SPINAL CORD DYSFUNCTION IN PAGET’S DISEASE OF BONE
HAS MEDICAL TREATMENT A VASCULAR BASIS?

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The medical treatment of eight patients with paraparesis associated with Paget’s disease of the vertebrae is described. Treatment, for 3 to 87 months, with calcitonin or with diphosphonates produced marked clinical improvement in seven of these patients. From this series and a review of 19 additional case reports it is concluded that favourable clinical response is seen in about 90 per cent of patients, and that this may occur very rapidly. Results are as good or better than those obtained by surgical decompression. It seems possible that paraparesis in some cases may be due to diversion of blood supply from the spinal cord to the highly vascular Pagetic bone giving rise to a vascular “steal” syndrome. It is suggested that medical treatment should be used more widely to avoid or delay the need for operation and reduce the risks of recurrence. These patients, however treated, require lifelong follow-up because relapses are common.

The cause of Paget’s disease (osteitis deformans) is unknown, although the recent identification of nuclear inclusion bodies in osteoclasts suggests that it may have a viral aetiology (Rebel, Malkani and Baslé 1974; Mills and Singer 1976; Gherardi, Lo Cascio and Bonucci 1980; Rebel et al. 1980). The common complications of the disease include deformity, pain, fractures and deafness. Dysfunction of the spinal cord or cauda equina secondary to Paget’s disease of the vertebrae is usually attributed to bony compression and is fortunately rare, although more than 100 cases have been described since the first report by Wyllie (1923). Other neurological complications of Paget’s disease have been reviewed by Schmidek (1977).

Effective medical treatment for Paget’s disease has only recently become available and until now the treatment advocated was surgical decompression of the spinal cord or cauda equina (Klenerman 1966). In the last decade several new drugs have become available (Russell 1979). These include the calcitonins, the diphosphonates and mithramycin. These drugs are effective in reducing both the pain and the biochemical indices of disease activity, thus indicating the possibility that relief of neurological symptoms and signs might be achieved by medical treatment alone, and that this might avoid subsequent relapse.

We report eight patients aged from 30 to 75 years with paraparesis associated with Paget’s disease of the vertebrae, treated in Sheffield since 1970, and describe their response to salmon calcitonin (Calsynar); to porcine calcitonin (Calcitare); to ethane-1,1-hydroxy-1,1-diphosphonate (disodium etidronate, EHDP, Didronel); and to dichloromethylene diphosphonate (Cl:MDP) (Fig. 1).

CASE REPORTS

Case 1. A retired teacher presented in September 1975 with a history of weakness in her legs for four months, temporarily improved by a course of steroids for bronchitis, and associated with the feeling as of a tight band around the abdomen. She could not walk more than 300 metres. On examination she had a mid-thoracic kyphosis, which had been present for three years, and sensory loss from the eleventh thoracic segment distally. Romberg’s test was positive, and a straight leg raise could be sustained for two minutes on the right, but only for one and a half minutes on the left. Radiographs showed fusion of the sixth, seventh and eighth thoracic vertebrae which was thought to be due to old tuberculosis (Fig. 2): a myelogram, performed with difficulty, did not show compression of the cord. She was allowed home, but became worse and was readmitted five months later when she was no longer able to stand unaided. Radiographs showed Paget’s
disease of the left humerus, of the pelvis, and of the second and fifth lumbar vertebrae. Myelography now showed a complete block in the mid-thoracic region (Fig. 3). The spinous processes and laminae from the sixth to the ninth thoracic vertebrae were excised at operation by one of the authors (A.A.J). The bone was hard and bled profusely. Pulsation of the dura returned after operation. Histology showed Paget’s disease of bone. Immediately after operation the patient became totally paraplegic.

Treatment with salmon calcitonin, 100 international units daily, was started two weeks after operation and she gradually recovered, being able to walk 120 metres with the aid of sticks after six months. Fifteen months after operation deterioration took place despite continued treatment with calcitonin. The serum alkaline phosphatase which had initially fallen with treatment again rose (Fig. 1). No antibodies to calcitonin were detected. A course of EDHP, 1600 milligrams per day by mouth, gave a good biochemical response but little clinical improvement. The patient became depressed and refused further treatment being confined to bed and wheel-chair.

