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METABOLIC AND ORTHOPEDIC TREATMENT OF A CASE OF ADULT NONFAMILIAR HYPOPHOSPHATEMIA WITH SEVERE OSTEOMALACIA

By

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The first adult case of the Fanconi syndrome was described by *Stowers & Dent in 1947* (1). The syndrome consists of osteomalacia with hypophosphatemia, glucosuria, aminoaciduria, and frequently acidosis. There is sometimes a defect in the water-retaining ability of the kidney as well. *Wallis & Engle* (2), who reported on eighteen adult cases of the syndrome, clained that multiple familial occurrences are rare in adults, whereas a hereditary tendency is common in children with the syndrome.

A condition which shares many features with the Fanconi syndrome is renal tubular osteomalacia, in which the serum calcium is usually normal, the serum phosphorus always low, and the alkaline phosphatases increased and in connection with which there is no aminoaciduria and usually no glucosuria. Familial instances of this disease are common but isolated cases also occur. High doses of vitamin D can improve the patient's osteomalacia. The first case of vitamin-D-resistant osteomalacia is said to have been presented by *Albright et al.* in 1937 (3) but the case described by *Milkman* in 1934 (4) which had osteomalacia, hypophosphatemia and glucosuria probably belongs to the group of vitamin-D-resistant osteomalacia with hypophosphatemia. Most investigators have found a low tubular reabsorption of phosphate in these cases. In children the disorder causes rickets resistant to treatment with vitamin D in doses sufficient to cure nutritional rickets and is therefore often called vitamin-D-resistant rickets. In adults, the hypophosphatemia causes osteomalacia and these adult disorders have

been called phosphate diabetes, essential hypophosphatemia, idiopathic osteomalacia, Milkman's syndrome etc.

There seems to be some controversy in the literature with regard to the classification of the various clinical conditions characterized by osteomalacia (or rickets in children) and hypophosphatemia due to decreased tubular reabsorption of phosphate. Many textbooks describe the Fanconi syndrome and hypophosphatemic osteomalacia in different chapters (5, 6). What seems ultimately to differentiate the Fanconi syndrome from hypophosphatemic osteomalacia is the aminoaciduria which, according to most authors, is an integral part of the Fanconi syndrome.

Dent (7) has suggested a classification of clinical conditions with "rickets and osteomalacia from renal tubule defects" in six different types. According to his classification, type 1 denotes osteomalacia in which there is only one human tubular reabsorption defect, namely that of phosphate. In type 2, renal glucosuria occurs, as well. The different types of the Fanconi syndrome and hypophosphatemic osteomalacia with renal tubular acidosis are classified as types 3–6. In our opinion, this classification is very useful from diagnostic, therapeutic, and prognostic viewpoints.

The main problem with vitamin D treatment in hypophosphatemic osteomalacia lies in the fact that high doses are required in most cases and are accompanied by the constant risk of intoxication with the vitamin. It was consequently of great interest when *Fraser* (8) reported in 1957 that intravenous phosphate had a beneficial effect in vitamin-D-refractory rickets in children. In 1958 and 1961, *Frame et al.* (9, 10) showed that oral phosphate supplement was effective in hypophosphatemic osteomalacia and it was further shown in 1963 by *Wilson & Yendt* (11) that two cases with the adult Fanconi syndrome were improved with oral phosphate treatment alone without vitamin D supplement. The role of phosphate therapy in hypophosphatemic rickets and osteomalacia has also been stressed by *Rose* (12). Oral phosphate supplementation is also appealing from the point of view that phosphate administration seems to protect against hypercalcemia of all etiologies (13) and, therefore, also against the hypercalcemia due to vitamin D intoxication.

In the present paper we will report on a case of very severe hypophosphatemic osteomalacia in a man of 27 and the gratifying effect of orthopedic correction in combination with long-term treatment with high doses of vitamin D and sodium monophosphate.

METHODS

Phosphorus in serum, urine, feces and food specimens was determined by the method of *Fiske-SubbaRow* (14). *Calcium* in the same media was estimated with flame photometry. *Alkaline phosphatase* was determined by the method of *Bessey, Lowry & Brock* (15) as modifed by *Jacobsson* (16). Quantitative analysis of the amino acids in the urine was performed by means of an automatic amino acid analysor (17) as by *Spackman, Moore & Stein* (18). Trace element determinations were performed with a recently developed ion-exchange technique with subsequent γ-spectrometry (19) after neutron activation.

For long periods the patient underwent studies of calcium and phosphorus balance. For shorter periods balance studies were also undertaken with respect to 25 different trace elements. During the balance study the patient was kept on a constant daily menu that he had chosen himself. Feces and urine was collected during five day periods. Calcium and phosphorus (and, during certain periods, trace elements) were determined on aliquots of urine and homogenates of feces. The intake of calcium and phosphorus and trace elements was determined by analysis of homogenates of duplicates of each day's meals. All drugs given were added to the model diet before homogenization. The balance data obtained were charted as by *Reifenstein et al.* (20).

CASE REPORT

On admission the patient was 26 years old. Up to early 1965 he had worked as a mechanic. The patient has two brothers and one sister, all healthy. The father has six healthy brothers and sisters, the mother has two healthy brothers and one brother who died from an unknown heart disease at the age of 25.

The patient had developed normally as a child and there is no history of rickets.

The symptoms started at the age of 16. During 1956–59 there were slowly increasing skeletal pains in the ribs, lower back, the left knee and the right shoulder, but the patient was still able to participate in football and other vigorous activities. In 1959, at the age of 19, he called the local hospital and during that year several roentgenograms were taken which revealed fourteen Milkman fractures, some in a state of healing, others showing no callus. In late 1959 the patient developed pains in the hip joints. X-rays showed fractures in the pelvis ring and in both tibiae and fibulae.

In 1959, hypophosphatemia and renal glucosuria were detected and the disorder was considered thereafter to be a Fanconi syndrome. The same year, treatment with approximately 50.000 I.U. vitamin D daily was started and was maintained during the four years preceding the development in 1963 of gastric ulcer which led to a Billroth II gastrectomy. Thenceforth, the vitamin D therapy was omitted for unclear reasons. During the period between 1959 to 1963, there were no gross changes in body stature. His body height decreased only slightly during this period from 176 to 173 cm. There were constant skeletal pains, however, which were especially severe in the hip joints. X-ray revealed bilateral Milkman fractures of collum femoris.

During 1964 the patient's symptoms did not progress despite the lack of vitamin D therapy.

