CALCIUM AND PHOSPHORUS METABOLISM IN OSTEOMALACIA.

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Osteomalacia is very prevalent throughout the northern and western parts of China. Maxwell (13) has found it is endemic in the northern three-quarters of the province of Shansi, the northern half of Shensi, the middle portion of Kansu, and the whole of Manchuria. There is a small focus of the disease in Hunan. Recently, Dr. Maxwell has had reports that Canton province and the northern part of Honan are also affected. Sporadic cases occur throughout north China but the incidence in the areas mentioned is especially heavy, variously estimated at from 1 to 5 per cent of all females over the age of puberty. Wampler (25) has made an intensive survey of the region surrounding P'ing Ting Chow in Shansi and reports that 1 adult woman out of 45 is afflicted in the cities while 1 in 173 is afflicted in the small villages. The Chinese themselves say that the incidence is much higher than these figures indicate, claiming that the incidence may be as high as 10 per cent. Wampler has had for observation and treatment in the Church of the Brethren Hospital in P'ing Ting Chow over 50 cases in the last 2 years.

P'ing Ting Chow was selected for a special study of the calcium and phosphorus metabolism of these patients. Beds in the women's ward of the Church of the Brethren Hospital were reserved, a large room was provided for a laboratory, special nurses, and a special kitchen and cook were provided so that the work could be conveniently and accurately carried on. Laboratory supplies, chemicals, and apparatus were taken to the hospital from the Peking Union Medical College in Peking.

One of us (Miles) studied the blood chemistry of 10 patients throughout the month of May in 1923 and made an attempt to determine the calcium and phosphorus balance. Difficulties led to the abandonment of the latter work.

In order to determine the calcium and phosphorus of the blood under the ordinary conditions it has been our purpose to place the patients on an approximate home diet, which in the case of these people is meager, consisting entirely of cereals and a limited amount of vegetables, with no milk, meat, or eggs. The principal article of diet is millet eaten at least once a day in the form of a thin gruel made of the whole seeds, which have been partially hulled, boiled in water to which may

be added a few chopped pieces of onion or garlic, or some other vegetable. A small quantity of "salt vegetable," usually a variety of turnip or radish which has been preserved in salt brine, is eaten with the millet gruel. Another vegetable eaten in the same way is prepared by placing the green leaves of bean plants in brine, thus making a sort of sauerkraut of the bean leaves from which comes the entire salt of the diet. Only about 10 to 15 gm. of this salt vegetable are consumed at a meal. Millet is also prepared by "dry steaming" the seeds.

Wheat flour products are eaten once a day by those who can afford them. Steamed bread is made of wheat flour; or the dough is rolled thin and baked in unleavened cakes; or wheat flour is eaten in the form of noodles with usually a certain proportion (about 25 per cent) of flour made from green soy beans. There are a few vegetables in the regular dietary. The so called Chinese celery-cabbage, pai ts'ai, is eaten in large quantities throughout north China, but pai ts'ai is not cultivated extensively in the region affected by osteomalacia, and poor women obtain little of it. Only the bleached inner leaves are eaten, boiled or fried. Onions, garlic, and another variety of salt vegetable prepared from the leaves and stalks of the mustard plant are used extensively. Small quantities of bean curd are eaten by those who can afford it.

Preliminary Observations.

Ten patients with osteomalacia were placed on a breakfast consisting of millet gruel, two steamed wheat flour bread rolls, and about 10 gm. of salt turnip; a dinner of wheat and bean flour noodles with pai ts'ai and garlic; and supper of dry steamed millet. This diet was not varied until therapeutic measures were instituted at the second stage of the experiment. This diet is not exactly similar to the home diet in two important respects, in the first place three meals were served in

TABLE I.

Patient No.	Blood calcium per 100 cc. serum.	Blood phosphorus per 100 cc. plasma.	CO_2-combining power of plasma reduced to 0°C. and 760 mm. pressure.
	mg.	*mg.*	
1	5.2	2.5	51.3
2	6.0	1.9	57.0
3	7.4	1.8	47.5
4	5.6	2.3	54.1
5	5.8	3.0	51.3
6	7.0	3.8	54.1
7	5.8	3.4	52.2
8	7.0	2.4	49.4
9	5.0	2.0	54.0
10	5.4	3.2	56.0

the hospital to these patients as to all others while at home the patients ate only twice a day, and often in far more restricted amount.

At the end of the 1st week on the diet the blood was analyzed for calcium and phosphorus and the carbon dioxide-combining power of the plasma was ascertained. The blood calcium was determined by the Kramer-Howland (9) method; the phosphorus, by the Briggs (1) modification of the Bell-Doisy method; and the CO_2-combining power, by the Van Slyke (24) method. The results are presented in Table I.

It will be seen that the calcium content of the serum was in some cases less than half the quantity considered as normal and in the highest determination only about three-quarters of the normal.

The phosphorus in the blood varied greatly, some of the patients showing a marked deficiency while others had a content within normal limits. Maxwell (13) quotes a theory of Read that the diet of osteomalacia patients, being rich in an acid-producing ash, might cause changes in the acid-base equilibrium of the body fluids with result in an acidosis and removal of the lime from the bones. The results of the determination of the carbon dioxide-combining power of the plasma do not indicate an acidosis.

