HEREDITARY PSEUDO-VITAMIN D DEFICIENCY RICKETS
(“Hereditare Pseudo-mangelrachitis”)

C. E. Dent, M. Friedman, and Lyal Watson, London, England*

From the Metabolic Ward, University College Hospital, London

Since the classic work of Mellanby (1920), of McCollum, Simmonds, Becker and Shipley (1922) and of the Medical Research Council team in Vienna (1923), rickets of nutritional origin has virtually disappeared from the indigenous population in this country, though it has been seen more recently in certain groups of immigrant children (Dunnigan, Paton, Haase, McNicol, Gardner and Smith 1962; Benson, Stroud, Mitchell and Nicolaides 1963). The clinical, biochemical and radiological manifestations of nutritional rickets may be rapidly reversed by the administration of relatively small amounts of vitamin D₂ or other similar compounds—namely, 50 µg or less daily (1 µg vitamin D₂=40 international units).

With the disappearance of this once common disease more notice can be taken of other kinds of rickets which are still rarely seen and which are neither associated with malnutrition nor healed by small doses of vitamin D. The original studies were soon followed by the first clear descriptions of renal rickets (Parsons 1927a) and of coeliac rickets (Parsons 1927b). The observations of Fanconi (1936) and of Albright, Butler and Bloomber (1937) drew attention to a still further group of patients who presented with apparent rickets but who, unlike those with classical vitamin D deficiency, required amounts a thousand times larger (milligram rather than microgram doses) to produce healing. The term “vitamin D resistance” was used to describe this phenomenon. It is now realised that this situation may also be manifest in the latter group of patients, for steatorrhoea, chronic renal glomerular failure, and a large number of diseases associated with renal tubular abnormalities, can all produce “vitamin D resistant” rickets in the sense that the term was used by Albright et al. (1937).

The various renal tubular disorders (classified into six types by Dent in 1952) are now the commonest cause of rickets in this country (Stewart, Mitchell, Morgan, Lowe and Thomson 1964). By far the commonest type shows an isolated renal tubular defect for the reabsorption of phosphate (Type 1 of Dent), a defect now known to be shared by several clinically different diseases. The commonest of these (called phosphate diabetes by Fanconi and Girardet 1952, and hypophosphataemic rickets by Winters, Graham, Williams, McFalls and Burnett 1958) is inherited as a sex-linked dominant gene (Winters et al. 1958; Burnett, Dent, Harper and Warland 1964). The case of Albright et al. (1937) was probably one of these. It manifests itself as a chronic rachitic process of rather variable severity from case to case which may be indistinguishable radiologically from vitamin D deficiency rickets in the early stages of the disease, although clinically and biochemically there are a number of important differences between the two diseases. For instance, muscular weakness and hypocalcaemic tetany are common features of vitamin D deficiency, but never occur in this form of vitamin D resistant rickets. Furthermore, in the latter the plasma phosphorus level is always low before treatment and rises only a little (never to normal) when healing is produced by prolonged administration of large doses of vitamin D. In contrast, the plasma phosphorus level returns rapidly to normal on treatment of vitamin D deficiency rickets with small doses of vitamin D. It has not been sufficiently stressed in the past that in this form of vitamin D resistant rickets even when healing is produced by large doses of vitamin D, and consequent deformities are avoided, growth rate seldom becomes normal, and the patients remain considerably dwarfed.

* Professor of Human Metabolism, Senior Registrar in Paediatrics and Honorary Consultant Physician, respectively.
We have recently investigated a boy who did not present all the typical features either of this latter form of vitamin D resistant rickets or of ordinary vitamin D deficiency rickets. The rickets was severe, both clinically and radiologically (much more severe than seen with untreated Type 1 rickets) and he had marked generalised muscular weakness, simulating a myopathy. With administration of vitamin D the rickets healed, muscle power returned to normal, and the plasma phosphorus level (which was very low before treatment) rose to within the low normal range. In these respects the disease resembled a vitamin D deficiency state. However, this child had had a normal intake of vitamin D and large doses were required to heal the rickets, this feature resembling the common forms of vitamin D resistant rickets. Clinical, radiological and biochemical observations, including metabolic balance studies, have been carried out on this patient over the past four years and form the basis of this report.

