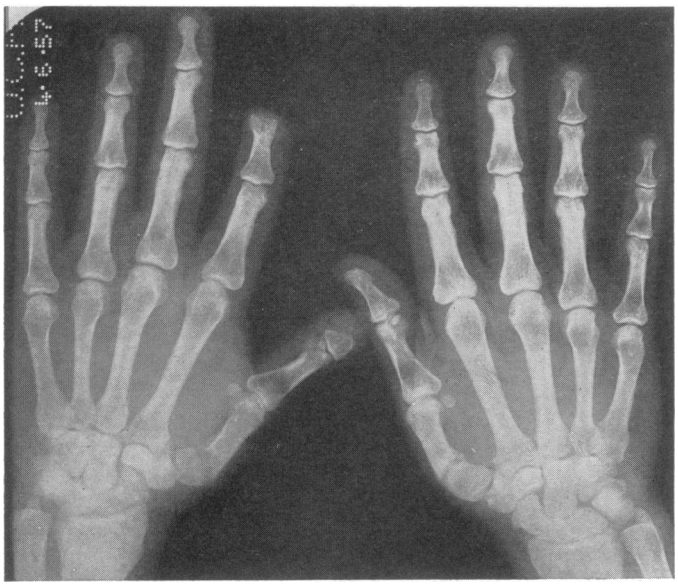

FIG. 1

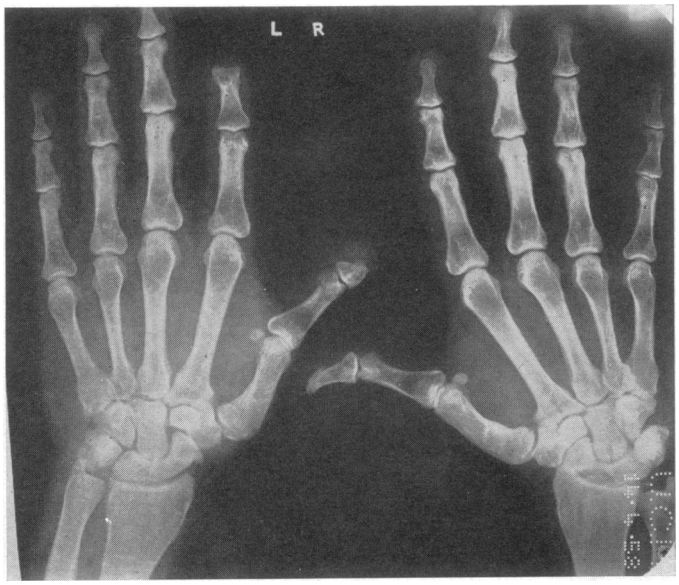

FIG. 2

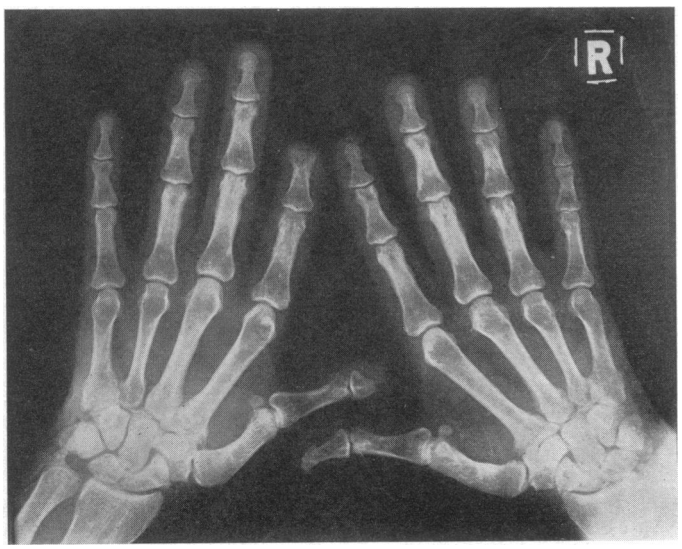

FIG. 3

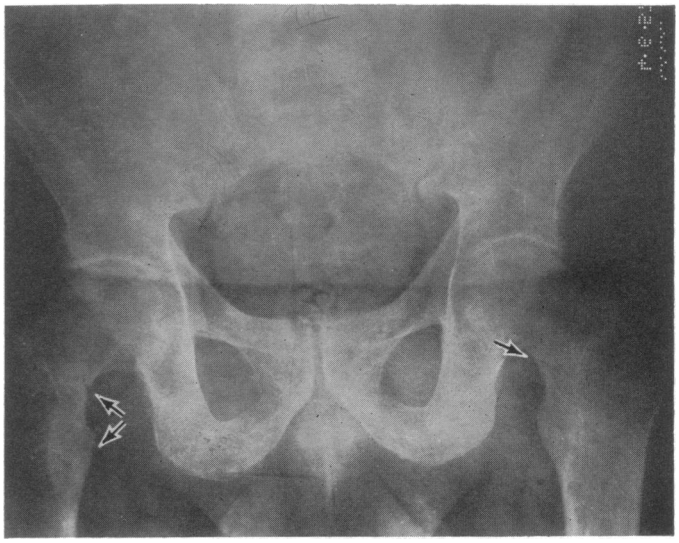

FIG. 4

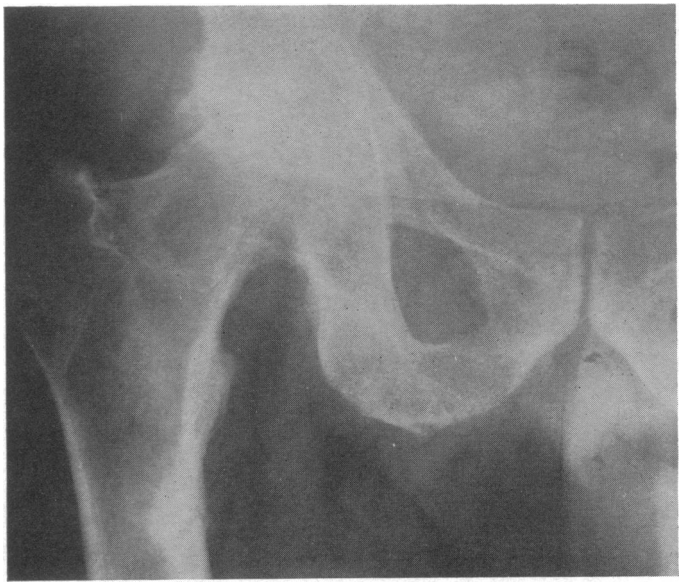

FIG. 5

FIG. 1.—Pseudo-fractures of first metacarpals in 1957.

FIG. 2.—Complete healing of metacarpal fractures in 1958.

FIG. 3.—Metacarpal fractures still healed in January 1964. No subperiosteal erosions have developed as a result of the hyperparathyroidism, indicating that this is the type that affects plasma levels without producing specific bone disease.

FIG. 4.—Femoral pseudo-fractures (arrowed) in June 1957. The fractures healed completely with treatment.

FIG. 5.—Recurrence of femoral Looser zones in July 1963 after reduction in dose of dihydrotachysterol.

show little evidence of damage in this rather indefinite condition. Lee and Holden supposed that tubular damage was secondary to interstitial infiltration and oedema, but the occurrence of acute tubular necrosis without major infiltrate in Cases 2 and 4 of the present series suggests that this is not necessarily so. It seems possible that the infiltrate and the tubular damage are both independent features of hypersensitivity, and not dependent on one another.

The other reported features of phenindione sensitivity shown by patients with acute renal failure are set out in the Table. Only one patient (Case 6) did not have an obvious skin lesion, but all showed one or more of the signs reviewed by Perkins (1962). In the present cases the time between starting the drug and the first evidence of hypersensitivity ranged from 10 to 56 days, with oliguria appearing between 4 and 21 days later. In all of them oliguria developed after phenindione had been stopped but before the initial sign of hypersensitivity had subsided. This time-scale in the clinical course is much the same in all reported cases. Lee and Holden (1964) and Baker and Williams (1963) produce some evidence that there may be residual renal damage, and in this context it is interesting that of the three survivors from this unit one still has a blood urea of 60 mg./100 ml. four months after discharge (Case 1).

