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Osteomalacia Associated with Renal Bicarbonate Loss

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Severe osteomalacia of uncertain etiology was observed in a 44-year-old woman. There was no evidence of chronic renal insufficiency, malabsorption, or of the renal tubular defects classically associated with osteomalacia. However, the dietary history suggested vitamin D deficiency and most of the biochemical findings were compatible with this condition. The unusual feature of the case was a decrease in plasma bicarbonate levels which appeared to be due to a lowered renal tubular threshold for bicarbonate reabsorption. There was no renal tubular defect with respect to hydrogen ion excretion.

Rapid symptomatic and radiologic improvement occurred when the dietary intake of vitamin D was increased to approximately 200 I.U. per day and the acidosis was simultaneously corrected with sodium bicarbonate. Although no firm conclusions could be drawn about the relative importance of vitamin D deficiency or chronic acidosis in the production of the osteomalacia, the possibility that the chronic acidosis may have been a major contributing factor is discussed.

OSTEOMALACIA is usually caused by intestinal malabsorption, chronic renal insufficiency or renal tubular disorders, and rarely by vitamin D deficiency. This paper describes the occurrence of osteomalacia in a woman whose history strongly suggested the possibility of vitamin D deficiency but who in addition had persistently low plasma bicarbonate levels probably due to a renal tubular defect of bicarbonate reabsorption. Unlike cases of renal tubular acidosis or of the Fanconi syndrome with associated acidosis, she was able to acidify urine normally. Striking clinical and radiological improvement occurred with a diet containing 200 I.U. vitamin D per day and correction of the acidosis with sodium bicarbonate. The pathogenesis of the acidosis and osteomalacia is discussed.

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On a observé chez une femme de 44 ans, une ostéomalacie grave d'étiologie incertaine. On n'a constaté aucun signe d'insuffisance rénale chronique, de malabsorption ou de troubles des tubes rénaux qui sont les causes classiques d'ostéomalacie. Cependant, l'étude du régime alimentaire permettait de croire à une carence de vitamine D et les examens biochimiques étaient compatibles avec cette hypothèse. La caractéristique exceptionnelle du cas en question était une diminution de la concentration plasmatique de bicarbonate qui se révéla être causée par une diminution du seuil de réabsorption du bicarbonate par les tubes rénaux. On n'a pas trouvé de trouble des tubes rénaux en ce qui concerne l'excrétion de l'ion hydrogène.

On a obtenu une amélioration rapide, tant symptomatique que radiologique, en portant l'apport alimentaire de vitamine D à environ 200 U.I./jour et en corrigeant simultanément l'acidose par administration de bicarbonate de sodium. Bien qu'il soit impossible de tirer de conclusions définitives quant à l'importance relative de la carence de vitamine D ou de l'acidose chronique sur la genèse de l'ostéomalacie, la possibilité que l'acidose chronique puisse avoir constitué un élément majeur de la pathogénie est quand même évoqué.

Case Report

Y. LeM., a 44-year-old French Canadian housewife, was referred to the Toronto General Hospital in May 1962 for the investigation of osteomalacia. She had a normal birth and grew and developed normally as a child. She reached her maximum height (61 in.) and weight (130 lb.) during adolescence. At the age of 17 years she had a full-term pregnancy and delivered a normal male infant who died at the age of 6 months from an unknown gastrointestinal disorder. At the age of 19 years she had a spontaneous abortion during the second or third month of pregnancy. At the age of 27 years she had roentgen therapy to the pelvic area for uterine fibroids and had no further menstrual periods. It is believed that she received hormone injections for an eight-month period after the pelvic irradiation. She then began to complain of periods of alternating constipation and diarrhea, each lasting four to five days. The stools were described as being watery, pale and foul-smelling but not greasy. At the same time she developed postprandial epigastric fullness and bloating, dull epigastric pain, and thirst. These complaints persisted until admission to hospital. Because of the gastrointestinal complaints she avoided meat,

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TABLE I.—BIOCHEMICAL DATA IN Y. LEM.

	First admission, May 1962 (no treatment)	*Second admission, Sept. 1962 (on $NaHCO_3$)*	*Third admission, April 1963 (no treatment)*	*Fourth admission, Sept. 1963 (on $NaHCO_3$)*
Hemoglobin (g./100 ml.)	10.4	10.0	12.5	10.7
White blood cell count (No./c.mm.)	3500 - 5000	4300 - 4400	5200	4400
Erythrocyte sedimentation rate (mm./hr.)	17 - 25	8 - 19	5	—
Serum sodium (mEq./l.)	141 - 145	142	136	133
Potassium (mEq./l.)	4.4 - 5.1	3.9	4.4	4.2
Chloride (mEq./l.)	106 - 110	106 - 107	105 - 107	104 - 107
Calcium (mg./100 ml.)	8.7 - 8.9	8.9 - 9.1	9.4 - 9.8	9.6 - 9.8
Magnesium (mg./100 ml.)	2.0	2.1 - 2.2	2.1 - 2.4	2.2 - 2.3
Phosphorus (mg./100 ml.)	1.9 - 3.2	3.8 - 4.6	4.1 - 4.3	3.7 - 4.7
Citric acid (mg./100 ml.)	1.2	2.4 - 3.2	1.8 - 4.0	1.9 - 2.3
Uric acid (mg./100 ml.)	4.1	—	3.2	—
Creatinine (mg./100 ml.)	0.7 - 0.8	0.9	1.1	1.0
Alkaline phosphatase (K.-A. units)	30 - 42	23 - 25	8 - 11	6 - 8
Blood pH	7.36 - 7.38	7.41 - 7.42	7.35 - 7.45	7.43 - 7.45
P_{CO_2} (mm.Hg)	31 - 35	35 - 38	32 - 46	40 - 46
Urea nitrogen (mg./100 ml.)	7.5 - 11	6	—	—
Plasma bicarbonate (mM./l.)	17.2 - 17.5	21.2 - 22.5	20.3 - 22	25 - 29
Plasma ultrafilterable calcium (mg./100 ml.)	5.0, 5.3	5.2, 5.4	—	—
Total plasma calcium (mg./100 ml.)	8.6, 8.4	9.0, 9.2	—	—
Serum albumin (g./100 ml.)	3.2		4.1	4.1
Globulin (g./100 ml.)	2.3		2.1	2.2

fish, eggs, bread, milk, butter and margarine and lost about 50 lb. in weight over the ensuing 15 years.

At approximately age 37 the patient first noticed aching pains in her low back which progressed to involve the arms, hips and chest, and she obtained relief with codeine. The pain persisted and worsened and resulted in her being largely confined to her home for three to four years before her admission. Consequently, she received little exposure to sunlight during this time. Two years before admission (age 42) she required crutches to walk and finally was partially confined to a wheelchair. She also noted a gradual loss of height. Fourteen months prior to admission roentgenograms showed a generalized decrease in bone density. She was treated with estrogens, and androgens and physiotherapy, but at no time before admission to our hospital was she given supplementary calcium or vitamin D.

Five months before admission roentgenograms taken elsewhere showed a healing fracture of the medial third of the right ulna, two partial fractures of the left ulna and another incomplete fracture of the left radius. There was decreased bone density with thinning of the cortex of the femora, pelvis and spine. At that time the levels of serum calcium and phosphorus (performed in our laboratory) were 8.9 and 2.5 mg./100 ml., respectively. The levels of hemoglobin, serum proteins and blood urea nitrogen were normal. Fat absorption (I^{131}-triolein) was normal.

The patient had never experienced tetany and gave no history of kidney stones or of other renal disturbance. There was no family history of bone disease. Her parents, both dead, had been well developed and were about 61 and 67 in. tall. Two brothers, measuring approximately 65 in. in height, are well and have no skeletal complaints. Serum calcium, phosphorus, creatinine, alkaline phosphatase and bicarbonate as well as blood pH have all been found to be normal in one brother. Serum chemistry has not been performed in the other brother.

TABLE II.—BIOCHEMICAL DATA IN Y. LEM.

	May 1962 (no treatment)	*Sept. 1962 (on $NaHCO_3$)*	*April 1963 (no treatment)*	*Sept. 1963 (on $NaHCO_3$)*
Urine volume (l./24 hr.)	1.9 - 2.7	2.2 - 2.9	2.4 - 2.8	2.7 - 3.4
Calcium (mg./24 hr.)	16 - 21	12 - 23	44 - 88	74 - 136
Magnesium (mg./24 hr.)	60 - 97	91 - 117	44 - 85	60 - 103
Phosphorus (mg./24 hr.)	849 - 889	662 - 840	455 - 696	597 - 720
Citric acid (mg./24 hr.)	195 - 294	696 - 1117	290 - 558	715 - 995
Uric acid (mg./24 hr.)	527	—	387	—
Ammonium (mEq./24 hr.)	41 - 45	3.2 - 6.2	20 - 25	3.0 - 3.7
Titratable acidity (mEq./24 hr.)	20	0	16 - 21	0
Bicarbonate (mEq./24 hr.)	9 - 11	113 - 194	5 - 10	178 - 223
pH	5.0 - 7.0	7.0 - 7.5	5.0 - 5.5	—
Protein (mg./24 hr.)	59	0	0	100
Glucose (mg./24 hr.)	—	34 - 72*	0	0
Urinalysis	Neg.	Neg.	Neg.	Neg.
Urine culture	Neg.	Neg.	Neg.	Neg.
PSP excretion: 15 min. (%)	29	30	—	20
120 min. (%)	76	79	—	50
Urine maximum specific gravity	1.019	1.017	—	1.025
Endogenous creatinine clearance (Ccr (ml./min./1.73 sq.m.))	80	62	60	65
Phosphorus clearance (Cp) ml./min.	11	5	5	4
Cp/Ccr	0.20	0.11	0.13	0.10
Phosphorus excretion index (PEI)	+0.08	−0.03	−0.03	−0.04
Tubular reabsorbed phosphorus (%)	80	89	88	90

* Glucose oxidase method.

