6	1937	13	1384	+ 540	1041	126	494	+421	12.00	8.40	1.13	+2.47
Y.W.L.	11–18	22–23‡	6	1937	23	1034	+ 880	1041	140	403	+498	12.00	8.38	0.93	+2.69
	19–30	24–26	7	1937	91	888	+ 958	1041	42	468	+531	12.00	8.41	1.19	+2.40
	31–January 15	27–30	7	1937	119	797	+1021	1041	12	422	+607	12.00	8.77	1.22	+2.01
	January 16–23	31–32	8	1937	92	990	+ 855	1041	52	470	+519	12.00	8.82	1.23	+1.95
	February 5–12	36–37	8	1945	202	1030	+ 713	1108	12	658	+438	12.16	8.55	1.32	+2.29
	13–28	38–41	9	1945	202	1086	+ 657	1108	12	736	+360	12.16	9.33	1.42	+1.41
	March 1–12	42–44	9	1943	81	1158	+ 704	1091	165	515	+411	12.00	8.89	1.21	+1.90
	13–24	45–47	10	1945	51	1047	+ 847	1108	214	429	+465	12.16	9.22	0.87	+2.07
	25–April 9	48–51	10	1945	95	1472	+ 378	1108	275	605	+228	12.16	9.24	1.22	+1.70

* Vigantol during Periods 6–13. † Vigantol in this period. ‡ Vigantol during Periods 22–51.

rather than by the presence or absence of slight bony rarefaction.

Group III. Advanced osteomalacia

Case 8, Mrs. L. H. M. This subject, aged 33 years, was admitted for study at the seventh month of her fourth pregnancy. She had severe osteomalacia with symptoms dating back eleven years, which was shortly after the birth of her first child. The metabolic data of 20 periods are presented in Figure 3 and Table IV. In the first 2 periods on an intake of 273 mgm. of calcium per day, the output, all in the stools, almost balanced the intake. Beginning with Period 3, the intake was raised to 1473 mgm. daily. During the first 3 periods on the augmented intake, there was, on the average, a daily retention of 323 mgm., or 22 per cent of the intake. This degree of retention may not be abnormally low for a person with a normal skeleton, but for a patient like this with such extensive bony decalcification, together with absence of urinary calcium and low serum calcium and phosphorus, it indicates poor intestinal absorption or severe vitamin D deficiency. The correctness of this interpretation is shown by her response to Vigantol therapy which was given from Period 6 to 13. From Period 7 onward there was a progressive decrease of stool calcium and, at the same time, the appearance of a considerable amount of calcium in the urine. The average daily retention from Period 11 to 20 was over 1 gram or 70 per cent of the intake. If the last 4 periods, in which the phosphorus intake was raised, were considered alone, the retention averaged 1133 mgm. a day or 77 per cent of the intake. The amount retained would enable the patient not only to meet the requirements of pregnancy, but also to repair her depleted skeleton. Her symptoms were considerably improved.

Phosphorus balances were generally parallel with calcium balances. Serum calcium, 6.58 to 7.18 mgm. per cent during the low calcium periods, was raised to a maximum of 7.90 mgm. per cent during high calcium periods. After Vigantol administration, a slight further rise occurred, but the highest figure reached was only 8.36 mgm. per cent. Serum inorganic phosphorus, 1.45 mgm. per cent to start with, remained at this level until vitamin D administration, after which it showed steady elevation, the maximum being

3.06 mgm. per cent. Serum phosphatase, 4.2 to 6.70 Bodansky units per 100 cc., was lowered to 2.35 to 3.54 units after Vigantol therapy.

This patient, who had a severe osteomalacia, showed evidence of vitamin D deficiency in the early part of the metabolic observations. With vitamin D therapy there resulted remarkable calcium and phosphorus retention. Over and above what was required by the fetus, a substantial part of the retained minerals must have been deposited in the depleted skeleton. In this case, serum calcium and phosphorus failed to rise to perfectly normal levels in spite of adequate vitamin D therapy. Thus it seemed as if the urgent requirement of the skeleton, as well as of the fetus, had to be fulfilled at the expense of the serum concentration of these elements.