Some Features of Phenindione Sensitivity

Case	Skin Rash	Fever	Diarrhoea	Granulopenia	Jaundice	Eosinophilia
Case 1	+	+	−	−	−	+
Case 2	+	+	−	−	−	−
Case 3	+	+	−	−	−	−
Case 4	+	−	+	−	−	+
Case 5	+	+	−	−	−	+
Case 6	−	−	−	−	+	−
Kirkeby (1954) ..	+	+	−	+	+	+
Barritt and Jordan (1960)	+	+	+	−	−	−
Baker and Williams (1963)	+	+	−	−	+	+
Galea *et al.* (1963) ..	+	−	+	−	−	−
Lee and Holden (1964)	+	+	−	−	−	+

The possibility that drugs other than phenindione were involved in the sensitivity reaction has been carefully explored, and in only two patients was this at all likely. Short courses of sulphadimidine and Crystamycin (a combination of penicillin and streptomycin) were given in Case 2 at least three weeks before the onset of the rash, and Case 4 received a short course of penicillin 19 days before the rash. In neither instance was any form of sensitivity-testing thought justifiable, but circumstantial evidence is very much in favour of a phenindione reaction.

With regard to treatment, it clearly is important to stop the offending drug at the first definite signs of hypersensitivity. If acute renal failure occurs it may be prolonged, but it is potentially reversible, and therefore some form of dialysis should not be delayed. Corticosteroids were used for three patients, two of whom survived, but it is impossible to give an objective assessment of their value in a situation where spontaneous recovery may occur.

Summary

Acute oliguric renal failure due to phenindione sensitivity has been seen on six occasions in the past five years in a busy renal unit. In the four cases where histological material was available the underlying renal lesion was a severe tubular necrosis accompanied in two cases by gross interstitial cellular infiltration. Five patients had a severe skin lesion and one had jaundice as the first sign of their hypersensitivity.

I wish to thank Dr. O. M. Wrong and Professor R. Shackman for permission to publish these cases, and Dr. H. K. Weinbren, who kindly reviewed the pathological material.

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Case of Renal Tubular Osteomalacia (Dent Type 2) with Later Development of Autonomous Parathyroid Tumours

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[WITH SPECIAL PLATE]

Brit. med. J., 1965, **2**, 26–29

It is now well known that osteomalacia may comprise an important part of a number of different clinical syndromes. Apart from the classical variety due to deficiency of vitamin D, there are three main types not always fully separable from each other. The first is the osteomalacia associated with the large group of malabsorption syndromes, which presumably should include that following partial gastrectomy, though the evidence for malabsorption is often minimal. The second is the osteomalacia from renal disease, subdivided into those cases with gross glomerular failure and those without glomerular but with mainly tubular dysfunctions. The third comprises a motley collection of hereditary and idiopathic osteomalacias which usually demonstrate a lessened renal-tubular phosphate reabsorption as part of the biochemical findings and which could therefore also be classified in the second group.

In an attempt to stress the importance of renal tubular dysfunction as the cause of rickets and osteomalacia Dent (1952) attempted a classification of the various types recognized at that time. The type that he calls Type 2, in which a renal-tubular reabsorption defect for both phosphate and glucose occurred in the presence of normal glomerular function, is very rare and has not as yet been described in detail but is of considerable theoretical importance where the possible mechanisms of renal tubular function are concerned.

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A patient who fulfils the criteria for a diagnosis of Type 2 renal-tubular osteomalacia is described here. He showed a further unusual feature while under treatment for his osteomalacia in that he developed autonomous parathyroid tumours, which prevented further adequate control and led to the necessity for surgical intervention.

Case History

The patient is a man now aged 46, a bus driver, who attended an orthopaedic out-patient department in January 1956 and was seen by one of us (R. B.). At this time the patient was 38 years old and complained of "pain and weakness in the back and legs" and pain travelling to the buttocks and thighs. These symptoms had been present for three years. When sitting or lying there was no pain, but it came on immediately he started to move or on first rising from a sitting position. It would lessen on moving about.

