BONE AND BONE DISEASE

A SYMPOSIUM on “Bone and Bone Disease” was held in the Medical Biology Centre (Q.U.B.) on Friday, 14th February, 1975, under the joint auspices of the Royal College of Physicians of Edinburgh, the Northern Ireland Council for Postgraduate Medical Education, and the Ulster Medical Society. The Symposium proved extremely popular and was attended by over two hundred doctors. The large attendance was commented upon by Dr. R. F. Robertson (Vice-president of the Royal College of Physicians of Edinburgh) who opened the symposium. He remarked that the occasion was unique in that it was the first time the Edinburgh College had “crossed a sea” to participate in a symposium.

The programme was divided into three sessions: Session 1 was chaired by Professor J. J. Pritchard (Department of Anatomy, Q.U.B.), Session 2 by Dr. R. F. Robertson (Royal College of Physicians of Edinburgh), and Session 3 by Professor R. H. Girdwood (Department of Medicine, Edinburgh University). The culmination of the symposium was the annual Sir Thomas and Lady Edith Dixon Lecture, delivered by Professor H. F. DeLuca (Chairman of the Department of Biochemistry, University of Wisconsin, Madison), who gave an erudite and enlightening exposition of the present state of knowledge of the metabolism of Vitamin D. For the lecture the chair was taken by Professor J. E. Morison (President of the Ulster Medical Society).

The following are abstracts of the papers presented. After each session relevant points from the discussion are given.

SESSION 1

A. THE CLASSIFICATION OF METABOLIC BONE DISEASE (RICKETS AND OSTEOMALACIA)

Professor C. E. DENT, F.R.S., Ph.D., M.D., F.R.C.P. (Lond.)
Department of Human Metabolism, University College Hospital Medical School,
London

The discovery in 1919 that rickets was due to a dietary deficiency led to important improvements in bone disease classification. The superficially similar chondrodystrophies could be adequately distinguished. Classical rickets, healing readily with a few hundred units of vitamin D daily, could be distinguished from the metabolic forms requiring about 100 times more vitamin D, sometimes with other drugs too. Progress in the next 10 years comprised the first classic descriptions of coeliac and renal rickets and then soon after the extension of the latter into three types, “Vitamin D resistant” rickets, renal tubular acidosis and the Fanconi syndrome (in which renal tubular rather than glomerular dysfunction occurs). After this still further subdivisions of these types occurred and in addition quite new causes were and are
still being found. There are now over 30 different types of metabolic rickets, of such diverse origins as phosphate lack from overdosage with aluminium hydroxide, heavy metal poisoning of the renal tubule, as part of the bone disease in primary hyperparathyroidism, from various hereditary renal tubular syndromes, varieties of malabsorption syndromes and perhaps most interesting of all theoretically, from an obscure chemical complication clearly attributable to certain tumours of bone and soft tissue.

B. INVESTIGATIVE APPROACH TO BONE DISEASE

Professor D. L. GARDNER, M.D., F.R.C.P. (Edin.), F.R.C.Path., M.R.C.P. (Lond.)
Professor of Pathology and Director of the Institute of Pathology,
The Queen's University of Belfast

A full understanding of the nature of a generalised disease of bone often comes only from the use of a wide variety of diagnostic laboratory procedures. Among the most valuable is iliac crest bone biopsy. A cylindrical specimen of dense cortical and of cancellous iliac bone is obtained by a motor driven trephine. The material, which is suitable for x-ray, for microincineration, for scanning—and for direct electron microscopy, is divided longitudinally. This gives (1) a block decalcified in EDTA or in a formic acid/sodium citrate mixture and used to prepare paraffin sections that establish the presence or absence of neoplastic and haemopoietic diseases; and (2) a block embedded in epon wax or araldite to give undecalcified sections. Alternatively, one of the two blocks may be rapidly frozen and used to prepare undecalcified sections at low temperature in a bone cryostat.

Undecalcified sections enable the recognition of the extent of osteoid seams and the diagnosis of the osteomalacic syndromes. The survey of sections from bone in which tetracycline has been incorporated during life as a measure of bone growth is facilitated. Cryostat sections can be used for enzyme histochemistry, in the diagnosis, for example, of hypophosphatasia.

