be pointed out that the disease had already shown signs of spreading outside this area, and there were many parts of the city which were as vulnerable, if not more so, than the one that was affected. There will obviously be considerable interest in the trend of poliomyelitis in Dundee over the next few years. The population had probably a high degree of natural protection, and this had already been reinforced by the fairly extensive use of inactivated vaccine before being boosted still further by the widespread use of trivalent attenuated live vaccine in the 1962 outbreak.

Summary

An outbreak of poliomyelitis involving 40 patients occurred during the early summer of 1962 in the city of Dundee, particularly in certain new housing areas in the north-eastern part of the city. The causal virus was poliovirus type 1. An interesting feature was that the main attack was on children below the age of 6 years ; it is suggested that this was perhaps not surprising in view of the probable age distribution of both natural and acquired antibody in the population.

Trivalent attenuated vaccine, given orally, was used on a large scale in an effort to cut short the outbreak ; within three weeks of the start of an intensive campaign, and when approximately half of the population had received a single dose of vaccine, the outbreak came to an abrupt end. An intratypic serodifferentiation method was used to distinguish between wild and vaccine type poliovirus isolated from patients who had received live vaccine.

It is a pleasure to acknowledge our indebtedness to our respective staffs in the City of Dundee Public Health Department, in King's Cross Hospital, and in the virological section of the bacteriology department, Queen's College, Dundee. We are particularly grateful to Dr. N. R. Grist and Dr. Eleanor Bell, Virus Laboratory, Ruchill Hospital, Glasgow, for the intratypic serodifferentiation of some of the strains of virus, and to Mr. J. Hutchison, orthopaedic surgeon, for his independent assessment of severity in the paralytic cases.

References

Duncan, I. B. R., and Bell, Eleanor J. (1961). *Brit. med. J.*, **2**, 863.
Goffe, A. P., and Bell, Eleanor J. (1963). 9th European Symposium on Poliomyelitis and Allied Diseases, September 1963. Stockholm.
Green, D. M., and Bell, Eleanor J. (1963). Ibid.
Hale, J. H., Doraisingham, M., Kanagaratnam, K., Leong, K. W., and Monteiro, E S. (1959). *Brit. med. J.*, **1**, 1541.
MacLeod, R. C., MacGregor, Lilias, G., Larminie, Helen E., and Grist, N. R. (1958). *Scot. med. J.*, **3**, 76.
Mair, Hélène, J., and Tobin, J. O'H. (1960). *Mth. Bull. Minist. Hlth Lab. Serv.*, **19**, 49.
Ministry of Health (1963). Reports on Public Health and Medical Subjects No. 107. H.M.S.O., London.
Shand, F. L. (1961). *J. med. Lab. Technol.*, **18**, 75.
Wallis, C., and Melnick, J. L. (1962). *Virology*, **16**, 122.

Role of Phosphate in Treatment of Renal Tubular (Hypophosphataemic) Rickets and Osteomalacias

G. ALAN ROSE,* D.M., F.R.I.C.

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Rickets and osteomalacia continue to occur in this country. Vitamin-D deficiency, once thought to be an extreme rarity here, has now recurred (Dunnigan *et al.*, 1962 ; Benson *et al.*, 1963 ; Arneil and Crosbie, 1963). Chronic renal failure and steatorrhoea both continue to cause syndromes in which the affected persons behave as though they were vitamin-D-deficient, even though they are not. Such individuals have therefore been termed vitamin-D-resistant. The vitamin-D-resistant state described by Albright *et al.* (1937) is probably still, however, the most common cause of rickets and osteomalacia in this country to-day (Stewart *et al.*, 1964). In this disease many observers have found a low renal tubular reabsorption of phosphate, and there is clearly a renal tubular leak for inorganic phosphate. It is stressed, however, that the term " renal tubular leak " implies nothing about the mechanism by which this leak occurs. Because of the leak, the plasma phosphate is always low and the disease has been named hypophosphataemic rickets by some (Winters *et al.*, 1958), and phosphate diabetes by others (Fanconi and Girardet, 1952). An alternative system of nomenclature, and the one to be used here henceforth, was devised by Dent (1952). Using this system, six types of renal tubular osteomalacia are recognized. Type 1 cases show only the one renal tubular abnormality—that is, the phosphate leak ; type 2 cases show two tubular abnormalities—namely, renal glycosuria in addition to the phosphate leak ; while types 3–6 show more tubular abnormalities, such as renal tubular acidosis.