He had first noticed backache after falling from the back of a lorry in 1948. Since then there had been exacerbations and remissions of symptoms. These became so severe that he was forced to give up work in May 1955 when pain and weakness made it impossible for him to climb into the cab of his bus, and he had eventually to press on the knees with his hands to work the pedals. He had also become unsteady on his feet, had the greatest difficulty in rising out of a chair, and found it nearly impossible to walk upstairs. He remembered noticing weakness in the upper limbs in 1947 when working in a timber-yard, and believed that he had lost about 3 in. (7.6 cm.) in height in the last few years.

In January 1956 the main clinical features were as follows: his height was 5 ft. 7 in. (3.3 m.), and he was very obese, weighing 101 kg. The lumbar curve was flattened, he had noticeably poor posture, and movements of the spine were restricted, with pain at the extremes. There were no abnormal neurological findings, but weakness of active hip movements was noted and attributed at least in part to pain. Radiographs at this stage showed normal lumbar appearances, an old intertrochanteric fracture of the left femoral neck, with callus formation, and an early stress fracture of the right femoral neck.

He was treated with a weight-relieving calliper on the right leg. This was followed by partial healing of the fracture of the right side and some relief of pain. He was referred for rehabilitation, and it was decided to embark on training him for a new occupation (as a machinist) while healing of the fractures proceeded. Routine follow-up from the hospital rehabilitation department, however, was unsatisfactory, in that the initial improvements in the pain and weakness were short-lived. He was therefore recalled for re-assessment. Examination of the blood and urine gave the the following results: urine, albumin nil, sugar 1% ; blood urea, 28 mg./100 ml. ; serum calcium, 10.1 mg./100 ml. (lab. normal 9–11 mg./100 ml.) ; alkaline phosphatase, 22.8 units.

The raised alkaline-phosphatase level, the stress fractures of the femoral necks shown on radiography, the loss of height, and pain were evidence of an error of calcium metabolism on biochemical, radiological, and clinical grounds.

The patient was referred to Professor C. E. Dent, who kindly undertook his further investigation and treatment, and he was admitted to the metabolic ward at University College Hospital, London, in June 1957. The findings at this time are summarized as follows.

He was an obese cheerful man (Figs. 3*a* and 3*b*), who progressed with a gross shuffling gait, preferring to stand because of pain and difficulty in getting up from the sitting position. He was the only son of a non-consanguineous marriage, and had one child, a boy of normal stature and body proportions whose plasma gave normal values for calcium, phosphorus, and phosphatase.

Examination of the musculo-skeletal system showed his height to be 5 ft. 6½ in. (3.2 m.) and weight 89.9 kg. From crown to pubis measured 28 in. (71 cm.), from pubis to heel 36½ in. (93 cm.), and span 70 in (1.9 m.). Actual loss of height was thus about 7 in. (17.5 cm.).

There was a smooth increase of thoracic kyphosis. Compression of the thoracic cage and palpation over the tibial crests were painful. There was marked weakness of the hip and shoulder-girdle muscles without wasting. The peripheral limb muscles were all normal. Active and passive movements of the hips and shoulders were both accompanied by pain.

Investigations

Renal Function.—Clean specimen of urine, no proteinuria, occasional pus cells. Concentration/dilution test, maximum S.G. 1025, minimum S.G. 1002. Urea concentration test, 1.5 g./100 ml. of urea ; blood urea, 24 mg./100 ml.; standard urea clearance, 119 and 139 ; insulin clearance, 120 ml./min. ; glucose T_m, 169 mg./min. (Dr. H. M. Lloyd) para-amino hippuric acid clearance, 449 ml./min. After 5 g. of ammonium chloride his urine acidified to *p*H 5.1 with normal rise in ammonium excretion.

Plasma.—CO_2, 24.5 ; chloride, 103.5 ; sodium, 143 ; potassium, 4.1 ; calcium, 9.6 (lab. normal 9.5–10.0) ; phosphorus, 1.8 ; phosphatase, 48. Fasting blood sugar, 88 mg./100 ml.; ionized calcium, 5.9 (Dr. G. Alan Rose. Normal less than 6.2).

