Myopathy in hypophosphataemic osteomalacia presenting in adult life

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SYNOPSIS Three cases of hypophosphataemic osteomalacia presenting in adult life, in which a myopathy was a prominent presenting feature, are described. In one, a nasopharyngeal haemangioma was also present. Possible mechanisms underlying the myopathy are discussed briefly.

Muscle weakness as a major or even the presenting symptom of metabolic bone disease has been recognized for many years. Whistler (1645) in the first clearly documented description of rickets referred among the *Signa Diagnostica* of this disease to the profound weakness that occurs in the limbs and trunk, and similar observations were made in the earliest account of osteomalacia by the French surgeon Jean Louis Petit (1726). Since then, it has become apparent that there exists an important group of myopathic disorders associated with osteomalacia and which are due to either a deficiency of vitamin D or as a consequence of 'resistance' to its biological effects.

During the 1950s, a rare form of primary non-familial osteomalacia presenting in adult life characterized by hypophosphataemia and high phosphate clearance was established. The syndrome was defined by Dent and Stamp (1971) who described in detail nine patients and reviewed all previously reported cases. The essential clinical features of this unusual cause of osteomalacia comprise an often prolonged history of widespread bone pains, loss of stature from vertebral collapse, and muscular weakness. The weakness predominantly affects proximal muscles and, since bony disorders of the spine and pelvis frequently coexist, may markedly affect the trunk and lead to a waddling gait. The muscles are painless, the limbs usually hypotonic, but the

tendon reflexes are characteristically brisk. The degree of muscle weakness may be difficult to assess because of coincidental bone pain. As well as the hypophosphataemia and relative hyperphosphaturia—that is, high renal phosphate clearance—investigations typically reveal elevated alkaline phosphatase activity, radiological changes of osteomalacia, and in some patients an excess of glycine on urine amino-acid chromatography. The plasma calcium concentrations are consistently normal. In addition to the phosphaturia, renal glycosuria has been found in some cases, enabling the tubular defect to be classified as a type II osteomalacia (Dent, 1952). In a few instances electromyography has been performed on affected muscles and myopathic features noted (Smith and Stern, 1969; Dent and Stamp, 1971); nerve conduction studies have always proved normal. The relationship of tumours to this condition is discussed below, as are aspects of therapy. No familial case has yet been described, contrasting with the much more common dominant, sex-linked, childhood-onset vitamin D deficient rickets, in which myopathy is absent (Williams and Winters, 1972).

Three adult patients with hypophosphataemic osteomalacia are reported here in which a myopathy was the prominent presenting symptom. In all patients the myopathy responded to appropriate treatment for the osteomalacia.

CASE 1

A 31 year old white woman, born in 1942, presented

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here in May 1974 with a history of intermittent pain around the rib cage particularly precipitated by coughing and sneezing, which had developed over the preceding seven years. Three years before admission she had complained of episodes of acute pain in the metatarsal area of both feet on walking, especially in tight shoes, and radiography of the feet at that time revealed healing fractures of two metatarsal heads. Also at that time she became aware of muscular weakness, initially causing difficulty in climbing high steps and in manoeuvring her legs when getting into a car. The weakness of both thighs subsequently progressed, and was associated with intermittent hip and low back pain. She was investigated in another hospital one year before admission here, when proximal muscle weakness and a waddling gait were noted, together with brisk tendon reflexes and bone tenderness on palpation. An electromyogram performed at that time was normal, and the only significant abnormal investigation found was a low renal threshold for glucose. The symptoms were considered to be hysterical and she was discharged. Her weakness, however, became more profound, and she had to pull herself upstairs, a task that became increasingly difficult with the development of proximal weakness in the arms, and for six months before admission she had been unable to raise her arms above her shoulders. She was admitted at that time to a second hospital for investigation, and was again thought to be psychoneurotic and no specific therapy was prescribed. She continued to deteriorate, commenced walking with a Zimmer frame, and was admitted to this hospital for further assessment.

On direct questioning, she had noted that her nails had become brittle, and that she had had a tendency to vomit occasionally over the preceding 10 years. Her weight had fallen by about 13 kg over four years, although she had always eaten an adequate and normal diet. Her sister reported that the patient had 'shrunk' over the preceding two years. The patient's family have been in good health, and there is no consanguinity.