Many recent papers have shown that type 1 renal tubular rickets and osteomalacia can be cured by large doses of vitamin D. Dent and Harris (1956), however, pointed out that the resistance to vitamin D affects only the therapeutic effect of the vitamin and not the toxic effects. Therefore the therapeutic range may become very small and the treatment correspondingly hazardous, with the risk of hypercalcaemia always present. Not only is this treatment hazardous, but it is hard to control, the dose required to cure the rickets being very much larger than the dose required to maintain the patient healed. Sometimes it has been found impossible to heal the osteomalacia with vitamin D alone (Frame and Smith, 1958). At other times healing may occur, but it may take a remarkably long time for the treatment to be effective in relieving symptoms, as illustrated by Case 1 below. For these various reasons other possible therapies have been under investigation in this unit, and the effects of phosphate therapy in two further patients are now reported.

Methods

All investigations were carried out in an air-conditioned metabolic unit. The methods used in the balance studies were as previously described (Rose, 1964a) except that the balance study in Case 1 was carried out without the use of chromium sesquioxide marker, and calcium was determined by oxalate

* From the Metabolic Unit, Department of Medicine, Leeds General Infirmary.

precipitation methods and not by the flame photometry as used later in the other cases. In Cases 2 and 3 faecal values have been corrected for chromium recovery (Rose, 1964a). Plasma calcium was measured by the ethylenediamine tetra-acetic acid titration method of Fales (1953) as modified by Kenney and Toverud (1954). Plasma inorganic phosphate (referred to as phosphorus) was measured by the method of Fiske and SubbaRow (1925).

Case 1

This case illustrates the inability of vitamin D to raise the plasma phosphorus* to normal or to promote retention of absorbed calcium.

The patient was well and an active farmer until 1956, when at the age of 51 he developed pains around the ankles and then around the knees as well. The joints were never swollen, but the pains got worse, and after six months he was forced to stop work and take to his bed. Despite treatment with analgesics, Durabolin injections, various forms of heat, massage, and a two to three months' course of cod-liver oil he got worse and the pains spread to the lower ribs. He had no special food fads. He had one normal bowel motion a day and there was no nocturia. He had had no previous illnesses. His height was 6 ft. 1 in. (185 cm.). He had three brothers and two sisters alive and well. His parents were unrelated and died at 82 and 76 years respectively. No one else in the family was affected with bone pains. On admission to the metabolic unit he was a large healthy-looking man. He could remain seated in a chair without pain, but he had great pain on attempting to stand. He could walk a few yards with two sticks, but the effort made him sweat with pain.

Investigations.—Pulse was 72/min. and B.P. 150/110. Crown to pubis was 32 in. (81 cm.), pubis to heel 38 in. (96 cm.), and span 77 in. (195 cm.). There was marked bone tenderness over the lower ribs and shins, but movements of the knees, ankles, or hips did not themselves cause pain. Chvostek and Trousseau signs were negative. Corneal calcium was not present. Other systems showed no significant abnormalities. Plasma calcium was 9.9 mg./100 ml. ; phosphorus 1.5 mg./100 ml. ; alkaline phosphatase 23 K.A. units ; urea 30 mg./100 ml. ; albumin 3.6% and globulin 2.3% ; sodium 137, potassium 4.8, and bicarbonate 24 mEq/l. Urine: this repeatedly showed a trace of glucose but no other abnormality ; the 24-hour glucose was 3 g. ; urinary amino-acid chromatogram showed no abnormality ; maximum S.G. 1020 ; *p*H of morning urine 4.0 (Universal test paper). Creatinine clearance was 102 ml./min. Renal tubular reabsorption of phosphate was 63%. Glucose-tolerance test was normal. Faeces contained 18 g. of fat in six days. *X*-ray films showed Looser zones in the pubic rami and in several ribs. The lateral view of lumbar spine showed regularly biconcave vertebrae. Osteoporosis was shown by subarticular rarefaction plus raindrop pattern around the knees and femoral heads. These *x*-ray pictures have already been published (Rose, 1964b, Figs. 16 and 17). There were no subperiosteal erosions in the hands or elsewhere.