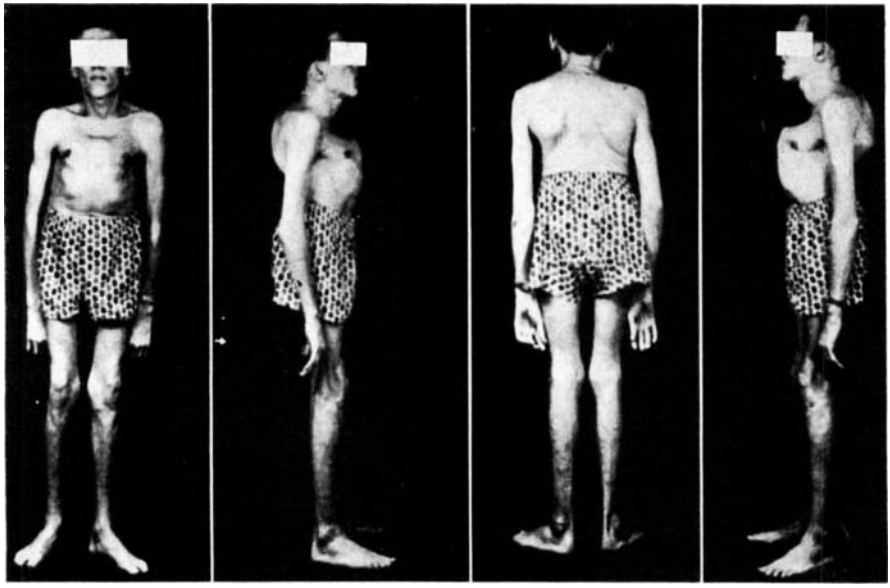

Figure 1. The patient on admission to the metabolic ward.

In early 1965, however, the symptoms progressed rapidly and within two or three months the patient had developed a severe thoracic kyphosis and the sternum was fractured at a 90° angle. Body height decreased from 173 to 159,5 cm, a dramatic change in three months (Figure 1). Severe pains as well as muscular fatigue in the legs and hip joints bound him to the wheelchair. A compound tablet containing 4.800 I.U. vitamin D and 600 mg calcium daily was then prescribed but the patient had lost all confidence in doctors and took the tablets only sporadically. He was severely depressed.

The patient was admitted to the metabolic ward, Serafimer hospital, in January 1966 with the diagnosis of Fanconi syndrome. He was mentally depressed and severely crippled by marked thoracic kyphosis, pidgeon chest, generalized muscular weakness, and constant skeletal pain. The pains were alleviated by lying down. He could not walk unaided and had, for several months, required analgesics constantly.

X-ray showed 36 fractures of the Milkman type of variable age, as illustrated in Figures 2 and 3. Serum phosphorus was extremely low, whereas serum calcium was normal. There was also renal glucosuria but no pathological aminoaciduria. As a result of these findings it was suggested that this was a case of hypophosphatemic osteomalacia with glucosuria, thus being a hypophosphatemic osteomalacia of type II by the Dent classification (7) rather than a Fanconi syndrome. More detailed information on roentgenographic and laboratory findings is given under separate headings later in the text.

After routine examination the patient was subjected to metabolic balance studies during 22 consecutive, 5-day balance periods, *i.e.* 110 days. During the first two control periods he was given the same dose of vitamin D, 4500 I.U., as pre-

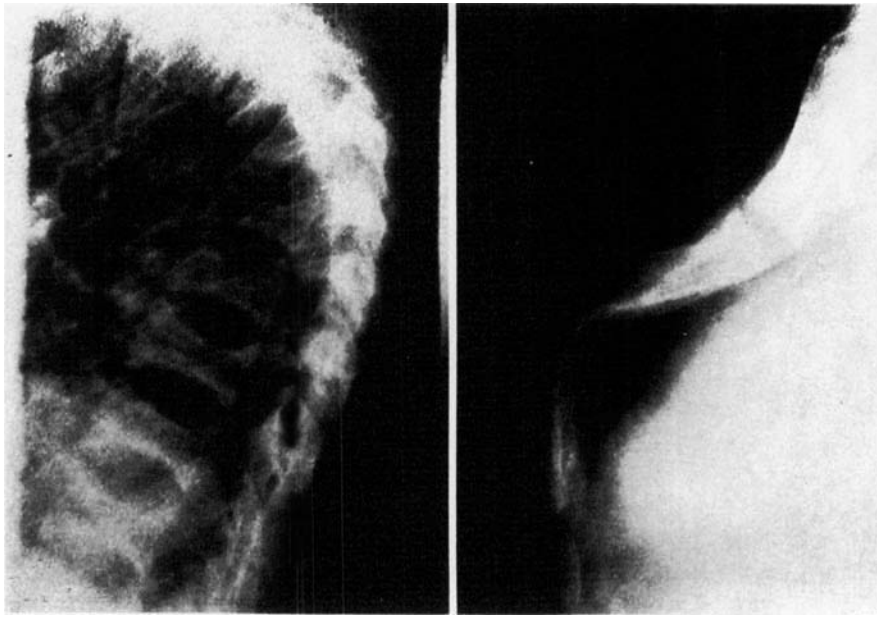

Figure 2. The roentgenogram to the left illustrates the cod-fish vertebra typical for advanced osteomalacia. Note the collapse of T6, resulting in a gibbus of approximately 90°. The right figure shows the fracture of the sternum causing pidgeon chest.

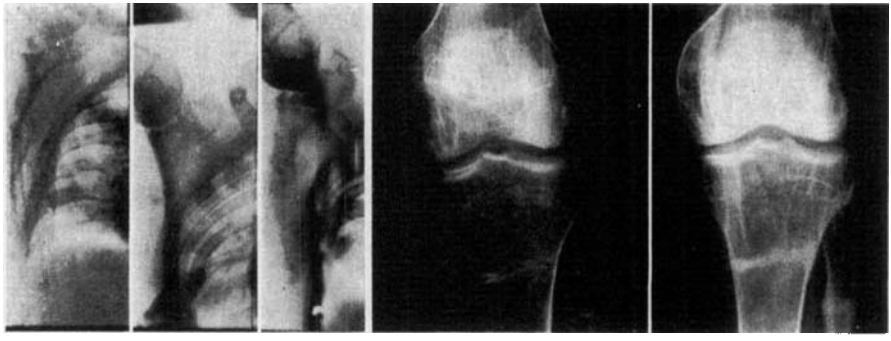

Figure 3. Roentgenograms showing Milkman fractures in the scapulae and in the tibia and fibula before and after metabolic treatment of the osteomalacia. After treatment the fractures are healed.

scribed before admission. During the following periods increasing amounts of vitamin D_2, calcium and phosphate were given. After five months the medication consisted of 545.000 units of vitamin D_2, 3 g calcium and 15 g sodium monophosphate.

The patient first noticed a decrease in pain after about four weeks of effective treatment. After about two and a half months, the muscular weakness and pain

had diminished and the patient was able to walk without walking-sticks, although he had marked waddling gait. After a few minutes of walking pains would develop in the hips and force him to rest. In late April, he was able to be up and about for several hours during the day and experienced pains only in the afternoon. After a little more than five months of a combined regimen of phosphate, calcium, and vitamin D_2, the patient was discharged from the metabolic ward for a planned three months "summer vacation". He was fully mobilized with no pain and scarcely any waddling gait. The patient was optimistic and his depression had vanished. The orthopedic treatment had been quite successful (see under orthopedic treatment), the patient's body height having been increased from 159.5 to 165 cm.