The variations from normal in blood calcium and phosphorus seemed to depend directly on the severity of the disease and its duration. Salient points in the histories of these patients together with their pelvic measurements are presented in Table II. It will be seen that in the three patients, Nos. 3, 6, and 8, having the disease for 1 year or less, the calcium and phosphorus contents of the blood were more nearly normal than in any of the others, and further that the degree of pelvic deformity was not so great. While most of the patients had symptoms first during lactation, two of them had never been pregnant, in one the symptoms coming on after the menopause; while another had had two early abortions before the fetus could have caused a severe calcium drain; and in yet another the disease began at the onset of the menstrual function. The menstrual flow in these patients was uniformly scanty and the cycle irregular. It would seem, therefore, that the drain on calcium incident to pregnancy and lactation is not an absolutely essential factor in producing the disease. Nor does it appear that the functioning of the ovaries or the menstrual activities play a major causative rôle since in all of these pa-

tients the ovarian function was faulty as evidenced by scanty menstruation and irregularities in the menstrual cycle.

After completion of the blood analyses on the standard diet the patients were treated as follows, without variation in the diet save as noted below:

Patients 1 and 4 received 30 cc. cod liver oil and 2 gm. calcium lactate per day; Patients 2 and 3 had 3 gm. calcium phosphate per day;

TABLE II.

Patient No.	Age.	Duration of disease.	No. of pregnancies.	Relation of onset of disease to pregnancy.	Tetany.	Pelvic measurements.				
						Interspinous.	Intercristal.	External conjugate.	Interischial.	Intertrochanteric.
	yrs.					*cm.*	*cm.*	*cm.*	*cm.*	*cm.*
1	23	5 yrs.	None.	None.	No.	24	26	18.5	2.5	25
2	57	10 "	"	"	Yes.	22	25.5	18	3.0	23.0
3	30	8 mos.	2	During last lactation.	"	22	24	17	7.0	25.5
4	34	20 yrs.	5	Began before first pregnancy at onset of menstruation.	"	20	23	21	3.0	22.0
5	32	12 "	2	After first delivery.	No.	20	25	17	2.0	24
6	35	1 yr.	5	During last lactation.	Yes.	22.5	26.5	20.5	6.0	30
7	25	7 yrs.	3	" first "	No.	21	25.5	19	2.0	22
8	19	1 yr.	1	" lactation. Pregnant 3 mos. on admission; marked exacerbation of all symptoms. Aborted in hospital.	Yes.	19	23	19	9	29
9	37	9 yrs.	2 abortions.	None.	"	21	27	19.5	3	29
10	24	6 "	3	During first lactation.	"	—	—	—	—	—

Patient 5 had 2 gm. calcium lactate per day; Patients 6 and 8 were placed on a liberal diet including milk, eggs, and plenty of fresh vegetables; Patients 9 and 10 had 30 cc. cod liver oil per day. Patient 7 left the hospital at the end of the first period. After 12 days of the treatment the blood was again analyzed for calcium and phosphorus. The results are presented in Table III.

It will be seen that the four patients, Nos. 1, 4, 9, and 10, to whom was given cod liver oil, either alone or with calcium salts added, all show a net gain in blood calcium as compared with the first findings. Those receiving calcium salts with no oil also showed in two cases an increase in the blood calcium with no alteration in the third. The two patients on liberal diet showed by contrast a decrease in blood calcium. The variations in the phosphorus content of the blood were without regularity.

The four women treated with cod liver oil alone, or combined with calcium lactate felt much improved and said that their pains were less. We observed that they moved about the ward and took more interest

TABLE III.

Patient No.	Blood calcium per 100 cc. serum.	Blood phosphorus per 100 cc. plasma.
	mg.	*mg.*
1	6.0	2.61
2	5.8	2.9
3	8.7	1.0
4	6.21	3.5
5	7.7	2.3
6	4.6	4.1
8	6.6	3.57
9	6.6	2.95
10	7.57	1.95

in life than formerly. Patient 2 who had received only calcium phosphate was decidedly worse, complaining more of pain, and could hardly move. Patients 6 and 8 who had been on liberal diet were both clinically worse than at the beginning of the experiment. As these women were both suffering from an early acute attack of the disease the finding is not strange especially in the case of Patient 8 who had a spontaneous abortion of a 3 months fetus and did not take her diet well afterwards.

While this first experiment gave suggestive results as to treatment of the disease, we felt that we would not be satisfied until the work was repeated and a complete metabolism experiment carried out. We returned to P'ing Ting Chow for the purpose in March of 1924. In the interim Dr. Wampler had been pushing a campaign of treatment

along the lines indicated, with such successful results that most of the women knew they could obtain medicine for relief of their pain, and were loth to be experimented upon. Finally, Dr. Wampler subsidized four women to enter the hospital and to stay there until such time as we were satisfied with our results. The same arrangements were made for their accomodation as in 1923. They were kept in a well ventilated ward but not exposed to direct sunlight throughout the experiments.

Final Observations. Control Period.

