total calcium with overt bone disease is hard to explain. The history of constipation, nocturia and polyuria, albeit mild, do suggest hypercalcaemia and it may be that the ionized calcium was elevated without the total calcium being raised.

There are many points of similarity in the patient reported here with the case reported by Mather in 1953. His patient was a 39-year-old woman who had developed diffuse aching pains in the lower limbs and back 6 months before admission to hospital. His patient was shown to have evidence of osteitis fibrosa both by skeletal X-ray survey and sternal bone biopsy. Four values for the serum calcium concentration during the 3 months prior to the removal of a Wasserhelle cell parathyroid adenoma were all within the normal range. Studies of intestinal function were not, however, reported. Mather's patient is of considerable interest, not only because of the short duration of symptoms but also because, as far as we are aware, it is the only other reported case that was persistently normocalcaemic until the time of operation.

The importance of the detection of cases of normocalcaemic primary hyperparathyroidism is stressed by the report of Nichols & Flanagan (1967). They reported six patients, with this syndrome, which represented 37% of all the patients in whom they had made a diagnosis of parathyroid hyperfunction in a 3-year period. Similarly the occurrence of eleven

cases with this syndrome seen in one centre (George *et al.*, 1965; Wills *et al.*, 1969) over a 9-year period suggests a high incidence among patients with recurrent renal calculi. The patient reported here, together with that of Mather (1953), suggest that normocalcaemia in primary hyperparathyroidism may also be present in some patients with osteitis fibrosa.

Acknowledgments

We wish to thank Professor C. B. Perry and Dr M. Hartog for permission to report this case.

References

- DAVIES, D.R., DENT, C.E. & WATSON, L. (1968) Tertiary hyperparathyroidism. *British Medical Journal*, **3**, 395.
- EISENBERG, E. & GOTCH, F.A. (1968) Normocalcaemic hyperparathyroidism culminating in hypercalcaemic crisis. *Archives of Internal Medicine*, **122**, 258.
- GEORGE, J.M., RABSON, A.S., KETCHAM, A. & BARTTER, F.C. (1965) Calcareous renal disease and hyperparathyroidism. *Quarterly Journal of Medicine*, **34**, 291.
- MATHER, H.G. (1953) Hyperparathyroidism with normal serum calcium. *British Medical Journal*, **2**, 424.
- NICHOLS, G., Jr & FLANAGAN, B. (1967) Normocalcaemic hyperparathyroidism. *Transactions of the Association of American Physicians*, **80**, 314.
- WILLS, M.R. (1969) The urinary calcium/creatinine ratio as a measure of urinary calcium excretion. *Journal of Clinical Pathology*, **22**, 287.
- WILLS, M.R., PAK, C.Y.C., HAMMOND, W.C. & BARTTER, F.C. (1969) Normocalcaemic primary hyperparathyroidism. *American Journal of Medicine*, **47**, 384.

Axial osteomalacia

JOHN R. CONDON
B.Sc., M.B., M.R.C.P.

*St George's Hospital,
London*

J. R. NASSIM
F.R.C.P.

*Royal National Orthopaedic Hospital,
London and St George's Hospital, London*

In 1961 Frame and his co-workers reported three patients who presented with mild back discomfort and in whom radiological studies showed a coarsening and distortion of the trabecular pattern of the cervical vertebrae, lumbar vertebrae, ribs and pelvis. Iliac crest biopsy in each of these patients showed widening of the osteoid seams and because all the known causes of osteomalacia were excluded, the disorder was called 'atypical osteomalacia involving the axial skeleton'. With the exception of a slightly raised plasma alkaline phosphatase in one subject, plasma calcium, phosphate and alkaline phosphatase values were normal in all patients; 24-hr urinary calcium

estimations were also normal. Only two other examples of this syndrome have been reported (Arnstein, Frame & Frost, 1967).