Case 2. An engineering consultant aged 30 gave a history of backache for four years and pain radiating down both legs for three months. Other than weakness of the dorsiflexors of both feet he had no abnormal neurological signs. Radiographs showed expansion of the body of the first lumbar vertebra characteristic of Paget’s disease (Figs 4 and 5). A myelogram showed complete obstruction at the level of this vertebra (Fig. 6). A laminectomy was performed in October 1970, by Mr D. K. Evans, who noted that the bone was very soft and bled profusely. The dura had been pushed back by the expanded body of the first lumbar vertebra. Removal of the spinous process and laminae decompressed the cord. Biopsy from the vertebral body showed Paget’s disease (Fig. 7). Recovery after operation was complete but in July 1971 pain recurred in the legs and in September 1973 both legs became weaker, with the later development of sensory impairment, and weakness of the buttock and hamstring muscles.

In February 1976, two and a half years after operation, the patient started medical treatment by injections of porcine calcitonin, 160 international units daily (Fig. 1). Within two months he was able to walk without a stick, but 14 months later weakness in both feet recurred, and after a fall he became chair-bound with complete flaccid paralysis of both legs. Treatment was changed from porcine to salmon
calcitonin without clinical or biochemical improvement. When EHDP became available, this was added to his treatment at a dosage of 1600 milligrams per day for seven months. This produced some return of power in the legs. In March 1979 he started a course of CI:MDP, 1600 milligrams per day. He is now able to move about with crutches but still has a reflex bladder. His recent radiographs show marked kyphosis and fusion of adjacent vertebrae.

Case 3. In September 1975 a 72-year-old man developed weakness in the arms and legs followed one week later by acute retention of urine. On examination he was confused and dehydrated with loss of motor power distal to the seventh cervical segment. Radiographs showed sclerotic lesions at C4–5, T2–3, and L2 (Figs 8, 9 and 10). Serum acid phosphatase was elevated at six international units per litre (normal, less than four international units per litre) and serum alkaline phosphatase was elevated at 422 international units per litre (normal, 35 to 105 international units per litre).

The initial diagnosis was of prostatic carcinoma with bony secondaries and stilboestrol treatment was started, but after a few days the diagnosis of Paget's disease was made and later confirmed by bone biopsy. Treatment was started with salmon calcitonin, 100 international units daily (Fig. 1). After three days he was able to move his feet a little. A cervical myelogram was performed and no block was seen on screening, although detailed radiographs could not be taken. In view of his general condition and the “negative” myelogram no surgery was undertaken and he remained on calcitonin treatment. He improved dramatically over the next few weeks and his serum alkaline phosphatase level fell. By May 1976 he had full power in all his limbs, although the legs remained spastic. He later failed to attend for follow-up and was reported to have died after a myocardial infarction.

Case 4. In September 1976 a 65-year-old retired hospital gardener gave a history of five months' progressive weakness of the legs. On examination he showed a lower thoracic kyphosis and weakness in both lower limbs, with brisk leg reflexes and extensor plantar responses. A straight leg raise could be sustained for 20 seconds on the right and 35 seconds on the left. Radiographs and bone scans (Figs 11, 12 and 13) showed Paget’s disease of the mandible, the bodies of T9, T10, and T11 vertebrae, the pelvis, and several ribs. A myelogram showed a complete block at the level of T10 vertebra (Fig. 14). The serum alkaline phosphatase level was 425 international units per litre. A course of treatment with salmon calcitonin, 100 international units daily, was started with a short course of dexamethasone, four milligrams three times daily, and two days later catheterisation was required for urinary retention. After nine days he was able to walk with a stick, and a further myelogram showed free flow throughout the spinal canal. A straight leg raise was sustained for two minutes on each side. Transurethral resection of the prostate was performed by Mr D. Thomas, and the patient was able to micturate normally. After three months of calcitonin treatment he was walking almost normally, the only abnormal neurological sign being bilateral extensor plantar responses. The serum alkaline phosphatase level had fallen to 118 international units per litre.