Patient 1.—Li Liu Shih, aged 37 years, married at 19 years, and has had osteomalacia 12 years. The onset of symptoms was in the later months of her first pregnancy and the symptoms became much worse during the puerperium. Menstruation began at the age of 15 and has been quite regular, the cycle being 28 days with a moderate flow of 3 to 4 days. She has had six pregnancies from which two children are living, the oldest now 12 years of age while the youngest was delivered by Caesarean section 3 years ago. Two other pregnancies terminated prematurely, and of the other two one child lived 6 days and the other was born dead.

She has had no other severe illnesses, her personal habits are good, her diet is the usual one for this region and she does no work but a little hand sewing. Her feet are bound. Her mother was also afflicted with osteomalacia but no other members of the family have had the disease and no one in her husband's family.

Physical Examination.—Height 127.5 cm.; sitting height 68 cm.; leg length 75 cm.; weight 34.8 kilos. The head is normal except for some teeth that are loose but without caries. The lymph glands in the posterior triangle of the neck, the epitrochlear, and inguinal region are all enlarged and hard. The skin on the back and the anterior surfaces of both tibiæ has many pigmented scars.

The dorsal spine has a marked curve which is uniform without any sharp angles and the sternum has a pronounced anterior convexity, the head and neck have sunken between the shoulders, the chest is greatly increased in anteroposterior diameter and the ribs are flattened at the sides with a marked groove and thickening at the costochondral junction. The thoracic and abdominal organs are normal.

The patellar reflex is exaggerated, patellar and ankle clonus are easily elicited, the biceps tendon reflex and the forearm reflexes are lively. Signs of tetany are not present.

Pelvic Measurements.—Interspinous 19.5 cm.; intercristal 24 cm.; intertrochanteric 23 cm.; external conjugate 17.5 cm.; interischial 2.5 cm.

Laboratory Findings.—The urine is normal. The blood count shows red blood corpuscles 3,200,000; white blood corpuscles 9,100. The Wassermann reaction is 4 +.

Diagnosis.—Osteomalacia and syphilis.

Patient 2.—Sun He Shih, age 29 years, married at 17 years of age; has had osteomalacia for 6 years. She has had only one pregnancy, 6 years ago. The child lived 1 year. Her symptoms began in the puerperium. Symptoms are worse in winter and milder in summer. Menstruation began at 16 years of age, and has always been irregular and scanty. She may have an interval of several months without a period.

There has been no other sickness, her habits are regular, and her diet is the usual one. Her feet are bound. No other members of her family have been afflicted.

She denied tetany but during her stay in the hospital had a typical attack.

Physical Examination.—Height 125.5 cm.; sitting height 68.5 cm.; leg length 71 cm.; weight 31.1 kilos. The head is negative except for looseness of the teeth, which do not show caries. The lymph glands are not enlarged. The back is bowed forward but the compensatory lordosis is not marked. The sternum is convex anteriorly but not marked. The chest is flattened laterally but the costochondral junction is not thickened externally. Thoracic and abdominal organs are normal. The patellar, biceps, and forearm reflexes are lively, no clonus could be elicited. Signs of tetany were absent. (Owing to other pressing work this patient was not examined until after the conclusion of the therapeutic experiment.)

Pelvic Measurement.—Interspinous 18 cm.; intercristal 21.5 cm.; intertrochanteric 24 cm.; interischial 5 cm.; external conjugate 17 cm.

Laboratory Findings.—The urine is normal. The blood count shows red blood corpuscles 2,400,000; white blood corpuscles 7,300. Wassermann negative.

Patient 3.—Jen Li Shih, age 37 years, married at 16 years of age, has had osteomalacia for 15 years. She had had five pregnancies. The oldest two children are living, aged 15 and 12 years, while the other three children were still-born. The onset of her disease was in the later months of her first pregnancy with pain in her back and hips, which became much worse during the puerperium. The symptoms are worse in winter. She has also had attacks of tetany.

Two of the patient's sisters also have the disease but no other members of family are afflicted. Menstruation began at 15 years of age, and has always been irregular with frequently a 2 to 3 months interval. The flow is scanty and lasts only 2 days.

Physical Examination.—Height 132.5 cm.; sitting height 71 cm.; leg length 73 cm.; weight 42.8 kilos. The head is normal and the regional lymph glands are not enlarged; the vertebral column is bowed forward but to a lesser degree than most patients present. The sternum is convex anteriorly, the chest flattened laterally, and the costochondral junctions are thickened. The thoracic and abdominal organs are normal. Reflexes are exaggerated but no clonus is elicited. Signs of tetany are absent.

Pelvic Measurements.—Interspinous 22 cm.; intercristal 25 cm.; intertrochanteric 24 cm.; interischial 2 cm.; external conjugate 20 cm.

Laboratory Findings.—The urine is normal. The blood count shows red blood corpuscles 4,000,000; white blood corpuscles 11,000. Wassermann negative.

Patient 4.—Ch'en Fa Shih, age 49 years, married at 16 years of age, has had the disease for eight years. She has never been pregnant. Her symptoms are worse in winter. She has never had tetany. Menstruation began at 16 years, always irregular. The menopause came 1 year ago, and there has been no improvement since. One sister died of osteomalacia; no other members of family afflicted.