Examination revealed dry, scaly skin and dry hair; her finger nails were brittle and cracked, and she had mildly carious teeth. There was bone tenderness on palpation over the left chest wall, hips and both tibiae. A marked thoracic kyphosis was present. Her skeletal measurements were: crown to pubis 67.5 cm, pubis to heels 87.5 cm, span 85.5 cm, giving an estimated height loss of 16 to 20 cm. Trousseau's and Chvostek's signs were absent, as were corneal calcification and Kayser-Fleischer rings, the latter observations being confirmed by slit-lamp examination. Her apex beat and heart sounds were apparent to the right of the midline; the trachea was central, but there were absent breath

sounds and a diminished percussion note inferiorly over the left side of the chest.

Neurological abnormalities were confined to the motor system. There was moderate diffuse wasting of the shoulder and upper arm muscles, and moderate wasting of the leg muscles particularly proximally, sparing those of the feet; the muscles were not tender. The muscles of the face were normal, but there was gross weakness of neck movements, especially flexion. Striking symmetrical weakness of all shoulder movements was apparent, and elevation of the arms was impossible above 45°. There was moderate weakness of elbow movements, but the hands were normal. A similar distribution of profound proximal weakness was noted in the legs, with sparing of ankle and toe movements. She was unable to turn over in bed, stand unaided, or sit up without much assistance; she could walk only a few yards using a Zimmer frame. All the tendon reflexes were very brisk, and the plantar responses were flexor.

Radiological examination of the skeleton showed generalized, severe loss of bone density with multiple fractures of the ribs, hands, and feet, and Looser zones in both pubic rami; no tumours were detected, and the lamina dura appeared intact. The chest radiograph showed displacement of the normally orientated heart to the right, and a very high left hemidiaphragm consistent on radiographic screening with congenital eventration of the hemidiaphragm. Radiography of the abdomen was normal, as were an intravenous urogram and barium meal and follow-through examinations.

The fasting plasma calcium ranged from 9.2 to 9.4 mg/dl, phosphorus 0.7 to 1.3 mg/dl, and alkaline phosphatase 32 to 43 KA units per dl. On a normal ward diet, 24-hour urinary calcium excretion ranged from 72 to 250 mg and urinary phosphorus 350 to 850 mg. Glycosuria was consistently present and was shown to be of renal origin; a urine amino-acid chromatogram showed an excess of glycine. Urine osmolality was 530 to 629 mOsmol/kg, and a 24-hour urine pH was 5.8. Urine culture was sterile. The following investigations were normal: blood picture, ESR, parathyroid hormone, serum folate, vitamin B₁₂, vitamin A, copper and caeruloplasmin, protein bound iodine, creatine phosphokinase and aldolase, total protein, albumin, globulin and protein electrophoresis, creatinine clearance, urine urea and electrolyte excretion, and glucose and xylose tolerance tests. Blood serological tests for syphilis were negative. The plasma electrolytes were normal, although the plasma bicarbonate was at the lower limit of normal. An electrocardiogram and electroencephalogram were normal. Electromyography with concentric needle samplings of the right deltoid, triceps, vastus medialis, and tibialis anterior muscles

demonstrated at all sites a proportion of brief, polyphasic and low amplitude motor units consistent with a myopathy. A biopsy of the left triceps muscle showed randomly scattered, rather small angulated fibres, with evidence of non-specific fibre atrophy on electron microscopy; histochemical examination revealed atrophy of type IIB fibres.

In view of the investigations, which confirmed a myopathy associated with osteomalacia, the diagnosis was made of adult presenting primary hypophosphataemic osteomalacia. She was also seen at that time by Professor C. E. Dent who confirmed the diagnosis, and she was subsequently started on treatment with vitamin D₂, 5 mg daily, disodium hydrogen phosphate, 10 g daily, and calcium supplements as bone meal, 8 g daily, together with physiotherapy. Within a month the weakness had started to improve: she was able to raise her arms above her head and walk with less difficulty. Her bone pain also lessened considerably. Within a few months she was walking unaided and able to look after herself at home.

CASE 2

A 56 year old woman, born in 1918, first developed stiffness and heaviness in both legs at the age of 48 years. Initially the weakness affected her when climbing stairs or rising from a chair, but shortly afterwards she became aware of weakness when raising her arms above her head and a tendency for them to tire easily with prolonged use. At that time she was referred on two separate occasions to psychiatrists, since her condition was thought to be hysterical in origin. The weakness gradually increased in severity causing progressive difficulty in walking, and she was virtually confined to a wheelchair by the age of 50 years. She was admitted in 1969 to the National Hospital, Queen Square. During the months before her admission she had in addition developed intermittent deep cramp and tenderness in the legs related to movement, and this was followed by the development of thoracic and lumbar pain on bending quickly, coughing, or sneezing. She had also complained of nasal obstruction of some months' duration with occasional purulent discharge from the left nostril. There was no significant family history.