After one year the alkaline phosphatase level rose to 380 international units per litre and continued to rise despite doubling the dose of calcitonin (Fig. 1). Treatment was changed to EHDP, 1600
milligrams daily for four months. This reduced the serum alkaline phosphatase level to 210 international units per litre and the patient remained well after this course of treatment. Ten months later, because of biochemical relapse he was started on a course of CI.MDP, 1600 milligrams daily, and within one month could descend stairs more easily. He remains fully mobile after three and a half years of medical treatment, and his alkaline phosphatase level is now normal. An interesting feature of this patient was the presence of a paravertebral mass which was at first feared to be an osteosarcoma (Fig. 15). Since the mass did not enlarge it probably consisted of Paget’s osteoid and bone tissue as described by Siegelman, Levine and Walpin (1968).

Case 5. A 64-year-old sales manager developed progressive weakness and numbness in both legs over a period of three months. He was known to have Paget’s disease in the lumbar vertebrae, pelvis and right femur, and had received a course of porcine calcitonin in 1971 with relief of pain in the right hip. In January 1979 there was loss of sensation to pin-prick over both feet, and absent vibration sense at both ankles. The dorsiflexor muscles of the feet and the hamstrings were weak. Ankle jerks were absent and plantar reflexes were extensor. Serum alkaline phosphatase was markedly elevated at 1026 international units per litre and radiographs showed Paget’s disease of T9, T10, T11 and T12 vertebrae, and in the pelvis and right femur, and severe osteoarthritis in the right hip. Tomograms of the thoracic vertebrae showed the characteristic changes of Paget’s disease and a myelogram showed a complete block at T11 level (Fig. 16).

Treatment was started with CI.MDP, 1600 milligrams daily, and the serum alkaline phosphatase fell rapidly to normal (Fig. 1); the clinical improvement was dramatic. Within one month he was walking normally, apart from pain due to arthritis, and he was once again able to drive his car. Six months after the end of a seven-month course of treatment serum alkaline phosphatase level remained normal. Examination in March 1980 showed no motor loss, normal plantar responses and free flow of contrast medium (Fig. 17).

Case 6. A 66-year-old man developed progressive weakness, lack of co-ordination and numbness in both legs over a six-month period following acute back pain caused by heavy lifting. In February 1979 he had brisk reflexes in the lower limbs although no sensory loss was apparent. The serum alkaline phosphatase level was increased to 755 international units per litre, and radiographs showed extensive Paget’s disease of the lumbar spine and pelvis. A short course of treatment with porcine calcitonin produced modest biochemical and clinical improvement. In August 1979, he got worse with increased muscle tone and hyper-reflexia in the legs, no obvious weakness, but sensory loss in stocking distribution. In September 1979 the spinous processes and laminae of L4 and L5 were removed by Mr B. S. Sylvester, and at the end of operation the dura showed pulsation. Histology confirmed Paget’s disease.

After operation his symptoms did not improve and in January 1980 he was referred for further investigation. He had blunting of pin-prick sensation below T11 level, both legs were spastic and both plantar reflexes were extensor. Power was reduced including hip flexion (MRC Grade 3 right, Grade 4 left). A myelogram showed no compression in the lumbar region but major obstruction in the flow of Myodil at T10 level where Paget’s disease was present in both the body and the laminae of the vertebrae (Figs 18 and 19).

![Fig. 18](image18.jpg)

Fig. 18. Figure 18—Myelogram showing almost complete block to flow at T10 level (arrowed). Figure 19—Myelogram showing Paget’s disease involving the laminae as well as the body of the vertebra (arrowed).

Treatment was started with CI.MDP, 3200 milligrams daily (Fig. 1), and three weeks later power in the flexor muscles of both hips was recorded as MRC Grade 4 to 5, and the patient was up and about with a walking frame. After three months’ treatment, he could walk about 300 metres unaided. The right plantar response was flexor, and the left was equivocal. Pin-prick sensation was felt in both legs, although reduced over the feet. After six months’ treatment both plantar responses were flexor. Power was improving and sensation to pin-prick had returned to normal. The serum alkaline phosphatase level was normal.