First Admission (May 1962)

On admission she was a small, thin, chronically ill woman weighing 78½ lb. and measuring 58 in. in height. Her length from crown to pelvis was 30 in., pubis to heel 28 in. and span 59 in. There were no bone deformities. She was very weak and walked with difficulty; her gait was waddling. She had severe diffuse pain in her lumbar area, hips and ribs and diffuse bone tenderness over the vertebral column, pelvis, forearms and rib cage. Her teeth were in poor condition. There was slight tenderness in the epigastrium but no masses were felt. The liver, spleen and kidneys were not enlarged. Trousseau's and Chvostek's signs were not present. There were no cataracts or conjunctival calcium deposits. The remainder of the physical examination was normal.

Investigations performed on the ward and later in the Farquharson Clinical Investigation Unit are shown in Tables I and II. The noteworthy biochemical abnormality on admission was a persistent lowering of the plasma bicarbonate, which ranged between 17 and 19 mM./l. Serum chloride levels were in the upper normal range, varying from 106 to 110 mEq./l. The blood pH was 7.36 to 7.38 and partial pressure of carbon dioxide (P_{CO_2}) was 31 to 35 mm. Hg. Initially the levels of serum calcium were 8.7 to 8.9 mg./100 ml., and serum phosphorus 2.1 to 2.8 mg./100 ml., but three weeks after admission serum phosphorus levels had risen to 3.2 to 3.3 mg./100 ml., with little change in the serum calcium level. The patient had received no medications and was eating a normal diet. Ultrafilterable calcium levels were 5.0 and 5.3 mg./100 ml. with corresponding total plasma calcium of 8.6 and 8.4 mg./100 ml., respectively. The level of serum citrate was 1.2 mg./100 ml., and serum alkaline phosphatase 30 to 42 King-Armstrong (K.-A.) units. The serum levels of magnesium and uric acid were normal.

Studies of gastrointestinal function were as follows: Schilling test—20.8% excretion of oral dose of Co^{57}-vitamin B_{12}, serum carotene 228 and 254 μg./100 ml., prothrombin time 13 seconds (control: 13 seconds). An oral glucose tolerance test gave the following results: fasting blood sugar 70 mg./100 ml., one-half hour 107 mg./100 ml., one hour 58 mg./100 ml., two hours 87 mg./100 ml. All urine specimens were negative for sugar. During an oral xylose tolerance test the following blood xylose levels were obtained: one hour 53 mg./100 ml., two hours 70 mg./100 ml., three hours 25 mg./100 ml., four hours 19 mg./100 ml. and five hours 8 mg./100 ml. A five-hour urine collection contained 6 g. of xylose (normal test). Cultures of stools were negative for pathogenic bacteria or parasites. Roentgenographic examinations of the stomach, small bowel and colon were normal. Fecal fat excretion while the patient ate a constant diet containing 100 g. of fat/day was 1.7 g./day.

Microscopic examination of the urine was normal and a urine culture was sterile (Table II). The pH of freshly voided urine ranged from 5.0 to 7.5 over several days. The urine was negative for cystine (cyanide-nitroprusside test). Determinations of 24-hour urines were as follows: volume 1.9 to 2.7 l., protein 59 mg., calcium 16 to 21 mg., citrate 195 to 297 mg. and bicarbonate 9 to 11 mM. The levels of magnesium, uric acid, ammonia and titratable acid were normal in 24-hour urine collections. The maximum

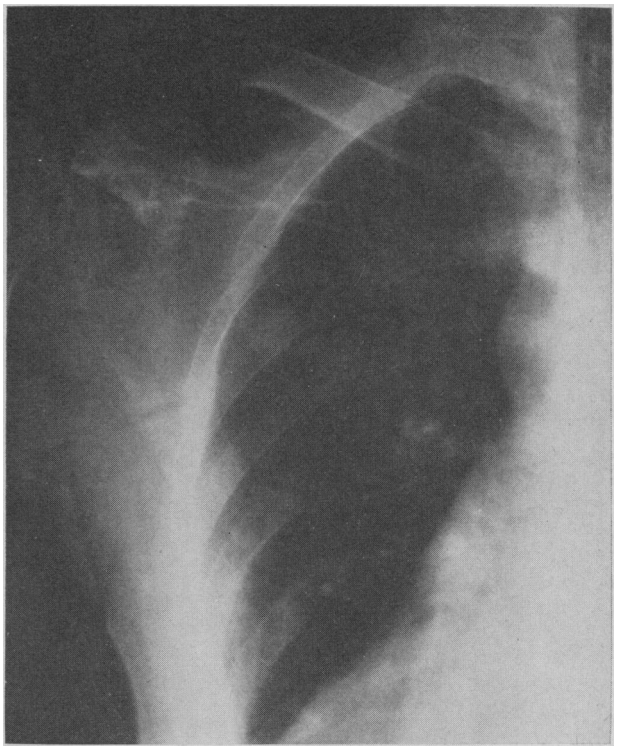

Fig. 1.—First admission prior to treatment. Pseudofracture in right scapula.

specific gravity of urine after 18 hours without fluids was 1.019. Phenolsulfonphthalein excretion was 29% in 15 minutes and 76% in two hours. A two-hour endogenous creatinine clearance was 80 ml./min./1.73 m^2. No abnormalities were noted on intravenous urography.

Roentgenograms showed a generalized decrease in bone density with pseudofractures of the scapulae (Fig. 1), upper femora and the superior and inferior pubic rami (Fig. 2), several metatarsal and phalangeal bones of the hands (Fig. 3), and midshafts of both ulnae (Fig. 4). A percutaneous renal biopsy showed normal kidney tissue. Other studies included an

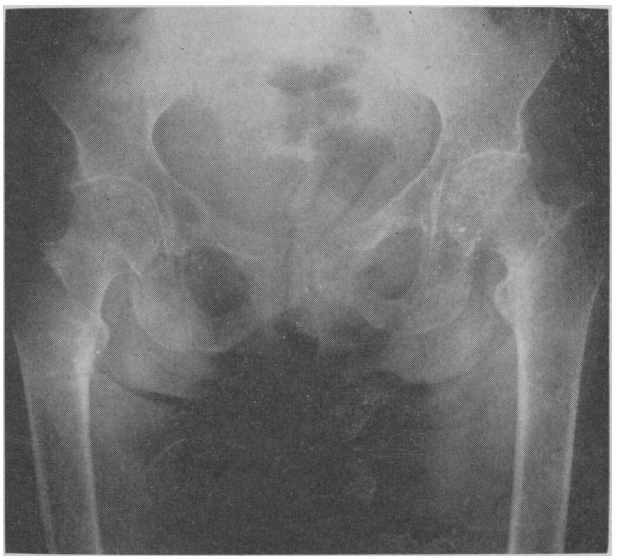

Fig. 2.—First admission prior to treatment. There is a generalized decrease in bone density with pseudofractures in the pubic rami, the upper shaft of the right femur, and the neck of the left femur.

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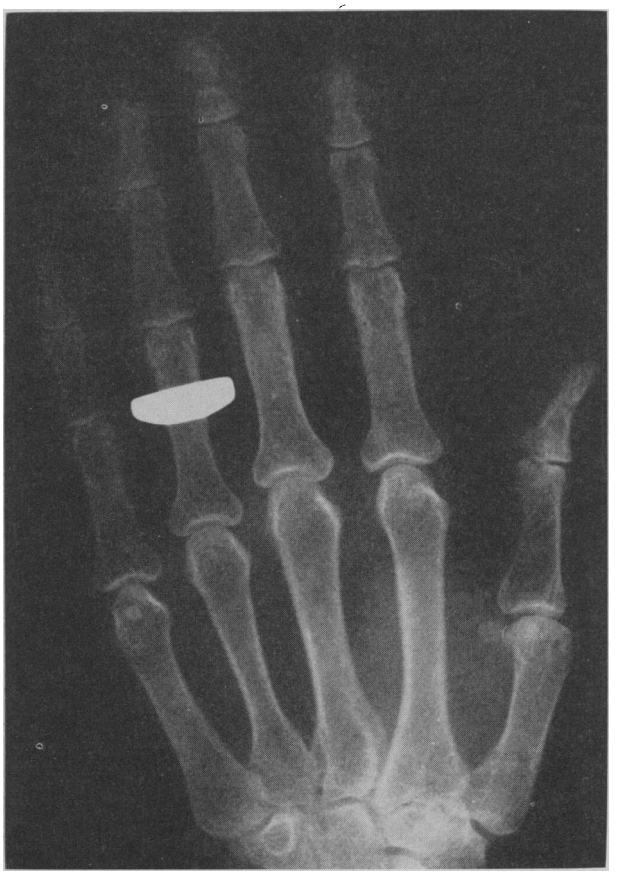

Fig. 3.—First admission prior to treatment. There is decreased density of the bones of the right hand and wrist with pseudofractures in the first metacarpal and in the first and third terminal phalanges.

ammonium chloride test which was normal (see DISCUSSION), an intravenous calcium test, and tests of renal handling of phosphate. These results will be outlined later.