We are reporting a sixth patient who has had this disorder for 18 years and, therefore, gives some indication of the natural history of the disease. The results of calcium, phosphorus and nitrogen balance studies are documented; the effect of prolonged therapy with vitamin D on the symptoms, radiological picture and bone biopsy histology are reported. The possibility that the disorder is not due to any abnormal metabolism of calcium, phosphorus, alkaline phosphatase and vitamin D is discussed.

Case report

The patient, a 71-year-old man, was first admitted to hospital when aged 53 years. At this time he complained of low back pain which had been present for 18 months.

On examination there were no abnormal physical signs but radiographic examination of the vertebrae showed a marked coarsening of trabeculations throughout all areas of the spine with some flattening and biconcavity of the dorsal and lumbar vertebrae.

The intervertebral discs were widened. The trabecular pattern of the pelvic bones was also coarser than normal (Figs. 1-4).

Investigations. Plasma calcium 9.5 mg/100 ml, phosphorus 3.0 mg/100 ml. Alkaline phosphatase 6.3 phenol units. Urine calcium varied from 114 to 160 mg/24 hr.

In 1952, calcium, phosphorus and nitrogen balance studies were performed and these are represented graphically in Fig. 5. It should be noted that unlike

FIGS. 1 AND 2.

FIGS. 3 AND 4.

patients with 'typical osteomalacia' this individual was in strongly positive calcium and phosphorus balance with a normal urinary calcium.

In 1959, the patient had acute pancreatitis which was confirmed at laparotomy. In 1960, he had a right middle cerebral artery thrombosis and in 1963 an impacted fracture of the left femur. Three years later he began developing bilateral Dupuytren's contractures.

In 1966, a bone biopsy examination was performed. Normal bone trabeculae were replaced by a network of thickened structures which gave the specimen a grossly abnormal appearance on naked eye examination. Examination of decalcified sections

showed thick irregular bone trabeculae. Much of the trabecular surface was covered by osteoid tissue which in places formed layers of up to 100 μ in thickness. Some areas of bone resorption were present but there was no evidence of fibrous replacement of bone. Microradiographs showed the smudgy outline of osteocytic lacunae found in rickets and osteomalacia. All the osteoid tissue had a normal lamellar structure; there was nothing to suggest a diagnosis of fibrogenesis imperfecta ossium.

Increased bone density is known to occur in some examples of long standing osteomalacia and the present case appears to be an example of this association.

From 1952 to 1970 plasma calcium, phosphorus and alkaline phosphatase levels were measured at 3-6-monthly intervals and were invariably normal. Twenty-four-hour urine hydroxyproline values were all within the normal range.

Treatment. Treatment with vitamin D at a dosage of 1500 units and later 10,000 units/day, was begun in 1952 and continued for 6 months. This was followed by stilboestrol 1 mg/day combined with methyltestosterone 10 mg/day and later methyltestosterone alone. There was no improvement of symptoms and no change in radiological appearances of the bone following this therapy.

In 1966, the dosage of vitamin D was increased to 20,000 units/day and continued for 3 years. There was still no improvement in symptoms and the radiological bone picture remained unchanged. Repeat iliac crest bone biopsy was performed in 1970 and reported as follows:

'The material, a small piece of thin cortical bone and a few narrow widely separated trabeculae was inadequate for proper histological assessment. There were few osteoid seams, but the width of those present was similar to the width of seams seen in areas of the bone biopsy taken in 1966.

Microradiographs again show the smudgy outline of the osteocyte lacunae to be present.'

It is difficult to draw any definite conclusions concerning the effect of therapy.

Discussion

The patient we have reported came under medical supervision when aged 53 years, because of back pain. At that time the abnormal trabecular pattern of the axial skeleton was noted but regarded as a form of osteoporosis. In 1966, the radiological evidence was reviewed and a diagnosis of fibrogenesis imperfecta ossium (Baker *et al.*, 1966) suggested. Bone biopsy, which was performed in 1966 to confirm this diagnosis, revealed histological features which are generally accepted to be diagnostic of osteomalacia.