Case 9, Mrs. W. H. S. This patient, aged 29 years, was observed for 10 four-day periods during the last part of her fourth pregnancy. While the history of osteomalacia and tetany had been of eleven years' duration, and bony deformities were marked, the degree of skeletal rarefaction was not as extensive as in the preceding case, partly on account of previous treatment. As shown in Table IV, the average calcium balance on an intake of 1483 mgm. per day during the first 4 periods was 155 mgm., or approximately 10 per cent of the intake. The poor calcium retention, together with low serum inorganic phosphorus and relatively low calcium, indicates definite vitamin D deficiency. Vitamin D in the form of Vigantol 5 cc. daily was given for four days during Period 5. The response during the subsequent 5 periods consisted of an increase of the average calcium retention to 324 mgm. per day, or 23 per cent of the intake, and a considerable increase of urinary calcium. The response, however, was probably not the best of which the patient was capable in view of the unusual manner in which vitamin D was given. Large doses of Vigantol given for a few days might not be as efficient as smaller doses spread over a longer period of time, although single massive doses of vitamin D have been claimed to be effective in the treatment of rickets (12). It is possible that this patient with a lesser degree of skeletal mineral depletion might not require a higher degree of calcium retention than she showed. However,

this explanation is not likely, because patients with slight skeletal decalcification (Case 7), or without obvious bone lesions (Case 3), exhibited better retention of calcium under adequate vitamin D therapy.

Retention of phosphorus corresponded with that of calcium. Serum calcium was slightly but definitely raised and inorganic phosphorus was markedly elevated after Vigantol therapy.

Case 10, Mrs. Y. W. L. This woman of 43 years of age with severe osteomalacia of four years' duration was observed continuously from the third to the tenth month of her fifth pregnancy. For a year previously she went through detailed metabolic studies during which Vigantol 1 cc. daily (12,000 international units of vitamin D per cc.) was given for forty days (ending January 28, 1934) with considerable improvement in metabolic behavior, as well as clinical symptomatology. Observations during the present pregnancy were begun on September 19, 1935, on a diet containing 304 mgm. calcium per day (Figure 4 and Table IV.) On this diet (Periods 1 to 4) more than half of the intake of calcium was retained. This was true of the next diet containing 461 mgm. calcium per day (Periods 5 to 7), indicating satisfactory circumstances. Even when the diet calcium was reduced to 88 to 126 mgm. per day (Periods 8 to 16), balances, on the whole, were even, showing the remarkable power of conservation of calcium in a patient with osteomalacia when a prior store of vitamin D had been present.

From Period 17 on, the calcium intake was raised to 1959 mgm. per day. During the first 2 periods of high calcium intake, associated with very low phosphorus intake, the calcium retention averaged 907 mgm. per day, or 47 per cent of the intake, and the urinary calcium 233 mgm. per day, or 22 per cent of the total output. In distinct contrast were the results of Periods 20 and 21, during which both calcium and phosphorus intakes were high. Here the calcium retention was not as good and the urinary calcium was negligible. It was thought that at this point the patient might be showing an early vitamin D depletion. Therefore, Vigantol 2 cc. daily was started from Period 22. Subsequently, the calcium balances showed slight improvement and the urinary calcium gradually returned (Periods 22 to 32). Likewise, the phosphorus balances in-

FIG. 4. CASE 4. CALCIUM AND PHOSPHORUS METABOLISM IN A CASE OF ADVANCED OSTEOMALACIA OBSERVED FROM THE THIRD TO THE TENTH LUNAR MONTH OF GESTATION, SHOWING THE EFFECTS OF VITAMIN D ADMINISTRATION, AND THOSE OF FERRIC AMMONIUM CITRATE AND HYDROCHLORIC ACID GIVEN AT THE SAME TIME FOR THE ANEMIA

creased correspondingly, mainly at the expense of urinary phosphorus.

In view of the presence of anemia, ferric ammonium citrate, 6 grams daily, was given during Periods 34 to 41. The anemia did not respond to the iron therapy; both calcium and phosphorus balances were adversely affected by it. The absorption of phosphorus seemed to be particularly impeded by the presence of large amounts of iron in the intestinal tract, probably on account of the formation of insoluble ferric phosphate. Since the absorption of phosphorus was impaired, the calcium balance would decrease mainly on account of a shortage of phosphorus for simultaneous deposition in the bone; hence the undeposited calcium was eliminated in the urine. The discontinuation of iron administration in Period 42 was followed by improved balances both in calcium and in phosphorus, and by decreasing amounts of calcium and increasing amounts of phosphorus in the urine.

The last 4 periods prior to delivery, however, were associated with poorer retention of both calcium and phosphorus. The explanation was not clear, although the discontinuation of hydrochloric acid administration, which had been given during Periods 39 to 45, might conceivably have removed a factor that promoted absorption. An alternative would be that with prolonged high calcium intake the skeletal store was gradually being replenished, rendering mineral retention less urgent. In support of this supposition, there seemed to be a slight general trend toward decreasing retention throughout the periods of high calcium intake.

Both serum calcium and inorganic phosphorus were within lower limits of normal at the commencement of the observations. Serum calcium varied but slightly except for a tendency to decrease during periods of low calcium intake, and a tendency to increase after vitamin D addition and after iron therapy. Serum inorganic phosphorus fluctuated more widely. In general, it varied directly with the phosphorus intake. While the latter was maintained on a constantly high intake, vitamin D administration was associated with a definite rise and iron therapy with a distinct lowering of serum phosphorus.