CASE REPORT

The patient, a boy, was born in June 1958. He was the second child of unrelated parents, both well and of normal height. His elder sister is well and growing normally. He was delivered normally at full term and his birth weight was 3-1 kilograms. Since birth he has been taking an adequate mixed diet appropriate for his age. He was given vitamin D and C supplements by the local child welfare clinic from the age of three months. Although the parents thought that his early development was normal he only started to walk at the age of eighteen months, when he was noticed to have bow legs. At the age of two years he was seen at an orthopaedic hospital where radiographs showed the changes of rickets associated with marked rarefaction of the long bones and severe retardation of bone age. No epiphyses were visible at the wrists, hands or knees. The lateral view of the spine showed flattened vertebral bodies with anterior protrusions as in Morquio's disease. A tentative diagnosis of osteochondrodystrophy was made. When the child was two and a half years of age the deformity of both tibiae was corrected by osteotomy. The osteotomies failed to unite by visible callus and he was kept in hospital for nine months. During this time he gradually developed generalised muscular weakness and was unable to walk again.

In July 1963, at the age of five years, he was referred to University College Hospital for further investigation. He was still unable to walk and was almost completely confined to bed, though he was able to propel himself about on level surfaces by means of a small tricycle. He had not grown in height since the age of two years, and over the previous three years his weight had also remained constant at about 10 kilograms. The parents said that, apart from bony deformities and muscular weakness, he was very well. His appetite was good; he ate all foods. He had one bowel action daily, and there was no evidence of steatorrhoea or diarrhoea. Intellectual and mental development were normal.

Physical examination revealed a bright, alert child, very stunted in both height and weight. Height was 76 centimetres (the third percentile for his age was 99 centimetres) and weight 10·6 kilograms (the third percentile for his age was 14·6 kilograms). There was marked bowing of the lower limbs with expansion of both ends of the tibiae and the lower ends of the femurs. Healed osteotomy scars were present over both tibiae. The upper limbs showed bowing of the radius and ulna with expansion of the bones at the wrists and elbows. A well developed rickety rosary was present. There was frontal bossing. A striking feature was generalised severe muscular weakness. He was not able fully to support the weight of his head, which tended to flop about. He was able to sit up from the lying position only with great difficulty. He had considerable bone tenderness which interfered with movement and caused great pain. He appeared to be above average in intelligence and he made good social contact with both adults and other children. There was no evidence of a lesion of the nervous system.
Figure 1—Radiographs (July 1963) at age 5 years. Epiphyses are not visible and the ragged ends of the metaphyses are difficult to define. The density in the medulla of the bones is hardly greater than the surrounding soft tissue shown in this radiograph. The important diagnostic feature here is the absence of callus or other signs of healing around the two-and-a-half-year-old osteotomies, which were nevertheless clinically united. This excluded chondrodystrophy and was fully consistent with, if not diagnostic of, active chronic rickets.

Figure 2—Radiographs of hands (July 1963). No carpal bones or epiphyses are seen. The ends of all the metaphyses are ragged.

Figure 3—Spine (October 1963). The vertebral bodies are flattened and show anterior beaking. Though resembling that in Morquio’s disease the beaking was ascribed to the exceptionally severe and prolonged rickets.
Initial investigations—The plasma calcium level was 8.9 milligrams per 100 millilitres (specific gravity 1.026–7), the plasma phosphorus level 1.3 milligrams per 100 millilitres, and plasma alkaline phosphatase 27 King-Armstrong units per 100 millilitres. The twenty-four-hour urinary excretion of calcium was 7 milligrams and of phosphorus 168 milligrams. The plasma level of sodium was 139 milli-equivalents per litre, of potassium 4.3 milli-equivalents per litre, of chloride 109 milli-equivalents per litre, of bicarbonate 18.3 milli-equivalents per litre, and of urea 36 milligrams per 100 millilitres. Serum total protein levels were 6.6 grammes per 100 millilitres with a normal electrophoretic strip. The erythrocyte sedimentation rate was 9
millimetres in the first hour. The haemoglobin level was 11·8 grammes per 100 millilitres, white blood count 5,600 per cubic millimetre; the bone marrow was normal and contained no cystine or other crystals. The urine contained no protein, reducing substances or cells, and was sterile on culture. The urinary amino-acid chromatogram was normal, the maximum urinary concentration was 1,020 and dilution 1,000. Intelligence quotient using the Stanford-Binet intelligence scale was 107. Six-day stool collection revealed fat excretion of 1·5 grammes per day. Resting plasma vitamin A level was 145 i.u. per 100 millilitres, plasma vitamin A four hours after 95,000 i.u. by mouth was 5,100 i.u. per 100 millilitres. Assessment of the dietary intake before admission to hospital showed normal intakes of calcium (600 milligrams per day) and of vitamin D (250 i.u. per day).

