HEREDITARY HYPOPHOSPHATAEMIC RICKETS WITH AUTOSOMAL RECESSIVE INHERITANCE AND SEVERE OSTEOSCLEROSIS

A REPORT OF TWO CASES

W. PERRY, T. C. B. STAMP

From the Metabolic Unit, Royal National Orthopaedic Hospital, Stanmore

We have observed congenital hypophosphataemic rickets in two sons of a marriage between first cousins, their mother being clinically and biochemically normal. Both patients are now approaching middle age. In addition to severe childhood rickets and lifelong hypophosphataemia, their disease is characterised by gross osteosclerosis with extraskeletal ossification, clinically persistent osteomalacia in one and spinal cord compression in the other.

The genetics of this disease can be satisfactorily explained only on the basis of autosomal recessive inheritance, a mode which has only once before been reported in the literature. The severity of certain features, which would be expected in a homozygous state, may help our understanding of the more usual X-linked form.

Hereditary hypophosphataemic rickets is a fairly common condition characterised by X-linked dominant transmission, childhood rickets which is resistant to treatment with vitamin D in the physiological dose range, and lifelong hypophosphataemia (Albright, Butler and Bloomberg 1937; Winters *et al.* 1958; Williams and Winters 1972). The disease is usually associated with an unaccountable increase in bone density which occasionally progresses to severe osteosclerosis, extraskeletal ossification and premature fusion of cranial sutures. Spinal cord compression has been known to result.

Up to one-third of cases appear to arise by spontaneous mutation, depending on the vigour with which maternal hypophosphataemia is sought (Burnett *et al.* 1964). Autosomal dominant transmission has been referred to but has never been adequately documented (Harrison *et al.* 1966). We report two adult brothers in whom autosomal recessive transmission is the only satisfactory explanation of inheritance. The severity of their disease, particularly in relation to its osteosclerosis, is consistent with a homozygous state and highlights the inadequacy of most current explanations of pathogenesis in the X-linked form.

CASE HISTORIES

Case 1. The elder brother was born in March 1935. Bowing of his legs was first noticed when he began walking at the age of nineteen months. Up to the age of eighteen years he underwent numerous bilateral osteotomies: of the upper tibiae in 1942, of the femora in 1951 and of the upper tibiae again in 1953. From 1943 to 1953 he was said to be receiving 100 000 units of vitamin D (2.5 mg) daily but radiographs of both tibiae in 1947 showed persisting rickets at the ankles (Fig. 1).

In June 1976 he was admitted to the metabolic ward complaining of tingling and numbness down the back of the thighs for eighteen months, occurring only after walking or spinal over-extension, and pain in the lower lumbar spine for three years. On examination his height was 159 cm and skeletal measurements were crown to pubis 87 cm, pubis to sole 73 cm and span 194 cm; he was severely bow-legged. There was no bone tenderness or myopathy. No abnormality was detected in his central nervous system while at rest but audiometry demonstrated a high-tone sensorineural deafness in both ears. Other systems were normal.

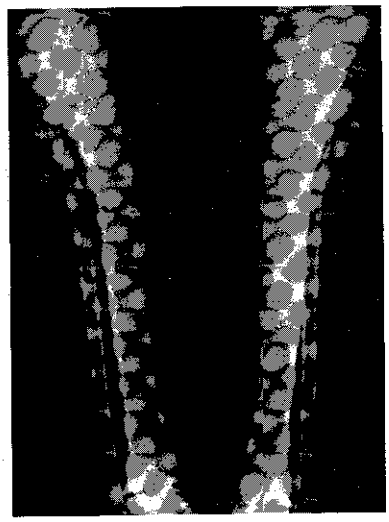

Fig. 1

Case 1. Radiograph at the age of twelve, showing that the deformity has been largely corrected by previous osteotomies, but at the ankles there are multiple Harris lines and persistent rickets.

W. Perry, M.R.C.P., Senior Medical Registrar
T. C. B. Stamp, M.D., F.R.C.P., Consultant Physician
The Metabolic Unit, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex HA7 4LP, England.