Physical Examination.—Height 126 cm.; sitting height 63 cm.; leg length 76 cm.; weight 30.5 kilos. The head is negative except for pyorrhea. There are no enlarged glands. The back is very much bowed and the head is sunken between the shoulders. The sternum is markedly convex anteriorly and the chest is flattened laterally. The costochondral junctions are thickened. Her feet are bound. Reflexes are exaggerated but there are no signs of tetany.

Pelvic Measurements.—Interspinous 22 cm.; intercristal 24 cm.; intertrochanteric 23 cm.; interischial 2 cm. (practically in apposition); external conjugate 15 cm.

Laboratory Findings.—The urine is normal. The blood count shows red blood corpuscles 3,400,000; white blood corpuscles 10,000. Wassermann negative.

It will be noticed that three of the four cases give a definite history of the onset of the disease during the first pregnancy or the puerperium, while the fourth patient had never been pregnant. The symptoms may have begun during pregnancy but were all exaggerated in the puerperium, owing undoubtedly to the custom of placing parturient women on a diet limited to thin millet gruel, the patient consuming not over 4 ounces of millet per day for 30 to 50 days. The menstrual cycle in all was irregular and the flow scanty. All have more or less constant pain but the condition is alleviated in summer. Two of the four have had tetany. By the physical measurements it will be seen that the deformity is greatest in the bones of the trunk, the pelvis, the vertebral column, the sternum, and the ribs. The normal relation of the length of the sitting height to the leg length is reversed. The deformity of the chest is marked and resembles that of rickets in that the sternum is convex anteriorly and the chest is flattened laterally so that the anteroposterior diameter is greater than the transverse. In two instances the costochondral junctions are thick and present a "rosary."

The Diet.—Chinese diet and Chinese women do not adapt themselves well to metabolism experiments. After a week's effort, a diet was selected which satisfied the patients and the exact amount each could and would eat per meal was determined. This having been accomplished the patients cooperated well to the end of the experiment.

The diet consisted of preparations of wheat and green soy bean flour, millet, pai ts'ai, garlic, salt vegetable, and salt mustard leaves.

Allowing for individual differences in quantities eaten per day, which was determined beforehand, the average daily ration of each patient was as follows:

Breakfast: 133 gm. of wheat flour in the form of steamed bread; 50 gm. of millet in gruel; 10 gm. of salt turnip.

TABLE IV.

	Wheat flour.	Millet.	Bean flour.	Garlic.	Pai ts'ai.	Mustard.	Salt vegetable.
Calcium, *per cent*.....	0.07415	0.07664	0.10705	0.042	0.03525	0.1896	0.1214
Phosphorus, *per cent*.....	0.3295	0.3349	0.3828	0.02024	0.0431	0.0386	0.060

Dinner: 150 gm. of wheat flour made into a thick dough, rolled thin, and baked; 170 gm. of pai ts'ai, and 8 gm. of garlic boiled together.

Supper: 100 gm. of wheat flour and 30 gm. of green soy bean flour rolled into noodles and boiled; 40 gm. of mustard leaves and stalks, and 8 gm. of garlic boiled together.

Numerous samples of these foods were dried in a water bath drier and taken to Peking for analysis. The average percentages of calcium and phosphorus contained in the foods are shown in Table IV.

Analysis of the calcium was performed by the gravimetric method of McCrudden (12) and the phosphorus determinations were done by the standard ammonium molybdate-magnesia mixture method. All analyses were in quadruplicate.

The diet and the quantities of each article of food together with the total quantity of both calcium and phosphorus contained in the total food consumed by each

TABLE V.

Patient No.	Wheat flour.	Millet.	Bean flour.	Pai ts'ai.	Garlic.	Mustard leaves	Salt turnip.	Total calcium.	Total phosphorus.
	gm.	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*
1	2,681	350	210	1,190	110	280	70	3.5630	11.4857
2	2,331	350	140	1,190	110	280	70	3.2285	10.0657
3	2,681	350	210	1,190	110	280	70	3.5630	11.4857
4	2,331	350	140	1,190	110	280	70	3.2285	10.0657

patient for 7 days are shown in grams in Table V. The diet is adequate from the caloric standpoint, yielding as it does over 2,000 calories per day.

The food was prepared under our personal supervision, each person's food being prepared separately. Distilled water was used to prepare and cook the food and to make the tea provided.

Shohl and Sato (20) estimate that the calcium requirement of the average person per kilo of weight per day is 0.0153 gm. in order to remain in a state of calcium balance. Ehrström (3) considers that the minimum of phosphorus pentoxide required by an individual is 0.06 gm. of P_2O_5 per kilo per day, or 0.0261 gm. of phosphorus per kilo per day. Table VI presents the actual daily consumption of calcium and phosphorus in grams and also the quantities of both as calculated from the above figures, which are required by the patients per day, judging from their weights. The diet as given, though

TABLE VI.

Patient No.	Intake of calcium per day.	Daily required calcium.	Daily diet balance calcium.	Intake of phosphorus per day	Daily required phosphorus.	Daily diet balance phosphorus.
	gm.	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*
1	0.5090	0.53244	−0.0234	1.6408	0.9282	+0.7126
2	0.4612	0.4758	−0.0146	1.4365	0.8117	+0.6248
3	0.5090	0.6548	−0.1458	1.6408	1.1170	+0.5238
4	0.4612	0.4666	−0.0054	1.4365	0.7960	+0.6405

TABLE VII.