Radiographs of the skeleton showed generalised rarefaction of bone with gross rickets. No epiphyses were visible at the wrists, hands or knees (Figs. 1 and 2). The sites of the osteotomies of both tibiae showed no evidence of healing by calcification. There was considerable varus deformity of the femoral necks with distortion of the shape of the pelvis producing a triangular pelvis. The vertebral bodies were much distorted of shape (Fig. 3). The skull was normal.

**Metabolic studies and progress**—Calcium and phosphorus balance studies were carried out according to the principles of Reifenstein, Albright and Wells (1945) as modified by Dent, Harper and Philpot (1961) and the results are shown in Figure 4. In August 1963, before treatment was begun, analysis in two six-day collection periods showed that he was in negative calcium balance of 37 milligrams a day. The stool calcium was greater than the dietary calcium intake of 746 milligrams per day and the daily urinary calcium varied between 6 and 14 milligrams. He was approximately in phosphorus balance, with a daily urinary phosphorus of about 300 milligrams, though the plasma phosphorus level was only 1·2 milligrams per 100 millilitres. On September 6, 1963, he was started on 0·25 milligrams (10,000 i.u.) vitamin D₂ (Calciferol) daily, prepared by the same method as described for dihydrotachysterol by Dent and Friedman (1964a). Although this dose has been shown to produce full and rapid clinical and biochemical responses in adults with dietary vitamin D deficiency (unpublished results), it produced no change in the plasma calcium and phosphorus levels of this patient after eighteen days; the dose of vitamin D₂ was then increased to 2 milligrams daily. This produced a gradual rise in his plasma phosphorus level to 3 milligrams per 100 millilitres (Fig. 5).

The dose of vitamin D₂ was further increased to 5 milligrams daily at the end of October 1963 because radiographs at this stage showed only very slight improvement. Three further six-day balance studies were carried out during November 1963 while he was taking 5 milligrams of vitamin D₂ daily. The results showed a marked improvement when compared with the pre-treatment balances (Fig. 4). With a daily calcium intake of 765 milligrams the urinary calcium had risen to about 180 milligrams daily and the faecal calcium had fallen to about 190 milligrams a day. This gave an average positive calcium balance of 389 milligrams a day during the eighteen-day study. The phosphorus balance showed an average daily retention of 226 milligrams phosphorus. Radiographs at this stage showed a marked improvement (Figs. 6 and 7).

In December 1963 he was given 50 μg vitamin D₂ daily by intravenous injection for two periods of seven and four days respectively, to exclude the possibility of gastro-intestinal malabsorption of vitamin D. This produced no acute effect on the plasma levels of calcium or phosphorus. At the end of December the dose of oral vitamin D₂ was reduced from 5 milligrams to 2 milligrams daily. Further improvement in the radiographic appearance was noted (Figs. 8 and 9). However, since it was hoped to increase the rate of improvement still further, he was given a daily supplement of 4 grammes calcium phosphate, which contained 930 milligrams calcium and 722 milligrams phosphorus. This produced surprisingly little change in the overall balance picture (Fig. 4).
After treatment with vitamin D was begun there was a gradual improvement in muscle power, which was particularly marked when the vitamin \( D_2 \) was increased to 5 milligrams daily and the plasma phosphorus level subsequently rose (Fig. 4). Bone pain and tenderness gradually improved and after four months' treatment had completely disappeared. The patient went home on February 15, 1964, having spent six and a half months in hospital. He was then able to walk with the aid of sticks, and could take a few steps without support. He could support the weight of the body on the lower limbs, and his head without effort.

The effects of treatment on the calcium, phosphorus and alkaline phosphatase values are shown in Figure 5. In June 1964 he became hypercalcaemic while taking 2 milligrams vitamin \( D_2 \) and 4 grammes calcium phosphate daily. Both were therefore stopped for a short period and then vitamin \( D_2 \) was reintroduced in a daily dose of 1 milligram, soon reduced to 0.5 milligram daily; this appears to be a satisfactory maintenance dose. The plasma phosphorus level has remained constantly above 3 milligrams per 100 millilitres. The plasma alkaline phosphatase, initially 30 King-Armstrong units per 100 millilitres, fell to 15–20 King-Armstrong units per 100 millilitres. Radiographs of the wrists and knees in April 1965 (Figs. 10 and 11) showed that the rickets had healed, but the epiphyses were still abnormal, with an irregular fragmented appearance. In December 1965, when he was seven and a half years old, his height was 93.5 centimetres (third percentile for his age 112.5 centimetres), muscle power was completely normal, and he was able to join in games with other children, to play football and to walk a mile without difficulty. There is still considerable bowing of the lower limbs. The spine was not fully reformed in August 1966 (Fig. 12).

