Among 46 patients who had been treated for thyrotoxicosis between one and nine years previously there were four with complete or nearly complete achlorhydria, of whom two had latent pernicious anaemia.

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ADRENAL CORTICAL AND PITUITARY FUNCTION AFTER INTRARECTAL STEROID THERAPY

BY

S. G. FLAVELL MATTS, M.B., Ch.B., M.R.C.P.Ed.
 Senior Registrar in Medicine

J. KELLEHER, M.Sc.
 Biochemist

B. A. WHARTON, M.B., Ch.B., D.C.H.
 Senior House Officer in Medicine

G. WALTERS, M.D., M.R.C.P.
 Consultant Pathologist

The Royal Hospital, Wolverhampton

Intrarectal steroids are being used more and more frequently in the treatment of ulcerative colitis. The two methods most commonly used are the slow-infusion method of Truelove (1956), using hydrocortisone hemisuccinate, and the single-dose bag method of Matts, using prednisolone phosphate (Matts, 1960a, 1960b, 1961a, 1962a) or betamethasone phosphate (Matts, 1962b). It is clearly desirable to know whether significant absorption occurs, because of the possibility of adrenal cortical suppression. There have been a few reports which show that hydrocortisone and methylprednisolone are absorbed (Liddle, 1956; Nabarro, Moxham, Walker, and Slater, 1957; Spencer, Kirsner, and Palmer, 1960), but we could find no information on the absorption of prednisolone phosphate or betamethasone phosphate, which are the two steroids used in this hospital. This paper reports our observations on the effect of rectal administration of these two steroids on adrenal cortical and anterior pituitary function.

Materials and Methods

Eighteen patients with ulcerative colitis were studied, the criteria for diagnosis being those laid down elsewhere (Matts, 1961b, 1962a).

Six patients were given enemata containing 5 mg. of betamethasone phosphate and 12 were given enemata containing 20 mg. of prednisolone-21-phosphate; both steroids were given in buffered aqueous solution. The

therapeutic procedure was the same in all cases, the steroids being administered rectally by the single-dose bag method of Matts. During the first week one enema was given night and morning, and for a further three weeks enemata were given at night only.

Adrenal Cortical Function.—This was assessed immediately before and immediately after treatment in 14 patients by determining the response to A.C.T.H. In 12 this was done as follows: three consecutive 24-hour urines were collected, after which 80 units of corticotrophin zinc (Jenkins, 1958) was given daily for three days by intramuscular injection. The urinary 17-hydroxycorticosteroids (17-O.H.C.S.) were estimated by the method of Norymberski (1961). In the other two cases A.C.T.H. was given intravenously (Eik-Nes, Sandberg, Nelson, Tyler, and Samuels, 1954); 25 units were infused in 500 ml. of 0.9% saline over a six-hour period, and the plasma 17-O.H.C.S. was determined by the method of Silber and Porter (1954), as modified by Rudd, Cowper, and Crawford (1961).

Anterior Pituitary Function.—The capacity of the anterior pituitary to secrete A.C.T.H. was tested before and after treatment in four patients treated with prednisolone. After treatment the test was begun 24 hours after the last enema had been given. After two control 24-hour urines the 11-beta-hydroxylase inhibitor metyrapone ("metopirone") was given for 48 hours in a dosage of 750 mg. four-hourly. The pituitary response to the fall

in blood cortisol thus produced was assessed by the increase in urine 17-O.H.C.S. (Liddle, Estep, Kendall, Williams, and Townes, 1959).

Urine Creatinine.—This was estimated in all urines by the method of Bonsnes and Taussky (1945).

Results

The daily variation in creatinine excretion in the male patients was similar to that in normal subjects, but greater variation was found in some of the females. We attribute this to the difficulty of collecting all the urine in females with frequent bowel actions. The urine steroids are nevertheless expressed as mg./24 hours, and where large variations in creatinine excretion affect the interpretation of results this is stated.

