MYOSITIS OSSIFICANS PROGRESSIVA
CLINICAL FEATURES OF EIGHT PATIENTS AND THEIR RESPONSE TO TREATMENT

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The clinical features of eight patients with myositis ossificans progressiva are described and the effects of treatment with the diphosphonate EHDP, together with surgical removal of ectopic bone, are assessed. Early correct diagnosis remains unusual, mainly because the significance of the short great toes is unrecognised, and because myositis may be mistaken for bruising, sarcoma or mumps. The diphosphonate disodium etidronate (EHDP) was given to all patients in an attempt to suppress calcification of new lesions; in five of them ectopic bone was removed during the treatment. EHDP sometimes delayed the mineralisation of newly formed bone matrix after surgical removal but this delay could not be predicted. The variable effect of EHDP may depend particularly on the amount absorbed and on the activity of new bone formation.

Myositis ossificans progressiva, also known as fibrodysplasia ossificans progressiva, is a rare disorder, dominantly inherited. It is characterised by skeletal abnormalities, particularly of the toes and fingers, and ectopic ossification mainly in the connective tissue of muscle (Lutwak 1964; Illingworth 1971; McKusick 1972). It produces a catastrophic and crippling illness in young people for which there is no effective treatment. This paper summarises the clinical features and treatment of eight patients with myositis ossificans and the effect of the diphosphonate disodium ethane-1-hydroxy-1, 1-diphosphonate (EHDP), an inhibitor of calcification (Francis, Russell and Fleisch 1969; Russell and Smith 1973).

PATIENTS
The clinical features are summarised in Table I. All of the eight patients had characteristic phalangeal abnormalities. The plasma calcium, inorganic phosphate, alkaline phosphatase and urinary total hydroxyproline were normal for age at the start of diphosphonate treatment in all cases. The effects of treatment are shown in Table II and amplified in the text where necessary. Plasma phosphate showed the expected increase on treatment with diphosphonate. The term ossification is used where this was demonstrated histologically; otherwise the less precise term calcification is employed, particularly when referring to radiographic appearances.

CASE REPORTS
Cases 1 and 2 have been briefly described elsewhere (Russell, Smith, Bishop, Price and Squire 1972).

Case 1—In 1970 this severely affected woman (Fig. 1) began treatment with oral EHDP (20 milligrams per kilogram per day). After five weeks ectopic bone 1.5 centimetres in length was removed from the right calf. Radiographs showed no calcification, and a larger piece of bone was therefore


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Morgan 1968). There was no cellular evidence of increased resorption or formation. A block of tissue was removed from the region of the operation on the left elbow; the ectopic bone in the muscle was of two types. Lamellar bone, away from the operation site, contained much osteoid, in some places five or six lamellae wide, but the cellular appearance did not suggest excessive rates of deposition or of resorption at the time of sampling. Microscopic areas of fibre bone, only a proportion of which was calcified, were seen in the scar tissue at the site of operation. Material like cartilage was also found alongside some of the bone, and plump osteoblasts were present in some of the surfaces.

**Case 2**—In 1962 this patient was put on a vitamin D-free diet (Professor C. E. Dent) and instructed to keep away from sunlight in an attempt to delay ectopic mineralisation. In 1963 a series of operations began with removal of a bony bar from the right foot; recalcification occurred after three months and the operation was repeated in 1964. In 1965 recalcification occurred after attempts were made to remove bone in front of the left hip and again from the foot.

In April 1970 EHDP was begun in a daily dose of 200 milligrams (body weight 51 kilograms). This was increased to 400 milligrams after four months, and then to 1,000 milligrams in September 1970, a week before ectopic bone was removed from the right foot. Histologically this showed little cellular activity and no excess osteoid (see Table II). The absence of significant calcification in this region six months later has been reported previously (Russell et al. 1972), and three years after the removal of bone only slight recalcification was visible on the radiograph. The dose of EHDP was continued at 1,000 milligrams a day until May 1972 and then reduced.