Figure 13 shows the alteration in the renal phosphate threshold with the varying doses given of vitamin \( D_2 \). The early-morning fasting plasma phosphorus has been plotted against the twenty-four-hour phosphorus excretion in the urine on the same day (Dent and Friedman...
Figure 8—Knees in December 1963. Irregular deposition of calcium salts in the epiphyses is now seen. The epiphysial plate is of almost normal width. Figure 9—Right arm in December 1963. Much more healing is evident in the three weeks since the radiograph in Figure 7 was taken. Carpal bones are appearing and subperiosteal bone around the shafts of the long bones is being laid down eventually to thicken the cortex.
Figure 10—Radiograph of leg in April 1965. There is no sign of rickets now. The bone density is normal, with marked buttressing of the cortex on the inner side of the bent tibia as the bone straightens. A bulge some way up the shaft of the femur marks the position of the expanded metaphysis when treatment began and illustrates the amount of growth in length since then. The epiphyses are still spotty.

Figure 11—Hands in April 1965. No rickets is seen. The phalanges appear stumpy from lack of growth in length, some have epiphyses at each end.

1964b). The initial values before treatment gave points very close to the dotted line. They were obtained during alterations in phosphorus intake achieved by the administration first of 10 millilitres Aludrox five times daily for five days, followed by 5 grammes of disodium hydrogen phosphate daily. The dotted line illustrates the behaviour to be expected of a substance like inulin which shows no renal tubular reabsorption. With increasing doses of vitamin D\textsubscript{2} there was a rise in the renal threshold (that is, in renal tubular reabsorption) for phosphorus and the points therefore move to the right. The rise in the urinary phosphorus excretion in the last four values in Figure 13 is due to the addition of 4 grammes of calcium phosphate daily. This has made little difference to the tubular reabsorption of phosphorus as the points lie along a line roughly parallel to the dotted line.

DISCUSSION

The patient presented a considerable problem in diagnosis as we had not previously seen metabolic bone disease of such severity. Nevertheless, the biochemical changes were quite typical of rickets and the uncalcified but clinically healed tibial osteotomies were also
diagnostic. These latter were particularly helpful in diagnosis since fine structure of the bones was not easily seen at the metaphyses owing to their radiolucency. The dietary history and biochemical investigations excluded classical rickets and the various forms associated with renal disease or steatorrhoea. Thus he appeared to have an unusual type of "resistant rickets," obviously one of the forms with an isolated abnormality of phosphate reabsorption in the renal tubule, for no other tubular disorder could be discovered.

Whereas the age of incidence of the disease in the patient was similar to that in the common sex-linked form of "resistant rickets," other features made this diagnosis unacceptable. The rickets was far too severe and there was an associated gross myopathy, but the most distinguishing feature was the excellent clinical and biochemical response to treatment. Indeed the response was as spectacular as that occurring in severe classical rickets, although we found it necessary to use much larger doses of vitamin D. It could be said therefore that he showed a true "vitamin D resistant rickets"—that is, a quite normal response when the dose was large enough. However, we do not suggest that this term be applied to our case because it was originally applied by Albright et al. (1937) to the common form which does not become
fully normal with large doses of vitamin D and also has other distinguishing features mentioned earlier. These distinguishing features make it most unlikely that our patient merely represents an extreme degree of severity of the relatively common disease, although this does vary a great deal from case to case, and in particular males are nearly always more severely affected than females.