During the summer of 1966, the patient's subjective well-being continued and the serum calcium and phosphorus values were normal. In the middle of August, however, there was a bout of hypercalcemia and the patient was therefore immediately admitted to the metabolic ward. The patient was in excellent condition physically (he was now able to run and to jump from 50 cm heights without pains) and his muscular strength was normal. The vitamin D_2 was omitted for about one month in order to restore normal calcium values. The patient again underwent metabolic balance studies for two and a half months and was discharged in late November. Some adjustment of the medication (see under laboratory findings) was made subsequently and the patient is currently (August 1967) receiving 105.000 units of vitamin D_2 and 15 g sodium monophosphate daily. He is fully rehabilitated and works as an electronic technician.

FAMILY STUDIES

No other case of rickets, osteomalacia or other metabolic bone disease is known in the patient's family. Blood and urine specimens from both parents and all siblings (2 males and 1 female) were investigated for the presence of glycosuria and aminoaciduria and determinations were made of serum concentrations of calcium, phosphorus, creatinine and alkaline phosphatase. All these tests were found to be normal.

EFFECT OF THERAPY ON CALCIUM AND PHOSPHORUS METABOLISM

A few days after admission in January 1966, the patient was put on a balance diet with an intake of exactly 1000 mg calcium and 1100 mg phosphorus. The vitamin D intake was 9,300 I.U., imitating the medication he had taken at home. Only two 5-day control periods were studied due to the patient's poor condition which required treatment. Both calcium and phosphorus balances were negative (see Figure 4) initially, the calcium loss being 120 to 160 mg per day. The urinary calcium did not exceed 120 mg per day. The phosphorus balance was close to equilibrium and the urinary phosphorus approximately 700 mg per day, a rather normal value.

During the following three balance periods, the vitamin D_2 dose was

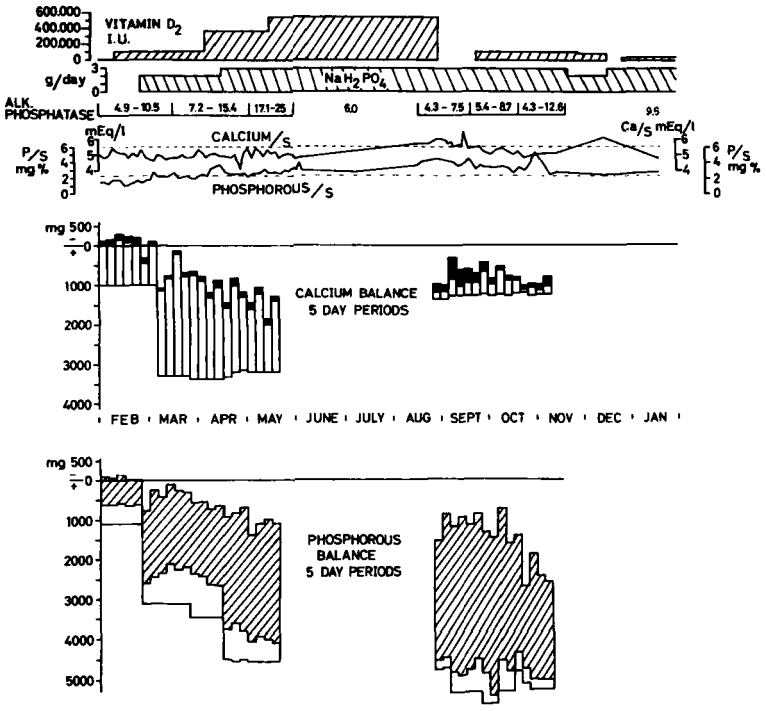

Figure 4. Balance studies of calcium and phosphorus in the patient. Intake is plotted downwards from the base line, output is plotted from the bottom of the intake upwards. The solid and the open parts of the columns represent urinary and fecal excretion, respectively. In the case of a positive balance all parts of the columns are below the base line but if the balance is negative a part of the columns is above the baseline.—The figure also shows the alterations in treatment with vitamin D_2, oral phosphate, and calcium as well as variations in the serum calcium, phosphorus, and alkaline phosphatase.

increased to 120,000 units. That dose of vitamin D_2 obviously failed to change the phosphorus balance, and the calcium balance did not become positive. The patient reported no subjective improvement.

During balance periods 6 and 7, sodium monophosphate, 10 g per day (corresponding to about 2 g phosphorus), was given orally. The salt was given three times a day in fruit juice, and the patient found the taste of this mixture to be acceptable (he has taken it for more than a year now without serious objections). The pH of the divided salt doses in distilled water was 4.8. On the combination of 10 g sodium monophosphate and 120,000 units of vitamin D, the phosphorus bal-

ance became strongly positive, and during one of the two 5-day periods on this regime the calcium balance was positive.

During the following six balance periods the treatment was unchanged except for an increase of the calcium intake from 1000 to 3300 mg per day (Calcium Sandoz, effervescent tablets). Thereafter, the patient was in positive phosphorus and calcium balance. The urinary calcium never exceeded 200 mg per day on this medication, but the urinary phosphorus was very high, 2500 to 2900 mg.

The serum phosphorus was low despite of the positive calcium and phosphorus balances. The dose of vitamin D_2 was therefore increased from 120,000 to 370,000 units in balance periods 14 and 15 (April) while the phosphate and calcium intakes were unchanged. This normalized the serum phosphorus. The patient was then able to walk without support during short periods, and the skeletal pains had decreased. The muscular weakness had improved.

At the end of the third month (balance period 16), the phosphate dose was increased to 15 g per day (corresponding to 3 g phosphorus) and with that dose serum phosphorus has been constantly normal. One month later (balance period 2, beginning of May), the dose of vitamin D_2 was further increased to 545,000 units a day. By now the patient was able to move around without crutches or support, although he had a typical waddling gait. After 15 minutes or so of walking, the patient developed pains in the hip joints and had to rest. At the end of May, however, muscular strength was nearly normal (as was the electromyogram) and the patient was completely mobilized. There was still a slight waddling gait. The patient left the hospital in the beginning of June after almost six months in hospital. The patient was now in strongly positive calcium and phosphorus balance, retaining about 1500 mg of calcium and about 1000 mg of phosphorus. The serum calcium and phosphorus were normal and the extremely large dose of D_2 (545,000 units) had not produced hypercalcuria.

During two and a half months at home, the rather heavy medication was kept constant (545,000 units of vitamin D_2, 3000 mg phosphorus, and 2280 mg calcium as tablets). Check-ups of serum calcium, phosphorus and alkaline phosphatase and creatinine were made at four week intervals and the urinary calcium was also determined. Physically the patient improved steadily. In the beginning of August, however, a high serum calcium value (5.7 mEq/l) was seen for the first time and the patient was therefore readmitted to the hospital.