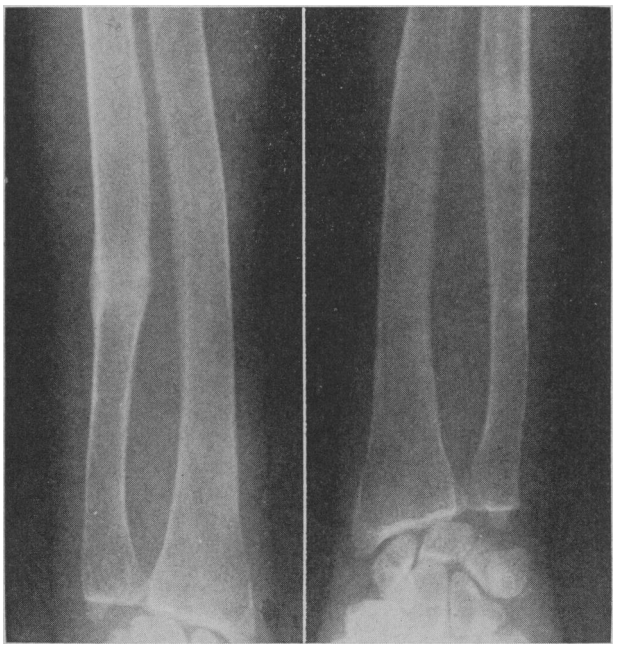

Fig. 4.—First admission prior to treatment. There is decreased density and thinning of the cortex of the bones of both forearms with a pseudofracture of the shaft of each ulna.

The patient was given a constant diet containing 750 mg. calcium, 1.7 g. phosphorus, 100 g. fat and 2100 calories, and balance studies were performed which will be discussed later. The estimated vitamin D content of this diet was 200 units per day. After a period of six days the patient requested to be discharged because of family problems and agreed to return at a later date. In the absence of a firm diagnosis it was decided that the initial treatment should consist only of the correction of the serum bicarbonate level in an effort to determine whether or not this abnormality was in any way related to the osteomalacia. She was given sodium bicarbonate 24 g. daily in four divided doses without supplementary calcium or vitamin D. Balance studies were carried out for a further six days on this regimen before her discharge from hospital on June 29, 1962. During the short period of bicarbonate therapy she improved markedly. She was able to walk without crutches and her bones were much less tender on palpation. In addition she felt better generally and slept much better. However, despite this dramatic improvement there was little change in her serum chemistry or calcium balance.

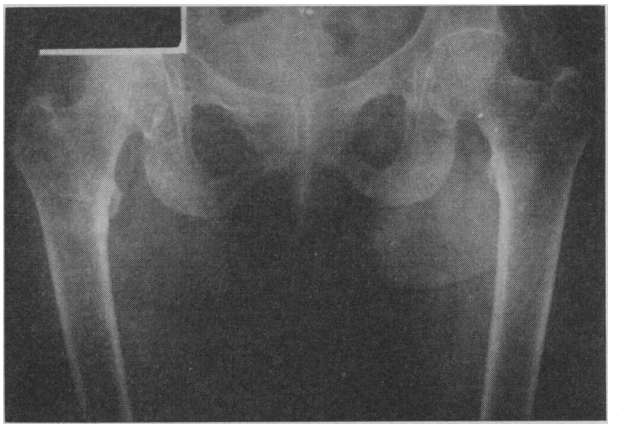

Fig. 5.—Second admission four months later. The pseudofractures of the pubic rami and femora have healed.

Second Admission (September 1962)

The patient returned for further studies two and one-half months later, on September 16, 1962. After her discharge from hospital she did not revert to her former eating habits and her diet since then has included one quart of milk and one serving of meat per day as well as four to five eggs per week and one lb. of butter per week. However, she still avoided cheese and fish and ate no margarine. She reported that two weeks after discharge she was practically free of pain and after one month was able to walk about unaided. At the time of admission she was able to walk several blocks without aid and without pain. She no longer was weak and felt better than she had for several years previously, although she continued to have a postprandial feeling of fullness in the epigastrium. She had gained 5 lb. since discharge (weight: 88 lb.) and was eating better. There were no other complaints. There was no tenderness over the long bones or rib cage but there was slight tenderness to percussion over the lower lumbar vertebrae. Her muscle strength was good. There was no abdominal tenderness. The remainder of the physical examination was normal.

Laboratory studies were carried out while the patient was receiving sodium bicarbonate (Tables I and II). Despite this, plasma bicarbonate levels were still below normal (21.2-22.5 mM./l.). Serum calcium levels were slightly higher and serum phosphorus levels were considerably higher than on the previous admission. Serum alkaline phosphatase levels had fallen significantly but were still elevated (23-25 K.-A. units).

Roentgenograms showed marked healing of previously noted fractures and pseudofractures (Figs. 5, 6 and 7). Undecalcified preparations of a bone biopsy from the iliac crest showed abnormally wide osteroid borders diagnostic of osteomalacia.

The patient was placed on a constant diet and balance studies were carried out for 16 days while she was receiving sodium bicarbonate, followed by 32 days without medication. Tests of renal handling of phosphate were also performed. Results of these studies will be discussed later. No change in her physical condition occurred during the study apart from a weight gain of 2 lb.

The patient was discharged from hospital on November 9, 1962, with instructions to take no sodium bicarbonate, calcium or vitamin D while at home. Frequent determinations of serum calcium and phosphorus were performed when she was seen as an outpatient, and no changes were noted. She continued to feel well.

Third Admission (April 1963)

She was readmitted on April 21, 1963, for further studies. She had taken no sodium bicarbonate for six and one-half months. She still complained of postprandial epigastric fullness, poor appetite, mild low back ache and occasional aching in the tibiae, femorae and humeri. The remainder of the functional enquiry was negative. Physical examination showed that she weighed 81½ lb. (an 8½-lb. weight loss since the previous admission). There was no tenderness over the long bones or ribs and no epigastric tenderness. The remainder of the physical examination was normal.

Investigations were done while the patient was receiving no medications and are shown on Tables I and II. The plasma bicarbonate levels were still below normal, ranging from 20 to 22 mM./l. Since the previous admission, serum alkaline phosphatase levels had fallen to normal. Serum calcium levels and urinary calcium excretion were somewhat higher than on previous admissions. Polyuria was still present.

Roentgenograms showed no fractures or pseudofractures. A bone biopsy from an iliac crest showed small amounts of osteoid tissue in undecalcified preparations. The amount of osteoid tissue was much less than on the previous admission.

The patient was again placed on a constant diet and balance studies carried out. Tests of renal handling of phosphorus were also carried out. These results will be discussed later. After 16 days on no therapy, she again was given sodium bicarbonate 24 g./day in four divided doses. The patient was discharged with instructions to continue taking the same dose of sodium bicarbonate at home. During hospitalization she gained 2 lb. and there was no change in her clinical condition.

Fourth Admission (September 1963)

At the time of this admission for follow-up studies her health was unchanged and she was active and quite free of pain except for low backache when tired. She still had occasional postprandial epigastric distress and poor appetite, and had lost 8 lb. since discharge. Physical examination was unchanged from the previous admission and there were no bone deformities or tenderness.

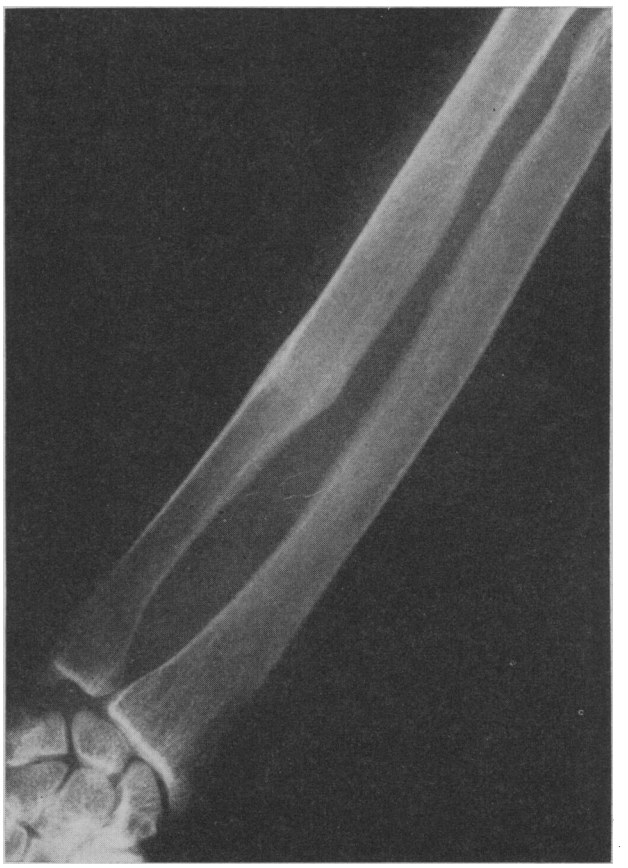

Fig. 6.—Second admission four months later. The pseudofracture in the right ulna has healed.