Important systematic studies of bone disease by these and other techniques have been made by Frost. This survey concluded by illustrating the microscopic appearances of some of the principal forms of generalised bone disease and outlined the methods Frost has advocated in their assessment.

After Session 1, Professor J. J. Pritchard (Q.U.B.) made the point that anatomically bones were simple things but they had become "mixed up" with a major portion of the body's metabolic activity and this helped to explain the variety of disorders affecting the skeleton. Professor Pritchard asked how bones bent in osteomalacia/rickets and Professor Dent in reply stated that in children the bending of the femora occurred at the growing ends but that deformity of the femoral neck could occur at the site of a Looser fracture.
C. **Metabolic Bone Disease**

**Dr. M. G. McGeown, M.D., Ph.D., F.R.C.P. (Edin.)**  
Honorary Reader in Nephrology, The Queen's University of Belfast

In the introduction to her paper Dr. McGeown emphasised the importance of clinical examination in the diagnosis of metabolic bone disease.

| Disease             | Histology                                      | Clinical                  | Radiology                                   | Blood Chemistry | Aetiology                        | Treatment                  |
|---------------------|------------------------------------------------|---------------------------|---------------------------------------------|-----------------|----------------------------------|---------------------------|
| Osteoporosis        | Thin, sparse trabeculae, fully calcified.      | Brittle: fractures. Pain episodic. Central skeleton deformities fractures. | Poorly calcified spine, pelvis, femora.    | Ca → P → Alk phos → | Age types Hormonal Nutritional Disease | Unsatisfactory            |
| Osteomalacia        | Too little *calcified* bone. Trabeculae with osteoid borders. | Aching bones. Tender bones. Soft bone deforms. Muscle weakness. | Poorly calcified whole skeleton. Deformities marked. Looser zones. | Ca ↓ or → P ↓ Alk phos ↑ | Vitamin D deficiency Congenital Dietary Malabsorption Renal Tubular syndromes Dialysis osteomalacia | Vitamin D Treat cause     |
| Hyperparathyroidism | Osteitis fibrosa cystica. Bone destruction with fibrous repair. | Generalized bone pain. Bizarre deformities chest, spine, pelvis. “tumours” long bones. Fractures. | Whole skeleton involved—cortical bone loss. Subperiosteal erosions. | Ca ↑ P ↓ Alk phos ↑ | Excess PTH | Remove overactive parathyroid gland(s) |
| Paget’s Disease     | Osteitis deformans. Bone destruction with excessive bone formation. | Pain variable. Deformities with increased bone thickness. | Characteristic appearances with remaining areas of normal bone—“spotty” bone disease. | Ca → P → Alk phos ↑ | Unknown | ? any—calcitonin mithramycin glucagon diphosphonates |
SESSION 2

A. PAGET’S DISEASE OF BONE

DR. V. PARSONS, M.D., F.R.CP. (Lond.),
Physician, King’s College Hospital, London

James Paget’s disease of bone is a widespread disease which can affect all of the bones in the body with many features of a diffuse abnormality, not only of bone formation and modelling, but also affecting other connective tissue including the vascular supply to the bone and finer vessels, angioid streaks in the eye.

There is evidence for a familial and geographical incidence of the disease which suggests that it may be of genetic origin and there is evidence that it may be associated with other diseases such as pseudoxanthoma elasticum and possibly thyroiditis.

The presenting symptoms and signs are extremely varied, but patients may present to the orthopaedic surgeons and rheumatologists with arthritis, fractures and sarcoma, to the neurologist with cranial nerve lesions, cervical cord lesions and more rarely mid-brain and cerebral dysfunction, to the cardiologist with heart failure and heart block, to the dental surgeon with difficulties associated with the jaw and dentition and to the metabolic physician because of the derangements found in calcium metabolism when those patients are admitted for other reasons. A proportion of patients are asymptomatic and the disease is brought to light during routine X-rays and biochemical investigations. These latter show characteristic changes in alkaline and acid phosphatases and total urinary hydroxyproline. The radiological, histological and bone scan features are typical.