Case 7. A 59-year-old office worker was first seen in 1970 complaining of pain in the back and both calves. No neurological abnormalities were noted and radiographs showed Paget’s disease of the left hemipelvis and of the third and fourth lumbar vertebrae. Backache was relieved by a surgical corset but discomfort in the calves persisted after exercise. In 1978 the backache recurred and the serum alkaline phosphatase level was 600 international units per litre. A short course of porcine calcitonin, 160 international units per day, gave some initial benefit but relapse followed cessation of calcitonin. A course of salmon calcitonin failed to improve his symptoms.

In January 1980, he developed severe low backache radiating to both groins and to the posterior aspects of both legs with bilateral foot-drop. The pain in the legs was exacerbated by exercise and relieved by rest and he required bilateral foot-drop splints. He had weakness of both lower limbs, with complete loss of power of the dorsiflexors of the foot and absence of plantar responses. Radiographs showed Paget’s disease of the pelvis, of the lumbar spine and of T12 vertebra, where there was also a paraspinal mass. A myelogram showed complete obstruction at this level (Figs 20 and 21), and marked narrowing opposite the bodies of L3 and L4 vertebrae. He
started on a course of Cl-MDP, at a dosage of 3200 milligrams per day. His serum phosphatase level fell (Fig. 1) and his symptoms rapidly improved. After three months' treatment he was able to exercise without developing pain in the back or legs. Power in the hips and knees was normal, and foot dorsiflexion was MRC Grade 3 to 4 on both sides.

Case 8. A 75-year-old woman had developed bilateral leg weakness and sensory loss over four years which had been rapidly progressive in the four months before referral. She had brisk reflexes in both legs with equivocal plantar responses, and marked weakness from the hips downwards. Vibration sense was absent from the pelvis downwards and pin-prick sensation was reduced in both legs. Romberg's sign was positive. Radiographs showed Paget's disease in T11 and T12 vertebrae and a myelogram showed an incomplete block at this level. Serum alkaline phosphatase level was 205 international units per litre.

Treatment was started with Cl-MDP, 3200 milligrams per day, and after only six days the patient noticed improvement in power and coordination. She was able to rise from a chair without the help of her arms for the first time in four years, and could stand and walk without the stick which she had used for four months. After four weeks of treatment both plantar responses were normal, and sensory loss had recovered, and serum alkaline phosphatase level was 110 international units per litre (Fig. 1). There was continuing clinical improvement after three months and Romberg's sign had become negative.

DISCUSSION

The present series demonstrates that drug treatment can reverse neurological dysfunction caused by Paget's disease of the vertebrae. These results are particularly gratifying since several of the patients were referred with recurrence after surgical treatment and clearly had severe disease. The improvements are unlikely to be due to the natural history of the disorder since spontaneous recovery from cord compression due to Paget's disease has not been reported and probably does not occur.

Three types of drug are now available for the management of Paget's disease. The first, calcitonin, became available in the early 1970s following its discovery by Copp et al. (1962). It has since been widely used, particularly for the control of bone pain (DeRose et al. 1974; Kanis et al. 1974), and several authors have noted successful results in cord compression syndromes (Table 1). However, the long-term use of this agent has sometimes yielded disappointing results, when initial biochemical and clinical response has been followed by relapse. This may sometimes be due to antibody formation (Singer et al. 1972; DeRose et al. 1974; Woodhouse et al. 1977), but resistance can occur in the absence of significant antibody titres as was seen in two of our patients. In one (Case 1) no significant antibody titre was present when relapse occurred, and in the other (Case 4) the antibody titre to porcine calcitonin was elevated at 12 months; no improvement occurred when treatment was changed to salmon calcitonin, but improvement followed the use of diphosphonates. This suggests that the use of calcitonins alone requires to be carefully monitored during long-term treatment.

Mithramycin, which is an antibiotic with cytotoxic activity, has also been available for a number of years and its efficacy has been shown in the treatment of paraparesis due to Paget's disease (Hadjipavlou et al. 1977). Its potential toxicity in producing thrombocytopenia and impairment of renal and hepatic function have discouraged its widespread use. Like calcitonin it has to be given parenterally.