Patient No.	Total calcium in urine, 7 days.	Total phosphorus in urine, 7 days.
	gm.	*gm.*
1	1.6351	2.8598
2	0.2634	1.9879
3	0.3467	3.2646
4	0.6606	2.7657

TABLE VIII.

Patient No.	Total calcium in feces, 7 days.	Total phosphorus in feces, 7 days.
	gm.	*gm.*
1	2.4213	5.7847
2	3.0145	4.4503
3	2.7761	5.7758
4	3.4104	5.7543

undoubtedly more liberal than the home diet is still deficient in calcium, though adequate in phosphorus.

Metabolic Observations.—The urine of 7 days was collected in bottles and analyzed in 24 hour samples for calcium and phosphorus. McCrudden's (12) titration method was used for the calcium with one slight modification. When the precipitate of calcium oxalate was collected on the filter and washed according to his method, instead of punching the filter and washing the precipitate into a flask and then adding 10 cc. of concentrated H_2SO_4 we added directly to the filter without perforating it 50 cc. of solution containing 10 cc. H_2SO_4 dissolving the precipitate on the filter, then perforating the filter paper, washing thoroughly,

and titrating out. Phosphorus was determined by the Briggs (1) method. All was done in duplicate.

The feces of the 7 days were dried and taken to Peking where they were ground in a mortar, and thoroughly mixed. Samples were ashed, the calcium determined by McCrudden's (12) gravimetric method and the phosphorus by the standard gravimetric method in which ammonium molybdate is used, and the final precipitation effected with magnesia mixture. Table VII gives the total quantities of urinary calcium and phosphorus in grams for the week, and Table VIII gives similar data for the feces. Table IX shows the relation of intake to output of both calcium and phosphorus.

TABLE IX.

	Calcium.			Phosphorus.		
Patient No.	Intake.	Excretion.	Balance, 7 days.	Intake.	Excretion.	Balance, 7 days.
	gm.	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*
1	3.5630	4.0564	−0.4934	11.4857	8.6445	+2.8412
2	3.2285	3.2779	−0.0494	10.0657	6.4382	+3.6275
3	3.5630	3.1228	+0.4402	11.4857	9.0404	+2.4453
4	3.2285	4.0710	−0.8425	10.0657	8.5200	+1.5457

TABLE X.

Patient No.	Calcium per 100 cc. serum.	Phosphorus per 100 cc. plasma.
	mg.	*mg.*
1	7.503	1.83
2	6.395	1.24
3	6.175	2.42
4	5.810	1.55

In Table X are presented the calcium content of the blood serum and phosphorus content of the blood plasma as determined at the end of the 1st week. Calcium was determined in this and the subsequent experiment by the Tisdall (21) modification of the Kramer-Tisdall method, and phosphorus by the Briggs (1) method.

DISCUSSION.

Three of the four patients had a negative calcium balance and all had a positive phosphorus balance. These results are in accord with the previous findings. The figures of various authors will be found in Table XVI. There are two possible explanations for the negative calcium balance, one that it is the expression of the calcium deficiency

in the diet, the other that the diet lacks some element which serves as an activator in the retention of calcium.

Park (17) deduces from numerous experiments that the antirachitic vitamine is not that ordinarily designated as A but another element X closely related to A and found in the same substances, such as cod liver oil and animal fats, but not oxidized like A. Mellanby (14) has shown that animals fed on a cereal diet develop rickets although the diet contains an abundance of food elements in good proportion, with the sole exception of the fat-soluble vitamine. His experiments point to a toxic action of the cereals—the degree of toxicity varying directly with the quantity of cereals ingested. The toxic action is supposedly overcome by adding fat-soluble vitamine to the diet. Since the patients with whom we are concerned had lived almost exclusively on a cereal diet their failure to utilize calcium might be due to such a toxic influence. The positive phosphorus balance in spite of a low blood content may be accounted for on the assumption that, with rest in a good bed, improved hygienic conditions, a diet more liberal in quantity than that to which they were accustomed, and freedom from worry, the patients had taken on flesh. Von Noorden (23) says that with increase in weight the "flesh" takes up phosphorus in a certain proportion and phosphorus is retained. Unfortunately the patients were weighed only once during the experiment.

Patient 3 whose calcium intake deficiency was most marked of all was, nevertheless, in a state of positive calcium balance. She was an old patient of the hospital and had received two courses of treatment with cod liver oil and calcium phosphate, the last of which was in the fall of 1923, about 4 or 5 months before this experiment was begun. She was so much improved that she asked to come into the hospital on the metabolism squad. She was the most active physically of the four patients. Tso (22) has observed in rickets that, even after a short course of treatment by cod liver oil, the x-ray shows bone development to go on for as much as 2 or more months after cod liver oil has been discontinued. There may have been a similar happening in this patient.

The calcium and phosphorus in the blood of all the patients were below the normal limits. Other investigators have given various figures. According to Korenchevsky (8), Marquis found 12 mg. of

calcium; and Capellani (1909) 44.9 mg; Aschenheim, 15.9 mg. Adler (1912) alone found a nearly normal calcium content in the blood of an osteomalacia patient— 9.8 mg. CaO. Scott (19) investigating osteomalacia in India reports a blood calcium higher than in patients with other diseases. In her experiments the Wright method was used. In the Peking Union Medical College Hospital the blood of many patients not rachitic or osteomalacic has been studied and the calcium and phosphorus found to correspond to the standards for Europeans and Americans. It is more than likely that investigators using the latest methods will find that the blood calcium content in osteomalacia is low. The duration of the disease seems to be without any marked influence. In our first series of ten cases there was a diminished calcium content in all and three of these were early cases.