Elsewhere, however, calcification or recalcification after operation occurred. In March 1971 there was an active area of myositis in the right biceps, attributed to trauma, but no radiological evidence of calcification. Biopsy about a month after the onset of pain and swelling showed loss of striation and disintegration of the sarcoplasm, small collections of round cells and extensive fibrosis of interstitial tissue (Fig. 2). Early calcification was seen on the radiograph three months later in July 1971.

Subsequently, because there was no evidence of calcification at the site of the operation on the foot, an attempt was made by Mr J. Cockin to remove the bar of bone in front...
### TABLE I

**CLINICAL DETAILS OF THE EIGHT PATIENTS**

<table>
<thead>
<tr>
<th>Case number</th>
<th>Sex</th>
<th>Date of birth</th>
<th>Age and mode of onset of myositis</th>
<th>Unusual features</th>
<th>Treatments</th>
<th>Operation of removal of bone</th>
<th>Results of operation plus EHDP</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>March 1936</td>
<td>5 years. Swelling on back of neck</td>
<td>—</td>
<td>EHDP</td>
<td>Two. Also extraction of teeth</td>
<td>Recalcification delayed</td>
<td>Grossly disabled patient. Useful improvement in function</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>September 1953</td>
<td>2 years. Lumps on back and neck</td>
<td>Initial diagnosis of sarcoma</td>
<td>Radiotherapy. Steroids. EHDP</td>
<td>Several</td>
<td>Recalcification delayed</td>
<td>Some episodes of myositis considered to be due to trauma</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>May 1954</td>
<td>2 years. Lump on back of head</td>
<td>Extensive phalangeal deformity. Mentally retarded</td>
<td>Low vit. D diet. EHDP</td>
<td>—</td>
<td>—</td>
<td>Possible increase in mobility while on EHDP</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>September 1951</td>
<td>11 yrs. Stiff neck</td>
<td>—</td>
<td>Low vit. D diet. EHDP</td>
<td>One</td>
<td>Recalcification</td>
<td>Gross disability due to ossification near left hip at age 20</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>October 1963</td>
<td>21 years. Lump on back of neck</td>
<td>Initial diagnosis congenital hallux valgus</td>
<td>Prednisone. Cellulose phosphate. Low calcium diet. EHDP</td>
<td>—</td>
<td>—</td>
<td>Fixation of left hip joint. Mineralisation defect in metaphyses, possibly due to EHDP</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>October 1965</td>
<td>2 years. Lump on limbs: ulna, tibia, humerus</td>
<td>Initial diagnosis congenital hallux valgus: later, diaphysial aclasia</td>
<td>EHDP</td>
<td>Biopsy. Bilateral hallux valgus operation</td>
<td>Calcification at site of operation on toes</td>
<td>Progressive rigidity</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>July 1947</td>
<td>2 years. Torticollis</td>
<td>—</td>
<td>Prednisone. EHDP</td>
<td>Several</td>
<td>Recalcification</td>
<td>—</td>
</tr>
</tbody>
</table>