The genetic study in the family of this patient is inadequate to indicate whether this is an inherited disease. Both parents are clinically normal and have normal plasma phosphorus levels. This does not exclude the possibility of sex-linked inheritance in future generations since the patient may represent a new mutation, a frequent occurrence in the ordinary sex-linked resistant rickets (Burnett et al. 1964). We are not aware of surviving adults who have had a similar disease in childhood to that of our patient and whose children would now be available for study. However, we were asked to see at the Hospital for Sick Children, Great Ormond Street, a child aged nineteen months whom we think has the same disease as our patient. Her plasma calcium and phosphorus levels were 5.7 milligrams per 100 millilitres and 2.3 milligrams per 100 millilitres respectively. She was so grossly weak and rachitic that the ribs had collapsed and prevented normal breathing; she had to be kept in a respirator until the bones had hardened after the administration of large doses of vitamin D. She made an excellent biochemical and clinical recovery which has continued to the present time. The case was described by Wilkinson (1955) in the earlier stages of the follow-up. Recently we were kindly given the opportunity to review the case for comparison with ours. We were referred to another family with a similarly affected child and another normal one, by Dr A. Barlow. This latter child was treated at an earlier age than our patient and had not developed such severe clinical abnormalities with consequent spectacular reversal on treatment. But the important biochemical abnormalities became normal on treatment in both these cases and we think they must have had the same disease. We think it is important that the two other families had no other similarly affected members and that they both showed first cousin parentage of the affected children. A form of inheritance by a recessive gene seems therefore strongly suspect, and if confirmed by further work will provide final proof that the disease is quite different from ordinary resistant rickets. The literature contains a very few descriptions of a more severe form of "resistant rickets" which may refer to the same disease as that suffered by our patient. Royer, Lestradet, Frédéric and Dartois (1961) described four children with a severe form of "resistant rickets" responding well to large doses of vitamin D. More recently Royer, Habib and Mathieu (1963) have again distinguished this disease, which they call Type 2, from the commoner form (Type 1). Prader, Illig and Heierli (1961) also described two cases of a similar disease, closely mimicking classical rickets and healed only with large doses of vitamin D. They also stressed the presence of hypocalcaemia and the early age of presentation of the rickets (three to eight months), both of which helped to distinguish it from ordinary resistant rickets. In one case other affected members occurred in the family in a manner to suggest autosomal, dominant mode of inheritance.* They used the name "hereditäre pseudo-mangelrachitis" to describe the disease, and we prefer this term to describe our patient's illness; it illustrates well our similar way of thinking.

However, it must be emphasised that the hereditary aspects need much further study. Prader et al. (1961) went in some detail into the previous literature of this subject. They quoted possible similar cases from six other families containing one to four affected members in each. More recently, Rodriguez, Einhorn, Stark and Edelmann (1966) described a child with "deficiency-type rickets due to decreased sensitivity to vitamin D." There are minor differences between our patient and all these others—for instance no other publication stresses the severe myopathy. However, this was probably so severe only because the child was not diagnosed

* Professor Prader allows us to state that he is now doubtful about the dominant inheritance quoted in his 1961 paper. Furthermore, he now has a new family with one affected child having "pseudomangelrachitis." The parents are first cousins and are healthy, with normal plasma levels of calcium and phosphorus.

Vol. 50 B, No. 4, November 1968
or treated until he was five years of age. The important feature common to all these cases is that the biochemical abnormalities, as well as the clinical changes, were all fully corrected with a suitably large dose of vitamin D. We infer from this that we are dealing with the same disease.

It is hardly necessary to stress the importance of early diagnosis in the case of a severely deforming disease which responds so well to treatment. Our tiny, dwarfed, but very lively child remains with us to remind us of our responsibility here.

**SUMMARY**

1. A child is described who presented with very severe rickets and gross myopathy. The clinical, biochemical and radiological signs were identical with those to be expected of a very chronic and severe vitamin D deficiency. The child's diet, however, had been normal.
2. All the pathological signs, except for residual dwarfism and leg bowing, disappeared on treatment with very large doses of vitamin D₂. Ordinary anti-rachitic doses had no effect.
3. We suggest that this child demonstrates a true resistance to the action of vitamin D and that the defect is permanent. The findings in two similar patients that we have seen suggest that the condition is inherited as an autosomal recessive gene, and that it may be the same disease as that described in the continental literature as "hereditäre pseudo-mangelrachitis" and by other names.
4. The disease seems distinct clinically and biochemically from the disease originally described under the name "vitamin resistant rickets," which does not respond so well to massive vitamin D therapy and which is usually inherited as a sex-linked dominant gene.

We wish to thank Mr. H. H. Langston for referring his patient to us; Dr. A. J. Robertson, who cared for the patient during 1965-66 and who sent us his biochemical findings for incorporation in this paper; and the many doctors from the Hospital for Sick Children, Great Ormond Street, who gave us information and follow-up details of their similar patient. We are particularly grateful to the nurses, dietitian and biochemists of the Metabolic Ward for their appropriate help during our patient's first long admission and subsequent out-patient supervision.

**REFERENCES**


THE JOURNAL OF BONE AND JOINT SURGERY