Examination in 1969 revealed slight bilateral wasting of deltoid and quadriceps muscles and early contractures of the hamstrings. There was weakness of neck flexion and generalized but mainly proximal weakness in the upper and lower limbs, but pain made accurate assessment of muscle strength difficult. Weakness of a similar distribution was found in the lower limbs which again was accompanied by considerable pain. Tendon reflexes were brisk, and

the plantar responses were unobtainable because of previous arthroplasty operations on both halluces. Sensory examination was normal.

INVESTIGATIONS Full blood picture, erythrocyte sedimentation rate, plasma electrolytes, urea, phosphocreatine kinase, glutamic-oxaloacetic transaminase, and latex test for rheumatoid arthritis were all normal; the blood Wassermann reaction was negative. Electromyography showed no abnormality. A biopsy of the left triceps muscle showed some variation of fibre diameter, and many fibres demonstrated an increase in subsarcolemmal nuclei, but there were no pathognomic features; histochemical stains, however, revealed type II fibre atrophy, consistent with a myopathy. Radiographs of chest and spine were normal, but skull films and subsequent tomography showed opacification of the left frontal, ethmoid, and maxillary sinuses and of the left nasal cavity. The walls of the ethmoid sinuses were not visible and those of the maxillary sinuses were thin. A rounded filling defect protruding from the choanae into the nasopharynx was also visible. This defect was found to be due to a pedunculated growth of which as much as possible was removed surgically, although some polypoid material undoubtedly remained. The tumour proved histologically to be a haemangioma without evidence of malignancy.

She was readmitted in 1971 for further assessment. Despite a course of steroids, over the intervening two years her weakness had not altered significantly; she required assistance to walk even a few steps and spent most of her time in a wheelchair. Considerable proximal weakness was present in the arms as before. However, she had also noted an increasing bony deformity with a depression of the upper end of the sternum, and increasing bone pain over the chest wall on coughing or sneezing. Since commencing steroids, she had developed a dry, scaly erythema and tendency to bruise easily. On this admission, she was noted to have developed an appearance resembling Cushing's syndrome, with the skin and skeletal deformities of which she had complained. The neurological signs were similar to those noted on her earlier admission. Investigations at that time added the following information: serum calcium 9.9 mg/dl, serum phosphorus 1.3 mg/dl, alkaline phosphatase 187 i.u./l; her serum phosphocreatine kinase remained normal. Radiological examination of the chest, cervical and thoracic spine, pelvis, hips, and knees showed widespread bone rarefaction with numerous pathological fractures. Looser zones were present in the scapulae and right pubic ramus. Electromyography performed on the right deltoid, biceps, triceps, and vastus medialis muscles showed in all muscles a large proportion of low amplitude

motor unit action potentials of short duration; no spontaneous activity was seen, and there was no excess of polyphasic potentials; a few motor unit potentials were above the normal amplitude at 6 mV. The possibility of a myopathy in association with osteomalacia was considered, and the patient referred to Professor C. E. Dent at University College Hospital.

She was admitted under the care of Professor Dent in August 1971 for assessment of her metabolic state. Additional findings were of tender ribs on palpation and body proportions of: crown to pubis 66 cm, pubis to heel 76 cm on the right and 74 cm on the left, span 152 cm (confirming a height loss of 9 to 11 cm). Trousseau's and Chvostek's signs were negative. Investigations confirmed the reduced plasma phosphorus values and elevated alkaline phosphatase activity, and showed in addition increased urinary glycine excretion and a 24-hour urinary excretion of phosphorus of 252 mg and calcium 133 mg. A bone biopsy showed characteristic changes of osteomalacia.

The features of this case were considered to be consistent with adult presenting hypophosphataemic osteomalacia, and she was treated with daily doses of vitamin D₃ 5 mg, disodium hydrogen phosphate 10 g, and bone meal (Ossopan) 8 g. Thereafter she made slow but steady progress, with relief both from bone pain and muscle weakness. By the end of five weeks, she was able to walk again with two sticks. She has subsequently been followed up at University College Hospital, and over the past three years her vitamin D has been progressively reduced because of impending intoxication, and she is currently receiving 0.5 mg vitamin D₃ daily. Bone meal was discontinued after about a year and she has remained on the same dose of phosphate. Her symptoms continued to lessen, and she is now symptom free. These changes have been associated with a return to normal of her alkaline phosphatase activity and complete healing of her osteomalacia as demonstrated radiologically; her serum phosphorus concentration is maintained at 1.5–3.0 mg/dl.