There are several points of interest in this patient with advanced osteomalacia. First, while vitamin D was operative a minimal intake of calcium was associated with an even balance, and a high intake with a retention of 40 to 50 per cent. Second, as observations proceeded, there was a tendency to a decreasing retention. This was considered to be related to a gradual replenishment of the skeletal store rather than to any interference attributable to later stages of pregnancy. Finally, the adverse effects of iron on calcium and phosphorus balances deserve attention. While both calcium and phosphorus retention may be reduced under iron therapy, serum phosphorus may fall with a rise in serum calcium. This phenomenon has been utilized in the treatment of hypocalcemia and hyperphosphatemia associated with chronic advanced renal insufficiency (13).

Comment. The three patients in this group, though they were alike in showing marked skeletal decalcification, deformity and fractures, again varied in their metabolic behavior on admission on account of the varying store of vitamin D acquired prior to the studies. Thus Cases 8 and 9 were deficient in vitamin D, while Case 10 exhibited evidence of a considerable store when the studies were begun. Cases 8 and 10, under adequate Vigantol therapy and high calcium and phosphorus intake, consistently showed a retention of calcium and phosphorus considerably over and above the requirements of pregnancy, proving that in osteomalacia it is possible for the patients under such a regimen to gain sufficient minerals for the skeletal reparation as well. The mineral retention in Case 9 was not as much as expected, probably due to the inefficient manner of administering vitamin D. When large amounts of calcium and phosphorus are required for the growth of the fetus as well as for the replenishment of the depleted skeleton of the mother, as in Case 8, serum calcium and phosphorus may fail to rise to perfectly normal levels in spite of adequate vitamin D and high mineral intake.

The behavior that may be said to characterize this group of patients with extensive bone involvement consists of more marked metabolic evidence of vitamin D deficiency when untreated, unusually high retention of calcium and phosphorus under high mineral and vitamin D intake, and ocasional failure of the serum calcium and phosphorus to rise to normal in spite of such therapy.

DISCUSSION

Quantitative measurements of calcium and phosphorus metabolism in osteomalacia during pregnancy of the type here presented are not available in the literature except for the two cases which have been briefly reported by us (14). Such data are important in evaluating the rôle of pregnancy in the pathogenesis of osteomalacia in view of the frequent association of the two. A comparison of the metabolic behavior during pregnancy of patients with severe or mild osteomalacia with that of subjects showing no skeletal lesions reveals no essential differences. With adequate vitamin D supply and moderately high intake of calcium and phosphorus, subjects of various skeletal condition have no difficulty in retaining sufficient amounts of the minerals for the needs of gestation. In fact, under similar regimen, osteomalacic patients tend to retain more calcium and phosphorus in an attempt to replenish the depleted maternal store, as well as to provide for fetal growth. In other words, there is no inherent inability on the part of osteomalacic patients during pregnancy to utilize calcium and phosphorus in the midst of plenty of these minerals and vitamin D. Whatever metabolic defect they may show during gestation results from limited vitamin D and mineral supply just as it does during reproductive rest.

Furthermore, in contrast to lactation, where the physiological activity is such that mineral requirement has to be increased much above what is secreted in the milk, even in the presence of adequate vitamin D, there is no such factor in pregnancy. Cases 9 and 10 were subsequently observed during lactation and reported on as Cases 1a and 4a in paper IX of this series (2). In both instances, the mineral balances were much less favorable during lactation than during pregnancy under similar conditions of adequate vitamin D and high calcium intake. Moreover, in Case 5, where the termination of pregnancy was not followed by lactation, mineral retention did not improve after delivery, again showing that pregnancy itself has no excessively deleterious influence on mineral retention.

However, the minimal requirement for fetal growth of 200 mgm. calcium and 100 mgm. phosphorus per day during the last three months of gestation has to be met through the maternal mineral resources. The usual level of calcuim intake in Chinese dietary is approximately 0.337 gram and that of phosphorus 1.2 grams (15), although somewhat higher levels of intake have been recorded by others. Such a level of calcium intake, in the presence of vitamin D, may maintain an individual in balance under ordinary circumstances, but in pregnancy it cannot be expected to yield adequate mineral balance for the fetal requirement. The extent of drain on the skeletal store of the mother will depend upon her state of vitamin D nutrition. If there is adequate vitamin D supply—sometimes from the diet, but usually from sunlight (16)—a variable proportion of the total fetal requirement (21 to 23 grams of calcium) may have to be drawn from the maternal store. This alone may not constitute a serious loss to the mother. On the other hand, in the absence of vitamin D, the mineral loss will be much greater than that imparted to the fetus. Under such circumstances, pregnancy plays an important rôle in the causation of osteomalacia. Moreover, pregnancy is usually followed by prolonged lactation, which constitutes a much greater drain upon the maternal skeletal store. Such a reproductive cycle frequently repeated under an inadequate supply of calcium and vitamin D will inevitably lead to the development of osteomalacia.