Table I. Blood and urine analyses of the two patients and their first-degree relatives

Subject	Age	Serum analysis*			Renal tubular phosphate clearance (*ml/min*)	Tubular reabsorption of phosphate (*per cent*)
		Calcium (*mmol/l*)	Phosphorus (*mmol/l*)	Alkaline phosphatase (*i.u./l*)		
Mother	69	2.55	1.27	65.0		
Case 1	41	2.37	0.64	67.0	65.0	67.0
Case 2	39	2.42	0.62	126.0	24.0	78.5
Elder son of Case 2	10	2.32	1.32	180.0		
Younger son of Case 2	7	2.30	1.42	192.0		
Normal range		2.30–2.70	0.84–1.53	21–84	6.3–15.5†	80–91‡

**Conversion factors*
serum calcium mmol/l × 4 = mg/100 ml
serum phosphorus mmol/l × 3.1 = mg/100 ml
serum alkaline phosphatase i.u. ÷ 7.1 = King–Armstrong units
†Kyle, Schaaf and Canary 1958
‡lowest normal limits in literature (Reiss and Alexander 1959)

Investigations. Haemoglobin measured 15.3 g/dl with a normal blood count; levels of serum calcium and alkaline phosphatase, and of plasma urea and electrolytes were normal, but serum phosphorus was below the normal range (Table I). The plasma 25-hydroxycholecalciferol level was normal at 13 ng/ml (32.5 nmol/l). Twenty-four-hour urine calcium excretion was 144 mg (3.6 mmol) and the total hydroxyproline was normal at 35 mg (0.27 mmol). Tubular reabsorption of phosphate was severely reduced (Table I). Radiographs showed marked thickening of all bones very similar to that of his brother, and ossification of the posterior vertebral ligament; myelography demonstrated compression of the cord at the level of the disc between the second and third lumbar vertebrae (Fig. 2). There were multiple sites of stenosis of the spinal canal, also due in part to thickening of the posterior wall of the canal, which were clearly the cause of the tingling and numbness in the legs after exercise. Biopsy of the iliac crest showed wide osteoid seams. He was not given vitamin D and remains under observation for his spinal cord compression.

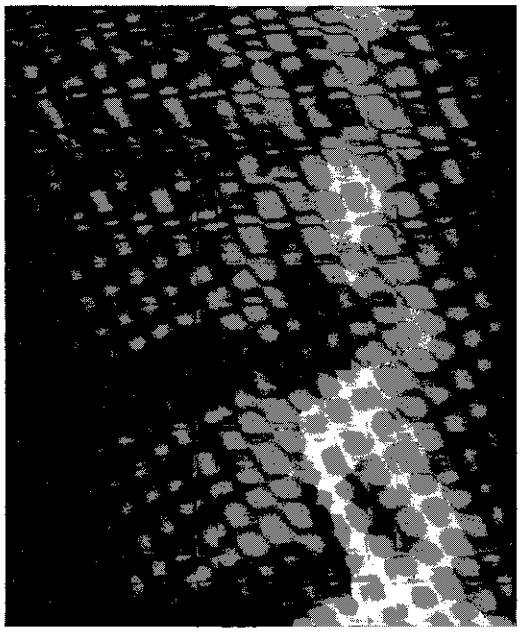

Fig. 2

Case 1. Myelogram at the age of forty-one showing ossification of the posterior vertebral ligament and compression at L2–3 level.

Case 2. The younger brother was born in May 1937. Bow legs were first noticed when he began walking. At the age of five years bilateral tibial osteotomies were performed and he began taking vitamin D. During childhood he travelled widely and vitamin D dosage was variable. Vitamin D was stopped in 1971. He has two normal sons.

In March 1975 he was admitted to the metabolic ward complaining of increasing stiffness and pain in the lower back and knees. On examination his height was 164.5 cm and skeletal measurements were crown to pubis 88 cm, pubis to sole 78.5 cm and span 176.5 cm. He was severely bow-legged (intercondylar separation was 10 cm). There was no bone tenderness or myopathy. Although he had no clinical evidence of deafness audiometry demonstrated a high-tone sensorineural deafness of the left ear. Other systems were normal.

Investigations. Haemoglobin measured 12.8 g/dl with a normal blood count; serum calcium, and plasma urea and electrolytes were normal; serum phosphorus was low but alkaline phosphatase was high (Table I). There was no glycosuria and the urinary amino acid chromatogram was normal. Twenty-four-hour urine calcium excretion was 236 mg (5.9 mmol) and total hydroxyproline excretion was normal at 33 mg (0.25 mmol). Tubular reabsorption of phosphate was reduced (Table I). Radiographs showed marked cortical thickening of the long bones and ossification of the intervertebral ligaments of the lumbar spine together with excessive ossification of many muscular attachments (Fig. 3). Biopsy of the iliac crest showed a marked increase in osteoid on the trabecular surfaces and no uptake of tetracycline at the calcification front. He was discharged on 1 mg vitamin D_2 daily and his plasma 25-hydroxycholecalciferol levels have since ranged between 144 and 201 ng/ml (360–502 nmol/l) which was consistent with this dose. By April 1976 his alkaline phosphatase had fallen to 11.8 K-A units (84 i.u.) per litre and he remains under observation.