The diphosphonates are a group of compounds which inhibit the growth and dissolution of hydroxyapatite crystals in vitro and inhibit bone resorption in organ culture and in vivo (Russell and Fleisch 1976). Ethane-1-hydroxy-1, 1-diphosphonate (EHDP, disodium etidronate) has been used for several years in the treatment of Paget's disease (Altman et al. 1973; Smith et al. 1973; Gunçaga et al. 1974; Russell et al. 1974; Meunier et al. 1975; Canfield et al. 1977; Khairi et al. 1977; Russell 1979), but when given in high doses (20 milligrams per kilogram per day) it can induce a mineralisation defect (Smith et al. 1973). These adverse effects are not seen with lower doses (five milligrams per kilogram per day) but these are less effective in suppressing pain and reducing the biochemical indices of disease activity (Meunier et al. 1975). Two other diphosphonates are under clinical trial in Paget's disease. These are disodium dichloromethylene diphosphonate (Cl-MDP) and 3-amino-1-hydroxypropylidene diphosphonate (APD). These drugs are more specific inhibitors of bone resorption and do not appear to induce mineralisation defects in man at the doses so far tested. Initial reports of their use in Paget's disease have shown that biochemical indices of disease activity can be effectively controlled in nearly all patients with these compounds (Frijlink et al. 1979; Meunier, Chapuy and Alexandre 1979; Douglas et al. 1980).

Long-term experience with the use of diphosphonates in treating nerve compression syndromes has not been as extensive as with calcitonin but our findings and those of Alexandre et al. (1979) suggest that substantial
clinical improvement can be produced in the majority of patients. The diphosphonates, particularly CI:MDP, have advantages over calcitonin in that they can be given by mouth and that biochemical and possibly clinical remission may be maintained for long periods.

The English and French literature now includes 10 reports (including this series) of the medical treatment of dysfunction of the cord caused by Paget’s disease and four reports of medical treatment for cauda equina or nerve root compression (Tables I and II). Twenty-seven patients with spinal cord complications have been treated with calcitonin (16), diphosphonates (four) or a combination or sequence of these (seven). Twenty-four (89 per cent) were improved and 22 (81 per cent) had either marked or complete reversal of their abnormal neurological findings. Two patients had only mild or moderate improvement and in three there was no response. No patient became worse. The follow-up period where stated, was from 3 to 87 months (mean 25 months). Eleven of the patients had undergone a total of 16 previous laminectomies, with recurrence in all but two patients. Improvements also occurred in 11 of the 20 patients treated medically for compression of the cauda equina or a nerve root and this recovery was

<table>
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<th>Treatment</th>
<th>Dose per day</th>
<th>Previous laminitomy</th>
<th>Recurrence after laminitomy</th>
<th>Result of medical treatment</th>
<th>Follow-up from start of treatment (months)</th>
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<td>—</td>
<td>Almost complete</td>
<td>42</td>
</tr>
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<td></td>
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<tr>
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<td></td>
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<td>—</td>
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<td>50–200u</td>
<td>NS</td>
<td>—</td>
<td>No change</td>
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<td>51</td>
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<td>Yes</td>
<td>Yes (became completely paralysed)</td>
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<td>12</td>
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<td></td>
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EHDP = sodium etidronate. CI:MDP = dichloromethylene diphosphonate or clodronate disodium. SCT = salmon calcitonin. PCT = porcine calcitonin. NS = not stated.
marked or complete in five patients. Follow-up was from 17 to 48 months (mean 32 months).