### TABLE II

**HISTOLOGY AND EFFECTS OF OPERATION IN FIVE PATIENTS HAVING EHDP**

<table>
<thead>
<tr>
<th>Case number</th>
<th>Date started</th>
<th>Dose at time of operation (mg/kg)</th>
<th>Type of operation</th>
<th>Date</th>
<th>Histology</th>
<th>Effect of operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.3.70</td>
<td>20</td>
<td>Removal of ectopic bone right calf</td>
<td>21.4.70</td>
<td>Lamellar and fibrous bone</td>
<td>No clear evidence of recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>and right elbow</td>
<td>17.6.70</td>
<td>Lamellar bone with few osteoblasts, no osteoclasts, no osteoid. Post-mortem (January 1971): Skeletal bone: porotic: no excess osteoid. Ectopic bone: partly mineralised fibre bone; lamellar bone with wide osteoid seams</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.4.70</td>
<td>20</td>
<td>Removal of bar of bone right foot</td>
<td>23.9.70</td>
<td>Inactive ectopic bone with no excess osteoid</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>Biopsy of right biceps muscle</td>
<td>27.4.71</td>
<td>Active myositis. Segmental disintegration of sarcoplasm</td>
<td>Recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>Removal of bone from left hip</td>
<td>11.10.71</td>
<td>Compact and cancellous ectopic bone with few osteoclasts and no osteoblasts or osteoid</td>
<td>Recurrence</td>
</tr>
<tr>
<td>3</td>
<td>14.4.71</td>
<td>20</td>
<td>Removal of bone around right thigh</td>
<td>8.9.71</td>
<td>Ectopic bone with increased thickness of osteoid up to 10 lamellae; few osteoblasts. Skeletal bone: excess osteoid</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>5</td>
<td>21.1.72</td>
<td>20</td>
<td>Removal of bone left quadriceps muscle</td>
<td>27.3.72</td>
<td>Compact and trabecular bone with osteoblasts and osteoclasts</td>
<td>Recurrence</td>
</tr>
<tr>
<td>6</td>
<td>12.71</td>
<td>20</td>
<td>Removal of bone over right scapula</td>
<td>5.72</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Case 3—A radiograph taken in July 1971 showing ectopic bone in front of the right hip. The appearance six weeks after resection of ectopic bone in September 1971. The sharp edge where bone has been removed (arrowed) was still present two years later.

Case 3. Figure 7—A histological preparation showing thick osteoid in the bone resected in September 1971. (Undecalcified; Von Kossa, neutral red, viewed under polarised light, × 320.) Figure 8—A similar preparation of ectopic bone, again demonstrating thick osteoid. Figure 9—A histological preparation of ectopic bone showing that even immature bone presents little evidence of osteoblastic activity. (Decalcified, haematoxylin and eosin, × 170.)
of the left hip which was fixing the joint (Fig. 3). Because the mass of ectopic bone surrounded the main neurovascular bundle, not all of it could be removed (Fig. 4) and no increase of movement was produced. The mixed compact and cancellous ectopic bone had a few areas of osteoclastic resorption; no osteoblasts or osteoid were seen. Four months after operation there was no evidence of recalcification, but at seven months recalcification had begun and gradually became more dense (Fig. 5). Progressive limitation of movement, especially of the left leg, now confines this patient to a wheel-chair.

Case 3—In this boy operations to remove ectopic bone began in 1963. Short courses of radiotherapy were also given and in 1969 he started to take prednisone 7.5 milligrams daily. Bone was excised from the right hamstring muscles in January 1970 and again in September 1970, with further recurrence. In April 1971 EHDP (20 milligrams per kilogram per day) was started and prednisone discontinued.

In May 1971 bone was removed from the biceps on both sides, which gave increased movement. In September 1971 a considerable amount of the bone which had developed around the right hip (Fig. 6) and in the right hamstring muscles was removed, with some improvement in function. Radiographs taken in 1973 showed no evidence of recurrence; EHDP was continued at the same dose.

Histology of the skeletal bone removed at the hip operation showed that up to half the bone surfaces were covered with osteoid, varying in thickness from two to eleven lamellae (Fig. 7); osteoblasts of active appearance were present on a small part of the osteoid surface. Ectopic bone removed from the thigh showed partly lamellar and partly woven bone, with islands of cartilage. Osteoid covered nearly all the surfaces of this ectopic bone (Fig. 8); it was up to ten lamellae thick and uncalcified woven osteoid was present. Osteoblasts were present only on a small part of the woven surfaces (Fig. 9). The presence of osteoid was attributed to the diphosphonate treatment.