THE FAMILY

The parents, who were both English, were first cousins and the family tree is shown in Figure 4. The father (III, 4), who is dead, was reported to have had normal stature with no clinical history of bone problems.

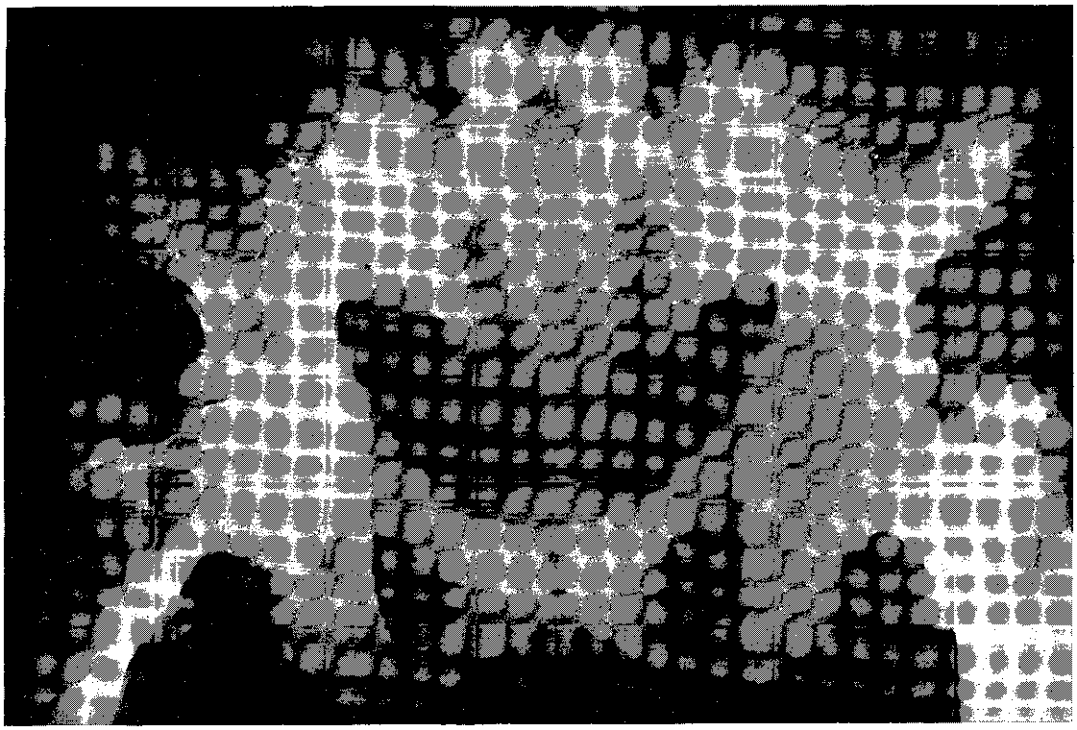

Fig. 3

Case 2, aged thirty-seven. Radiograph of the pelvis showing severe osteosclerosis and ossification of the muscular attachments.

The mother (III, 3), who was born in June 1908, was healthy and normally proportioned; her serum analysis was normal (Table I). The two sons (V, 1 and V, 2) of the younger patient (IV, 2) were born in October 1966 and December 1969, respectively. They were both of normal stature for their age and their serum analyses were normal (Table I). Full blood grouping was consistent with the stated maternity.

DISCUSSION

We have briefly described in two patients a severe hypophosphataemic rickets which closely mimics the X-linked "vitamin D-resistant" form of the disease but which appears to have been inherited as an autosomal recessive gene. Since the patients' father was deceased we could not completely exclude autosomal dominant transmission but in view of his reported clinical normality and of the fact that one affected son (IV, 2) has two normal children, it seems unlikely: certainly X-linkage could not have been involved. A theory of primary mutation in the oöcyte has been postulated to account for the rare occurrence of dominantly inherited disease, such as achondroplasia, in more than one sib from healthy parents. However, since first-cousin marriage was firmly established in our pedigree, such theory is unnecessary since one eighth of each parent's genes are identical.