On admission in August 1966 the serum calcium was high, 5.7–6.0

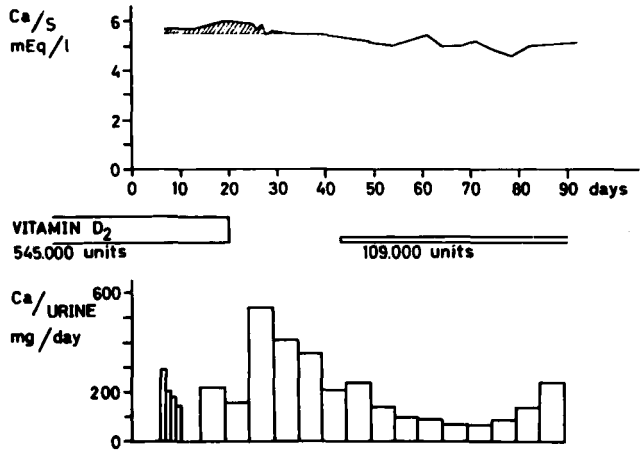

Figure 5. Serum and urinary calcium during a period of slight vitamin D_2 intoxication.

mEq/l, and the urinary calcium was 294 mg, also a high value. The patient's calcium and phosphorus balances were restudied for fifteen 5-day periods. Despite the omission of both vitamin D_2 and calcium the urinary calcium was high for three balance periods (Figure 5). The serum calcium became normal 1–2 weeks after omission of the vitamin (Figure 4). The calcium tablets and all vitamins were omitted for about one month and during this period calcium fell to 5.2–5.5 mEq/l. After four weeks without vitamin D_2, a dose of 109,000 units was instituted. For the ten following balance periods the calcium and phosphorus metabolism was acceptable as judged from the studies of balances and blood chemistry and the patient was discharged for out-patient control.

In December 1966 the phosphate intake was lowered to 10 g/day due to the possible interference by oral phosphate with iron absorption (see below). This was followed by a new bout of hypercalcemia (Figure 4). After 10 days omission of D_2 and reinstitution of 15 g phosphate/day, a lower dose of 45,000 units of D_2 was begun.

EFFECT OF TREATMENT ON TRACE ELEMENT BALANCES

The balances for the following trace elements were determined before (balance period 1) and during (period 22) treatment: As, Ba, Cd, Co, Cr, Cs, Cu, Fe, Hg, Rb, Sb, Se and Zn. Among the trace elements with known biological function (Figure 6), Co showed a negative bal-

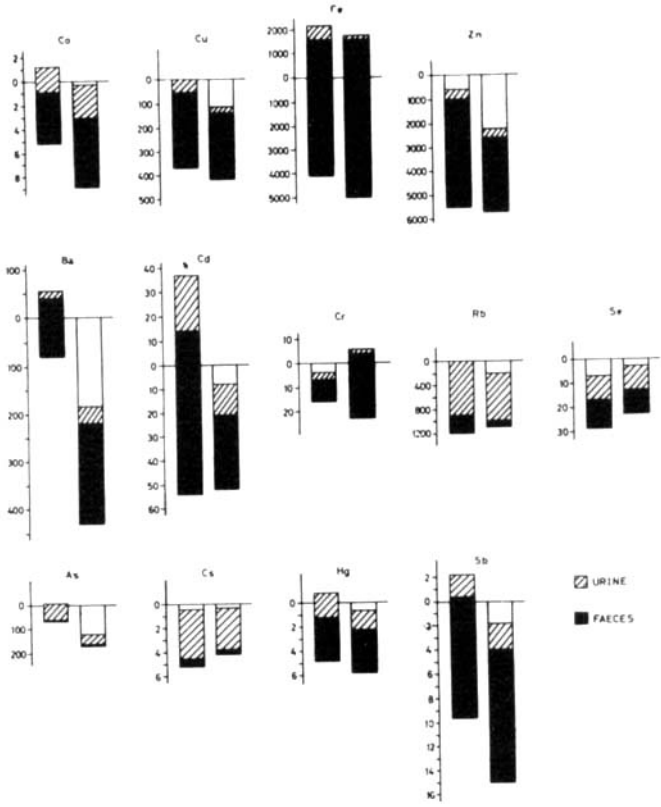

Figure 6. Trace element balances before and during treatment with oral phosphate and vitamin D_2 (for key see legend to Figure 4).

ance before and a positive balance during treatment. The balances of Cu and Zn were somewhat more positive after treatment than before. On the other hand, the Fe-balance was negative before as well as after treatment.

Among the balances of trace elements with suspected biological function the Cr, Rb, and Se balances were not changed in any definite way by treatment. The Ba-balance was very similar to the Ca-balance (Figures 4 and 6). The Cd-balance, like the Ba-balance, was negative before and positive after treatment.

Some trace elements without known biological function were also determined. Among these elements the balances of As, Hg and Sb became positive during treatment while the Cs balance was unchanged by treatment.

THE POSSIBLE EFFECT OF SODIUM MONOPHOSPHATE ON IRON ABSORPTION

On admission, the hemoglobin concentration was 13.2 g per 100 ml. Since the serum iron was normal (135 μg per 100 ml), little attention was paid to the slight anemia. Before phosphate administration began, the hemoglobin was only 11.0 g per cent and the serum iron was low, 28 μg per 100 ml. A series of intravenous iron injections (Ferrigen, 5 ml daily for 10 days) was given. This produced a reticulocytosis, and within one month the hemoglobin was 14.5 g per cent. The iron deficiency was then thought to be secondary to the gastrectomy. After six months of phosphate therapy, a significant anemia had developed, however, and the serum iron was again low, 25 μg per 100 ml. There were no traces of blood in the stools and no ulcer was visible on the roentgenograms.

It was suggested that large doses of oral phosphate might interfere with the absorption of iron by causing formation of insoluble iron salts. In order to clarify this point, a separate study of iron absorption by means of the double isotope technique of *Hallberg, Brise & Sölvell* (21) was undertaken.

The patient was given sodium monophosphate, 15 g, every other day for a period of ten days. On each of the five days when phosphate was given, the patient took 3.4 μg of $^{55}FeCl_3$ orally and on the other five days when no phosphate was given, the same amount of $^{59}FeCl_3$ was given orally. The incorporation of the two isotopes into hemoglobin was studied 2, 9 and 19 days after the end of the 10-day period of isotope administration. Almost twice as much of ^{59}Fe as of ^{55}Fe was found in the erythrocytes (Figure 7), suggesting that the sodium monophosphate can interfere considerably with the absorption of iron. Accordingly the patient has been given a daily dose of 220 mg iron (Ferromyn S, 6 tablets), and the hemoglobin concentration has remained normal on this therapy.