Case 4—This girl had severe skeletal abnormalities (Figs. 10 to 12), partial alopecia, webbing of the neck and mental retardation. Chromosome analysis was normal. In 1969 she began a vitamin D-free diet and regular physiotherapy; EHDP 10 milligrams per kilogram (600 milligrams) per day was started in 1970. Six months later there was said to be an increase in mobility but this was difficult to confirm. An active
focus of myositis had appeared in the left arm and partially subsided without any evidence of calcification. Subsequently EHDP was reduced to 200 milligrams daily and the improvement in mobility appeared to continue. In July 1973 a radiograph of the right upper arm, which had been the site of swelling and redness due to myositis four months previously, showed no calcification.

Case 5—This girl became rapidly disabled at the age of twenty due to fixation of the left hip by ectopic bone. In 1972 EHDP was started in a dose of 800 milligrams (20 milligrams per kilogram) daily and after two months ectopic bone was removed by Mr J. Cockin from the left quadriceps (Fig. 13). This improved flexion of the left knee by about 30 degrees but the left hip became less mobile. Seven weeks later there was some evidence of remineralisation at the operation site and this was more marked at five months (Fig. 14).

The bone removed consisted of compact and trabecular bone, partly lamellar and partly woven. On the surface of the trabecular bone were osteoblasts that looked active and occasional multinucleate osteoclasts. Some atrophic and degenerating muscle fibres were seen between the trabeculae (Fig. 15). In addition there was a large amount of cartilaginous tissue and immature bone with granulation and fibrous tissue which looked like fracture callus; large numbers of active osteoblasts were related to intramembranous ossification and to areas of appositional bone growth.

In July 1972 swelling, pain and stiffness of the right shoulder developed but radiographs showed no calcification. Because of the previous rapid recurrence after surgery the dose of EHDP was temporarily doubled to 800 milligrams twice daily. The pain and swelling gradually resolved but radiographs revealed progressive mineralisation (Figs. 16 and 17).

The disability has slowly increased, with limited movement of the mandible but no clear evidence of local myositis or calcification. The dose of EHDP has varied from 800 to 1,200 milligrams daily, and a diet low in vitamin D was begun in October 1972. Radiographs taken in February 1973 suggested increasing calcification in the region of the left hip.

In this patient the rapid remineralisation may be due to lack of absorption of EHDP. The histology of the removed bone supports this idea, showing cellular activity without the
thick osteoid seen in Case 3. However, the moderately raised level of plasma phosphate suggests that some EHDP was being absorbed.

**Case 6**—This boy was treated from January to June 1966 with prednisone 20 milligrams daily, later reduced to 5 milligrams daily and continued until 1971. In 1972 he was also given cellulose phosphate 5 G thrice daily and a low calcium diet.

Since October 1972, and during treatment with EHDP 250 milligrams (10 milligrams per kilogram) daily, occasional transient swellings around the mandible have given an appearance similar to mumps. Comparison of radiographs of the knees taken in 1972 and 1974 show the development of wider growth plates and dense metaphyses (Fig. 18). Similar dense metaphyses were seen in the wrists and hands (Figs. 19 and 20). These appearances may be due to EHDP. This boy has had no symptoms of vitamin D deficiency rickets such as bone pain or proximal myopathy.

**Case 7**—This boy was given EHDP 400 milligrams (20 milligrams per kilogram) daily from 1973 but his condition continued to progress; several areas of myositis over the back rapidly calcified. Swellings on both sides of the neck simulated mumps. The neck and trunk became very stiff as the myositis subsided and calcification appeared. This rigidity made him more liable to accidents; on a day at the seaside he fell into a few inches of water and nearly drowned.

**Case 8**—This patient has been seen only once (by R. S.) and is being followed elsewhere. The patient (Case 2 of Illingworth 1971) began to take cortisone 50 milligrams daily in 1955, which appeared to improve mobility; later this was changed to prednisone, but steroids were discontinued after two years. From 1960 to 1970 her condition changed little; in 1968 some ectopic bone was removed from the back. In 1972 she began to take EHDP 10 milligrams per kilogram daily; this was increased to 20 milligrams before ectopic bone was twice removed from near the scapula, with temporary improvement in movement but eventual recurrence of calcification.