Investigations carried out while she was taking sodium bicarbonate 24 g./day are shown in Tables

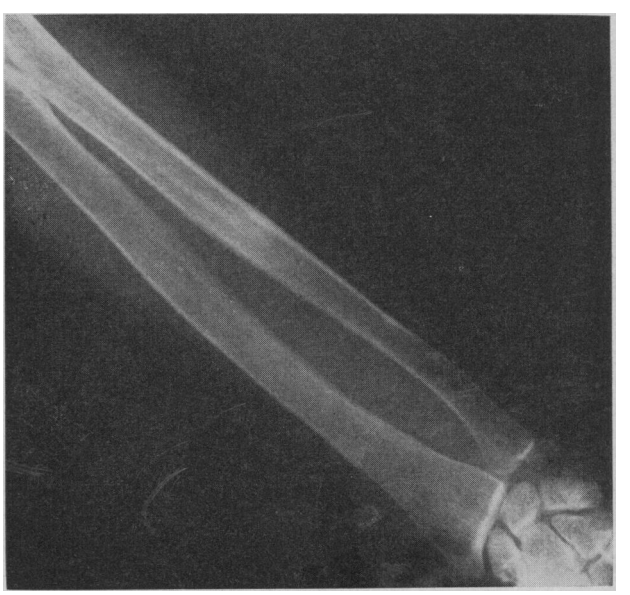

Fig. 7.—Second admission four months later. The pseudofracture in the left ulna has healed.

I and II. For the first time, plasma bicarbonate levels were now well within the normal range. Otherwise there were no striking biochemical changes since the previous admission.

Roentgenograms of the chest, scapulae, pelvis, femorae and ulnae showed good bone density and no pseudofractures. A bone biopsy from an iliac crest still showed small amounts of osteoid tissue in the undecalcified preparations. She continued to take sodium bicarbonate 24 g. daily for the initial part of this admission, and balance studies were performed for 16 days while she was receiving this therapy. Sodium bicarbonate was then discontinued, following which other studies, including an intravenous calcium test, response to intramuscular parathyroid extract and the response to acetazolamide, were performed. The results of these will be outlined later.

The patient's condition during her hospital stay was unchanged. She was discharged with instructions to take 24 g. sodium bicarbonate daily.

Follow-Up

Since the last admission she has been seen as an outpatient on two occasions. On June 29, 1964, she was feeling well and free of significant skeletal complaints and continuing to take sodium bicarbonate in the usual dosage. Her serum calcium level was 9.9 mg./100 ml., phosphorus 3.5 mg./100 ml., creatinine 1.3 mg./100 ml., serum sodium 135 mEq./l., serum potassium 4.0 mEq./l., chloride 90 mEq./l., blood pH 7.41, plasma bicarbonate 23.0 mM./l., P_{CO_2} 37.5 mm. Hg. The sodium bicarbonate was temporarily discontinued for 56 hours, at which time blood pH was 7.39, plasma bicarbonate 18.7 mM./l. and P_{CO_2} 32.0 mm. Hg.

On June 9, 1965, there was no significant change in her clinical state. Blood chemistry while she was taking sodium bicarbonate was as follows: calcium 9.2 mg./100 ml., phosphorus 3.4 mg./100 ml., creatinine 1.1 mg./100 ml., citrate 3.2 mg./100 ml., uric acid 1.9 mg./100 ml., sodium 140 mEq./l., potassium 3.2 mEq./l., chloride 108 mEq./l., alkaline phosphatase 9 K.-A. units. Blood pH 7.40, P_{CO_2} 37.5 mm. Hg, plasma bicarbonate 22.5 mM./l. After she temporarily discontinued sodium bicarbonate for 48 hours the blood pH was 7.37 with a P_{CO_2} of 35.5 mm. Hg and plasma bicarbonate 19.7 mM./l.

METHODS AND PROCEDURES

The following determinations were all performed in a research laboratory. Calcium and magnesium were determined by the method of Campbell,[1] phosphorus by a modification of the method of Gomori,[2] uric acid by a modification of the technique of Kern and Stransky,[3] citrate by a modified Natelson[4] method, and creatinine according to Folin and Wu[5] and Peters.[6] Chloride was determined with a Cotlove chloridometer. Sodium and potassium were measured by a Baird flame photometer. The Astrup method was employed to measure blood pH, plasma bicarbonate (actual) and P_{CO_2}. Ultrafiltration of calcium was performed by the method of Toribara,[7] urinary ammonia was determined by the method of Folin and Bell,[8] titratable acidity by the method of Henderson and Palmer[9] and bicarbonate by standard methods.[10] Normal serum values in our laboratory are as follows: calcium 8.9 to 10.3 mg./100 ml., ultrafilterable calcium 5.0 to 5.8 mg./100 ml., magnesium 1.7 to 2.4 mg./100 ml., phosphorus 2.8 to 4.5 mg./100 ml., and citric acid 1.8 to 3.0 mg./100 ml.

All metabolic studies were performed in the Farquharson Investigation Unit of the Toronto General Hospital. During the first admission the patient was placed on a constant diet calculated to contain 2100 calories, 100 g. of fat, and 200 units of vitamin D. During the second admission she received a similar but not identical diet which on analysis was found to contain calcium 870 mg., magnesium 200 mg., and phosphorus 1280 mg./day. During the third and fourth admissions the caloric content was reduced to 1820 calories with a decrease in phosphorus to 1050 mg. The calcium and magnesium content remained unchanged. Chemical analysis of the diet was performed at the beginning and end of each study. Blood for all determinations was taken at 8 a.m. in the fasting state. Daily 24-hour urine collections were analysed for creatinine, calcium, magnesium, phosphorus and citrate. In addition, during each period one 24-hour urine collection was collected under oil to minimize exposure to air. The urine was collected with a funnel connected to tubing extending under a layer of paraffin oil. The urine was analysed for pH, ammonia, titratable acid and bicarbonate content. On the same day a specimen of blood was analysed for pH, plasma bicarbonate and P_{CO_2}, using "arterialized" venous blood collected from the dorsum of the hand during the first admission. The hand was previously warmed and venostasis was avoided by using no tourniquet. During subsequent admissions these determinations were made on capillary blood from a fingertip using the Astrup micro-method. In all balance studies an equilibration period of five to 11 days was allowed before stool collections were commenced. During the first admission stools were collected in three-day periods but during the second and subsequent admissions stools were collected in four-day periods. The stool collections were analysed for calcium, magnesium and phosphorus.

RESULTS

Balance Studies

Balance studies were performed as described in "Methods and Procedures". The results are shown in Figs. 8 and 9. The fecal excretion of phosphorus and magnesium was not measured during the first four periods. The important features are as follows:

Periods 1 and 2 (first admission)

During these control periods the total excretion of calcium approximated the intake. However, the fecal excretion of calcium was quite high and the urinary excretion contributed only 15 mg./day to the total output. Also to be noted are the mild

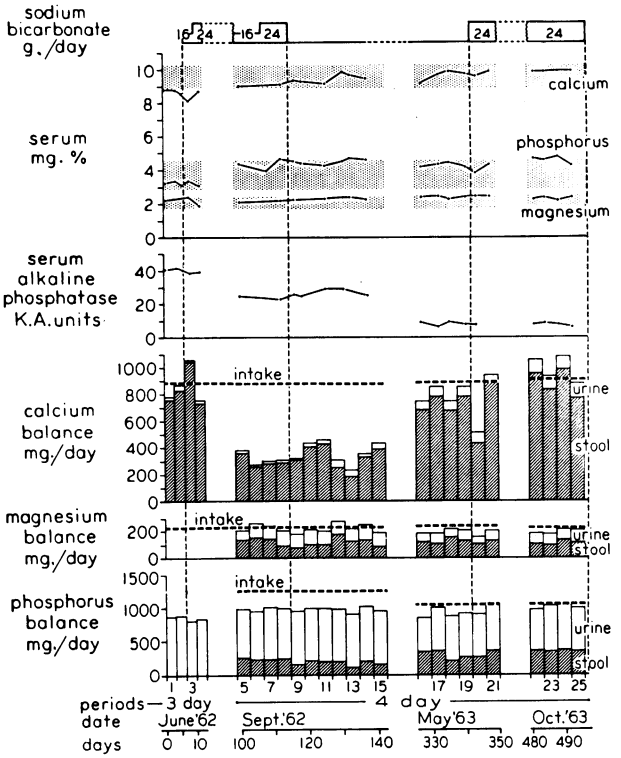

Fig. 8.—Balance studies. The shaded areas depict normal ranges for serum calcium, phosphorus and magnesium.