As to the actual level of calcium that may be considered adequate to meet the needs of gestation, our data do not give a clear-cut answer. In the first subject who was presumably normal from the standpoint of vitamin D nutrition, an intake of 1 gram of calcium was necessary to bring about sufficient retention for the fetal needs. In individuals (Cases 2, 3 and 6) in whom the vitamin D supply was limited, or beginning to be depleted, an intake of 1.0 to 1.3 grams of calcium seemed also adequate for the gestatory requirement. There was evidence that, in the presence of greater supply of vitamin D, they could acquire the same degree of retention on an intake level considerably lower than 1.3 grams (Case 3). However, in severe grades of vitamin D depletion, an intake of 1.3 grams, or higher, of calcium would not maintain the individual in balance (Case 4). These data all go to show that vitamin D is a more important factor than the actual level of

calcium intake in determining the extent of renten-tion, provided a reasonable amount of calcium is present in the diet. As to phosphorus, its utili-zation depends a great deal on that of calcium. As Chinese dietaries contain good amounts of phosphorus, adequate calcium retention usually means adequate phosphorus retention. Likewise, there is apparently no difficulty in nitrogen metab-olism with usual Chinese dietaries.

A comparison of the data of these subjects showing varying skeletal condition and vitamin D store with those of presumably normal women in pregnancy available in the literature shows greater degree of mineral conservation in our patients. Toverud and Toverud (17) made short periods of observation on thirty Norwegian women living in a home for expectant mothers during the last two to three months of pregnancy. Negative cal-cium and phosphorus balances were the rule on the usual home diets, but positive balances were sometimes observed after the intake of calcium and phosphorus had been increased to 1.6 to 2.0 grams. Coons et al. (5) reported the results on 2 groups of women, one in Chicago, the other in Oklahoma. With an average intake of 1.4 grams calcium and 1.6 grams phosphorus, adequate re-tention for gestatory needs occurred in the South-ern women, but not in the Chicago women, the difference being attributed to the influence of sun-shine. Macy and Hunscher (4), from a com-pilation of data in the literature on mineral utili-zation during pregnancy, concluded that during the last three months an intake of 1.4 to 1.5 grams of calcium and 2 grams of phosphorus was neces-sary to secure adequate retention for the demands of pregnancy. On the other hand, in our subjects 1.0 to 1.3 grams of calcium seemed adequate for the requirements of pregnancy, even when the supply of vitamin D was limited. With optimum vitamin D nutrition calcium requirement may be lowered.

This relative conservatism shown by our pa-tients cannot be entirely due to the depleted skele-tal store which would cause calcium to be re-tained with great avidity because the patients in the first group without obvious osseous decalci-fication exhibited the same phenomenon. Another important factor seems to lie in the previous level of intake. When the dietary habits accustom the subject to a lower intake, the added requirement

for reproductive activity will be correspondingly lower. Furthermore, vitamin D plays such an im-portant rôle in conserving calcium that its judicious use will make it possible to decrease the usually quoted requirement for a given state of physio-logical activity. The combination of previous low level of intake and existing vitamin D action probably explains the unusual ability on the part of five of the ten subjects in this series to retain calcium on intakes varying from 88 to 277 mgm. per day (Cases 3, 4, 6, 7 and 10). It is plain, then, that the so-called calcium requirement, con-trary to current conception, must be regarded as a variable quantity conditioned by such factors as the prior skeletal store, the previous dietary cus-tom, and the state of vitamin D nutrition.

SUMMARY

Data on calcium, phosphorus and nitrogen me-tabolism during the latter part of pregnancy were obtained on ten subjects showing various states of skeletal store and vitamin D nutrition. Given an adequate supply of vitamin D and calcium, pa-tients with osteomalacia showed no inherent in-ability to retain minerals during pregnancy, com-pared with those with no skeletal depletion. The added requirement during gestation, unlike that in lactation, did not seem to go beyond fetal needs. However, such needs had to be filled at the ex-pense of the maternal tissue, if the supply of vita-min D and minerals was inadequate. Under such circumstances, pregnancy plays an important pathogenetic rôle in osteomalacia inasmuch as it hastens the skeletal demineralization. While high calcium intake tends to ameliorate the effects of vitamin D deficiency, the latter conserves calcium. Of the two, vitamin D is probably more impor-tant, provided a reasonable level of calcium intake is available. The calcium requirement during pregnancy is conditioned by the prior skeletal store, the previous dietary intake, and the state of vitamin D nutrition.

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