The loss of height had increased by $\frac{1}{2}$ 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 osteomalacia 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

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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 (Betnovate¹) 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.

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.

¹ Oral Betnovate is not yet available for prescription.

The starting dose of Betnovate was usually 2 mg. daily in divided doses, and this was increased as required. The maximum daily dose was 8 mg. The clinical response to Betnovate was first assessed at the end of three weeks' treatment according to the following grades:—very good: complete remission, with rapid subsidence of symptoms, normal bowel actions with formed motions, increased appetite and weight without dietary restriction; good: progressive improvement towards normal, incomplete at three weeks; fair: slight improvement at three weeks; poor: no response. The present state was assessed as follows:—very good: full remission maintained; good: full remission, minor relapses, easily controlled; fair: partial remission only; poor: no improvement from start of treatment.

TABLE I.—Data Concerning 14 Patients Given Oral Betnovate

Case No.	Sex and Age	Diagnosis	Original Severity	Total History (Years)	Reason for Betnovate
1	M 20	Crohn's disease	Severe	2	New patient
2	M 45	"	"	1	Relapse during prednisolone withdrawal for depression
3	M 47	"	"	26	Relapse during prednisolone withdrawal for hypertension and depression
4	F 24	"	Moderate	2	Relapse during prednisolone withdrawal for recurrent staphylococcal abscess
5	F 45	Ulcerative colitis	Severe	11	New patient
6	F 39	"	"	2	" "
7	M 29	"	Moderate	3	" "
8	F 38	"	Severe	15	Relapse during prednisolone reduction
9	F 44	"	"	21	" "
10	M 51	"	"	11	Relapse during prednisolone withdrawal for osteoporosis
11	F 35	"	Moderate	15	Relapse during prednisolone reduction
12	M 63	"	Severe	7	" "
13	F 39	"	Moderate	13	Progressive hypercorticism on prednisolone
14	F 66	"	"	31	Severe bruising on prednisolone

In each patient the blood-pressure, body weight, E.S.R., plasma cortisol, and haemoglobin were known before treatment began. These values were checked at intervals of about two weeks in order to correlate objective evidence with clinical response. Full clinical data and x-ray and sigmoidoscopy results will be reported at a later date. Blood for cortisol estimation was always taken at 10.30 a.m. in order to minimize diurnal variations (De Moor *et al.*, 1962). Plasma cortisol was estimated by the method of Spencer-Peet *et al.* (1965).

INITIAL RESPONSE

Table II shows the results for each patient. The five "very good" initial responses comprised the four new patients and the patient (Case 2) who had received prednisolone therapy for 7½ months and who relapsed during progressive dose reduction.

TABLE II.—Clinical Results of Betnovate Therapy

Case No.	Length of Previous Steroid Therapy	Betnovate Therapy			
		Duration (Months)	Clinical Result		Dosage (Mg.)
			Initial	Present	Initial Final
1	Nil	13	Very good	Good	2 2
2	7½ months	8	"	Very good	2 3
3	"	5	Good	"	4 8
4	32 "	2	Fair	Poor	2 6
5	Nil	12	Very good	Good	2 2
6	Nil	8	"	Very good	2 2
7	Nil	1	"	Defaulted	2 —
8	8 years	10	Good	Good	2 2
9	7½ "	5	Fair	Fair	2 8
10	7½ "	1	"	Poor	2 8
11	6½ "	8	"	"	1 8
12	6½ "	7	"	"	2 4
13	6½ "	7	Remission. Prednisolone reduction still in progress	"	2 2
14	4½ "	5	"	"	2 2

Two patients had a "good" response. One of these (Case 3), with severe Crohn's disease, was undergoing prednisolone reduction during the first three weeks of Betnovate treatment; the withdrawal of prednisolone was made necessary by the development of hypertension and mental depression. The second patient (Case 8, with ulcerative colitis) had relapsed after prednisolone withdrawal. The initial response in the four relapsed colitis patients (Cases 9–12) who had received long-term prednisolone therapy was only fair. Case 4, with severe Crohn's disease in relapse, responded poorly. Two patients (Cases 13 and 14) changed from prednisolone because of hypercorticism and were in clinical remission at the start of Betnovate treatment.

PRESENT CONDITION

Three of the five patients showing very good response have maintained that status; one (Case 7) defaulted but is known to be in good health; and Case 1 developed sacro-ileitis in the last six months with slow general deterioration and is now in the good category. Of two patients initially in the good category Case 8 remains good and Case 3 is very good. Of the four fair-response patients one is still fair and three are graded poor, and Betnovate has been discontinued. Case 4 responded poorly initially and had failed to improve. The two colitis patients (Cases 13 and 14) who were in therapeutic remission at the start of Betnovate therapy are still undergoing prednisolone reduction. Case 14 remains in remission, but Case 13 appears to be slowly relapsing. Their ultimate status on Betnovate alone is therefore unknown.