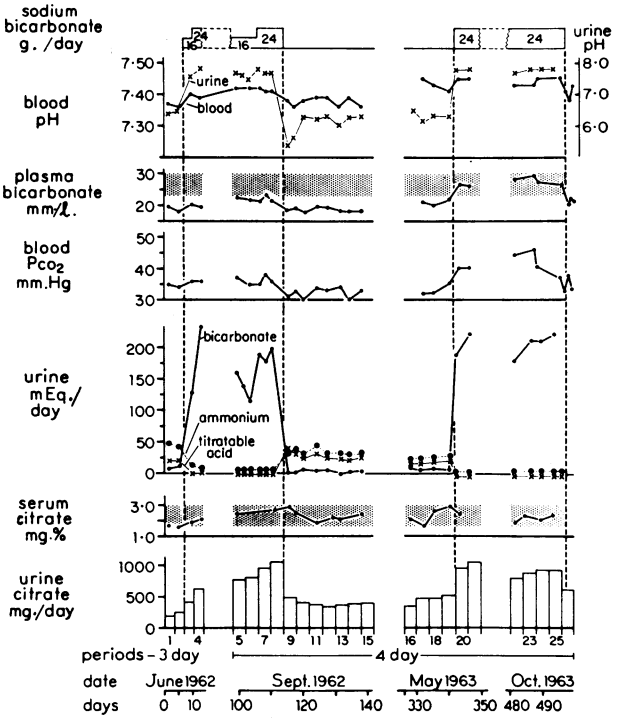

Fig. 9.—Biochemical data. The shaded areas depict normal ranges for plasma bicarbonate and serum citrate.

hypocalcemia, low normal levels of serum phosphorus, marked increase in serum alkaline phosphatase, decreased plasma bicarbonate levels, normal blood pH, and the presence of bicarbonate in the urine (8 and 11 mM./day). Serum citrate levels and urinary excretion of citrate were both in the low normal range.

Periods 3 and 4 (first admission)

The administration of sodium bicarbonate (6 g. four times daily) was associated with no change in urinary excretion of calcium, but there was perhaps a temporary increase in the fecal excretion of calcium. Serum calcium levels decreased slightly but there was no change in the levels of serum phosphorus, magnesium or alkaline phosphatase. Blood and urine pH increased. The plasma bicarbonate levels increased slightly but were still below the normal range. Despite the low plasma levels, the urinary excretion of bicarbonate increased greatly, suggesting a lowered renal threshold for bicarbonate. The urinary excretion of ammonium and titratable acid decreased. Levels of both serum and urinary citrate increased.

Periods 5 to 8 (second admission)

These studies were performed after 93 days of sodium bicarbonate administration. In the interval she had been given no supplementary vitamin D and the intake of vitamin D in the diet did not exceed 200 units/day. The fecal excretion of calcium had decreased greatly, resulting in a strongly positive calcium balance. The urinary excretion of calcium was still very low (15-20 mg./day). Phosphorus balance was positive and the excretion of magnesium equalled intake. The serum phosphorus levels were considerably higher than on the previous admission, whereas serum calcium levels had risen only slightly. Serum alkaline phosphatase levels had fallen considerably but were still above the normal range. Blood pH was normal but plasma bicarbonate levels were still below the normal range despite the large intake of sodium bicarbonate. Large amounts of bicarbonate were excreted in the urine, again suggesting a lowered renal threshold for bicarbonate. The serum citrate levels were slightly higher and the urinary excretion of citrate was also greater, but both were within the normal range.

Periods 9 to 15 (second admission)

When sodium bicarbonate was stopped no change was noted in calcium, phosphorus or magnesium balances, although the urinary excretion of calcium tended to increase slightly. Serum calcium levels rose slightly but there was no significant change in serum phosphorus, magnesium or alkaline phosphatase levels. Plasma bicarbonate decreased to pre-treatment levels and this change was accompanied by a slight decrease in blood pH and a marked decrease in urine pH. The urinary excretion of bicarbonate (3 to 7 mM./24 hr.), urinary ammonia and titratable acid also returned to previous levels. There was a slight decrease in serum citrate levels and a marked decrease in urinary citrate excretion.

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Periods 16 to 19 (third admission)

These periods were obtained 212 days after sodium bicarbonate was stopped. The patient was in much less positive calcium balance than during periods 5 to 15 and the urinary excretion of calcium had increased to 62 to 80 mg./24 hours. Less phosphorus was now being excreted in the urine but the fecal excretion of phosphorus had increased and phosphorus balance was slightly less positive than before. She was now in positive magnesium balance, owing mainly to a decrease in the urinary excretion of magnesium. The levels of serum calcium, magnesium, phosphorus and alkaline phosphatase were now all well within the normal range. The plasma bicarbonate levels were still below normal, while the urinary excretion of bicarbonate, ammonia and titratable acid was unchanged from initial studies (periods 1 and 2).

Periods 20 and 21 (third admission)

When oral sodium bicarbonate was resumed, no changes were noted except for the previously observed increase in blood pH, plasma bicarbonate levels and urinary excretion of bicarbonate. The urinary excretion of ammonia and titratable acid decreased as before (periods 3 and 4).

Periods 22 to 25

These periods were obtained 138 days after initiating the second course of sodium bicarbonate therapy. Calcium balance was slightly negative. No other changes were noted since the previous admission (periods 20 and 21).

SPECIAL STUDIES

Excretion of acid (ammonium chloride load test)

The short test of urine acidification described by Wrong and Davies,[11] which utilizes an oral dose of ammonium chloride (0.1 g./kg. body weight), was performed. The urinary pH, titratable acidity, and ammonia and bicarbonate content were determined hourly for two hours before and eight hours after the dose. In normal subjects all urine specimens passed more than two hours after administration of ammonium chloride have a pH of 5.3 or less, the excretion of titratable acid is 27 to 51 μEq. (micro-equivalents)/min. and the excretion of ammonia is 33 to 75 μEq./min. The results obtained in our patient are shown in Fig. 10. The blood pH was 7.34 and plasma bicarbonate 18 mM./l. before the test. Four hours later the blood pH was 7.33 and plasma bicarbonate 16.8 mM./l. The minimum urinary pH was 4.7 with all values below 5.3. Titratable acidity ranged from 24 to 32 μEq./min., while the urinary excretion of ammonia ranged from 46 to 77 μEq./min. None of the urine specimens after the ammonium chloride load contained bicarbonate.

This test was interpreted as being normal.

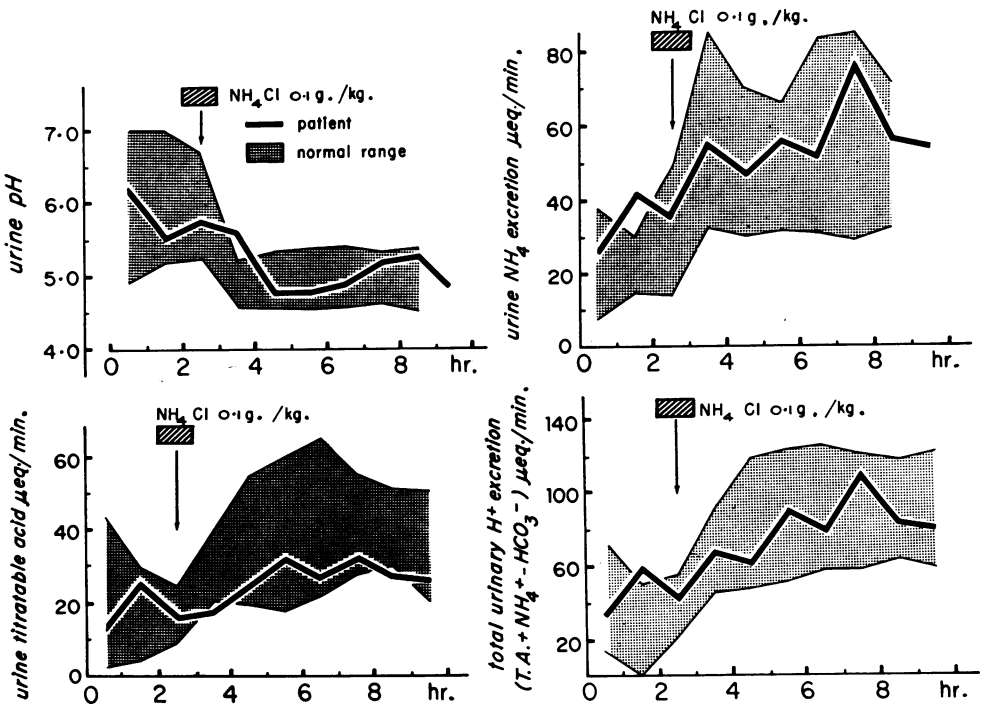

Fig. 10.—Response to ammonium chloride load. The shaded areas designate the range of the normal response as described by Wrong and Davies.[11] The heavy black line depicts the response of the patient.