A diagnosis of type 2 renal tubular osteomalacia was made and he was treated with vitamin D in the form of dihydrotachysterol 10 mg. a day for 12 days, then 5 mg. a day for four days, and then with 3 mg. a day. The balance data obtained have already been published (Rose, 1964c) and need not be reproduced here. The striking feature was that, although the faecal calcium fell from 925 to 210 mg. a day, there was virtually no improvement in the overall balance picture, because the urinary calcium simultaneously rose from 180 to 800 mg. a day. This was not due to overdosage with vitamin D, since the plasma calcium did not change. It seems that the resistance to vitamin D was overcome at the gut, permitting absorption of dietary calcium, but this was not sufficient to make the absorbed calcium enter the bones. The failure to enter bones might have been because there was still resistance to vitamin D at this point, or because there was a failure of plasma phosphorus to reach the normal range. Even with the high dose of vitamin D the plasma phosphorus values remained in the region 1.8–2.2 mg./100 ml.

Eventually his Looser zones healed, his bone pains disappeared, and he was restored almost to normal activity, but it took many months to achieve this, and the hypercalciuria persisted unless he was given supplementary phosphate therapy.

* The term "plasma phosphorus" refers to inorganic phosphate.

Comment.—Type 2 renal tubular osteomalacia developing suddenly in a previously healthy man of 51. High doses of vitamin D enabled him to overcome the resistance of the gut to vitamin D, but this alone was insufficient to permit rapid skeletal recalcification. The plasma phosphorus failed to rise to normal, and there is a suggestion that phosphate therapy might have been a valuable supplementary therapy.

Case 2

This case illustrates the limitations of phosphate therapy alone but the value of phosphate as a supplement to vitamin D.

The patient was born in 1896. She had bow legs at 4 years, and at 6 years was put in splints and taken off her feet for six months. She did not improve despite splinting and administration of cod-liver oil and sunshine therapy during the whole of her childhood. At 20 years her legs stopped aching and she became well. In 1940 she developed painful swellings of the joints of the hands, and there was a recurrence in 1953, for which she was treated with forms of heat therapy. In 1959 she began to feel stiff in the hips and knees. Soon she developed aches in the shoulders and then a low backache. These symptoms got progressively worse and she gave up walking, becoming almost bedridden from January to November 1961. Then she again attempted walking and found she had a marked waddling gait. Stairs were extremely difficult and she could go up only on all fours. Her shins started to ache and she noticed that her bow legs were getting even more bowed. She had no special food fads, one normal bowel motion a day, and no nocturia. Her only brother was over 6 ft. (183 cm.) tall. Her parents were unrelated and of medium height and there was no family history of bone pains or dwarfism. When admitted to the metabolic unit in February 1962 she was able to waddle around the ward, but only with some difficulty and with the use of a stick.

Investigations.—Pulse was 80/min. and B.P. 140/80. Crown to pubis was 32 in. (81 cm.), pubis to heel 25 in. (63 cm.), and span 57½ in. (146 cm.) ; there was marked bowing of legs with 4½ in. (11.5 cm.) between knees. Definite bone tenderness was present at lower end of left femur. Chvostek and Trousseau signs were negative. Corneal calcium was not present. Other systems showed no significant abnormalities. Plasma calcium was 8.9 mg./100 ml. ; phosphorus 2.2 mg./100 ml. ; magnesium 2.1 mg./100 ml. ; alkaline phosphatase 8 K.A. units, and repeatedly normal on independent measurements in two laboratories, both before and during vitamin-D therapy. Plasma sodium was 138, potassium 4.2, chloride 104, and bicarbonate 27 mEq/l. Plasma albumin was 3.7% and globulin 2.9%. Urine: no protein or reducing substance ; amino-acid chromatogram showed raised excretion of glycine ; maximum S.G. 1026. Urea clearance was 78% ; plasma urea 20 mg./100 ml. The 25-g. xylose absorption test was normal. Hb 88%. Faeces contained 13.8 g. of fat in six days. *X*-ray films showed Looser zones in both femoral necks and another in the upper part of the left femoral shaft (Rose, 1964b, Fig. 13). The lateral view of the lumbar spine revealed regular biconcave vertebrae ; there were no subperiosteal erosions in the hands or elsewhere. The hands showed some arthritic changes and some rarefaction, but elsewhere the bones did not seem especially rarefied. Bone biopsy of the iliac crest disclosed an excessive number and width of osteoid seams ; osteoblasts and osteoclasts were present in normal numbers ; the Haversian seams of the cortical bone had enlarged canals suggesting some osteoporosis in addition to osteomalacia.

A diagnosis of type 1 renal tubular osteomalacia was made, despite the finding of a normal serum alkaline phosphatase. The diagnosis of osteomalacia rested firmly on radiological and histological findings. Normal plasma alkaline phosphatase in osteomalacia has been described previously by Pedersen and McCarroll (1951) and Frame and Smith (1958).