**Discussion**

The cause, diagnosis, natural history and possible treatment of myositis ossificans progressiva merit brief discussion.

**Case**—This is quite obscure. The disorder is undoubtedly inherited and has been reported in monozygotic twins (Eaton, Conkling and Daeschner 1957). The relation of the skeletal abnormalities is likewise mysterious: reports of ectopic bone formation with multiple congenital abnormalities (Rosborough 1966) and with pseudohypoparathyroidism (Malter and McAlister 1972) do little to clarify the situation. Chromosomes in two patients were found to be normal (Lettis 1968). The pathology suggests that the primary lesion is in connective tissue around the muscle. Eaton et al (1957) consider that there is exaggerated proliferation of connective tissue with subsequent dystrophic calcification and ossification; in contrast, Smith, Zeman, Johnston and Deiss (1966) provide evidence that the muscle tissue is intrinsically abnormal before overgrowth of connective tissue. The striking appearance of the muscle in the biopsy from Case 2 suggests that not all the changes in this tissue are secondary to connective tissue proliferation. For these reasons, and because doubt still exists, we have continued to use the established term of myositis ossificans progressiva.

**Diagnosis**—The phalangeal abnormalities are essential to the diagnosis. They are present at birth and are usually followed by acute episodes of myositis and subsequent extraskeletal ossification. The abnormal big toes may be dealt with surgically as a form of congenital hallux valgus without recognition of their possible significance (Case 7). Erroneous diagnoses may be given for the myositis. Pain, redness, and general systemic disturbances may suggest infection; myositis around the neck and angle of the mandible may simulate mumps (Cases 6 and 7); the lesions may be mistaken for bruises, which stresses the possible relation to trauma (Case 2); and soft-tissue sarcoma may be suggested and apparently confirmed by the histology (Case 3). When progressive rigidity is the most marked aspect of the disorder the delay in diagnosis may be prolonged (Case 2).
Natural history—We are ignorant of the normal outcome of the acute episodes of pain and swelling within the muscles. Although it is clear that in some episodes ectopic bone formation follows, it is not known how often this occurs or how often the lesions subside spontaneously. Because radiographs only show mineralisation and because pathological findings are relatively few, these answers will not be easy to obtain, but bone scanning agents may help, for example, Sr, Tc-polyphosphates or Tc-EHDP. If the pathology of the acute lesion in Case 2 is characteristic, it is very unlikely that complete healing could occur, but healing of milder recurrent myositis without marked local symptoms or systemic disturbance is a possibility.

The condition is thought to be more active in childhood than in adult life, but our patients demonstrate that crippling myositis followed by ossification can occur in late adolescence after many years of comparative quiescence (Case 5), and that even in children the rate of progression may be very variable (Cases 6 and 7). Moreover there is a suggestion from Case 2 that the tendency to mineralise or to remineralise ectopic bone varies in different sites. Lutwak (1964) has pointed out that different parts of the body are variably affected by ectopic ossification. Early lesions often occur around the neck and over the back (Cases 1, 3 and 6), whereas the most crippling ossification around the hip may occur in late childhood or early adult life (Case 5). Ossification is uncommon in smaller muscles and in those of the abdomen. One must also consider the possibility of spontaneous improvement, however unlikely this would seem when joints are fixed by extensive bridges of extraskeletal bone. For instance it seems that fixed flexion of an elbow may improve in the years following the first episode of myositis. This may appear to follow strong forced movement by the patient, with a sudden increase in mobility as in Case 2, or possibly vigorous physiotherapy as in Case 4.