EFFECT OF TREATMENT ON SKELETAL MUSCLE FUNCTION

Muscular weakness was a very striking symptom on admission. The patient was unable to stand without support for more than a few minutes and could not walk unaided. When rising from a chair he "climbed" with his hands on his legs. He was unable to rise from the floor without supporting himself on a chair or some other piece of

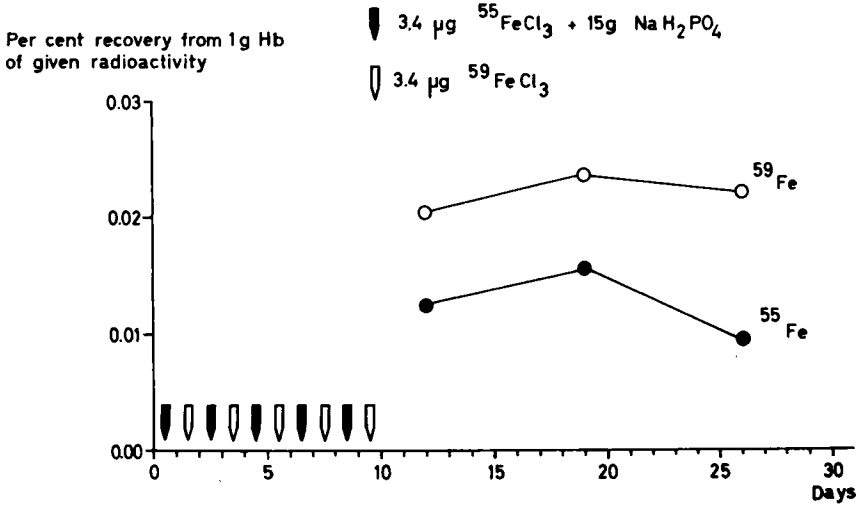

Figure 7. Double isotope study with regard to the effect of oral phosphate therapy on iron absorption. The Fe isotope given together with phosphate was incorporated more slowly into hemoglobin than the other isotope which was given without phosphate.

furniture. Although the muscle weakness was generalized, it was obvious that the muscles of the shoulder and the pelvis were most severely affected. There were, however, no contractures.

A definite improvement in muscular strength was experienced by the patient after he had been in positive calcium and phosphorus balances for about one month. After 6–9 months of treatment the muscular strength could be considered as normal.

Electromyography was performed at three occasions, before treatment was started and after six and nine months of treatment. In the first recording, typical signs of myopathy were found. In the second there was an obvious improvement but still a slight overrepresentation of "thin" action potentials. The third recording, after 9 months of treatment, was considered to be normal.

RENAL FUNCTION

Before treatment was started, serum creatinine was 0.75 mg per 100 ml and the glomerular filtration rate 140 ml/min (endogenous creatinine clearance). During the first 4 months of hospital treatment, the serum creatinine was checked every week and was lower in all instances than 0.9 mg per cent. At the peak of hypercalcemia in August the

same year, however, (Figure 4) the serum creatinine was 1.2 mg per 100 ml and the filtration rate 92 ml/min. In April of 1967 renal function tests were as follows: serum creatinine 0.8 mg per cent, endogenous creatinine clearance 88 ml/min, inulin clearance 80 ml/min.

ALKALINE PHOSPHATES

On admission the alkaline phosphatase was 3.9 Bessey-Lowry units (upper limit of normal = 2.5 units). It stayed only moderately elevated (6–10 units) until the calcium and phosphorus balances had been positive for about three weeks, at which time it rose to 16.5 units but fell again to a level of around 10 units. After the dose of 545,000 units of vitamin D was instituted in May, the alkaline phosphatase reached its highest value of 25 units and remained high, around 20 units, for two months. When the hypercalcemia occurred in late August of 1966, the alkaline phosphatase had dropped to 6 units. Since then, the value has been only moderately increased, 5 to 10 units.

ROENTGENOGRAPHIC FINDINGS

On admittance to the metabolic ward in January 1966, 35 Milkman fractures were present in the skeleton in most sites where such fractures have been described in osteomalacia (22). The collum femoris showed varus position bilaterally. The sternum was fractured at an angle of 90°. There was a pronounced thoracic deformity with marked gibbus of 90°, pidgeon chest, and cod-fish vertebrae. There was also general and severe demineralization of the bone.

The first roentgenographic evidence of osteomalacia, such as patchy rarification of bones and Milkman fractures, were observed in 1959 after a six month history of low back pain. The roentgenological findings are summarized in Table 1.

After five months of treatment with vitamin D_2, calcium, and phosphate, there was generally increased callus formation in the fractures, and after seven months all of the Milkman fractures had healed completely. The low mineralization of the skeleton was still rather evident at this time, however.

MICRORADIOGRAPHY OF THE BONE TISSUE

Biopsy of the bone was taken twice, before effective therapy was started in January 1966, and after about half a year of treatment, in October

Table 1.

1959 Body height 176 cm	*Febr.:* Fractures of transverse processes of L_2, L_3, and L_4, with moderate callus formation. Fracture of the right 9th rib. Rarefications in the 9th, 10th, and 11th ribs on right side. Normal X-ray of the pelvis, hip joints, and upper parts of femors. *Nov.:* Additional destruction in the right 8th rib and the 8th and 9th ribs on the left side. *Dec.:* Generalized demineralization of the skeleton. "Old" fractures bilaterally in the upper parts of the tibiae and fibulae and in the fifth right metatarsal, all of them showing callus formation.
1960 Body height 175 cm	*March:* Fracture without dislocation in the sacrum at the S_4 level. Now also fractures in the right superior and inferior rami of the pelvis, no dislocation.
1963 Body height 173 cm	*Febr., March:* Demineralization of the skeleton, more pronounced than in March 1960. Compression of the thoracic vertebrae, which now have a wedge-like appearance. The fractures in the pelvic ring are healed relative to March 1960. Fracture of the right femoral neck with slight varus dislocation, visible callus. The old fractures in the tibiae and fibulae are still visible, but largely healed. *May:* Additional fracture of the right 6th rib.
1965 Body height 163 cm	*Jan.:* Marked deformity of the thorax with pidgeon chest. The left lateral portion of the rib cage is pressed medially. The thoracic kyphosis has increased to almost 90°, and there is a fracture of the sternum with an angulation of 90°. The fracture of the right femoral neck is still visible as in 1963, but the varus dislocation is more pronounced. There is now an almost identical type of fracture in the left femoral neck with a similar dislocation. Fracture with callus of the right tibia 10 cm below the knee joint. The "old" fractures in the tibiae and fibulae from 1959 are still visible.
1966 Body height 159.5 cm	*Febr.:* The whole skeleton is reexamined, and compared with Jan. 1965. None of the fractures are healed. Recent multiple fractures in both scapulae. Extensive demineralization of the whole skeleton.
Body height 165 cm	*Sept.:* Continued low mineralization of the skeleton. All fractures are healed.