CASE 3

Born in 1927, a 46 year old woman presented in October 1968 with a nine month history of increasing 'curvature of the spine' and several months' inability to raise her arms above her head. She had also noticed some lower back pain for many years and more recently a tendency to limp while walking. Apart from a hysterectomy and oophorectomy for uterine fibroids, her previous health had been good. There was no family history of neuromuscular or

bone disease, or of consanguinity. She had always eaten a normal diet.

On examination, there was a thoracolumbar kyphoscoliosis, wasting of the shoulder girdle musculature, especially of both deltoids, with weakness of abduction at the hips. The tendon reflexes were noted to be brisk, and the plantar responses flexor. Sensory examination was normal.

Electromyography at that time was performed on the right supraspinatus, deltoid, triceps and biceps muscles, and the left deltoid muscle, and was reported as normal. However, radiological assessment demonstrated widespread demineralization, Looser zones in both pubic rami and medial aspect of the right femur, and a diagnosis of osteomalacia was made. Further investigation revealed low serum phosphorus values (1.5 to 2.4 mg/dl) in the presence of a normal urine phosphorus excretion (680 to 1 280 mg/day) and elevated alkaline phosphatase activity (21 to 48 KA units per dl). The plasma calcium values were consistently normal. A blood count, erythrocyte sedimentation rate, plasma electrolytes, urea, proteins, and liver function tests, and a barium meal and intravenous urogram were all normal. No Bence Jones proteins were found in the urine and a urinary amino-acid chromatogram demonstrated normal amino-acid excretion. Glycosuria was absent.

A diagnosis of osteomalacia of unknown cause was made and treatment commenced with a high calcium diet, calcium gluconate, and 50 000 units vitamin D daily. Within a month she was feeling considerably better, and was asymptomatic apart from some minor stiffness in the left leg. This improvement was temporary, however, for within a few weeks she complained of lumbar pain, generalized muscular weakness, and required the aid of a stick for walking, but refused further assessment and defaulted from follow-up on many occasions.

In February 1971, she was admitted as an emergency after a fall in which she sustained a fracture of the right femoral shaft. Since her previous admission she had developed widespread bone pain and more diffuse muscular weakness was evident. The fracture failed to unite and required temporary insertion of a pin and plate, a procedure that produced three other fractures nearby resulting from the extreme friability of the bone. Further investigation of her underlying osteomalacia was undertaken, and the additional relevant results were of a normal ability to acidify her urine after an acid loading test with ammonium chloride, normal faecal fat excretion, and normal serum folate and vitamin B₁₂ values. The plasma calcium, phosphorus, and alkaline phosphatase values found previously were confirmed; histological examination of a bone biopsy obtained from

around the fracture site showed the characteristic features of osteomalacia. In view of the clinical features, biochemical, radiological, and histological findings and previous response to therapy, a diagnosis of adult-onset hypophosphataemic osteomalacia was made. She was started on phosphate supplements (3.5 g daily as Phosphate-Sandoz) in addition to the calcium supplement (2 g daily of Calcium-Sandoz) and high dose of vitamin D (calciferol 50 000 u daily) she was already receiving. Within a few weeks of commencing the phosphate supplement her fractures began to heal, her bone pain started to improve, and her strength gradually increased. She has been followed up since this time, and has maintained this slow progress, now walking with the aid of a stick, remaining free from pain and muscle weakness. The plasma calcium, phosphorus, and alkaline phosphatase values have remained very variable, and appear throughout to be unrelated to her clinical condition: there has been a tendency for her hypophosphataemia and raised alkaline phosphatase values to persist, despite continuation of therapy and her satisfactory symptomatic state.

DISCUSSION

The aetiology of the hypophosphataemia in these cases of osteomalacia is unknown. Certain features of the accompanying myopathy, however, pose some questions of relevance with regard to muscle disease.