Haematology.—Haemoglobin, 126% ; P.C.V., 52.5%.

Vitamin-D Absorption.—Fasting level, 118 I.U. four hours after 350,000 I.U. orally ; 24-hour urinary glucose excretion varied from 4 to 7 g./day.

Glucose-tolerance Curve.—Normal.

Urine Amino-acid Chromatogram.—Slight increase in glycine, otherwise normal.

Radiographs.—Those of the skeleton revealed bilateral pseudo-fractures (Looser zones) of the first metacarpal (Special Plate, Fig. 1) and of both femoral necks (Special Plate, Fig. 4). There were changes, possibly pseudo-fractures, in several ribs.

From these findings it was deduced that this was a case of Dent Type 2 osteomalacia, in which glycosuria of renal type is associated with phosphaturia. There was no evidence of other renal tubular abnormality and renal glomerular function was normal.

Progress and Treatment

Calcium-balance studies in the untreated patient showed that he was in negative balance (Fig. 1) with a high faecal and low urine-calcium output. Treatment was started with 2 mg. a day of pure dihydrotachysterol (D.H.T.) This produced a positive calcium

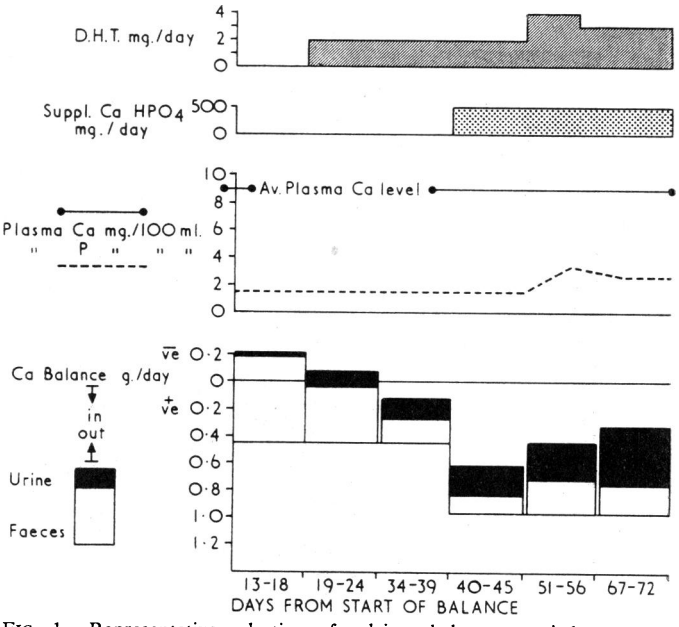

FIG. 1.—Representative selection of calcium balances carried out continuously in six-day collections over a period of 1 to 72 days.

balance of 200 mg. a day, but clinical improvement was slow. This was thought to be due to the effect of a reducing diet which contained a calcium intake of only about 450 mg. a day. Correction of this error with the addition of calcium phosphate was followed by rapid clinical improvement and a positive balance of 400–500 mg. a day. The patient was discharged virtually free of pain on a dose of 2 mg. of dihydrotachysterol and 2.5 g. of calcium phosphate a day.

He was followed up at regular intervals (Fig. 2) from September 1957, when the above investigations were completed, and he remained in good health until June 1963, resuming work as a machine operator

and then as a bus driver. He had made a complete clinical and radiological recovery by the middle of 1958 (Special Plate, Fig. 2).

Though there was never evidence of renal stone formation, the fact that the urinary calcium level rose to 900 mg./24 hr. (Fig. 2) as a result of treatment gave cause for alarm. The dose of dihydrotachysterol was therefore reduced gradually from December 1958. The reduction was followed by a fall in the urine-calcium levels, but there was a tendency, at the time not fully understood, for the plasma-calcium levels to rise as the dihydrotachysterol was reduced to 0.5 mg. a day over the period September 1962 to July 1963, and then withdrawn altogether.