1966. The specimens were taken from the lateral part of the iliac crest. Thus, the material studied was composed mainly of cancellous bone. At the first biopsy the bone was very soft and elastic, and was felt by the palpating finger as a piece of rubber. The bone specimen could be

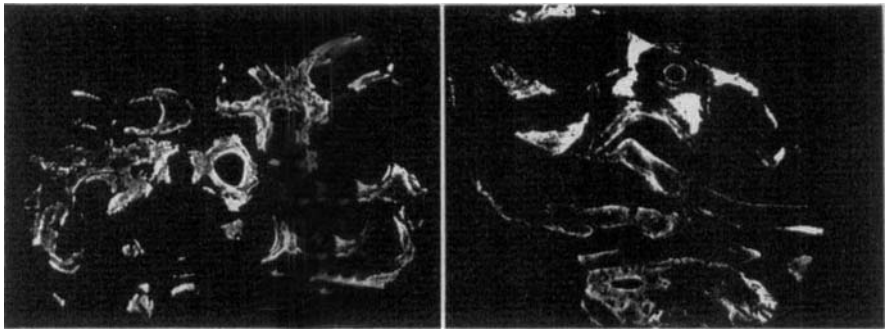

Figure 8. Microradiography of the bone tissue before (left figure) and after (right figure) treatment with phospate, vitamin D_2 and calcium. For explanation see the text.

cut out with scissors. At the time of the second biopsy the bone had normal hardness and appearance. The specimens were ground to a thickness of 40 microns and microradiographs were made in order to study the distribution of mineral salts.

The left part of Figure 8 shows the microradiographic appearance of the iliac bone before treatment. The most striking feature is the disorganization of the trabecular system, which is thin and irregular and lacks the normal lamellar structure. The trabeculae are separated by wide nonmineralized regions, but no distinct resorption cavities can be seen. The trabeculae also show marked homogeneity in the distribution of mineral salt, the osteons being very few and with small variations in mineralization. Thus, the microradiographic pattern before treatment is mainly that of pronounced inactivity of the remodelling of the bone.

Figure 8, right part, is a microradiogram of the iliac bone tissue after treatment. The trabeculae are now course and tightly packed and show a typical lamellar structure with a wide variation of the calcium content in different areas. The amount of osteons is greatly increased as compared with before therapy. Centrally in the trabeculae the degree of mineralization is very high. These areas have a homogenous structure and distribution of bone salt, analogous to the only calcified structures that were to be seen before treatment. Thus, the microradiographic picture shows a very varied distribution of the calcification indicating both absorption and new deposition of bone-salts in the different structures. The pattern after treatment is similar to that of the callus in fractures (28) or bone-grafts (29).

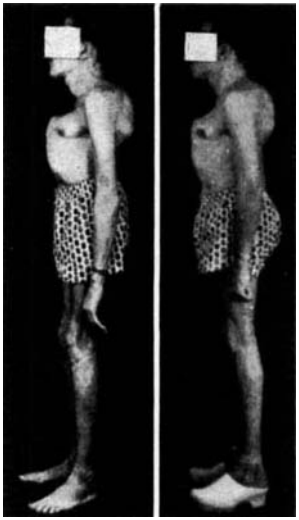

Figure 9. The effect of orthopedic and metabolic treatment on body stature of the patient. Left figure: on admission, before effective treatment. Right figure: after 3½ months of therapy including 12 traction treatments.

ORTHOPEDIC TREATMENT

A tragical sequel of the long-standing osteomalacia was the severe thoracic deformation with the pidgeon chest and marked kyphosis (Figure 9). Between 1959 and 1966 the body height had decreased from 176 to 159.5 cm. Orthopedic treatment of this deformity seemed worth trying and was performed as described in the following. The treatment was undertaken early in the vitamin D_2 and phosphate therapy (Febr.–May–66), *i.e.* while the skeleton still was in the osteomalacic state.

Twelve successive traction treatments and plaster fixations were made. Traction of the spine was applied with the patient standing and a suspension sling around his head. After each extension treatment a plaster brace was used to fix the trunk in the resulting position. In the beginning, the procedure had to be performed with considerable haste due to the patient's poor condition and muscular weakness. For the same reason, measures were taken to make the plaster brace as light as possible. Later in the course of treatment there were no such difficulties.

The therapy resulted in an increase in body height from 159.5 to 165 cm and in some correction of the thoracic kyphosis (Figure 9). The anterior part of the thoracic deformity, the pidgeon chest, was nevertheless only very slightly improved. The possibility of surgical correction of the sternal deformity was discussed with the thoracic surgeons.

The possible gains from such an operation were considered small relative to the risk of impairment of respiratory function.

The loss of body height could not be attributed to the thoracic deformity alone. The fractures of the femoral necks, resulting in a marked varus position in both hip joints, caused shortening of the legs which could be estimated as 3 to 5 cm. The varus deformity also constitutes a risk of future osteoarthritis of the hip joints. Although this possibility could be considered an indication for corrective osteotomy of the femoral necks, the procedure has not been done thus far. Furthermore, it was considered unwise to immobilize the patient for another prolonged period by such operations and thus again delay his rehabilitation. It is possible, however, that orthopedic surgery will have to be performed at some time in the future if signs of arthrosis should appear in the hip joints.

DISCUSSION

The characteristic features of the present case, osteomalacia, hypophosphatemia, renal glucosuria in the absence of aminociduria, and other tubular reabsorption defects fit well with the diagnosis of hypophosphatemic osteomalacia of Type II, according to *Dent*'s (7) classification with the important exception of the absence of a positive family history. This particular disturbancy in renal tubular reabsorption must be extremely rare. A survey of the pertinent literature has thus far revealed only six cases (4, 7, 12), comparable with the actual case. In at least one of these cases, no family history of metabolic bone disease was found. Furthermore the type II tubular defect has occurred only in adults, in contrast with the more common type I defect which obviously is far more common in children than in adults.

The present case was complicated by a bleeding ulcer that necessitated gastric resection four years after the onset of symptoms of metabolic bone disease. It is quite clear from the hospital records that the disease progressed rapidly after the gastric resection. Two main factors seem to have contributed to this, namely the lowering of the vitamin D_2 dose (for unknown reasons) from 50,000 to 5,000 units/day and the patient's dislike for dairy products which seems to have decreased his postoperative calcium intake to about 500 mg/day. The gastrectomy did not seem to cause any significant malabsorption since the daily fecal fat excretion was found to be within normal limits.

Compared to most reported cases of osteomalacia, the generalized skeletal destruction observed in this case, including a very rapid thor-

acic deformation in the course of three months, was remarkable. Nevertheless, the results of combined therapy with vitamin D_2, oral phosphate and calcium, and orthopedic treatment was very gratifying and resulted in a total rehabilitation of the patient in less than one year.