Allowing for the difficulties of comparing retrospective results from different centres, it would appear that medical treatment can be as effective as surgical intervention and further experience will be needed to determine whether, and for how long, recurrence can be avoided. Sadar, Walton and Gossman (1972) collected 90 cases, 64 of whom had been explored surgically. Improvement had occurred in 55 of these (85 per cent) but this had been only slight in four patients, three of whom were found to have sarcomatous change. Two site for Paget's disease apart from the sacrum is in the lumbar spine (Schmorl and Junghans 1959), but paraparesis is more common with thoracic involvement. This may be because the canal is narrowest in comparison with the diameter of the spinal cord in this region (Hartman and Dohn 1966), but dysfunction of the cord can occur at any level below the occiput. At operation the cord is usually found to be compressed by the expanded bodies of the vertebrae as was noted in two of our patients. Occasionally expansion of the pedicles and laminae can cause compression (Turner 1940). In some cases, however, no convincing cord compression

<table>
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<tr>
<th>Author</th>
<th>Number of patients</th>
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<th>Dose per day</th>
<th>Result of medical treatment</th>
<th>Follow-up from start of treatment (months)</th>
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<td>50u</td>
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<td>PCT = porcine calcitonin, SCT = salmon calcitonin, NS = not stated.</td>
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patients were unchanged and one was made worse. There were seven operative deaths (11 per cent) and six patients underwent more than one laminectomy. The review did not discuss the long-term outcome of these cases.

This comparison suggests that medical treatment is a good alternative to surgical intervention in many cases, particularly those of gradual onset; that it may become the treatment of choice when the newer diphosphonates become widely available; and may also be a valuable adjunct to surgical treatment where this remains necessary, as in rapidly progressive lesions. All cases require follow-up with repeated biochemical and clinical assessment for life after their initial treatment, whether it has been surgical or medical. An increase in serum alkaline phosphatase often precedes clinical relapse and may be an indication for further treatment.

The aetiology of the neurological complications of Paget's disease is not entirely clear. The most common can be demonstrated by radiography and the cause of paraparesis may then be related to vascular changes in the adjacent soft tissues and bone. In one reported case of paraparesis without complete myelographic obstruction medullary angiography demonstrated delay in filling and emptying of the anterior spinal artery at the level of the involved vertebra (Mathe et al. 1976). The speed of response to medical treatment, within two weeks in some of our patients, suggests that the response could not have been due to remodelling of bone but rather due to a decrease in soft-tissue swelling or to a redistribution of blood flow. In three of these patients (Cases 6, 7 and 8) repeated ultrasound measurement of the spinal canal during treatment (Porter, Wicks and Ottewell 1978) showed no change in bony diameter while marked clinical improvement took place.

Vascular perfusion through bone affected by Paget's disease is known to be high (Wootton, Reeve and Veall 1976) and to fall rapidly in response to
calcitonin before reduction in the plasma alkaline phosphatase level. This suggests that in some cases the spinal cord may be compromised by diversion of blood to the adjacent highly vascular diseased bone. This view is consistent with the anatomical relationships noted between blood supply to the vertebral and the cord (Crock and Yoshizawa 1977).

Our patients also illustrate some of the difficulties encountered in management. The diagnosis was commonly delayed, and one patient (Case 1) was thought to have tuberculosis of the spine. The presence of a narrow disc space and of a paraspinal mass may support the mistaken diagnosis of Pott’s disease (Siegelman et al. 1968). Another patient (Case 3) with acute retention of urine, sclerotic vertebral, and elevated serum acid phosphatase was erroneously thought to have carcinoma of the prostate although the acid phosphatase level is often raised in Paget’s disease. Occasionally the patient may be thought to have a demyelinating disease (Hartman and Dohn 1966).

The detection of Paget’s disease elsewhere in the skeleton may expedite the diagnosis of the cause of paraparesis; and a radiographic skeletal survey and a bone scan may be helpful (see Figs 11 to 13).

The diagnostic features are elevation of the serum alkaline phosphatase in the presence of normal liver enzymes, together with typical radiographic changes: perhaps the most helpful feature in differentiating from secondary carcinoma is that Pagetic bones are often enlarged (Fig. 4).

Surgical decompression has been the only effective treatment in the past but may present technical problems and often needs to be repeated. The disease is often present at more than one level so that it may be difficult to decide at which level to operate, and even after extensive laminectomy recurrence can be due to envelopment of the cord in a layer of fibro-osseous material (Kleinerman 1966). These considerations, together with the experience thus far gained with the use of drugs, suggest that medical treatment may provide a valuable new approach to this uncommon but distressing complication of Paget’s disease.

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