The special studies carried out are indicated in Fig. 1. During the first two six-day balance periods with no treatment she was in negative calcium balance, the faecal calcium being virtually equal to the dietary calcium and the urinary calcium being about 80 mg. a day. During the next five days she was given a continuous and steady intravenous infusion of neutral sodium phosphate in order to maintain the plasma phosphorus at normal if possible. There was a slight fall in plasma calcium to 8.1 mg./100 ml. and the plasma phosphorus was raised to 4.4 mg./100 ml. The urinary calcium fell by one-half to 40 mg. a day, but the faecal calcium was unchanged. Because of signs of irritation to the veins, the mode of phosphate administration was changed to the oral route.

It was possible to give enough of the same neutral phosphate mixture to keep the plasma phosphorus at 2.9 mg./100 ml. The urinary calcium continued at the low level, but the balance was slightly worse on account of a small rise in faecal calcium. The net result on the calcium balance of 18 days of phosphate therapy and a restoration to normal of the calcium phosphorus product was virtually nil. Phosphate therapy was then stopped and vitamin D started as 8 mg. of vitamin D_3 a day orally. The faecal calcium started to fall, but the urinary calcium rose to match it, as occurred in Case 1, and there was no improvement in the overall calcium balance. Note that the plasma phosphorus again fell to subnormal values as soon as the phosphate therapy was stopped. Therefore in

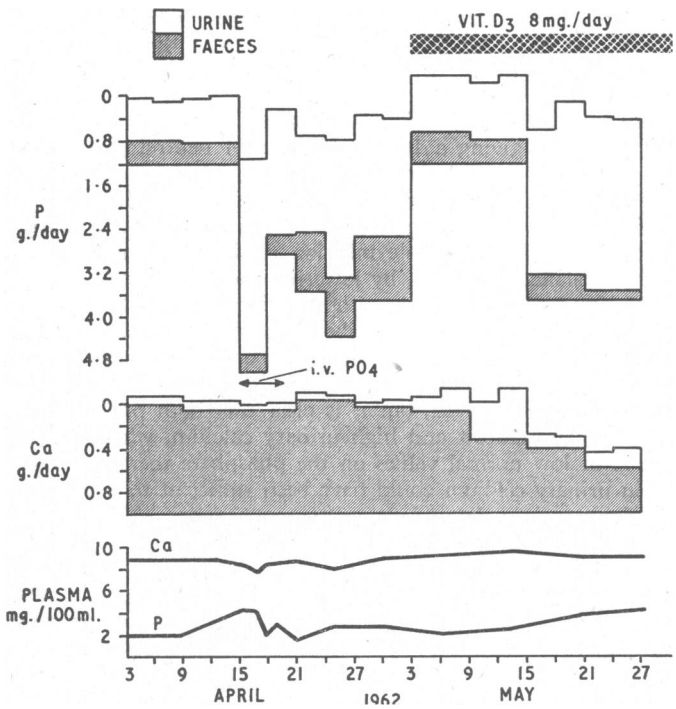

FIG. 1.—Studies in Case 2 (Type 1 renal tubular osteomalacia; corrected for chromium). The balance charts both here and in Fig. 2 are constructed according to the practice of the Albright school—that is, the baselines represent the dietary intakes, the shaded portions represent faecal excretions, and the clear portions urinary excretions.

the last 12 days of the balance study the vitamin D therapy was supplemented with neutral phosphate mixture by mouth. During these 12 days the plasma phosphorus rose to normal levels again, the fall in faecal calcium continued, the urinary calcium was lowered to normal values, and a positive calcium balance of 200–400 mg. a day was established. Subsequently she went home on this regimen, her bone pains disappeared, and the Looser zones healed.

Comment.—In this case type 1 renal tubular osteomalacia had presented initially in childhood, and now re-presented in late adult life but with a normal plasma alkaline phosphatase. Phosphate therapy alone was without benefit, although it did lower the urinary calcium. Vitamin-D therapy alone might have been effective but would probably have taken a long time. The combination of vitamin D and phosphate therapies was dramatically successful biochemically and clinically.

Case 3

This case illustrates the advantage of supplementing vitamin D therapy with phosphate.