The clinical picture is occasionally confused by other diseases occurring with Paget’s disease, such as carcinoma of the prostate, multiple myelomatisis, osteomalacia, sarcoidosis, all of which need to be disentangled in the particular patient. Treatment involves a full assessment of the patients symptoms. How much of the pain is due to degenerative arthritis? The extent of deformity and periosteal distension, fracture, increased bone blood flow, diversion of blood from muscle to bone, and finally, malignant change. The range of treatment involved include local radiotherapy, antimitotic agents such as mithramycin, diphosphonates and calcitonin (porcine, salmon and human).

B. MINERAL METABOLISM IN RHEUMATOID ARTHRITIS

Professor W. W. BUCHANAN, M.D., F.R.CP. (Glasgow), F.R.CP. (Edin.)
The Centre for Rheumatic Diseases, Glasgow

It has been recognised for many years that one of the earliest radiological features of rheumatoid arthritis is juxta-articular osteoporosis. However, the pathogenesis of this and generalised osteoporosis has not been explained.

This paper described studies of osteoporosis in a large group of patients with
rheumatoid arthritis, employing three radiological indices—metacarpal, femoral and clavicular. The results show that a significant degree of osteoporosis occurred in both males and females. Osteoporosis was particularly marked in those over 45 years of age, those with arthritis of long duration, and those who had been treated with corticosteroid therapy. Of particular interest was the fact that osteoporosis occurred to the same degree in bones close to joint inflammation e.g. the metacarpal, and those some distance from inflammed joints e.g. mid-point of femur. Studies on the role of zinc in osteoporosis in rheumatoid arthritis were also described. The plasma zinc has been found to be low in patients with the disease, especially those treated with corticosteroid therapy, and the plasma zinc concentration correlated with the degree of osteoporosis.

Finally, the results of more recent studies of serum calcium, phosphorus, alkaline phosphatase, albumin and chloride, were reported which suggest that patients with rheumatoid arthritis have a significant increase in parathyroid activity.

Discussion on Dr. Parson's paper after Session 2, emphasised that Paget's disease could be associated with vitamin D deficiency.
It is well established that Vitamin D₃ must be hydroxylated on C-25 in the liver and subsequently on C-1 in the kidney to form 1,25-(OH)₂D₃ before it can function...
at physiological doses. Without apparent further metabolism, the 1,25-(OH)₂D₃ stimulates the intestine to transport calcium and phosphate, the mobilization of calcium and phosphate from bone and the reabsorption of calcium in the kidney. In true endocrine fashion, the biogenesis of 1,25-(OH)₂D₃ in the kidney is feed-back regulated by 1,25-(OH)₂D₃ itself, by serum calcium concentration through the parathyroid hormone and by serum inorganic phosphorus. Although the cellular and molecular mechanisms of this regulation are not known at present, it is clear that the physiologic need for calcium and for phosphorous as revealed by low serum levels of these ions results in stimulation of 1,25-(OH)₂D₃ synthesis which then mobilizes these ions from intestine and bone. The level of 1,25-(OH)₂D₃ also plays a regulatory role which may be permissive in nature. In the absence of 1,25-(OH)₂D₃, the parathyroid hormone and inorganic phosphate of the serum do not regulate the 25-OH-D₃-hydroxylase activity of kidney which is very high in the vitamin D-deficient state regardless of the serum levels of Ca=, PO₄= and parathyroid hormone.

Hypoparathyroid patients probably produce little 1,25-(OH)₂D₃ in response to hypocalcemia and are easily treated with 1 µg/day of 1,25-(OH)₂D₃ plus 1 gram of dietary calcium. Renal failure patients who probably lack the ability to synthesise 1,25-(OH)₂D₃ are also markedly improved by treatment with 1,25-(OH)₂D₃ (1 µg 3 times per week). Vitamin D dependency rickets is also treated with 1,25-(OH)₂D₃ (1 µg/day) successfully. In all such treatments a synthetic analog of 1,25-(OH)₂D₃, namely 1-alpha-OH-D₃, is also effective, but the successful treatment level is about twice that of 1,25-(OH)₂D₃. Additional clinical applications of the metabolites of vitamin D₃ were discussed.