There are many reports of myopathy associated with osteomalacia from a variety of causes and these have recently been reviewed (McArdle, 1974; Pallis and Lewis, 1974). Vicalè (1949) studied 33 patients with primary hyperparathyroidism and three patients with osteomalacia associated with renal tubular acidosis, and found muscular weakness affecting 21 patients in the former group and two in the latter. She also described the salient features that occur in the myopathy of metabolic bone disease, and drew attention to its proximal distribution, the slow waddling gait, the discomfort and pain that muscular effort produces, the very active reflexes that occur in the absence of pathological reflexes, and the bone tenderness on pressure. Vicalè also differentiated between a number of diseases with which this myopathy could be confused, and noted that 'the most difficult diagnostic differentiation is undoubtedly from the neurotic muscular disorders which may clinically

closely resemble the syndrome...'. Vicalè's findings contrast with those of Smith and Stern (1967), who in a retrospective study found definite muscle weakness in only six of 91 patients with primary hyperparathyroidism (three of whom had osteomalacia), although they confirmed the high incidence of weakness in their patients with osteomalacia; similar findings were obtained in their subsequent prospective study (Smith and Stern, 1969).

The weakness which may develop insidiously over many years results in severe disability, although formal testing may not correlate well with the symptoms experienced. The apparent delay in appearance and frequent absence of florid myopathic changes on electromyography, despite severe or even gross disability, is of interest. Histological examination revealed little of significance in the patients reported here, as Smith and Stern (1969) found in their cases. The histochemical findings consistent with type II fibre atrophy in two of the present patients are compatible with a metabolic myopathy, but are of no diagnostic significance (Dubowitz and Brooke, 1973). In all of the patients with this syndrome, the phosphocreatine kinase activity has either been normal or minimally elevated, and the activity of this enzyme in the plasma clearly does not correlate with the degree of weakness.

Calcium, phosphorus, and vitamin D may play an important part in the aetiology of the muscle weakness. The critical role of calcium in muscle function has been known since the classical experiments of Heilbrunn and Wiercinski (1947), who using a micropipette injected calcium-containing Ringer solution into muscle fibres of the frog adductor magnus and observed the ensuing contraction. It is recognized that both intra- and extracellular calcium concentrations are of critical importance to muscle cell function, particularly contractility (Frank, 1965). The plasma concentrations of calcium (and phosphorus) are, however, unlikely to be the sole factors of importance in the genesis of muscle weakness occurring in several metabolic bone diseases, a problem discussed by Henson (1966). For instance, in the present report there was little correlation between the myopathy and the plasma phosphorus concentration, and the calcium concentration remained normal through-

out. This lack of correlation between plasma calcium concentration and the severity of myopathy was noted by Prineas *et al.* (1965) in their report of two myopathic patients, one with a parathyroid adenoma, osteomalacia, and osteosclerosis, and the other with osteomalacia associated with idiopathic steatorrhoea. Smith and Stern (1967; 1969) were also unable to establish any relationship between proximal myopathy and plasma calcium or phosphorus values in their reviews of patients with metabolic bone diseases from a variety of causes.

The role of plasma phosphorus is also uncertain. It is clear that isolated hypophosphataemia induced iatrogenically (Baker *et al.*, 1974), by self-medication (Dent and Winter, 1974) and in normal volunteers (Lotz *et al.*, 1968) may produce muscle weakness together with myopathic changes on electromyography (Baker *et al.*, 1974); the weakness responds rapidly to phosphate repletion, and in these instances it is reasonable to assume that the weakness is attributable to hypophosphataemia. Moreover, the myopathy associated with primary hypophosphataemic osteomalacia has been successfully treated with phosphate replacement alone (Nagant de Deuxchaisnes and Krane, 1967), although Dent and Stamp (1971) found the greatest benefit using a combination of vitamin D, phosphate, and calcium supplements. Perhaps surprisingly, symptomatic improvement in adult-onset hypophosphataemic osteomalacia does not appear to correlate with the plasma phosphorus concentration in the present cases or in others reported. It is also recognized that myopathy does not occur despite longstanding hypophosphataemia in sex-linked familial hypophosphataemia.

It is possible that disordered metabolism of vitamin D could play an important part in the genesis of osteomalacic myopathy. Smith and Stern (1967) found low plasma vitamin D levels in three out of four patients in whom this was measured, but in their subsequent publication (1969) a definite correlation between myopathy and low plasma vitamin D activity was not demonstrated. More recently, understanding of vitamin D metabolism has increased considerably, and with it an appreciation of the number of possible derangements which might occur. It is apparent that vitamin D₃ (cholecalciferol),