The patient was born in 1947, and was diagnosed as having vitamin-D-resistant rickets in 1950. From then on he was treated with calciferol, mostly in the dose of 2.5 mg. a day. He grew well, climbing from below 2 standard deviations below the mean at age 4 to only 1 standard deviation below the mean at age 15. The rickets had healed well and for most of the time the plasma calcium had been normal, although there had been four periods of hypercalcaemia when he had been on a higher dose of vitamin D. Plasma phosphorus, however, had always been low for his age, falling from about 3.5 mg./100 ml. at the age of 6 to about 2.5 mg./100 ml. at 14. In the last year before admission to the metabolic unit he had failed to grow at all despite continued treatment with vitamin D, and he was admitted to see if a final growth spurt could be produced by phosphate therapy. He had no complaints apart from the lack of growth. He led an active life with no aches or pains, and no disturbance of bowel function or of micturition. He had two sisters of 18 and 12 years who were 5 ft. 5 in. (165 cm.) and 5 ft. 1 in. (155 cm.) respectively. His father, 5 ft. 7 in. (170 cm.), and mother, 5 ft. 1 in. (155 cm.), were unrelated. There was no family history of rickets or bone pains. He was a muscular boy.

Investigations.—Pulse was 68/min. and B.P. 120/75. Crown to pubis was 33 in. (84 cm.), pubis to heel 29 in. (74 cm.), span 63½ in. (161 cm.). Slight antero-lateral bowing of the femora was present, but no space between knees. There were no other bone deformities and no bone tenderness. Other systems showed no abnormality. Plasma calcium was 10.4 mg./100 ml.; phosphorus 2.0 mg./100 ml.; alkaline phosphatase 21 K.A. units; magnesium 2.1 mg./100 ml.; and sodium 140, potassium 4.9, and bicarbonate 30 mEq/l. Urine showed no protein or reducing substances. Urine amino-acid chromatogram showed an abnormally strong glycine spot. Maximum urine S.G. was 1024, and urea clearance 55%. Hb 100%. Faeces contained 7.7 g. of fat in a six-day collection period. *X*-ray examination of wrists, knees, and ankles showed no evidence of active rickets and no subperiosteal erosions.

There was no reason to doubt the diagnosis of type 1 renal tubular rickets. Although this did not appear to be active by radiological criteria, the raised plasma alkaline phosphatase suggested that there might still be some undertreatment. It was decided to continue the vitamin D as before—that is, 2.5 mg. of calciferol a day—and explore the effects of adding phosphate therapy to it. The

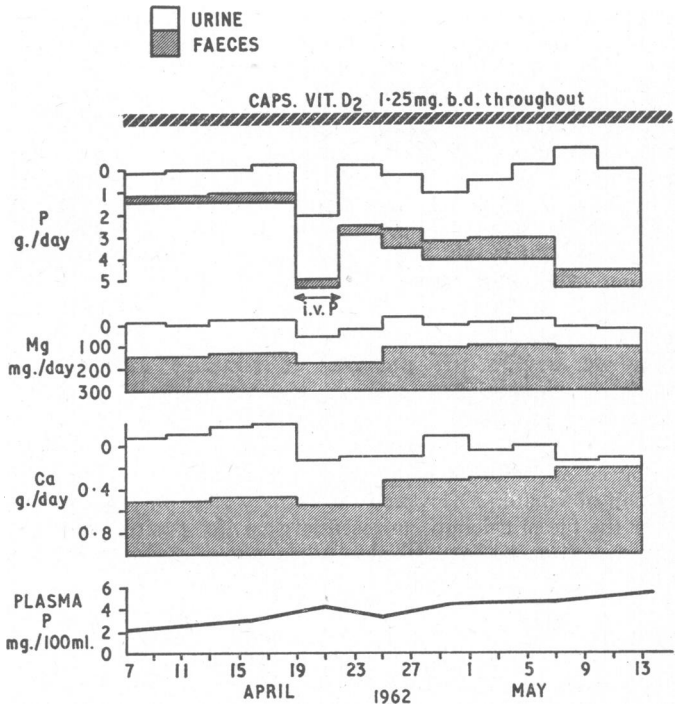

FIG. 2.—Studies in Case 3 (type 1 renal tubular rickets; corrected for chromium). Chart constructed as in Fig. 1. Plasma calcium values are not shown because the variations were so small. Values were all about 10.2 mg./100 ml. except for a fall to 9.6 mg./100 ml. during intravenous therapy.

results are summarized in Fig. 2. During the first two six-day balance periods he was absorbing dietary calcium well but was nevertheless in slight negative balance because of a urinary calcium as high as 600 mg. a day. This was associated with a plasma phosphorus of 2–3 mg./100 ml. He was then given neutral phosphate for five days intravenously and subsequently orally. The plasma phosphorus rose to 3.5–5.5 mg./100 ml. and the plasma calcium showed a slight fall during the intravenous therapy to 9.6 mg./100 ml. During the period of intravenous therapy the faecal

calcium was unaffected but the urinary calcium fell to 400 mg. a day. With the oral therapy there was a marked rise in faecal calcium, but since the urinary calcium fell progressively to 100 mg. a day he ended up in positive calcium balance. It was concluded that the phosphate therapy was a valuable supplement to the calciferol and he was discharged on the combined therapy.