Effect of Calcium Infusion

An intravenous calcium test was performed on two occasions. Both tests were performed in an

identical fashion while the patient was on a constant calcium and phosphorus intake, and the procedure used was similar to that originally described by Howard, Hopkins and Connor.[12] The infusion consisted of 15 mg. calcium ion (as calcium gluconate) per kg. of body weight in 1000 ml. saline and was given between 8 a.m. and 12 noon. Serum calcium and phosphorus levels were determined at 8 a.m., 12 noon and 4 p.m. on the day of infusion and at 8 a.m. on the following day. Urine was collected in 24-hour collections on the day before the infusion, the day of the infusion and the day after the infusion. In normal subjects the increment in serum phosphorus on the day of infusion is 1.2 mg./100 ml. or more, and there is a decrease in the urinary excretion of phosphorus of at least 15% on the infusion day (when compared to the pre-infusion day), with a rebound increase of at least 12% in the urinary excretion of phosphorus on the post-infusion day.[13] From 36 to 53% of the infused calcium appears in the urine (as excess calcium compared with the control day); i.e. calcium retention is 47 to 64% of the infused calcium.[12]

TABLE III.—EFFECT OF INTRAVENOUS CALCIUM

Date	Dose of I.V. calcium	Serum calcium (mg./100 ml.)				Serum phosphorus (mg./100 ml.)				Urine phosphorus					Urine calcium		
	mg. Ca++	0 hr.	4 hr.	8 hr.	24 hr.	0 hr.	4 hr.	8 hr.	24 hr.	Control day (mg./24 hr.)	Test day (mg./24 hr.)	% change	Post infusion day (mg./24 hr.)	% change	Control day (mg./24 hr.)	Test day (mg./24 hr.)	Retention (%)
June 7, 1962.....	540	8.4	9.9	8.1	8.0	3.3	3.6	4.1	3.0	942	870	−8	964	+3	18	94	86
Oct. 28, 1963.....	530	9.6	13.7	11.9	9.8	4.1	4.8	5.5	4.2	744	653	−12	780	+5	165	432	50

The results obtained in our patient are shown in Table III. The test was performed during the first admission before any treatment had been given, and again 17 months later after clinical improvement had occurred. On the second occasion the test was performed during a period when no sodium bicarbonate had been received for four days.

On the first occasion the increase in both serum calcium and phosphorus was less than normal, while the urinary phosphorus excretion decreased less than normal on the infusion day and had a smaller rebound than normal on the post-infusion day. The retention of calcium was abnormally high. These results are similar to the response to calcium infusion seen in patients with osteomalacia secondary to steatorrhea.[14] On the second occasion the serum calcium and phosphorus levels increased in a normal fashion and calcium retention was normal, but the changes in urinary phosphorus excretion on the day of infusion and on the following day were still somewhat abnormal.

Phosphorus Excretion

Phosphorus and endogenous creatinine clearances were determined simultaneously in the early morning fasting state (8 to 10 a.m.). The range of normal for phosphorus clearance in our laboratory by this method is 6 to 16 ml./min. Using the phosphorus:creatinine clearance ratio, the per cent of tubular reabsorbed phosphate (%TRP) can be determined (%TRP=(1−CP/Ccr) x 100) and in our laboratory the normal range is 82 to 97%.[15] The results in our patient are shown in Table II. With the exception of a slightly low %TRP prior to sodium bicarbonate administration, there was no evidence of excessive urinary phosphate excretion.

Response to Parathyroid Hormone

The response to parathyroid hormone was observed during the fourth hospital admission at a time when the osteomalacia was in clinical and radiological remission. Parathyroid extract (Parathormone) was administered intramuscularly in a dose of 200 I.U. every six hours for 12 doses while the patient was eating a constant diet. Early morning fasting bloods and 24-hour urine collections were analysed for calcium and phosphorus before, during and after administration of the hormone. The results are shown in Table IV, and are similar to those occurring in normal subjects studied under similar conditions.

Response to Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor, was given to the patient during the last admission to hospital when the osteomalacia was in clinical and radiological remission and after she had received no sodium bicarbonate for 14 days, and to one normal adult. Urine was collected under oil from 8 to 10 a.m. on the day before the test, and from 8 to 10 a.m. and 10 to 12 noon on the day of the test. The urine was analysed for pH, bicarbonate, titratable acid and ammonia. Blood pH, plasma bicarbonate and P_{CO_2} levels were measured at the midpoint of each urine collection. The results of the first day were used as control values. Acetazolamide (250 mg.) was taken orally at 8 a.m. on the day of the test. The results are shown in Table V. During the third and fourth hours after administration of acetazolamide, the normal control

TABLE IV.—EFFECT OF PARATHYROID EXTRACT IN Y. LEM.

Day	Parahormone (I.U./day)	Serum*		Urine	
		Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Calcium (mg./24 hr.)	Phosphorus (mg./24 hr.)
1	0	9.8	4.0	159	735
2	800	9.8	4.5	225	995
3	800	11.0	3.7	363	1080
4	800	11.8	3.6	456	1068
5	0	11.9	3.2	253	553
6	0	9.5	3.0	192	699

*Tak en at 8 a.m. in the fasting state.

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TABLE V.—EFFECTS OF ACETAZOLAMIDE IN Y. LeM. AND ONE NORMAL SUBJECT

Subject	Time	Acetazolamide (mg.)	Urine pH	Urine bicarbonate (μEq./min./1.73 sq.m.)	Change in bicarbonate excretion (μEq./min./1.73 sq.m.)	Plasma bicarbonate (mM./l.)
Y. LeM. 1.20 sq.m.*	pre-test day 8-10 a.m.	0	6.74	21	—	25.0
	test day 8-10 a.n.	250	7.16	30	—	24.5
	10-12 a.m.	0	7.40	115	+94	22.7
Normal ♂ 1.87 sq.m.	pre-test day 8-10 a.m.	0	6.40	9	—	29.9
	test day 8-10 a.m.	250	7.60	238	—	27.2
	10-12 a.m.	0	7.33	220	+211	24.5

*Surface area in square metres.

excreted over 200 μEq./min./1.73 m.² of bicarbonate. Despite the difference in procedure and smaller dose of drug, this response is within the range reported in 10 normal subjects by Webster *et al.*[16] The increase in urinary bicarbonate excretion following acetazolamide in our patient was much less than in normal subjects but does not differ significantly from the changes observed by Webster *et al.*[16] in normal subjects loaded with ammonium chloride or in patients with renal tubular acidosis.

DISCUSSION

1. *Differential Diagnosis*

The diagnosis of osteomalacia in this patient was established by the radiological evidence of generalized decrease in bone density in association with numerous pseudofractures and elevated serum alkaline phosphatase levels. A bone biopsy performed three months after clinical and radiologic remission had begun still showed the wide borders of uncalcified osteoid which are characteristic of this disorder.

The osteomalacia was associated with a number of biochemical abnormalities, the most striking of which was the persistent depression of plasma bicarbonate levels. Initially she also had mild hypocalcemia and hypophosphatemia, although the serum phosphorus level rose to normal shortly after admission to hospital and remained normal thereafter. Other biochemical abnormalities included markedly diminished excretion of calcium in the urine as well as low levels of citrate in serum and urine. The fecal excretion of calcium almost equalled the dietary intake, and calcium balance was neither significantly positive nor negative.

General renal function was not seriously impaired, although there was perhaps slight reduction of glomerular filtration rate and impairment of concentrating ability. Phenolsulfonphthalein excretion was normal. She had a moderate polyuria. There was no excessive glucosuria and the excretion of amino acids in the urine was within normal limits. The changes occurring in urinary pH and in the urinary excretion of ammonia and titratable acid following the oral administration of ammonium chloride were within the normal limits as described by Wrong and Davies.[11]

This patient probably developed osteomalacia in adult life rather than in childhood. Symptoms were of only seven years' duration, growth and development were normal and there were no deformities or evidence of early rickets. There was no family history of bone disease, and biochemical studies performed in one of two brothers were normal.

Osteomalacia in the adult is rarely produced by simple vitamin D deficiency and is most frequently associated with intestinal malabsorption and renal tubular disorders of various types. Osteomalacia may also be secondary to chronic renal failure, but then it is commonly associated with osteitis fibrosa and secondary hyperparathyroidism as well. It may also occur as a result of phosphate depletion induced by the prolonged and excessive use of unabsorbable antacids such as the aluminum hydroxide gels. Large amounts of uncalcified osteoid are also a histologic feature of hypophosphatasia.

Osteomalacia in adults due to vitamin D deficiency is rare in Canada and the United States. In 1948, Albright and Reifenstein[17] stated that they knew of no single case of osteomalacia in the United States due to simple vitamin D lack. However, in 1957 Dent[18] reported that he had seen three such cases in Great Britain. Van Buchem[19] also recorded the occurrence of clinical and radiographic signs of osteomalacia in 15 nuns whose nutrition was deficient during the war years 1943-45. Gough, Lloyd and Wills[20] described three additional cases of "nutritional osteomalacia" in 1964. Osteomalacia has occurred most frequently in areas where malnutrition was prevalent and where exposure to sunlight was minimal. These conditions formerly prevailed in the women of Northern

China, who were especially liable to develop osteomalacia during pregnancy and lactation.