Most cases of hypophosphatemic osteomalacia have, until now, been successfully treated with large doses of vitamin D and frequently with calcium supplements. In many cases this can bring about not only healing of fractures, but also normalization of serum phosphorus (23, 24). In this case 109,000 units of D_2 did not normalize the serum phosphorus. In view of the risks of vitamin D intoxication by higher doses as well as the protective effect of oral phosphate against hypercalcemia of all etiologies (13), it was decided to give oral phosphate in large amounts. Further support for the use of phosphate therapy was obtained from the papers by *Frame et al.* (9, 10) and *Rose* (12).

The course of the combined D_2 and phosphate treatment was fairly uncomplicated in spite of the fact that more than 500,000 units of vitamin D_2 were given for several months. Exceptions were two bouts of moderate hypercalcemia, one after 7 months of treatment with very large doses of vitamin D_2 (Aug., Figure 4) and the second during the administration of a moderate vitamin dose in connection with an attempt to lower the phosphate dose (Dec., Figure 4). The second episode of hypercalcemia offers some support for the abovementioned hypothesis that phosphate is of value in minimizing the risk of vitamin D-induced hypercalcemia. The question can be raised of whether, in this case, phosphate treatment alone could have produced the same good result, healing of fractures and rehabilitation of the patient, without the risk of vitamin D intoxication. In fact, two cases of the adult Fanconi syndrome are described where this has been tried, evidently, with good results (11). This type of therapy has been reported to be of little value in children with vitamin D-resistant rickets, however (25). The mentioned therapy was not systematically investigated in the present study.

In spite of the fact that only two short periods of moderate hypercalcemia occurred during the treatment, a slight impairment of glomerular filtration was induced by the therapy. A plausible explanation for this undesirable effect is the well-known vitamin D intoxication. It cannot be ruled out, however, that the phosphate treatment *per se* carries the risk of inducing renal injury. Some authors (5) have, in fact, reported unfavourable results with phosphate administration in renal tubular osteomalacia and they claim that it may cause renal in-

jury. The documentation for this is scarce, however. Of considerable interest in this connection is the recently published experimental study by *Herbert et al.* (26) indicating that the mechanism for the calcium-lowering effect of phosphate seems to be a decreased solubility of calcium in the body fluids.

The alkaline phosphatase was checked frequently during treatment. Starting from a slightly elevated level, the value increased markedly during the first four months of treatment and was roughly correlated with the calcium retention as judged from the balances, possibly reflecting increased osteoblastic activity. So far, (August 1967), after more than one year of treatment, the alkaline phosphatase has not been normalized. The most probable explanation for this is that full mineralization of the bone has not yet been achieved in spite of the complete clinical recovery.

On admission, the patient had a pronounced and generalized muscular weakness, and EMG recordings showed signs of myopathy. The symptoms disappeared completely on treatment and the EMG also became normal. Generalized myopathy of this degree is uncommon in osteomalacia although a slighter degree of muscular involvement causing the well-known waddling gait has often been reported in this group of diseases. The myopathy is difficult to explain as being caused by immobilization and skeletal pains alone. The mechanism for the development of the myopathy in osteomalacia is, however, unknown as is the often remarkable and rapid improvement seen with adequate treatment.

The microradiographic pattern of the bone tissue was interpreted as showing marked inactivity of the remodelling of bone before treatment. After treatment the bone tissue showed pronounced increase both of absorption and new deposition of bone salts. This view differs from the one of *Engfeldt et al.* (1956, 30), who in their cases of vitamin D resistant rickets came to the conclusion that there was "intense absorption and new deposition of mineral salts in both untreated and treated patients". Maybe the difference can be explained by the fact that their patients were young children from 3 to 6 years of age, our patient a grown-up person.

Iron balance studies performed before and during treatment showed that the iron balance was negative in both conditions. By means of a double isotope technique, data was obtained suggesting that oral phosphate in the dose used (15 g/day) might cause significant reduction in iron absorption from the intestine. It is possible that insoluble iron

salts are formed that are absorbed poorly. This phenomenon might be overcome by an adequate supplementation of iron as was done in the present case.

The trace element studies performed showed that the patient had negative balance of many trace elements before treatment, *e.g.* As, Ba, Cd, Co, Hg and Sb. The clinical significance of these findings must, however, await a more complete understanding of the physiological and metabolic role of these elements. Only recently have methods been made available which permit a systematic study of the full balances of various trace elements in selected cases of metabolic disorders (27, 28).

Orthopedic treatment has thus far been limited to extension and plaster fixation in a partly successful attempt to correct the thoracic deformity and improve the posture of the patient. Other types of correction which could be indicated have been postponed thus far.—On the basis of the experience acquired from the present case, the following statement seems justified. The orthopedic treatment of severe cases of osteomalacia with skeletal deformities of physiological or cosmetic significance should be carefully planned and synchronized with the metabolic treatment of the patient. This is necessitated by the fact that some of the orthopedic procedures (*e.g.* extension treatment) should be performed while the skeleton of the patient is in the soft and malleable osteomalacic state. It might even be desirable, in certain cases, to withhold treatment until maximal effect of the orthopedic procedures have been obtained. Other methods for orthopedic corrections, *e.g.* corrective osteotomies, should not be used until full metabolic control of the mineralization process and a partial or complete remineralization have been achieved in order to facilitate fixation and healing of the osteotomies.

For similar reasons, the physical rehabilitation by systematic training must be synchronized with the metabolic treatment of the patient.

SUMMARY

A case of very severe hypophosphatemic nonhereditary osteomalacia with renal glucosuria complicated by gastric resection is described in a 27-year old man. The first symptoms appeared at the age of 18. At 26 the patient was severely crippled after the loss of 16.5 cm in body height, the development of a thoracic deformity, and a marked proximal myopathy. After one year of treatment with high doses of vitamin

D_2, phosphate, and calcium, he was completely rehabilitated. By means of orthopedic extension treatment performed during the osteomalacic state, some correction of the thoracic deformity was obtained which included a gain in body height of 5.5 cm. The balances for calcium, phosphorus, and a number of trace elements were studied before and during treatment and are discussed. The experience from this case supports the view that oral phosphate has a place in the treatment of hypophosphatemic osteomalacia.

RESUME

Il est décrit un cas très grave d'ostéomalacie hypophosphatémique non-héréditaire, avec glucosurie rénale, compliquée de résection gastrique chez un jeune homme de 27 ans. Les premiers symptômes se sont manifestés à l'âge de 18 ans. A 26 ans, le malade était gravement invalide après une perte de hauteur du corps de 16,5 cm, le développement d'une déformité thoracique et une myopathie proximale marquée. Après un an de traitement avec de fortes de vitamines D_2, de phosphate et de calcium, il était entièrement remis. Au moyen d'un traitement par extension orthopédique pratiquée durant l'état ostéomalacique, une certaine correction de la déformité thoracique a été obtenue avec une récupération de 5,5 cm de la hauteur du corps. Les métabolismes du calcium, du phosphore et d'un nombre d'autres éléments ont été étudiés avant et pendant le traitement et sont discutés. L'expérience acquise de ce cas soutient le point de vue que le phosphate oral a une place dans le traitement de l'ostéomalacie hypophosphatémique.