Surgical removal of ectopic bone is thought to be followed inevitably by rapid recalcification at that site. The speed with which this occurs is not clearly documented, because radiographs, which hitherto have been the only practical way of detecting early remineralisation, are usually taken infrequently. Recurrence is probably less rapid and less certain after removal of old “inactive” ectopic bone rather than newly formed bone. From the limited data available one may still conclude that in myositis ossificans progressiva both the formation of ectopic bone matrix and its mineralisation are inevitable.

Treatment
The aims of treatment are to prevent the formation of ectopic bone causing fixation of joints and progressive immobility, and to increase mobility in patients already crippled. Because of our ignorance the many attempts at treatment discussed by Mair (1932) and by Lutwak (1964) remain largely empirical, none having been outstandingly successful. However, Eaton et al. (1957) noted that cortisone reduced the systemic effects of acute myositis, and Illingworth (1971) found apparently prolonged suppression of active myositis in one of two patients treated with corticosteroids. There is no clear evidence that these agents can prevent the formation of ectopic bone, although because of their known effects on fibroblasts they might be expected to suppress it. Dixon, Mulligan, Nassim and Stevenson (1954) found that ACTH and cortisone failed to prevent reossification.

Theoretically, measures to prevent mineralisation, however effective, could only produce partial improvement because it is unlikely that they would primarily affect the formation of either fibrous tissue or ectopic bone matrix. In practical terms the mobility of joints may be just as limited by unmineralised as by mineralised bone. Early use of the calcium chelating agent EDTA has been ineffective, and there is no evidence that dietary restriction of calcium can reduce mineralisation of ectopic bone. The effect of cellulose phosphate, as in Case 6, has not been fully assessed, but it is unlikely to differ significantly from that of a low calcium diet. A low vitamin D diet and restriction of sunlight is a different approach and represents an attempt to produce osteomalacia in ectopic bone, and presumably also in skeletal bone. We have no evidence that these measures have delayed ectopic mineralisation. It is also striking that there has been no clinical, biochemical or histological evidence of osteomalacia, although the possible effects of low calcium diets in retarding skeletal mineralisation in growing children should not be disregarded.

The main agent used in this series is the phosphonate EHDP (disodium etidronate), whose properties have been reviewed elsewhere (Russell and Smith 1973). Such compounds prevent the formation and dissolution of apatite crystals in vitro, and in experimental animals prevent both ectopic calcification (Fleisch, Russell, Bisaz, Mühlbauer and Williams 1970) and excessive bone resorption and turnover (Gasser, Morgan, Fleisch and Richelle 1972). The exact mechanism of their action is not known, and it is possible that they may have additional important effects on bone cells, either directly or indirectly reducing their activity. Thus early suppression of osteoblastic activity is a consistent histological feature of the bone of patients with Paget's disease treated with EHDP (Russell, Smith, Preston, Walton and Woods 1974).

In myositis ossificans progressiva EHDP has been used to prevent mineralisation of areas of active myositis (Bassett et al. 1969; Weiss et al. 1971; Schnakenburg et al. 1972) or remineralisation after surgical removal of established ectopic bone (Russell et al. 1972). The effect in fifty-two patients has been reviewed by Geho and Whiteside (1973). Our experience with Cases 1 and 2 (Russell et al. 1972) suggested that mineralisation could be delayed, if not prevented. Our subsequent experience has been mixed; thus in Case 3 there was good radiological
evidence of delayed mineralisation; but subsequent operations in Cases 2, 5 and 8 have been followed by recalcification despite high doses, and there is little evidence that EHDP has slowed down the natural progress of the disorder in children with active myositis (Case 7).

The response of the patient to EHDP, or to any other agent, may be influenced by the activity of the disorder, by possible variations between tissues in different parts of the body, and by the amount reaching the mineralising site, which in turn will depend on the amount and duration of oral dosage and on intestinal absorption.

Thus the failure of EHDP treatment in Case 7 might be related to the very active stage of the disease, because this patient has continued to take EHDP in a daily dose of 20 milligrams per kilogram without side effect, and there was a moderate increase in plasma phosphate suggesting good absorption.