Autosomal recessive inheritance of hypophosphataemic rickets has been reported once previously (Stamp and Baker 1976) and our patients show certain similarities: gross bony overgrowth with simultaneous defects in remodelling were features in both families, but craniostenosis was absent in the present report and nerve deafness was less marked. Extraskeletal ossification was present in our patients but absent in the previous report. Persistent clinical or biochemical osteomalacia was present in each family.

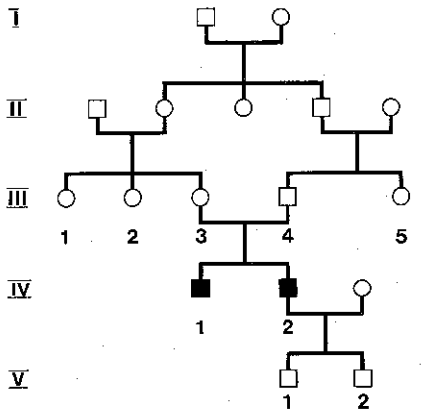

Fig. 4

Family tree showing the two affected sons (IV, 1 and 2) of a first-cousin marriage.

The pathogenesis of both X-linked and autosomal recessive hypophosphataemia is unknown. The rickets probably results, at least in part, from hypophosphataemia due to excessive renal tubular phosphate excretion. This renal phosphate "leak" is the cardinal biochemical abnormality and its precise cause is unknown. It was originally ascribed to secondary

hyperparathyroidism due to diminished intestinal calcium absorption and "a tendency to hypocalcaemia" (Albright and Sulkowich 1938; Avioli *et al.* 1967; Earp *et al.* 1970), but this view is no longer tenable: plasma calcium is always normal, usually in the upper range, secondary hyperparathyroidism as measured by serum immunoreactive parathyroid hormone appears mild (Arnaud, Glorieux and Scriver 1971; Lewy *et al.* 1972; Reitz and Weinstein 1973) and the phosphate "leak" is now more generally accepted as a primary abnormality (Robertson, Harris and McClune 1942; Dent 1952; Fanconi and Girardet 1952; Frame and Smith 1958; Winters and Graham 1960; Rey and Frézal 1966) due to loss of a "parathyroid hormone-sensitive component of phosphate transport" (Arnaud *et al.* 1971; Glorieux and Scriver 1972; Scriver *et al.* 1976).

In addition to the well-known actions of vitamin D or its active metabolites in promoting intestinal calcium absorption and bone calcium mobilisation, there is certain evidence of direct effects in the kidneys of stimulation of renal tubular phosphate reabsorption (Popovtzer *et al.* 1974; Puschett *et al.* 1972; Pechet and Hesse 1974), and in the parathyroid glands which may be suppressed directly by vitamin D metabolites (Rasmussen *et al.* 1974). An attempt was made to attribute the pathogenesis of hereditary hypophosphataemic rickets to multiple target-organ unresponsiveness to vitamin D, in the kidneys, in the intestine, in bone and in the parathyroid glands (Stamp and Baker 1976). According to this theory the renal tubular phosphate leak was due to loss of "the vitamin D-dependent element" of tubular phosphate reabsorption, and the additional skeletal abnormalities (poor remodelling and osteosclerosis) were due to a combination of vitamin D unresponsiveness and reactive hypertrophy from mild secondary hyperparathyroidism. Circumstantial evidence was derived from the experimental production of similar osteosclerosis by low doses of parathyroid hormone in growing animals (Kalu *et al.* 1970; Walker 1971), and a possible enhancement of bone density by low doses of human parathyroid hormone (1–34 fragment) in osteoporosis (Reeve *et al.* 1976).

The answer is still far from clear, however, partly because of uncertainty over the effect of vitamin D on phosphate transport in general and partly because of conflicting evidence regarding intestinal calcium and phosphate transport in X-linked rickets. Defective intestinal calcium absorption is often mild in X-linked rickets and may resolve in adult life (Stanbury 1976) although hypophosphataemia persists. Vitamin D may stimulate intestinal phosphorus absorption both in experimental animals (Harrison and Harrison 1961), and in man (Stamp 1972; Stanbury 1976). Evidence has therefore been sought for defective intestinal phosphate absorption in familial hypophosphataemia. Condon, Nassim and Rutter (1970) reported a diminished rise in serum phosphorus after oral phosphate loading in familial hypophosphataemia; Short, Binder and Rosenberg (1973) found defective phosphorus-33 uptake in biopsied jejunal mucosa in the disease. However, the findings of Condon *et al.* were not confirmed in a smaller series of patients (Dent and Stamp, unpublished data); Glorieux *et al.* (1974) also reported normal phosphate transport in some patients, and Stanbury (1976) has shown that faecal phosphorus excretion may bear a normal relationship to phosphorus intake.