ZUSAMMENFASSUNG

Ein Fall von schwerer hypophosphstämischer, nichterblicher Osteomalazie mit einer renalen Glykosurie, kompliziert mit Ventrikelresektion bei einem 27 jährigen Mann, wird beschrieben. Die ersten Symptome erschienen im Alter von 18 Jahren. Mit 26 Jahren war der Patient nach dem Verlust von 16,5 cm an Körperhöhe, der Entwicklung einer thorakalen Deformitet und einer ausgesprochenen, proximalen Myopathie schwer invalidisiert. Nach einer einjährigen Behandlung mit hohen Dosen von Vitamin D_2, Phosphat und Calcium war er vollständig wiederhergestellt. Mittels orthopedischer Streckung, die während des osteomalazischen Zustandes ausgeführt wurde, konnte eine gewisse Korrektur der Thoraxdeformitet erhalten und eine Zunahme der Kör-

perhöhe um 5,5 cm gewonnen werden. Die Werte für Calcium, Phophor und einer Anzahl von Spurelementen wurden vor und während der Behandlung untersucht und werden besprochen. Die Erfahrung aus diesem Falle unterstütz die Ansicht, dass orale Phosphatbehandlung einen Platz in der Behandlung von hypophosphatämischer Osteomlazie hat.

REFERENCES

1. Stowers, J. M. & Dent, C. E. (1947) Studies on the mechanism of the Fanconi syndrome. *Quart. J. Med.* **16**, 275.
2. Wallis, L. A. & Engle, R. L. (1957) Adult Fanconi syndrome. Review of eighteen cases. *Amer. J. Med.* **22**, 13.
3. Albright, F., Butler, A. M. & Bloomberg, E. (1937) Rickets resistant to vitamin D therapy. *Amer. J. Dis. Child.* **54**, 529.
4. Milkman, L. A. (1934) Multiple spontaneous idiopathic symmetrical fractures. *Amer. J. Roentgenol.* **32**, 622.
5. Williams, T. F., Winters, R. W. & Burnett, C. H. (1960) Chapter 36. Familial hypophosphatemia and vitamin D-resistant rickets. pp. 1177–1221 in "The metabolic basis of inherited disease". McGraw-Hill Co., Inc., New York.
6. Leaf, A. (1960) Chapter 37. The syndrome of osteomalacia, renal glucosuria, aminoaciduria, and hyperphosphaturia (The Fanconi syndrome), pp. 1222–1245 in "The metabolic basis of inherited disease". McGraw-Hill, New York.
7. Dent, C. E. (1952) Rickets and osteomalacia from renal tubule defects. *J. Bone Jt Surg.* **34B**, 266.
8. Fraser, D., Jaco, N. T., Yendt, E. R., Munn, J. D. & Liu, E. (1957) The induction of *in vivo* and *in vitro* calcification in bones of children suffering from vitamin D-resistant rickets without recourse to large doses of vitamin D. *Amer. J. Dis. Child.* **93**, 84.
9. Frame, B. & Smith, R. W. Jr. (1958) Phosphate Diabetes: A case study of osteomalacia. *Amer. J. Med.* **25**, 771.
10. Frame, B., Smith, R. W. Jr. & Wilson, G. (1961) Acquired nonfamilial osteomalacia of vitamin D-resistant type. *Henry Ford Hosp. Med. Bull.* **9**, 548.
11. Wilson, D. R. & Yendt, E. R. (1963) Treatment of the adult Fanconi syndrome with oral phosphate supplements and alkali. *Amer. J. Med.* **35**, 487.
12. Rose, G. A. (1964) Role of phosphate treatment of renal tubular (hypophosphataemic) rickets and osteomalacias. *Brit. med. J. ii*, 857.
13. Goldsmith, R. S. & Ingbar, S. H. (1966) Inorganic phosphate treatment of hypercalcemia of diverse etiologies. *New Engl. J. Med.* **274**, 1.
14. Fiske, C. H. & SubbaRow, Y. (1925) The colorimetric determination of phosphorus. *J. biol. Chem.* **66**, 375.
15. Bessey, O. A., Lowry, O. H. & Brock, M. J. (1946) A method for the rapid determination of alkaline phosphatase with five cubic millimeters of serum. *J. biol. Chem.* **164**, 321.
16. Jacobsson, K. (1960) The determination of tartrate-inhibited phosphatase in serum. *Scand. J. clin. Lab. Invest.* **12**, 367.

17. Hambraeus, L. (1963) A modified automatic aminoacid analyzor. *Svensk Kem. Tidskr.* **75**, 638.
18. Spackman, D. H., Stein, W. H. & Moore, S. (1958) Automatic recording apparatus for use in the chromatography of amino acids. *Analyt. Chem.* **30**, 1190.
19. Wester, P. O., Brune, D. & Samsahl, K. (1964) Radiochemical recovery studies of a separation scheme for 23 elements in biological material. *Int. J. Appl. Rad. Isot.* **15**, 59.
20. Reifenstein, E. C. Jr., Albright, F. & Wells, S. L. (1945) The accumulation, interpretation and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen. *J. clin. Endocrin.* **5**, 367.
21. Hallberg, L., Brise, H. & Sölvell, L. (1960) *Proc. VIIth Intern. Congr. Soc. of Hematol.* Rome.
22. Le May, M. & Blunt, J. W. Jr. (1949) A factor determining the location of pseudofractures in osteomalacia. *J. clin. Invest.* **28**, 521.
23. Albright, F. & Reifenstein, E. C. Jr. (1948) The parathyroid glands and metabolic bone disease. Williams & Wilkins, Baltimore.
24. Dent, C. E. & Friedman, M. (1964) Hypophosphatemic osteomalacia with complete recovery. *Brit. med. J. ii*, 1676.
25. Frame, B., Smith, R. W. Jr., Fleming, J. L. & Manson, G. (1963) Oral phosphates in vitamin-D-refractory rickets and osteomalacia. *Amer. J. Dis. Child.* **106**, 61.
26. Herbst, L. A., Lemann, J., Petersen, J. P. & Lennon, E. J. (1966) Studies of the mechanism by which phosphate infusion lowers serum calcium concentration. *J. clin. Invest.* **45**, 1886.
27. Wester, P. O. & Boström, H. (1968) Spårelementstudier vid några metaboliska rubbningar. *Nord. Med.*, in print.
28. Nilsonne, U. (1959) Biophysical investigations of the mineral phase in healing fractures. *Acta orthop. scand.* Suppl. 37.
29. Holmstrand, K. (1957) Biophysical investigations of bone transplants and bone implants. *Acta orthop. scand.* Suppl. 26.
30. Engfeldt, B., Zetterström, R. & Winberg, J. (1956) Primary vitamin-D resistant rickets. III. Biophysical studies of skeletal tissue. *J. Bone Jt Surg.* **38-A**, 1323.