Final Observations. Period of Treatment.

The patients were continued on the basal diet and to Patient 1 cod liver oil in doses of 8 cc. three times a day was given; Patient 2 received the same quantity of the oil and in addition 1 gm. of calcium lactate per day; Patient 3 received the oil and 1 gm. of calcium phosphate per day; Patient 4 received 8 cc. of olive oil three times a day and 1 gm. of calcium lactate per day.

The patients were kept on this régime for 12 days, and the feces and urine were collected on the last 7 days of the period.

The calcium salts were analyzed and in Table XI the actual amount of calcium and phosphorus thus administered in the week are added to the calcium and phosphorus taken in the food.

Patient 1 was still on a diet deficient in calcium as in the first experiment, while all the others had calcium added to the diet to provide more than a bare sufficiency. The urine and feces were examined as during the control period. In Table XII are shown the total calcium and phosphorus excreted for the 7 days urine; and Table XIII presents the figures for the feces. Table XIV shows the relation of the calcium and phosphorus intake to excretion and the balance of the two for the period.

The blood calcium and phosphorus are given in Table XV.

TABLE XI.

Patient No.	Total calcium ingested, 7 days.	Total phosphorus ingested, 7 days.
	gm.	*gm.*
1	3.5811	11.4983
2	4.4083	10.0783
3	5.4881	12.3195
4	4.4083	10.0783

TABLE XII.

Patient No.	Total calcium in urine, 7 days.	Total phosphorus in urine, 7 days.
	gm.	*gm.*
1	1.4034	2.8440
2	0.8276	2.0445
3	0.4157	2.9627
4	0.6638	2.5875

TABLE XIII.

Patient No.	Total calcium in feces, 7 days.	Total phosphorus in feces, 7 days.
	gm.	*gm.*
1	1.9801	5.6582
2	1.9445	2.6911
3	1.7854	3.2528
4	4.2530	4.5855

TABLE XIV.

	Calcium.			Phosphorus.		
Patient No.	Intake.	Excretion.	Balance, 7 days.	Intake.	Excretion.	Balance, 7 days.
	gm.	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*
1	3.5811	3.3836	+0.1976	11.4983	8.5022	+2.9961
2	4.4083	2.7712	+1.6371	10.0783	4.7356	+5.3427
3	5.4881	2.2011	+3.2870	12.3195	6.2155	+6.1040
4	4.4083	4.9168	−0.5085	10.0783	7.1730	+2.9053

TABLE XV.

Patient No.	Calcium per 100 cc. serum.	Phosphorus per 100 cc. plasma.
	mg.	*mg.*
1	8.62	1.83
2	8.197	2.10
3	9.57	3.02
4	8.58	1.64

DISCUSSION.

For the sake of clearness the cases will be taken up in order, and the results of the two periods compared.

Patient 1.—This patient was kept on an almost identical diet throughout—one deficient in calcium. After the addition of cod liver oil the calcium balance changed from a negative to a positive one and the blood calcium rose from 7.503 to 8.62 mg. per 100 cc. of serum. The weekly calcium output in the urine was very high in both periods but in the second the output in the urine and feces was less than in the first, which will account for the change in the balance and for the increase in blood calcium. The change in the phosphorus balance was very slight and there was no alteration in the blood phosphorus.

The findings suggest that there is in the cod liver oil some element which in osteomalacia materially influences the retention of calcium in the system even in the presence of a deficiency in the food. Clinically the patient was greatly improved. On admission she would not leave the bed and sat with head supported on a pillow held in the arms, but at the end of the second period she was voluntarily leaving her bed for a chair and would walk the length of the ward, though it was slow work.

Patient 2.—When cod liver oil and calcium lactate had been added to the standard diet the calcium balance changed from slightly negative to markedly positive. The calcium in the urine increased in the second period but in the feces there occurred a decrease. The blood calcium rose from 6.395 to 8.97 mg. The phosphorus balance was more strongly positive than in the first period and the blood phosphorus increased from 1.24 to 2.10 mg. The patient was clinically much improved.

Patient 3.—After calcium phosphate and cod liver oil had been added to the diet even more marked changes occurred. The calcium balance changed from + 0.4402 to + 3.2870 gm. and the phosphorus from + 2.24453 to + 6.1040 gm. while the blood calcium and phosphorus were as profoundly affected. Calcium phosphate contains more calcium in the molecule than the lactate so the patient got a correspondingly greater amount of calcium, and phosphorus in addition. In this case again the calcium in the urine was increased and that of the feces decreased. In this and the previous case we see an even more marked effect of the cod liver oil than in Case 1.

In both cases there was now no deficiency of calcium in the diet and the patient was enabled to utilize and retain relatively large amounts of calcium. The retention of the calcium called for a corresponding retention of phosphorus which was to be seen in the increase in the balance ratio and also in the blood.