FIG. 5. Open columns, faeces; hatched columns, urine.

The clinical and biochemical findings are, however, not those generally associated with osteomalacia. The plasma calcium, phosphorus and alkaline phosphatase were all normal. Urinary calcium estimations were normal and calcium and phosphorus balance was strongly positive. Furthermore, no Looser's zones were identifiable in the skeleton and the disorder had a prolonged clinical course with failure of response to vitamin D at doses varying from 1500 to 20,000 units/day.

Axial osteomalacia is difficult to distinguish from fibrogenesis imperfecta ossium on radiological grounds alone. Radiologically axial osteomalacia is characterized by a coarsening and distension of the trabecular pattern of the cervical vertebrae, lumbar vertebrae, ribs, and pelvis. (Figs. 1-4.) The more peripheral parts of the skeleton appear radiologically normal, unlike fibrogenesis imperfecta where they may not infrequently be involved. Histological examination of bone tissue from patients with fibrogenesis imperfecta ossium show a deficiency of collagen fibres as detected by the absence of birefringence with the polarizing microscope. There was, however, no histological evidence to suggest a diagnosis of fibrogenesis imperfecta ossium in the patient we have described. Urinary mucopolysaccharide and urinary hydroxyproline estimations were normal.

The prognosis of patients with 'axial osteomalacia' appears to be reasonably good. One patient followed up for 5 years is still well without treatment (Arnstein *et al.*, 1967) and the symptoms and radiological findings of our patient have not changed for 18 years.

Therapy with vitamin D, 20,000 units daily for 3 years has not induced any detectable alteration in bone biopsy histology and this fact together with the normal plasma biochemistry and positive calcium and phosphorus balance data strongly suggest that the disorder is not a true osteomalacia.

Acknowledgments

We thank Dr Paul Byers for reporting the bone biopsy histology and Dr E. H. Allen for radiological studies.

References

- ARNSTEIN, A. R., FRAME, B. & FROST, H. (1967) Recent progress in osteomalacia and rickets. *Annals of Internal Medicine*, **67**, 1296.
- BAKER, S.L., DENT, C.E., FRIEDMAN, M. & WATSON, L. (1966) Fibrogenesis imperfecta ossium. *Journal of Bone and Joint Surgery*, **48**, 804.
- FRAME, B., FROST, H.M., ORMAND, R.S. & HUNTER, R. (1961) Atypical osteomalacia involving the axial skeleton. *Annals of Internal Medicine*, **55**, 632.

Secondary amyloidosis in relation to carcinoma of the kidney

DAVID SPENCER*
M.B., Ch.B., M.R.C.Path.

Senior Registrar, Area Department of Pathology, Exeter

WITH the reduction in the incidence and duration of chronic inflammatory diseases such as tuberculosis and chronic osteomyelitis during the past 2 decades, the pattern of aetiological factors in the causation of secondary amyloidosis has been changing. As a consequence other conditions are assuming more importance in the pathogenesis of this disease, notably, of course, rheumatoid arthritis.

This case report illustrates another of the now relatively more important causes, carcinoma of the kidney, which produced a sufficiently severe degree of secondary amyloidosis for the patient to develop renal failure.

Case report

The patient was aged 59 at the time of his death in early 1969. He had been in Exeter on several occasions for minor ailments, the last of these being a Trendelenburg operation for varicose veins in August 1967. At this time the only other abnormality noted was that he also suffered from haemorrhoids, but sigmoidoscopy was normal. The haemorrhoids thrombosed and settled down in May 1968.

However, his general practitioner, who saw him at this time, was not satisfied with his general condition, mainly because of a weight loss of over a stone in a few months, with considerable hunger despite eating well. As he also looked ill he was readmitted for investigation in early June 1968.

On admission there was a pyrexia of 102°F, a

* Present address: Department of Pathology, Wycombe General Hospital, High Wycombe, Bucks.