By July 1963 the epiphyses were fusing and it was clear that no further growth could occur. Plasma alkaline phosphatase had fallen to 10 K.A. units and the urinary calcium was 437 mg. a day, so it was decided to stop therapy. The phosphate was stopped first, whereupon the urinary calcium rose to 813 mg. a day. The plasma phosphate, which had been maintained as an out-patient treatment at 2.5–4.8 mg./100 ml., dropped to 1.6 mg./100 ml. on stopping the phosphate therapy.

Comment.—A boy with type 1 renal tubular rickets controlled clinically with calciferol but with low plasma phosphorus and high urinary calcium. Phosphate therapy raised the plasma phosphorus, lowered the urinary calcium, and improved the calcium balance. The faecal calcium was unaffected by intravenous phosphate but raised by oral phosphate.

Discussion

Two patients (Cases 1 and 2) had each been treated with physiological doses of vitamin D without benefit and must therefore be considered to be vitamin-D-resistant. The third patient (Case 3) developed rickets despite a normal diet and is therefore also considered to be "resistant." In each of these patients it was demonstrated that the resistance to action of vitamin D in the intestinal canal could be overcome by the large doses of the vitamin administered. Thus each was forced to absorb dietary calcium with this therapy. This alone, however, appeared insufficient to cause absorbed calcium to be retained by the skeleton. It is true that in Cases 1 and 3 the bone lesions healed on vitamin D alone, but the healing process was very slow, and undoubtedly in Case 1, and probably in Case 3, most of the absorbed calcium was re-excreted in the urine rather than deposited in bone. There are two obvious possible reasons why this failure to retain absorbed calcium might have occurred. Firstly, there might still have been at the bone surface a resistance to vitamin D which was not overcome by the vitamin-D therapy. Secondly, the failure to establish a normal calcium-phosphorus product in the plasma because of the continued low plasma phosphorus might have prevented deposition of calcium phosphate despite the presence of adequate amounts of circulating vitamin D.

The results in Case 2 seem to indicate quite clearly that only the second possibility is tenable in this case. Thus restoration to normal of the calcium-phosphorus product without administration of vitamin D lowered the urinary calcium but did not lower the faecal calcium, an essential step if a positive calcium balance was to be established. When phosphate therapy was added to vitamin D the effect was a dramatic fall in urinary calcium and a positive calcium balance was established. The results in Cases 1 and 3 are compatible with the second possibility, although the proof is less rigid because it was not possible to carry out as extensive studies as in Case 2. In each case, however, it was demonstrated that phosphate therapy raised the plasma calcium-phosphorus product and lowered the urinary calcium. It is therefore concluded from these studies that phosphate therapy is a valuable supplementary therapy to vitamin D, its effect being to raise plasma phosphorus and lower urinary calcium. This second effect becomes valuable only when the absolute value of urinary calcium is high, as it might be if vitamin D alone is given. If this reasoning is correct then it follows that a similar valuable effect can be anticipated in the case of renal tubular acidosis where urinary calcium is high even without vitamin-D therapy.

Saville *et al.* (1955) showed in balance studies that the alkaline phosphate salt, Na_2HPO_4, lowered the urinary calcium and raised plasma phosphorus in patients under treatment with high doses of A.T. 10 for renal tubular rickets and osteomalacia. They thought that in one case phosphate therapy alone lowered the faecal calcium, but the evidence was not convincing. Fraser *et al.* (1957) seem to have been the first to have claimed the healing of vitamin-D-resistant rickets by phosphate therapy alone. The evidence was radiological and no balance data and no clinical or biochemical details were given. Frame and Smith (1958) described a case of what has here been called type 1 renal tubular osteomalacia. They were unable to heal the osteomalacia with vitamin D alone and therefore added oral phosphate as a second therapy. There was an improvement in overall calcium balance, and healing occurred radiologically and clinically. Their data show that the improvement in overall balance was due to a fall in urinary calcium rather than a fall in faecal calcium, these results therefore being very similar to those reported in Case 3.