Patient 4.—This patient was given, in addition to the regular diet, 8 cc. of olive oil and 1 gm. of calcium lactate per day. The olive oil was given because we did not want this patient to feel that she was treated differently from the others; and we felt that over so short a period the olive oil would probably produce no

effect on the calcium metabolism. The calcium balance remained negative, though to a less degree in the second period than in the first. The calcium of the urine remained almost stationary, with a big increase in the amount excreted in the feces, a reversal of the condition in the others. The blood calcium was increased almost in proportion to the others. This may be taken to mean that the calcium is absorbed from the intestine and goes to increase the blood calcium but unless utilized in the tissues is returned to the digestive tract and excreted. The change in the balance of calcium and the increase in blood calcium is probably due to a temporary storage of calcium in the blood and not to metabolized calcium. The blood phosphorus remained practically stationary with a small change in the total phosphorus balance. Clinically the patient was unimproved and she complained that the other women felt like moving a little while she did not.

We see that in these patients with osteomalacia there was a deficiency of calcium in the diet. This may have had an effect in producing the disease but there was another deficiency of greater importance than the calcium, namely that of some substance which enables calcium to be utilized. This substance appears to be present in cod liver oil. Increasing the calcium in the diet of Case 4 did not improve her condition nor produce an absolute positive balance. Yet in Case1 without an increase in the calcium of the diet and only the addition of the cod liver oil there were clinical improvement, retention, and utilization of calcium. In cases 2 and 3 with the deficiencies in the diet made up by the addition of both calcium salts and cod liver oil the changes were correspondingly marked.

The salient findings of previous workers are summarized in Table XVI.

The articles of von Limbeck (10), von Korczyński (7), and Sauerbruch (18) were not available in the original. In the other reports which are at hand no account was taken of the original diet of the patients. Neumann (15, 16) does not record the weights of his patients in either series of experiments so it is impossible to determine whether or not they were receiving sufficient calcium in the diet given. In the case reported by Goldthwait *et al.* (4) the calcium intake during the first period was 0.4073 gm. per day while the amount required by the patient per day was 0.4110. There was thus a deficiency. In their second period the intake was 0.5119 and the required calcium per day, taking into account the gain in weight, was 0.4345 gm. With this sufficiency and a diet containing all the necessary food elements including the vitamines, the change in calcium balance would probably have taken place without castration. In both of the cases described by Hotz (5) the calcium intake was sufficient, the first patient's requirement being 0.4681 gm. per day and the second, 0.6579 gm. per day.

The therapeutic measures did not meet with uniform results. Neumann (16) observed in his first case a change from a negative calcium balance to a positive following castration, whereas in a second there was less calcium retained by the patient after castration than before. von Korczyński (7) gave ovarian extract tablets and noted in one case a marked loss of calcium whereas in his second case there was more calcium retained than in the control period. After phosphorus Sauerbruch (18) and Hotz (5) observed a temporary retention of calcium but

TABLE XVI.

	Observation.	Calcium.			P_2O_5		
		Intake daily.	Output daily.	Balance daily.	Intake daily.	Output daily.	Balance daily.
	days	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*
von Limbeck (10), 1894.							
Early osteomalacia.	—	0.3501	0.6575	−0.3074	—	—	—
Neumann (15), 1894.							
Early puerperal osteomalacia. Diet, milk and soup.	7	2.8160	2.2710	+0.5450	3.89	6.20	−2.31
Same case 1 mo. later, same diet.	7	2.9800	2.5251	+0.4549	4.27	2.20	+2.07
Neumann (16), 1896.							
Early puerperal osteomalacia. Diet, milk, soup, eggs, wine, rolls.	5	1.6455	1.6795	−0.0340	2.80	3.99	−1.19
Same case 3 wks. after castration.	5	1.8520	1.0267	+0.8253	3.26	2.00	+1.26
Advanced osteomalacia. Same diet as above.	4	2.9362	2.8371	+0.0991	3.50	2.80	+0.70
Same case 8 days after chloroform anesthesia lasting 44 min.	5	0.9505	0.8862	+0.0643	2.19	1.55	+0.64
Same case 5 days after castration.	5	0.5217	0.4502	+0.0715	1.25	0.94	+0.31
Advanced case in 5th mo. of tenth pregnancy. Same diet as above.	5	1.7867	1.4224	+0.3643	2.94	2.65	+0.29
Same patient 20 days after hysterooophorectomy.	5	2.0082	1.3223	+0.6859	3.57	2.90	+0.67
von Korczyński (7), 1902.							
Puerperal osteomalacia.							
Mixed diet.	5	0.9004	0.6646	+0.2358	5.88	4.61	+1.26
Vegetable diet.	5	1.0050	0.9134	+0.0916	3.63	3.27	+0.35
Mixed diet.	5	0.7146	0.7146	+0.0000	4.14	2.94	+1.20
" "	5	0.7146	0.8290	−0.1144	4.14	3.33	+0.81
Ovarian extract tablets.	4	0.7146	0.9791	−0.2645	4.14	4.01	+0.13
Nullipara.							
Mixed diet.	5	0.3796	0.5431	−0.1635	3.72	3.39	+0.33
Vegetable diet.	5	0.7146	1.0220	−0.3074	4.09	3.94	+0.15
Mixed diet.	5	0.7146	0.6718	+0.0428	4.09	3.13	+0.96
Ovarian extract tablets.	4	0.7146	0.7789	−0.0643	4.09	3.25	+0.84