In the six patients treated with betamethasone (Fig. 1) the excretion of 17-O.H.C.S. was in the normal range

FIG. 1.—Effect of A.C.T.H. on urine 17-O.H.C.S. before (●—●) and after (○---○) treatment with betamethasone.

before treatment, and all cases gave a response to A.C.T.H., though in one case this was not large. After treatment the excretion was reduced in all cases, some showing a reduction from about 10 mg. to about 3 mg./24 hours. The response to A.C.T.H. was also greatly reduced in five cases, and appeared to be slightly reduced in the other.

The results were very different in those treated with prednisolone (Fig. 2). Before treatment the excretion of 17-O.H.C.S. was normal, and in all cases a good response to A.C.T.H. was obtained; Case P3 gave an exaggerated response. After treatment steroid excretion was decreased in only one case (from 10 to 4 mg./24 hours in Case P6), but all gave a good response to A.C.T.H., including the two in which A.C.T.H. was given intravenously (Table I). In

TABLE I.—Plasma 17-O.H.C.S. During Intravenous Infusion of 25 Units of A.C.T.H. over Six Hours, Before and After Treatment with Prednisolone

		Plasma 17-O.H.C.S. (μg./100 ml.)		
		0 Hours	3 Hours	6 Hours
Case P7	Before treatment	9.8	23	34
	After "	8.0	23	28
" P8	Before "	17	27	29
	After "	12	25	33

FIG. 2.—Effect of A.C.T.H. on urine 17-O.H.C.S. before (●—●) and after (○---○) treatment with prednisolone. In Case P3 the very low value on Day 3 was associated with a creatinine content of only 250 mg.

case P4 the response after treatment was greater than before, but this was associated with a larger increase in creatinine excretion. The response to A.C.T.H. in Case P2 was less after treatment than before, but was still very good.

The metyrapone tests for pituitary reserve in another four patients treated with prednisolone gave similar results before and after treatment (Table II).

TABLE II.—Effect of Metyrapone on Urine 17-O.H.C.S. in Patients Treated with Prednisolone. Metyrapone was Given on Days 3 and 4

	Urine 17-O.H.C.S. (mg./24 Hours)							
	Days Before Treatment				Days After Treatment			
	1	2	3	4	1	2	3	4
Case P9	—	8.1	19.1	33.0	2.8*	1.8*	18.6	34.2
" P10	7.2	5.8	7.4	26.4	6.7	13.9	21.7	31.7
" P11	11.0	9.5	18.2	42.0	16.5	14.2	17.2	37.6
" P12	16.8	15.3	11.5	40.4	10.5	10.8	38.4	39.8

* Creatinine output on Day 1 was 340 mg. and on Day 2 180 mg. The average for the succeeding four days was 850 mg.

Discussion

The striking decrease in excretion of 17-O.H.C.S. and in the response to A.C.T.H. in five cases treated with betamethasone indicates that this steroid was absorbed. Its therapeutic effect might therefore be partly due to a systemic effect, and patients treated with this preparation will be liable to the same complications as those treated with systemic steroids, and constitute the same operative risk (Sampson, Winstone, and Brooke, 1962).

Only one (Case P2) of the 12 patients treated with prednisolone showed a lower response to A.C.T.H. after

treatment than before. Even so, the 17-O.H.C.S. excretion rose from an average of 8 mg./24 hours to 23 mg. in the first 24 hours of A.C.T.H., despite the fact that the creatinine content of this urine was only two-thirds of the average output during the test. Though less than the corresponding value before treatment, this figure still represents a good response, and the difference between the two curves in this case could well be due to a somewhat exaggerated response before treatment. The similarity of the response to metyrapone before and after treatment demonstrates not only that A.C.T.H. secretion remained unimpaired but also that the adrenal cortical response to A.C.T.H. was not suppressed. These results indicate that prednisolone was not absorbed in amounts sufficient to cause pituitary or adrenal suppression, though according to the data of Shuster and Williams (1961) absorption of up to 30% of the dose given could have occurred without suppressing the adrenal cortex.