Many uncertainties clearly remain over the pathogenesis of familial hypophosphataemia. Genetic heterogeneity has been suggested in X-linked rickets (Glorieux and Scriver 1972; Scriver *et al.* 1976). The minor differences between our cases and those previously reported (Stamp and Baker 1976) are also consistent with genetic heterogeneity in autosomal recessive hypophosphataemia.

We are grateful to Sister Mary Dunsden and the nurses of the metabolic ward, and to Dr Ruth Sanger for undertaking the full blood grouping of the two patients.

REFERENCES

Albright, F., Butler, A. M., and Bloomberg, E. (1937) Rickets resistant to vitamin D therapy. *American Journal of Diseases of Children,* **54,** 529–547.

Albright, F., and Sulkowitch, H. W. (1938) The effect of vitamin D on calcium and phosphorus metabolism: Studies on four patients. *Journal of Clinical Investigation,* **17,** 305–315.

Arnaud, C. D., Glorieux, F., and Scriver, C. (1971) Serum parathyroid hormone in X-linked hypophosphataemia. *Science,* **173,** 845–847

Avioli, L. V., Williams, T. F., Lund, J., and DeLuca, H. F. (1967) Metabolism of vitamin D_3–^3H in vitamin D-resistant rickets and familial hypophosphataemia. *Journal of Clinical Investigation,* **46,** 1907–1915.

Burnett, C. H., Dent, C. E., Harper, C., and Warland, B. J. (1964) Vitamin D-resistant rickets. Analysis of twenty-four pedigrees with hereditary and sporadic cases. *American Journal of Medicine,* **36,** 222–232.

Condon, J. R., Nassim, J. R., and Rutter, A. (1970) Defective intestinal phosphate absorption in familial and non-familial hypophosphataemia. *British Medical Journal,* **3,** 138–141

Dent, C. E. (1952) Rickets and osteomalacia from renal tubule defects. *Journal of Bone and Joint Surgery,* **34–B,** 266–274

Earp, H. S., Ney, R. L., Gitelman, H. J., Richman, R., and DeLuca, H. F. (1970) Effects of 25-hydroxycholecalciferol in patients with familial hypophosphataemia and vitamin D-resistant rickets. *New England Journal of Medicine,* **283,** 627–630.

Fanconi, G., and Girardet, P. (1952) Familiärer persistierender Phosphatdiabetes mit D-vitamin-resistenter Rachitis. *Helvetia Paediatrica Acta,* **7,** 14–41.

Frame, B., and Smith, R. W., Jun. (1958) Phosphate diabetes. A case study of osteomalacia. *American Journal of Medicine,* **25,** 771–779

Glorieux, F., and Scriver, C. R. (1972) Loss of a parathyroid hormone-sensitive component of phosphate transport in X-linked hypophosphatemia. *Science,* **175,** 997–1000.

Glorieux, F. H., Travers, R., Delvin, E. E., Morin, C. L., and Poirier, R. (1974) Intestinal phosphate transport in familial hypophosphatemia. *Pediatric Research,* **8,** 381.

Harrison, H. E., and Harrison, H. C. (1961) Intestinal transport of phosphate: action of vitamin D, calcium, and potassium. *American Journal of Physiology,* **201,** 1007–1012.

Harrison, H. E., Harrison, H. C., Lifshitz, F., and Johnson, A. D. (1966) Growth disturbance in hereditary hypophosphatemia. *American Journal of Diseases of Children,* **112,** 290–297.

Kalu, D. N., Pennock, J., Doyle, F. H., and Foster, G. V. (1970) Parathyroid hormone and experimental osteosclerosis. *Lancet,* **1,** 1363–1366.

Kyle, L. H., Schaaf, M., and Canary, J. J. (1958) Phosphate clearance in the diagnosis of parathyroid dysfunction. *American Journal of Medicine,* **24,** 240–248.

Lewy, J. E., Cabana, E. C., Repetto, H. A., Canterbury, J. M., and Reiss, E. (1972) Serum parathyroid hormone in hypophosphatemic vitamin D-resistant rickets. *Journal of Pediatrics,* **81,** 294–300.