TABLE XVI—*Concluded.*

	Observation.	Calcium.			P_2O_5		
		Intake daily.	Output daily.	Balance daily.	Intake daily.	Output daily.	Balance daily.
	days	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*
Sauerbruch (18), 1902.							
Vorperiode.	11	0.5574	0.6146	−0.0572	2.02	1.62	+0.39
Phosphorperiode.	10	0.5717	0.3573	+0.2144	1.53	1.27	+0.26
Nachperiode.	7	0.6146	0.7361	−0.1215	1.81	1.61	+0.20
Goldthwait, Painter, Osgood, and McCrudden (4), 1905.							
Nullipara. 16 yrs. old Mixed diet.	8	0.4073	0.5074	−0.1001	1.50	1.54	−0.04
Same patient a few months after castration. Mixed diet.	14	0.5119	0.3675	+0.1444	—	—	—
Hotz (5), 1906.							
Advanced osteomalacia. Mixed diet.							
Vorperiode.	10	1.4364	1.3935	+0.0429	3.53	3.39	+0.13
1 mg. phosphorus daily.							
Phosphorperiode.	11	1.4650	1.3150	+0.1500	3.49	3.22	+0.27
Nachperiode.	10	1.3793	1.4150	−0.0357	3.47	3.10	+0.37
0.9 gm. fresh gland daily.							
Thyreoideaperiode.	8	1.3507	1.3435	+0.0072	3.77	3.25	+0.52
Longstanding advanced osteomalacia.							
Mixed diet. *Vorperiode.*	8	0.9576	1.1363	−0.1791	2.76	2.66	+0.10
1 mg. phosphorus daily.							
Phosphorperiode.	12	1.0505	1.0291	+0.0214	2.62	2.69	−0.07
Nachperiode.	7	0.9505	0.9505	−0.0000	2.62	2.58	−0.04
0.9 gm. fresh gland daily.							
Thyreoideaperiode.	8	0.9719	1.0545	−0.0826	2.85	2.64	+0.21

in the *Nachperiode* the loss was more marked than to begin with. The administration of thyroid extract tablets was followed in one of Hotz's (5) cases by a positive calcium balance and in the other by a marked negative balance.

The results of hystero-oophorectomy in Neumann's (16) third case are interesting but not unexpected. By this operation the patient was relieved of the drain on her system of a 5 months fetus, and beside this she was evidently not in a very active stage of the disease as her calcium balance was positive before operation.

There is a marked seasonal variation in the severity of osteomalacia which was observed in all our patients, corresponding with those

observed in rickets and in so called hunger-osteomalacia (2, 6). This summer remission might be explained on the ground that then the women are more exposed to the sun's rays. However, the patients all begin to improve in the early spring months, and do not get out into the sun until later. Their primary improvement is probably due principally to more fresh green vegetables. We have shown that even when confined to the hospital without sunshine these patients do improve when given the necessary vitamine in their diet.

It would seem, then, that osteomalacia is a deficiency disease. There is a lack of calcium in the food and also in a substance which enables the calcium to be utilized. The argument that because there was no corresponding increase in pregnancy-osteomalacia in Europe at the time the hunger-osteomalacia was prevalent, the two are separate entities, is far from convincing. As everyone knows, in times of general food shortage and famine the infants and aged suffer more severely than the strong people in middle life. The patients with hunger-osteomalacia were mostly old or of secluded life. Such persons would be the first to suffer and as the food shortage lasted less than 2 years, naturally the diet deficiency did not reach the women of child-bearing age. The term hunger-osteomalacia is a misnomer.

Food deficiency is a relative term. The very poor Chinese who are compelled to work hard in the fields are not afflicted with osteomalacia to the same degree as were our patients who were mainly of the middle class. Such women do no work, and in winter sit all day on a brick bed which is slightly warmed. In consequence their appetites and digestions are poor and they eat too little. Their sisters of the laboring class have to work and by bodily activity keep an appetite for more of the same kind of food. The deficiency in calcium is made up by the larger intake as is also the vitamine content to some extent and they escape the disease.

"'Hunger-osteomalacia' has been commonly held to be a manifestation in late life of the conditions that produce rickets in infants and rachitis tarda in adolescence" (26) Park (17) states, "Increasing knowledge concerning rickets has made it necessary to broaden the view in regard to the characteristic pathology and admit to the disease all disturbances in metabolism in which lime salts cease to be deposited

in the bones and cartilage." Is not osteomalacia also a manifestation of the same diet deficiency? Our results would bear out this assumption. The blood findings are like those of rickets with tetany. Tetany and hyperexcitability of the muscles, and reflexes are almost universal among these patients with osteomalacia. Our therapeutic test also tends to confirm the view.

CONCLUSIONS.

Osteomalacia is a diet deficiency disease of the same category as rickets. The deficiency is principally in the fat-soluble vitamine content of the diet, though there may be a calcium deficiency at the same time.

The disease may be prevented by providing a diet rich in the fat-soluble vitamine content, and may be cured by adding the same to the diet.

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