In view of the history of poor appetite and poor intake of food containing vitamin D and calcium, the possibility of osteomalacia due to simple vitamin D deficiency merits special consideration in this patient. The changes in serum calcium, phosphorus and alkaline phosphatase levels, the diminished excretion of calcium in the urine, the low levels of citrate in serum and urine as well as the high fecal excretion of calcium, are all compatible with this diagnosis. Although low serum bicarbonate levels and acidosis are not described in association with simple vitamin D deficiency rickets in children, we have noted these abnormalities in two adult patients with osteomalacia secondary to idiopathic steatorrhea. In both of these patients the abnormalities of serum bicarbonate spontaneously corrected themselves after treatment with gluten-free diet. Dietary deficiency of vitamin D remains a distinct possibility as a cause of the osteomalacia in our patient even though remission occurred when the intake of vitamin D was not in excess of 200 I.U./day. A daily intake of 200 I.U. probably exceeds the minimal adult requirement, although this requirement has never been clearly defined.[21] Chu *et al.*[22] found that 500 I.U. of vitamin D per day produced marked calcium and phosphorus retention in an adult woman with osteomalacia. Even the addition of three eggs to a diet otherwise deficient in vitamin D led to unequivocal improvement in calcium and phosphorus balance in their patient.

Osteomalacia secondary to malabsorption was also considered because of the complaints of indigestion and diarrhea. However, all investigations of gastrointestinal function were normal (serum carotene and prothrombin levels, glucose and xylose tolerance tests, absorption and radioactive B_{12}, fecal fat excretion and roentgenograms of the gastrointestinal tract).

The renal tubular defects which may cause osteomalacia are renal tubular acidosis, the de Toni-Fanconi syndrome, glycosuric rickets and hypophosphatemic "vitamin D refractory" rickets. Albright *et al.*[23] have also reported the occurrence of osteomalacia in one patient with idiopathic hypercalciuria; there have been no subsequent reports of similar cases. Our patient appears to have had none of these disorders. Although the finding of a low serum bicarbonate level suggested the possibility of renal tubular acidosis, the changes which occurred in urinary pH and in the urinary excretion of titratable acid and ammonia following the oral administration of ammonium chloride are not compatible with this diagnosis. The low urinary excretion of calcium in the absence of a marked reduction in glomerular filtration rate is further evidence against a diagnosis of renal tubular acidosis. Finally, the urinary excretion of citrate, although somewhat reduced in this patient, was considerably higher than that which we have observed in our patients with renal tubular acidosis, all of whom have excreted less than 100 mg. of citrate per day in the urine. Since our patient did not have glycosuria, significant aminoaciduria or persistent hypophosphatemia, the diagnoses of de Toni-Fanconi syndrome, glycosuric rickets or hypophosphatemic "vitamin D refractory" rickets need not be seriously entertained.

A number of patients with an apparent renal tubular defect and osteomalacia who fail to fit into any of the usual classifications have been described. Dent and Harris[24] described four patients with a condition of "severe osteomalacia presenting in early adolescence or adult life and very closely mimicking deficiency of vitamin D". In these patients, who had no previous evidence of rickets and no affected relatives, the osteomalacia was associated with moderately low plasma bicarbonate levels. However, they were able to acidify urine normally and had a high excretion of glycine in the urine. They had no evidence of renal damage or steatorrhea. Similar patients have been reported by Segar, Iber and Kyle[25] and Henneman *et al.*[26] It should be noted that the serum phosphorus level in our patient was not as low as in the patients previously reported. None of the previous reports comment on urinary bicarbonate excretion, but in all patients who received ammonium chloride loads there was a normal response. The patient reported by Henneman had mild hypercalcemia and hypercitricuria but had been receiving large doses of vitamin D until 30 days before the study. Vitamin D may have produced these findings, since it is known that the effects of vitamin D may last for many months.

Our patient also differs from previously reported cases in the form of her therapy and her response to it. Dent and Harris[24] considered the condition they described to be a form of vitamin D refractory rickets and treated their patients with doses of vitamin D ranging from 200,000 to 800,000 units daily which resulted in disappearance of muscle weakness and elevation of plasma bicarbonate to normal or low normal levels. However, the authors did not consider the treatment to be completely satisfactory because of hypercalcemia and attendant complications. Two of the patients were reported as being well about four years later[27] and spontaneous recovery has since been reported in one of them. Therapy with dihydrotachysterol was discontinued after three and one-half years and during the subsequent five years she has remained in clinical and biochemical remission.[28] The patient of Segar, Iber and Kyle[25] was also treated with vitamin D but no improvement in bones or symptoms occurred. The patient reported by Henneman *et al.*[26] received alkali (sodium citrate) for about 40 days with erratic increases of the serum bicarbonate levels but no effect on calcium or phosphorus balance. A subtotal resection

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of the parathyroids was performed, and vitamin D 200,000 units daily, neutral sodium phosphate and added milk were included in the diet. The osteomalacia healed and the patient felt well. In contrast, our patient received alkali alone and achieved complete healing of the osteomalacia with no additional vitamin D or calcium.

2. *Pathogenesis of the Acidosis*

Several excellent reviews of the current concepts of acid-base equilibrium have recently been published,[29-32] and these may be consulted for details of mechanisms to be mentioned. Under ordinary conditions the kidneys maintain acid-base equilibrium by reabsorbing bicarbonate ions and excreting hydrogen ions. A disturbance of either of these processes may result in metabolic acidosis. Retention of hydrogen ions may arise from the following: increased intake of acidifying substances such as acidifying salts, methionine or methyl alcohol; increased production of organic acids due to diabetes mellitus, starvation, hyperthyroidism, hypoxia or shock; or decreased excretion of hydrogen ions due to generalized renal failure, renal tubular acidosis and carbonic anhydrase inhibitors. Acidosis due to bicarbonate loss may arise from gastrointestinal losses (severe diarrhea, intestinal or biliary fistulae) or renal loss (renal tubular acidosis, Fanconi syndrome or carbonic anhydrase inhibitor administration). Our patient had no evidence of increased intake of acidifying substances, increased production of organic acids or decreased hydrogen ion excretion. Bicarbonate loss from the gastrointestinal tract was unlikely and, as mentioned previously, she did not have renal tubular acidosis or the Fanconi syndrome. Nevertheless, there was a persistent daily urinary loss of 9 to 11 mM. of bicarbonate when plasma bicarbonate levels were between 17 and 18 mM./l. When plasma bicarbonate levels were raised to approximately 22 mM./l. by sodium bicarbonate administration large amounts of bicarbonate were excreted in the urine even though renal bicarbonate reabsorption was not in excess of 2.0 mM. per 100 ml. of glomerular filtrate. These data suggest that in this patient there was defective reabsorption of filtered bicarbonate by the renal tubule.

Under ordinary circumstances very little bicarbonate is excreted in the urine. With normal plasma levels of bicarbonate of 26 to 28 mM./l., the normal kidney filters approximately 5100 mM. of bicarbonate each day, yet only 1 to 2 mM. of bicarbonate are excreted in urine of pH 6.0.[30] The normal kidney maintains plasma bicarbonate levels between 26 and 28 mM./l. by reabsorbing virtually all filtered bicarbonate until the Tm for bicarbonate reabsorption is exceeded. In man the normal Tm is about 2.8 to 3.0 mM. per 100 ml. of glomerular filtrate. Under normal conditions all filtered bicarbonate in excess of this amount is excreted in the urine. The main site of bicarbonate reabsorption is the proximal tubule but small amounts are reabsorbed in the distal tubules and collecting ducts. Proximal tubular bicarbonate reabsorption is thought to be a process of ion exchange in which hydrogen ions passively diffuse into the proximal tubular lumen in exchange for sodium ions which diffuse down a concentration gradient from tubular fluid into the tubular cells and are then actively pumped into the peritubular fluid.[28] In the tubular fluid the secreted hydrogen ions combine with bicarbonate ions to form carbonic acid which dissociates to carbon dioxide and water. The carbon dioxide diffuses back into the tubular cells where on hydration it forms carbonic acid which in turn dissociates to provide hydrogen ions and bicarbonate ions. The bicarbonate ions then diffuse out of the cell into the peritubular fluid. A similar process occurs in the distal tubules, but here hydrogen ions are thought to be actively secreted by tubular cells against a concentration gradient. The renal tubular reabsorption of bicarbonate is depressed by hypocapnia (respiratory alkalosis), increased stores of potassium and chloride, adrenal insufficiency and carbonic anhydrase inhibitors. None of these factors were present in our patient. Thus it would appear that the low "renal bicarbonate threshold" in our patient might be due to some intrinsic defect of tubular function or to external factors which are presently not understood.