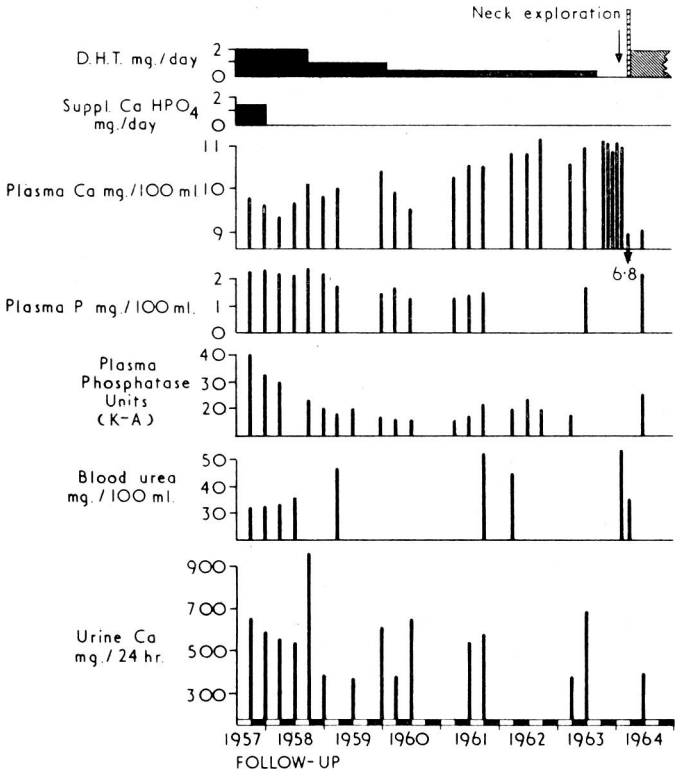

FIG. 2.—Results of follow-up examinations.

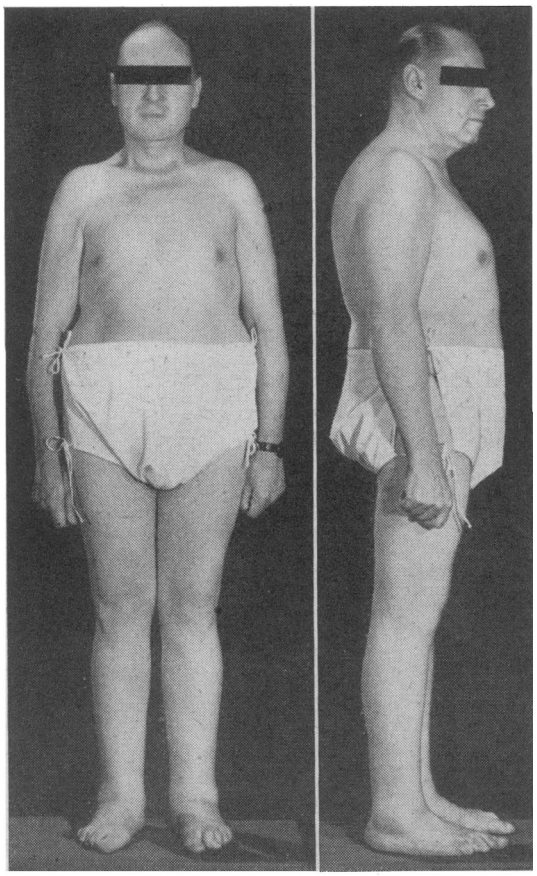

FIG. 3*a* FIG. 3*b*

FIGS. 3*a* and *b*.—Photographs of the patient.

In mid-1962 the patient had complained of indigestion, which was relieved by alkalis. He also began to be troubled by constipation and flatulence at about the same time. Otherwise he remained in excellent health. In June 1963 he fell heavily and subsequently complained of severe pain in the right knee and thigh, especially when weight-bearing. He was forced to give up work as a result. Films showed two Looser zones—one on the medial side right femur 10 cm. above the joint space, the other 3 cm. below the lesser trochanter (Special Plate, Fig. 5). It was concluded that reduction of the intake of dihydrotachysterol had led to a recurrence of his osteomalacia, but the high urine-calcium levels and the danger of raising them still higher contraindicated an increase in the dosage of the drug. Moreover, the slightly raised plasma calcium could not be explained away easily. It was thought at first to be due to a mild dihydrotachysterol intoxication—a state of affairs not compatible with recurrence of osteomalacia from under-dosage. At this stage Dr. R. Nassim (Royal National Orthopaedic Hospital, Stanmore) kindly offered a bed in his metabolic ward for further studies. During a control period after all treatment had been stopped the urinary calcium was around 630 mg./24 hr. and the faecal calcium 650 mg./24 hr. Negative calcium balance was 200 mg./24 hr., and the serum calcium remained persistently above 11 mg./100 ml. and serum phosphorus below 0.2 mg./100 ml.