There is a clear difference in the effect of these two enemata on the adrenal response to A.C.T.H. That this difference cannot be accounted for by variations in the severity of ulcerative colitis is shown by the fact that mild and severe cases behaved similarly with both preparations (Table III).

TABLE III.—Incidence of Adrenal Cortical Suppression After Treatment with Rectal Steroids in Mild and Severe Cases

Steroids Used	No. of Cases Showing Adrenal Cortical Suppression		
	Mild Cases	Severe Cases	Total
Betamethasone	3/4*	2/2	5/6
Prednisolone†	0/5	0/7	0/12

* Excluding one case with ? slight depression.

† Includes intravenous A.C.T.H. tests and metyrapone tests.

The explanation may be that the dose of betamethasone was equivalent to a much higher dose of prednisolone than was actually given. The relatively higher dose of betamethasone has been found to be necessary to achieve a satisfactory therapeutic effect (Matts, 1962b).

Previous reports on the absorption of rectally administered steroids in ulcerative colitis have given variable results, and these can be correlated with differences in the preparation used. Thus while an appreciable amount of hydrocortisone was absorbed when administered as the free alcohol in a variety of pharmaceutical preparations, the hemisuccinate was only very slightly absorbed from aqueous solution (Nabarro *et al.*, 1957; Schwartz, Cohn, Bondy, Brodoff, Upton, and Spiro, 1958). Liddle (1956) found hydrocortisone acetate to be readily absorbed when given in suppositories, but Nabarro *et al.* could not demonstrate absorption when this ester was used as a suspension. Spencer *et al.* (1960) and Sanbar and West (1961) found significant absorption of 6- α -methylprednisolone. In the present study both steroids were given as an aqueous solution of the 21-phosphate, and there are some differences in the buffer and preservatives used.

It seems unlikely that the different effects on adrenal cortical function are due to variations in the pharmaceutical presentation. Whether they are due to a difference in dosage or to the nature of the steroid has not been established. The important clinical application of the findings is that, since these doses are the ones necessary therapeutically and are contained in the commercially available enemata, the probability of adrenal cortical suppression must be kept in mind when using the betamethasone enemata.

Summary

The effect of rectal steroids on anterior pituitary and adrenal cortical function has been studied in 18 patients with ulcerative colitis. Six were treated with betamethasone enemata and 12 with prednisolone enemata.

Adrenal cortical and anterior pituitary function were assessed before and after treatment by the effect of A.C.T.H. and metyrapone respectively on plasma and urine 17-O.H.C.S.

Treatment with enemata containing 5-mg. of betamethasone was found to cause suppression of the adrenal cortex, whereas neither the adrenal cortex nor the anterior pituitary was suppressed after treatment with enemata containing 20-mg. of prednisolone.

We would like to thank the physicians under whose care the patients were admitted, the Birmingham Regional Hospital Board for a grant to one of us (S. G. F. M.), and Sister Martin and Sister Lovatt and the nurses of the wards concerned for their co-operation. Our thanks are also due to Glaxo Laboratories Limited for their generosity in supplying the enemata.

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"The Governors have been somewhat disturbed to find how little thought appears to have been given to the subject of the provision of accommodation for the mentally infirm aged. In general, the policy with which most will agree is that old people should not go into mental hospitals unless they need the special treatment and care which those hospitals can give but should be looked after within the community. But it seems to the Governors that local authorities will have to decide whether they are going to build special homes for these types of case or whether they can accommodate them in the existing homes for the physically infirm aged without too greatly upsetting the other residents. They may, too, have to create a closer contact with the geriatric units and the mental hospitals, so that assessments of some old people can be made in hospital to decide whether they need treatment there or only the care and supervision which a home can give." (*Annual Report for 1962*, National Corporation for Care of Old People.)