Steendijk (1961) treated a 9-month-old boy with cystinosis and rickets by giving a 10-day infusion of neutral phosphate. There was an improvement radiologically, but no balance data were obtained and rearrangement of skeletal calcium was admitted as a possible explanation. This boy had acidosis, however, and the phosphate infusion might have benefited the calcium balance, therefore, by lowering the urinary calcium by a significant amount and without affecting faecal calcium. Wilson and Yendt (1963) described two cases of adult Fanconi syndrome. They were both treated with oral phosphate without vitamin D, and healing of the osteomalacia occurred. No balance data were given, but it is clear that both patients had renal tubular acidosis and high urinary calcium, which fell to normal or low normal values on the phosphate therapy. This fall in urinary calcium could have been sufficient to have converted a negative calcium balance to a positive one. Frame *et al.* (1963) reported in detail the results of treatment of three cases of what is here called type 1 renal tubular rickets. Phosphate therapy without vitamin D was quite ineffective biochemically, radiologically, or clinically in curing the rickets. Those patients did not have renal tubular acidosis and had low urinary calcium values, and phosphate therapy did not lower faecal calcium.

The published work of others and the results reported here are therefore consistent with a single simple theory of the role of phosphate therapy in renal tubular rickets or osteomalacia. Phosphate therapy is a valuable means of raising plasma phosphorus, and this in turn will lead to a reduction of urinary calcium and therefore to a beneficial effect upon the calcium balance. However, this beneficial effect can be significantly great only if the urinary calcium prior to therapy was high, as is the case when large doses of vitamin D have been given or when renal tubular acidosis is present. Phosphate therapy does not affect faecal calcium when given intravenously, and may raise it when given orally. Therefore, phosphate therapy alone can be effective only when the faecal calcium is lower than the dietary calcium, and if this is not so vitamin D will also be required.

Summary

Three patients with types 1 and 2 renal tubular osteomalacia have been studied and the relative effects of vitamin D and phosphate therapies examined. One patient demonstrated the condition of undoubted osteomalacia with normal plasma alkaline phosphatase.

Phosphate therapy does not lower faecal calcium and is without significant benefit when faecal calcium is high. Phosphate therapy was found to be of great benefit in lowering the urinary calcium when high after vitamin-D therapy. It seems likely that the beneficial effects of phosphate therapy observed by others in renal tubular acidosis are due solely to a lowering of high urinary calcium. This effect of lowering urinary calcium is of no significant benefit when the urinary calcium is already low.

Case 1 was kindly referred by Mr. C. R. Berkin of the Westwood Hospital, Beverley ; Case 2 by Professor S. J. Hartfall ; and Case 3 by Dr. E. C. Allibone of the Leeds General Infirmary. I am grateful to Sister Thwaite, S/N Whan, and the dietetic, nursing, and technical staff of the metabolic unit for continual co-operation, without which studies such as these would be impossible. Miss V. Grayson and Mr. D. Newton carried out all the calcium and phosphorus measurements. Dr. F. W. Heaton and Dr. A. Hodgkinson of the urological research laboratories kindly carried out the magnesium measurements and the renal tubular reabsorption of phosphate respectively.