A possible cause of the impaired bicarbonate reabsorption in our patient might be decreased carbonic anhydrase activity. Such a mechanism has been suggested as operating in patients with renal tubular acidosis, but administration of carbonic anhydrase inhibitor has failed to indicate any difference between these patients, those with generalized renal disease and normal subjects made acidotic with ammonium chloride.[16] Also, Yaffe, Craig and Fellers[33] have assayed carbonic anhydrase activity in the kidney of a patient with renal tubular acidosis and found it to be normal. At the present time it is generally believed that the basic defect in renal tubular acidosis is neither a defect of hydrogen ion acceptors or hydrogen ion donors (including carbonic anhydrase activity) but a defect in the ability of the cells of the distal nephron to maintain a steep hydrogen ion gradient between luminal fluid and plasma.[29]

Following the administration of a single dose of a carbonic anhydrase inhibitor (250 mg. acetazolamide) to our patient, the resultant increase in urinary bicarbonate was less than that observed in a normal subject (Table V). The response was also less than that observed by Webster *et al.*[16] in normal subjects, although the dose of acetazolamide used by these workers was 10 mg./kg. of body weight whereas our patient received only 7 mg./kg. However, the increase in urinary bicarbonate excretion following acetazolamide in our patient did not differ significantly from the changes

observed by Webster *et al.*[16] in normal subjects loaded with ammonium chloride or in patients with renal tubular acidosis. As in patients with renal tubular acidosis, therefore, these data are inconclusive and neither rule in nor rule out carbonic anhydrase deficiency.

Relationship Between Acidosis and Osteomalacia

Although vitamin D deficiency is a possible cause of the osteomalacia in our patient, a consideration of the possible relationship between the chronic acidosis and the development of osteomalacia also seems pertinent. It is generally believed that newly formed osteoid undergoes normal mineralization when the extracellular fluids bathing it contain normal concentrations of calcium and phosphate ions but that osteomalacia results when the calcium x phosphate ion product is sufficiently depressed. In terms of this classic concept, acidosis would be expected to produce osteomalacia only indirectly as a result of decreased plasma calcium and/or phosphorus levels. However, Stanbury has suggested that "the mineralization of skeletal tissues is so complex a process that one cannot hope to explain the development of clinical rickets or osteomalacia in terms only of abnormal concentrations of calcium and phosphate in the plasma".[34]

Osteomalacia is associated with acidosis in three clinical disorders, namely renal tubular acidosis (alone or in association with the de Toni-Fanconi syndrome), chronic renal insufficiency (uremic osteodystrophy) and uretero-intestinal anastomoses. In none of these conditions is the cause of the osteomalacia clearly understood but in none is it currently fashionable to ascribe the bone disease directly to the acidosis. In renal tubular acidosis, for example, the osteomalacia is generally attributed to hypophosphatemia. Albright and Reifenstein[17] suggested the following sequence of events: acidosis produces hypercalciuria as a result of which the serum calcium tends to fall, leading to parathyroid hyperplasia, excessive urinary excretion of phosphate and finally hypophosphatemia. Objections have been raised to this theory because of the many cases which do not exhibit excessive urinary loss of calcium. It has been alternatively suggested that excessive urinary loss of phosphate and low serum levels of phosphorus are due to a separate defect of tubular function[35] or are secondary to acidosis[36] or to potassium deficiency.[37] All of these theories attempt to ascribe the osteomalacia of renal tubular acidosis to hypocalcemia and/or hypophosphatemia, and no satisfactory explanation has been offered for the occasional finding of osteomalacia in renal tubular acidosis when serum calcium and phosphorus levels are normal. Similarly, many theories have been advanced for the occurrence of osteomalacia in uremic osteodystrophy but none is convincing and the literature concerning osteomalacia associated with uretero-intestinal anastomoses is practically non-existent.

Experimental studies concerning the effects of metabolic acidosis on the skeleton are contradictory and scanty. Bernhardt and Rabl[38] reported that rickets occurred in young rats on a diet deficient in calcium and phosphorus to which 2% ammonium chloride as well as a small cod liver oil supplement was added. On the other hand, Jaffe, Bodansky and Chandler[39] found that the administration of ammonium chloride to puppies produced osteitis fibrosa. However, the amount of ammonium chloride given to the puppies was quite large, the degree of acidosis was probably very severe (although biochemical estimations are not given) and the experiments were relatively acute (the total duration being 11 weeks). The effects produced by this experimental situation can hardly be considered analogous to the changes produced in the skeleton of adult man by a mild acidosis of many months' or years' duration.

Recently Relman[32] has shown that in patients with chronic renal acidosis, total daily acid production may significantly exceed acid excretion without progressive exhaustion of extracellular buffer. He postulates that the retained acid is neutralized by the slow dissolution of bone salts. In our patient a chronic metabolic acidosis due to renal bicarbonate loss was associated with severe osteomalacia which improved rapidly and dramatically when sodium bicarbonate was administered by mouth. Unfortunately, we cannot with certainty rule out vitamin D deficiency as the chief etiologic factor in the pathogenesis of the osteomalacia in this patient. However, an attractive alternative explanation is that the bone disease was due to the direct effect of a long-sustained acidosis upon the skeleton. It is further suggested that since the current theories concerning the pathogenesis of osteomalacia associated with renal tubular acidosis and uremic osteodystrophy are unsatisfactory, the direct effect of acidosis on the skeleton should be the subject of renewed and vigorous study by those interested in metabolic bone disease.

SUMMARY

The occurrence of severe osteomalacia is reported in a 44-year-old housewife in whom there was no evidence of chronic renal insufficiency, malabsorption or the renal tubular defects classically associated with osteomalacia. The dietary history suggested vitamin D deficiency. An unusual feature of the case was a decrease in plasma bicarbonate levels, presumably due to a lowered renal tubular threshold for bicarbonate reabsorption. There was no renal tubular defect in hydrogen ion excretion. Rapid symptomatic and radiologic improvement occurred when the dietary intake of vitamin D approximated 200 I.U. per day with simultaneous correction of the acidosis with sodium bicarbonate.

The possibility that the osteomalacia in this patient may have been due to chronic metabolic acidosis rather than vitamin D deficiency is discussed.

It is further suggested that the occurrence of osteomalacia in association with chronic metabolic acidosis

is not necessarily dependent upon diminished levels of calcium and/or phosphorus in the extracellular fluids but may be due to a direct effect of the acidosis upon the skeleton.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

SUCH PRANKS . . . IN THE HUMAN BODY

The x-ray department has been a great success and, as there are no skiagrams possible in front of us, practically all patients who had been wounded were skiagraphed. It was not safe, we found, to accept the statement on the patient's tag, "operated upon and shrapnel removed", because often other pieces had not been removed. This meant a little delay, but the patient was generally better for that. The MacKenzie Davidson method of localizing the foreign body is very accurate and has been used in practically all such cases—and such pranks as foreign bodies do play in the human body! In one of our recent cases a bullet which had entered the right buttock, was located by x-ray in the left popliteal space, without a trace of any pelvic symptom. In times of very rapid evacuations, where there was no time to operate upon foreign bodies which could safely be left for a day, our radiographers very cleverly took the skiagrams direct upon bromide paper and these prints went home with the patient as part of his record, so that he might be operated upon as soon as he reached the base hospital in England. The same remark applies to fractures. Another great aid in definitely locating a foreign body, when operating, has been the telephone probe. This has proved especially serviceable in cases of removal of a bullet, or a piece of shell, from the brain, lung or liver, enabling us to extract the foreign body with a minimum of traumatism where trauma counts for so much. The instrument we now use has no battery, simply a small electro-magnet (like a telephone receiver) in the head piece, the necessary amount of electrical current being generated by the fluids of the patient's body.

In perforating gunshot wounds of the lung, associated with hæmothorax, our results have been surprisingly good. How many of these cases survive to come to us I have no means of estimating, but of those who did come we have lost very few. These cases, although admitted to the surgical wards, are always placed absolutely in the hands of the physicians, and the surgeon only interferes when requested to do so. Absolute rest and opiates to slow the respirations are the basic lines of treatment here. I have seen several cases showing all the clinical signs of traumatic asphyxia, due to intrathoracic pressure, quite recover with rest and repeated hypodermics of morphia. Any surgical interference at this time, I feel sure, would have proved fatal. When the hæmothorax has reached a certain stage (either come to a standstill or causing increasing symptoms) the pleural cavity is aspirated. We have always done this by the method of replacement. Our pathologist and the surgical majors very ingeniously arranged a mercury manometer tube attached to a "case sheet" board, and this instrument served our purpose admirably. Under local anæsthesia a small-sized aspirating needle is inserted into the pleural cavity at the upper level of the fluid and the manometer reading carefully taken. A larger needle is then inserted *at a lower level* and attached to an aspirating bottle. Between the smaller needle and the patient's body is a two-way stop-cock, one way goes to the manometer and the other is attached to an oxygen cylinder with a reducing valve, so that as the blood flows out into the aspirating bottle oxygen is forced into the emptying pleural cavity at such a rate that the intrathoracic pressure (as shown by the manometer reading) is kept constant. In this way further hæmorrhage is avoided and we had no symptoms of syncope follow this operation. The procedure is always carried out in the wards in order to disturb the patient as little as possible. I am quite convinced that the early removal of blood from the pleural cavity minimizes the danger of subsequent adhesions due to organizing fibrin.

Empyæmas treated by thoracotomy and free drainage, aided by posture, have also done well. In most cases we were able to resect the ribs under novocaine or anocain local anæsthesia.—J. M. Elder, *Canad. Med. Ass. J.*, 6: 495, 1916.