The high serum-calcium levels persisted in spite of withdrawal of dihydrotachysterol. Hydrocortisone 40 mg. t.d.s. for six weeks produced no alteration in the serum-calcium level, and at the end of three months without treatment the serum-calcium level was still raised and the urinary calcium had fallen to only 450 mg./24 hr.

By now it was presumed that the effect of the dihydrotachysterol had worn off. The ionized calcium was determined (Dr. L. Watson) with the following results: total calcium 10.8 mg/100 ml.; ionized calcium, 6.4 mg./100 ml. (normal less than 5.9 mg./100 ml.); complexed calcium, 0.5 mg./100 ml.; protein-bound calcium 3.9 mg./100 ml.

The ionized calcium level had been normal in 1957. The rising total calcium level was now accounted for by unambiguous elevation of the ionized calcium level, showing that a new situation had developed and indicating the development of hyperparathyroidism as the most likely explanation. The patient was transferred to University College Hospital, and his neck was explored on 16 February 1964 by Mr. D. R. Davies. Two parathyroid adenomata were found and removed, and two normal parathyroid glands found, identified by frozen section, and left behind. He made an uneventful recovery after the operation, and was discharged in March 1964 on 2 mg. dihydrotachysterol. On 15 June 1964 he was symptom-free and about to return to work. Radiographs taken in January showed healing Looser zones (Special Plate, Fig. 3), and at this time he showed a plasma-calcium level of 9.4 mg./100 ml.; phosphorus, 2.4 mg./100 ml.; and phosphatase, 28 units. The calcium level remains subnormal on a dose of 2 mg. a day of dihydrotachysterol.

Electromyographic studies carried out by Dr. E. D. R. Campbell in March 1964 were compatible with a myopathic process in the right and left vastus medialis and left deltoid. These findings were confirmed two months later (H. J. G.), though much clinical improvement had taken place in the meantime. Further tests by Dr. Campbell in June 1964 are summarized as follows: "The appearances show a marked improvement compared with the pattern obtained on 12 March 1964 and are now well within normal limits."

Discussion

The history illustrates first of all how cases of osteomalacia with symptoms over a prolonged period of time tend to be missed. The characteristic clinical features of loss of stature due to collapse and smooth kyphosis of the dorsal and lumbar spine and weakness of the girdle muscles are together responsible for the characteristic posture and Trendelenberg gait. The muscle weakness affects only the girdle muscles and is unaccompanied by wasting. Both pain and bone tenderness are almost constant features, and pain on active and passive movement of the hips and shoulders was also present in this case.

The loss of height had increased by ½ in. (12.7 mm.) from January 1956 to June 1957, and the total loss of height of 7 in. (17.7 cm.) was characteristically underestimated by the patient.

The radiographic appearances were typical, showing Looser zones together with generalized osteoporosis. The fact that osteoporosis may not be detectable until 30% to 60% of calcium has been removed needs to be appreciated when radiographs are used for diagnostic purposes.

The investigations in 1957 proved conclusively that this was a case of Dent Type 2 renal-tubular oestoemalacia in which phosphaturia and glycosuria due to renal-tubular defect coexist, renal function being otherwise normal. The condition is extremely rare. The development of autonomous hyperparathyroidism is presumed to be consequent upon a mild secondary hyperparathyroidism, present as a complication of the osteomalacia but not normally of much consequence. This is the first case in which parathyroid adenomata have been known to have developed while under treatment and while under full follow-up observation in Professor Dent's clinic. Less well-authenticated examples of this complication have been briefly mentioned by Dent (1962). It led to great difficulty in control in this case. Probably a state of hyperplasia of all four glands appeared first, followed by tumour formation in two of them. Presumably the condition of any patient with any type of osteomalacia can evolve in this way and will then require surgical intervention. As Type 2 is so rare this may be more than a coincidence, and one is tempted to consider whether any special biochemical situation was present in our patient that led to this particular complication.