REFERENCES

Albright, F., Butler, A. M., and Bloomberg, E. (1937). *Amer. J. Dis. Child.*, **54**, 529.
Arneil, G. C., and Crosbie, J. C. (1963). *Lancet*, **2**, 423.
Benson, P. F., Stroud, C. E., Mitchell, N. J., and Nicolaides, A. (1963). *Brit. med. J.*, **1**, 1054.
Dent, C. E. (1952). *J. Bone Jt Surg.*, **34B**, 266.
—— and Harris, H. (1956). Ibid., **38B**, 204.
Dunnigan, M. G., Paton, J. P. J., Haase, S., McNicol, G. W., Gardner, M. D., and Smith, C. M. (1962). *Scot. med. J.*, **7**, 159.
Fales, F. W. (1953). *J. biol. Chem.*, **204**, 577.
Fanconi, G., and Giradet, P. (1952). *Helv. paediat. Acta*, **7**, 14.
Fiske, C. H., and SubbaRow, Y. (1925). *J. biol. Chem.*, **66**, 375.
Frame, B., and Smith, R. W. (1958). *Amer. J. Med.*, **25**, 771.
—— —— Fleming, J. L., and Manson, G. (1963). *Amer. J. Dis. Child.*, **106**, 147.
Fraser, D., Jaco, N. T., Yendt, E. R., Munn, J. D., and Liu, E. (1957). Ibid., **93**, 84.
Kenny, A. D., and Toverud, S. U. (1954). *Analyt. Chem.*, **26**, 1059.
Pedersen, H. E., and McCarroll, H. R. (1951). *J. Bone Jt Surg.*, **33A**, 203.
Rose, G. A. (1964a). *Gut*, **5**, 274.
—— (1964b). *Clin. Radiol.*, **15**, 75.
—— (1964c). *Postgrad. med. J.*, **40**, 158.
Saville, P. D., Nassim, J. R., Stevenson, F. H., Mulligan, L., and Carey, M. (1955). *Clin. Sci.*, **14**, 489.
Steendijk, R. (1961). *Arch. Dis. Childh.*, **36**, 321.
Stewart, W. K., Mitchell, R. G., Morgan, H. G., Lowe, K. G., and Thomson, J. (1964). *Lancet*, **1**, 679.
Wilson, D. R., and Yendt, E. R. (1963). *Amer. J. Med.*, **35**, 487.
Winters, R. W., Graham, J. B., Williams, T. F., McFalls, V. W., and Burnett, C. H. (1958). *Medicine (Baltimore)*, **37**, 97.

Enlargement of Parotid Gland Due to Sarcoidosis

G. GREENBERG,* M.B., B.SC. ; R. ANDERSON,† M.B. ; P. SHARPSTONE,‡ M.B., M.R.C.P. ; D. GERAINT JAMES,§ M.A., M.D., F.R.C.P.

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Of 388 patients with histologically confirmed generalized sarcoidosis, 23 (6%) were observed to have enlargement of the parotid gland. This report analyses the associated clinical, radiological, histological, and immunological features so that one of the many causes of enlargement of the parotid gland may be more clearly delineated.

Patients and Methods

All patients were studied in a special sarcoidosis clinic by methods previously described (Anderson, James, Peters, and Thomson, 1962). They all showed clinical and/or radiological features of sarcoidosis, together with histological evidence of sarcoid tissue. Tissue for examination included biopsies of parotid gland, lymph nodes, skin, and liver. The Kveim test was carried out in 13 cases.

Results

The enlargement was bilateral in 19 (83%) cases, right-sided in three, and left-sided in one.

Presenting Features.—Sixteen patients (70%) presented with swollen glands or dryness of the mouth, or both ; 10 of these also mentioned pain or discomfort of the eyes at their first visit. The only initial complaint of three patients was of sore or dry eyes.

Age and Sex Incidence.—There was no significant difference between the incidence of enlargement of the parotid gland in the sexes ; 13 of the 23 patients were women, a trend which follows the overall distribution of sarcoidosis in the clinic. In 16 the onset was in the third or fourth decade of life, a pattern also similar to that seen in sarcoidosis as a whole. It occurred in men more commonly in the third decade compared with a mean age of onset of 44 years in women (Table I).

Other Tissues Involved.—There was widespread involvement of tissues other than the parotid glands (Table II). In 18 cases there were intrathoracic radiological changes ; the early stage of bilateral hilar lymphadenopathy was seen in seven, enlargement of hilar glands was associated with pulmonary mottling in nine, and in two the still older stage of diffuse pulmonary infiltration without hilar adenopathy had been reached ; subsequent complete resolution of the chest radiographic abnormalities was observed in nine (50%) cases.

TABLE I.—*Age and Sex of 23 Patients with Enlargement of Parotid Gland Due to Sarcoidosis*

Age at Onset	No. of Patients	
	Male	Female
11–20 years	1	0
21–30 „	5	3
31–40 „	4	4
41–50 „	0	3
51–60 „	0	3
Total	10	13

Mean age at onset : males 28 years, females 44 years.

TABLE II.—*Involvement of Other Tissues in 23 Patients with Enlargement of Parotid Gland*

System	No.	%
Intrathoracic	18	78
Peripheral lymph nodes	15	65
Skin	10	43
Spleen	9	39
Uveal tract	8	35
Lacrimal glands	4	17
Facial nerve	1	4

*Research Assistant, Royal Northern Hospital, London.
† Late Research Assistant, Royal Northern Hospital, London.
‡ Medical Registrar, Royal Northern Hospital, London.
§ Physician, Royal Northern Hospital, London.