whether obtained from the diet or by ultraviolet irradiation of 7-dehydrocholesterol in the skin, is converted to 25-hydroxycholecalciferol in the liver, and thence in the kidney to dihydroxy metabolites, of which 1,25-dihydroxycholecalciferol is the most biologically active (see Kodicek, 1974). The concentration and activity of the various metabolites of cholecalciferol have not been determined in hypophosphataemic osteomalacia, but it is tempting to postulate that, since impaired renal tubular function, as shown by the high renal phosphate clearance, appears to be an important factor in this disease, another renal function—the final conversion of cholecalciferol to its active dihydroxy metabolite—could also be impaired. This proposal is supported by the observation that the myopathy associated with osteomalacia from renal failure has been shown to improve after administration of small amounts of 1,25-dihydroxycholecalciferol (Henderson *et al.*, 1974). It is also pertinent that in the recessively inherited vitamin D resistant rickets, recent findings point to a defect in the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (Fraser *et al.*, 1973) and again a defect in the kidney is likely to be implicated.

The action of vitamin D with regard to muscle function remains at present unknown. Large doses of radioactive vitamin D given orally to rats have been found to be localized to a zone underneath the sarcolemma, and appear 'to sit in or on the muscle membrane' (Kodicek, 1963). In the present context it is perhaps no coincidence that this vitamin was also located in the first third of the proximal renal tubule, where the active reabsorption of phosphate is known to occur. The radioactive vitamin D available at that time required very large doses to be given to enable intracellular localization to be detected. However, later methods enabled Neville and DeLuca (1966) to synthesize a biologically active vitamin D compound with high enough specific radioactivity to enable physiological doses to be given. By such a technique, tissue distribution was estimated in a variety of organs in rats: although muscle accumulated a high percentage of the dose, the concentration was low when estimated as relative incorporation per weight of tissue. They considered, however, that, if corrections for non-cellular elements were

made, skeletal muscle and bone were the most radioactive.

It has recently been demonstrated that rachitic rabbits have a diminished rate of calcium uptake by muscle sarcoplasmic reticulum, which is independent of sarcoplasmic reticular magnesium- and magnesium-calcium-stimulated adenosine triphosphatase activity (Curry *et al.*, 1974), suggesting a link between vitamin D activity and calcium uptake by muscle sarcoplasmic reticulum. Such a link between vitamin D and calcium may nevertheless not be an exclusive one. There is now evidence possibly relevant to hypophosphataemic osteomalacia that the level of inorganic phosphorus within the renal tubule cell may underlie the regulation of synthesis of 1,25-dihydroxycholecalciferol, and both parathyroid hormone and calcitonin may exert their effect *via* control of the cellular phosphorus concentration (Tanaka and DeLuca, 1973).

The defect in hypophosphataemic osteomalacic myopathy may, however, be complex, or, alternatively, may comprise several different disorders. In the past few years, a few patients with hypophosphataemic osteomalacia associated with usually benign skeletal or soft tissue tumours have been reported (see Stanbury, 1972; Mankin, 1974). The features are similar to 'idiopathic' adult-onset cases, but the disease is generally reversible after the removal of the tumour, suggesting that the tumours might be producing an 'anti-vitamin D' substance, although such a substance has not yet been isolated. In this context, the presence of the nasopharyngeal haemangioma that was demonstrated in case 2 is likely to be of considerable significance. Since complete resection of the tumour was not feasible at the time, speculation remains whether complete removal would have resulted in 'cure' of the hypophosphataemic osteomalacia. Naturally, speculation must remain as to whether patients with 'primary' adult presenting hypophosphataemic osteomalacia are harbouring occult neoplasms, but at least one case has been described of spontaneous recovery from hypophosphataemic osteomalacia (Dent and Friedman, 1964) in which the presence of a neoplasm appears unlikely, and the follow-up of some cases has proceeded for over 25 years without any occult tumour having revealed itself (Dent, private communication).

The three patients reported here also illustrate some aspects of more general interest. In the first patient, the disorder had been diagnosed as hysterical and psychoneurotic, probably because of the lack of abnormality on electromyography, which, as has been discussed, may prove misleading. In the second patient, the possibility of polymyositis was entertained, a diagnostic difficulty that was pointed out by Vicale (1949); in this patient there was also the early mistaken impression that the condition was hysterical. In the third patient, although osteomalacia was recognized shortly after the patient had presented to hospital, her bone lesions and muscle weakness failed to improve until phosphate supplements were added to her treatment regimen.

The importance of elucidation of the disorder underlying these myopathies need hardly be emphasized, since, at least in idiopathic and tumour-associated hypophosphataemic osteomalacia presenting in adults, recovery with treatment may be anticipated.

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