Summary

A 38-year-old man who complained of weakness and pains in his limbs and back was found to have lost 7 in. (17.7 cm.) in height. Radiological examination showed pseudo-fractures of a metacarpal, both femurs, and possibly several ribs, while laboratory investigation shown a rise in the serum-alkaline-phosphatase concentration, and the urinary glucose and phosphate levels. He was found to be in negative calcium balance with a high faecal and a low urinary calcium excretion. A diagnosis of Dent Type 2 osteomalacia (osteomalacia with renal glycosuria and phosphaturia) was made and treatment with dihydrotachysterol and calcium phosphate produced a positive balance.

Six years after he was first seen he was found to be in negative calcium balance again, and to have a raised calcium and a lowered phosphorus concentration in the serum. The serum ionized-calcium level, which had previously been normal, was raised. This suggested that hyperparathyroidism had developed, and at operation two parathyroid adenomata were found and removed. Shortly after this, electromyography showed features of a myopathy, though three months later the findings were normal.

It is concluded that in this case autonomous hyperparathyroidism developed on the mild secondary hyperparathyroidism which is normally present in osteomalacia.

We are greatly indebted to Professor C. E. Dent for investigating and treating this case, for his advice in producing this report, and for allowing us access to his notes. The biochemical investigations and balance studies were carried out by the biochemists in the Metabolic Ward, University College Hospital, except during the autumn of 1963, when we have to thank those in the Royal National Orthopaedic Hospital, Stanmore. Dr. R. Nassim kindly took over clinical control during this latter period.

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Preliminary Communications

Oral Betamethasone 17-Valerate in Chronic Ulcerative Colitis and Crohn's Disease

Brit. med. J., 1965, **2**, 29–31

During 10 years' experience in the use of corticosteroids as the mainstay of treatment of 50 patients suffering from ulcerative colitis we have found that a drug lacking the potentially disastrous side-effects of these agents has become increasingly necessary. The ideal drug for the treatment of uncomplicated ulcerative colitis and Crohn's disease must control the intestinal lesion, exert minimal influence upon electrolyte and protein metabolism, and preserve normal adrenocortical function.

Betamethasone alcohol is a corticosteroid nearly 40 times more potent orally than cortisone (Glyn and Fox, 1961) and has in large measure all the characteristic effects of the more recently introduced analogues. Betamethasone 17-valerate (Betnovate[1]) has been shown clinically to have an exceptionally powerful anti-inflammatory action in skin disease (Williams *et al.*, 1964), but in animal experiments relatively weaker systemic effects (personal communication by Dr. T. B. Binns, 1963). The possibility arose that the disparity between topical and systemic potency could be exploited in other ways, even for the treatment of intestinal diseases. Tests comparing the ability of the alcohol and 17-valerate ester to suppress plasma cortisol will be reported separately.

[1] Oral Betnovate is not yet available for prescription.

Material and Methods

This report concerns the use of Betnovate in four patients with Crohn's disease and 10 with ulcerative colitis: six were males and eight females (Table I). Ten of the 14 patients had already received prednisolone for periods ranging from 3 months to 8 years. Betnovate was given to eight of these because they had relapsed during prednisolone reduction. Four of the patients had relapsed while undergoing routine prednisolone reduction, but in the remainder side-effects had made it necessary to withdraw prednisolone completely. Two patients undergoing prednisolone withdrawal for hypercorticism were in remission when Betnovate was begun. In nine of these patients Betnovate was started during the terminal phase of prednisolone withdrawal. Betnovate was also used in four unselected new patients, all of whom were admitted for investigation and general care before treatment began: one had Crohn's disease and three had ulcerative colitis. The other three patients with Crohn's disease had received prednisolone for 3, 7½, and 32 months respectively before being transferred to Betnovate. Seven patients with ulcerative colitis had received prednisolone for periods longer than four years and up to eight years.