FIG. 1.—Effect of Betnovate on number of daily stools. Four patients with Crohn's disease preceded the remaining 10 with ulcerative colitis. The new patients (Cases 1, 5, 6, and 7) and also Case 2 responded well to Betnovate. Patients previously on long-term prednisolone did less well, and four of them (Cases 4, 10, 11, and 12) did not improve at all.

The number of stools daily before and after Betnovate are compared in Fig. 1. The period of Betnovate therapy is given in months for each patient in Table II. Where the treatment failed the number given represents the period of treatment before Betnovate was withdrawn in favour of some alternative agent. It will be seen that Cases 4, 10, 11, and 12 responded incompletely and Case 13 is rather worse. Several patients who continue to pass three motions a day are located in different response categories. This is because at this level the number of stools alone is not a reliable criterion of severity. Thus Case 8 has three stools a day, which is regarded as a good response because they are formed and are not accompanied by urgency, blood, or mucus. Case 9, on the other hand, has three loose and urgent motions, while Case 13 has three semiformal motions with a little mucus. The patients who fell to one stool a day represent those showing very good response. Case 1, with Crohn's disease and recently developed

sacro-ileitis, continues to pass one stool a day, with occasional abdominal pain and looseness. He has fallen from the very good to the good grade.

The body-weight charts for five patients graded very good or good show an increase in weight from the start of treatment. Case 1 gained 50 lb. (22.7 kg.) in the first 10 weeks. Before he developed Crohn's disease his weight was 203 lb. (92 kg.) and had fallen to 120 lb. (54.4 kg.) before the beginning of treatment.

FIG. 2.—Plasma-cortisol levels in Cases 1, 2, and 5 fell precipitately after the start of Betnovate treatment. Case 6, despite a very good response, maintained high levels throughout. Case 3 achieved normal cortisol levels when his prednisolone had been completely withdrawn leaving only Betnovate. The increase in levels in Case 1 coincides with the development of sacro-ileitis.

Fig. 2 shows the plasma-cortisol levels during the first 200 days of treatment in the five patients with the best response. The levels in Cases 1, 2, and 5 fell precipitately during the three weeks of rapid improvement at the start of Betnovate therapy. Case 6, whose response was very good throughout, maintained higher cortisol levels, which fell to a generally lower level only in the second half of the period. The cortisol level seems to correlate with the clinical state in the curve of Case 1, who has developed low back pain and stiffness of his joints in the last few months, and in Case 5, who at about 100 days suffered a brief attack of infective hepatitis.

Case 3, whose plasma-cortisol levels seemed to have been depressed by three months of prednisolone treatment, showed a rise when the prednisolone was ultimately withdrawn, despite the fact that he was then receiving 8 mg. of Betnovate a day.

SIDE-EFFECTS

Mental elation, irritability and depression, mooning of the face, fluid retention, skin infection, and glycosuria have not occurred. In some patients the blood-pressure has fluctuated slightly in relation to increased doses of Betnovate, but the evidence is at present insufficient definitely to attribute the fluctuations to the treatment. One patient (Case 3) who received continuous prednisolone for three months remained hypertensive (170/115) on 8 mg. of Betnovate 10 weeks after prednisolone was discontinued.

DISCUSSION

These patients, most of whom were either acutely ill or in relapse, provided a severe test of any new treatment. The results indicate that in untreated patients with Crohn's disease or ulcerative colitis 2–4 mg. of Betnovate has produced an initial improvement comparable with that produced by about 40 mg. of prednisolone, so far without the side-effects usually associated with systemic corticosteroid treatment. The plasma-cortisol level of some patients has occasionally been found to be below the lower limit of "normal," but there has been no other evidence of adrenal suppression. The fall from rather high initial levels may have been due to recovery from the stress of the disease. Moreover, in the doses used Betnovate does not appear to inhibit increased adrenocortical activity in response to stress arising, for example, from complicating disease occurring in the course of treatment. The suppression of complicating disease, such as asthma and rheumatoid arthritis, is a feature of prednisolone treatment, but this has not been observed with Betnovate.

The results in patients treated previously with long-term prednisolone are disappointing. In such patients adrenocortical suppression is usual. Since Betnovate seems to have a low systemic activity, it may emerge that oral Betnovate is of greater value in the patient with an active suprarenal cortex.

SUMMARY

Four patients with Crohn's disease and 10 with ulcerative colitis have been treated with oral betamethasone 17-valerate (Betnovate). There was no evidence of the usual side-effects associated with oral corticosteroids. The response in new patients and in those who had received prednisolone therapy for relatively short periods was satisfactory. Most patients who had received long-term prednisolone treatment responded badly. Betnovate seems to have a low systemic activity, and may be unsatisfactory in patients whose adrenocortical activity is depressed or who develop the systemic complications of their disease.

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