In Case 2 variation between different tissues might also be a factor; the apparent prevention of remineralisation in the foot may have erroneously led us to think that we could achieve the same result in the thigh. It is possible that failure to prevent calcification around the thigh could be because this lesion was still active; indeed at the same time there was an episode of myositis in the right biceps which subsequently mineralised.

All the patients were on high doses of EHDP before, during and after operation. It is known that in normal persons the absorption is both low and variable, between 1 and 10 per cent of the administered dose, and that it is probably highest if taken when fasting. It is possible that in myositis ossificans progressiva absorption is less than normal, and in some patients even negligible. It is at present difficult to measure how much EHDP has been absorbed because urinary excretion is probably only indirectly related to it. However, if the urinary excretion measured after several months on EHDP is in any way an indicator of the dose, then the values obtained were as follows: Case 2, 1.27 per cent (three); Case 5, 0.33 per cent (four); Case 6, 0.75 per cent in May 1973 and 8.25 per cent in February 1974; and Case 7, 0.77 per cent, the values in each case being the percentage of the daily dose excreted in the urine and the figure in brackets the number of measurements. These values suggest that absorption in Case 5 may have been particularly low—a possible clue to the therapeutic failure. Similarly the absorption in Case 6 may have been high at the time he was developing signs of deficient mineralisation. An increase in plasma phosphate, which in Paget’s disease appears to be dose-related, may be a further indicator of how much EHDP has been absorbed.

Another way of assessing the effect of EHDP is by examination of its effect on tissues. Thus examination of the excised tissues from Case 5 showed that the ectopic bone was still active and that none of the usual effects on bone could be demonstrated; in retrospect, remineralisation was not therefore unexpected. By contrast, both ectopic and skeletal bone removed in Case 3 showed the excessive thickness of osteoid characteristic of treatment with high doses of EHDP.

Although we have been particularly interested in the possible ability of EHDP to prevent recurrent ectopic ossification, it is worth mentioning other possible effects. Thus, although it has been suggested that EHDP may improve mobility in myositis ossificans progressiva irrespective of its effect on calcification (Weiss et al. 1971; Geho and Whiteside 1973), we have not been impressed by this. It is known that EHDP produces hyperphosphataemia and our present patients show this. There is no evidence of a consistent effect on total hydroxyproline (THP) excretion, and some of the observed changes may be due to age. In only Case 3 did the THP fall significantly—from 93 milligrams per day in April 1971 to 23 milligrams in March 1972. Further, from the THP values there is no evidence of the increased collagen turnover in this disorder suggested by Bland, Kirschbaum, O’Connor and Wharton (1973). Another important aspect of the use of EHDP is its possible effect on the skeleton. Weiss, Fisher and Phang (1971) demonstrated decreased bone turnover by radioisotope measurement in their patient. Such effects may be most easily detected in the rapidly growing patient, and in one of our young patients (Case 6) there were changes in the metaphyses which point to a failure of normal mineralisation, though significantly other signs of classical rickets, such as muscle weakness and bone pain, were absent. The abnormal skeletal mineralisation in this boy may be attributable to treatment with EHDP but he also had his dietary intake of calcium restricted for a long time. For various reasons it seems that this inhibition of mineralisation is a direct effect of EHDP on calcifying tissues rather than due to interference with the conversion of vitamin D to its active metabolites (Russell et al. 1974).

Therapeutic progress in this disorder is likely to be slow while the underlying cause remains unknown, but the advantage of a relatively small increase in mobility in these young patients can be considerable.

We are indebted to the following who kindly referred patients to us: Professor C. E. Dent (Cases 2, 4 and 6), Mr J. A. Mantle (Case 3), Mr C. M. Squire (Case 1), Mr T. C. Howard Davies (Case 5), Mr T. A. English (Case 7) and Professor R. Kilpatrick (Case 8).

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