Pechet, M. M., and Hesse, R. H. (1974) Metabolic and clinical effects of pure crystalline 1α-hydroxyvitamin D_3 and 1α,25-dihydroxyvitamin D_3. *American Journal of Medicine,* **57,** 13–20.

Popovtzer, M. M., Robinette, J. B., DeLuca, H. F., and Holick, M. F. (1974) The acute effect of 25-hydroxycholecalciferol on renal handling of phosphorus. *Journal of Clinical Investigation,* **53,** 913–921.

Puschett, J. B., Fernandez, P. C., Boyle, I. T., Gray, R. W., Omdahl, J. L., and DeLuca, H. F. (1972) The acute renal tubular effects of 1,25-dihydroxycholecalciferol. *Proceedings of the Society for Experimental Biology and Medicine,* **141,** 379–384.

Rasmussen, H., Bordier, P., Kurokawa, K., Nagata, N., and Ogata, E. (1974) Hormonal control of skeletal and mineral homeostasis. *American Journal of Medicine,* **56,** 751–758.

Reeve, J., Hesp, R., Williams, D., Hulme, P., Klenerman, L., Zanelli, J. M., Darby, A. J., Tregear, G. W., and Parsons, J. A. (1976) Anabolic effect of low doses of a fragment of human parathyroid hormone on the skeleton in postmenopausal osteoporosis. *Lancet,* **1,** 1035–1038.

Reiss, E., and Alexander, F. (1959) The tubular reabsorption of phosphate in the differential diagnosis of metabolic bone disease. *Journal of Clinical Endocrinology,* **19,** 1212–1222.

Reitz, R. E., and Weinstein, R. L. (1973) Parathyroid hormone secretion in familial vitamin D-resistant rickets. *New England Journal of Medicine,* **289,** 941–945.

Rey, J., and Frézal, J. (1966) Pathogénie du rachitisme vitamine-résistant hypophosphatémique familial. *Revue française d'études cliniques et biologiques,* **11,** 771–776.

Robertson, B. R., Harris, R. C., and McCune, D. J. (1942) Refractory rickets: mechanism of therapeutic action of calciferol. *American Journal of Diseases of Children,* **64,** 948–949.

Scriver, C. R., Glorieux, F. H., Reade, T. M., and Tenenhouse, H. S. (1976) X-linked hypophosphataemia and autosomal recessive vitamin D dependency: models for the resolution of vitamin D refractory rickets. In *Inborn Errors of Calcium and Bone Metabolism,* pp. 150–178. Edited by H. Bickel and J. Stern. Lancaster: MTP Press Ltd.

Short, E. M., Binder, H. J., and Rosenberg, L. E. (1973) Familial hypophosphatemic rickets: defective transport of inorganic phosphate by intestinal mucosa. *Science,* **179,** 700–702.

Stamp, T. C. B. (1972) The intestinal absorption of phosphorus. Its relation to calcium absorption and to treatment with vitamin D in osteomalacia, parathyroid dysfunction and chronic renal failure. *Clinical Science,* **42,** 16P.

Stamp, T. C. B., and Baker, L. R. I. (1976) Recessive hypophosphataemic rickets, and possible aetiology of the 'vitamin D-resistant' syndrome. *Archives of Disease in Childhood,* **51,** 360–365.

Stanbury, S. W. (1976) Intestinal absorption of calcium and phosphorus in adult man in health and disease. In *Inborn Errors of Calcium and Bone Metabolism,* pp. 21–38. Edited by H. Bickel and J. Stern. Lancaster: MTP Press Ltd.

Walker, D. G. (1971) The induction of osteopetrotic changes in hypophysectomized, thyroparathyroidectomized and intact rats of various ages. *Endocrinology,* **89,** 1389–1406.

Williams, T. F., and Winters, R. W. (1972) Familial (hereditary) vitamin D-resistant rickets with hypophosphataemia. In *The Metabolic Basis of Inherited Disease,* pp. 1465–1485. Edited by J. B. Stanbury, J. B. Wyngaarden, and D. S. Frederickson. New York: McGraw-Hill Inc.

Winters, R. W., and Graham, J. B. (1960) Multiple genetic mechanisms in vitamin D-resistant rickets. *Pediatrics,* **25,** 932–934.

Winters, R. W., Graham, J. B., Williams, T. F., McFalls, V. W., and Burnett, C. H. (1958) A genetic study of familial hypophosphatemia and vitamin D-resistant rickets with a review of the literature. *Medicine,* **37,** 97–142.