Absorption of Cortisol from the Colon in Ulcerative Colitis.*† (23834)

RAPHAEL D. SCHWARTZ,‡ GEORGE L. COHN,§ PHILIP K. BONDY, MURRAY BRODOFF,** G. VIRGINIA UPTON, AND HOWARD M. SPIRO
Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn.

The successful use of topical steroid therapy for diseases of the skin, eye, and joints has led us to evaluate the effect of cortisol by rectum in iodiopathic ulcerative colitis. Truelove(1) and Allodi and Muratori(2) almost simultaneously reported good clinical results with cortisol enemas, but whether this was the result of systemic absorption of the steroid or a purely local effect was undetermined. Our experience with the clinical efficacy of this form of treatment will be reported in detail elsewhere; the present study is concerned with the absorption of rectally administered cortisol in ulcerative colitis.

Methods. A. *Mode of Administration*: Patients with ulcerative colitis of one to 4 years' duration, proven by sigmoidoscopy and x-ray, received daily enemas at about 10:00 a.m. of 100 cc. of normal saline for a period of 7 to 10 days prior to the administration of cortisol by rectum. After this control period, 200 mg of cortisol (hemisuccinate-sodium) dissolved in 100 cc of normal saline was administered as a rectal enema for a 20-minute period, at the rate of 3-5 ml per minute from an infusion bottle. Daily therapy with the steroid was continued for 2 weeks. Three patients received cortisol-4-C^{14} in a dose of 4,400,000 counts per minute (494 μg) as a tracer dose added to the 200 mg carrier cortisol.

B. Blood samples were obtained at 0, ½, 1, 2, 4, 6, and 24 hours after the administration of saline and cortisol enemas. The levels of plasma cortisol were measured quantitatively in duplicate on the initial day of therapy by the method of Bondy, *et al.*(3) and the presence of conjugated steroids was determined by the method of Cohn and Bondy (in preparation). In these experiments where cortisol-4-C^{14} was employed conjugated steroids were initially separated by paper electrophoresis of a butanol extract of plasma. The conjugated steroids were eluted with 70% methanol taken to dryness *in vacuo* and counted as the total conjugated glucuronide fraction in a gas flow windowless counter, shielded by steel, with a background of 1.8-2.0 counts/minute. Unconjugated cortisol-4-C^{14} was counted in a liquid phosphor scintillation counter (TMC Model LP-2).

Results. Table I illustrates the plasma

TABLE I. Plasma Levels of Cortisol.

Patient	Enema	Hr after enema: 0	½	1	2	4	6	24
S. F.	200 mg cortisol	7.3		3.4	1.4	12.7		4.9
L. D.	.85% saline*	28.5		21.8	16.2	44.2		18.2
	200 mg cortisol	18.2		24.0	37.6	49.5		21.4
M. I.	.85% saline*	12.1	10.0	13.1	13.2	9.4	14.4	15.1
	200 mg cortisol	15.1	18.5	18.2	16.3	24.5	25.3	17.2
P. K.	200 mg cortisol	10.1		17.3	9.0	21.1	14.8	11.2
A. K.	*Idem*	9.4	9.1	13.5	10.2	7.5		4.3
Mean of diff. from zero time conc. (μg/100 ml)				3.3	2.9	11.0		− .2
Upper confidence limit (95%)				8.6	14.9	26.4		4.1

* Statistics do not include cortisol values after saline.

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** Resident in Gastroenterology, V. A. Hospital, West Haven, Conn.

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‡ Dazian Foundation Fellow.

§ Trainee, Nat. Inst. of Arthritis and Metabolic Diseases.

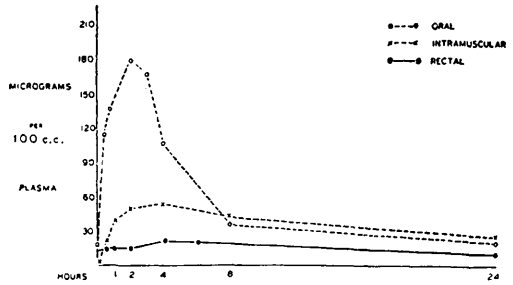

FIG. 1. Avg plasma cortisol concentrations after administration of 200 mg of cortisol.

levels of cortisol. There is a wide range of variation of these levels and no statistically significant differences occurred in the various time periods studied. The 95% confidence limits, assuming a normal distribution of plasma cortisol values(4), are also indicated.

Fig. 1 graphically illustrates the average plasma level radioactivity of cortisol after oral, intramuscular, and rectal administration. The data for oral and intramuscular levels were obtained from Peterson *et al.*(5), whose plasma values are similar to those reported from this laboratory. Peterson's data were obtained from healthy subjects.

Fig. 2 illustrates the levels of radioactive cortisol and conjugated steroids in plasma after the rectal administration of cortisol-4-C^{14} and carrier cortisol (200 mg). The radioactivity of the cortisol fraction is not significantly above the background. The peak of the radioactive conjugated steroids at one hour, however, is significant and is being further investigated.

Discussion. Five patients with idiopathic ulcerative colitis received 200 mg of cortisol daily for a period of 2 weeks. Clinical improvement was noted by sigmoidoscopy and the remission of symptoms. This may have been, in major part, a local effect since there were no statistically significant differences in the levels of plasma cortisol at the various time periods studied when compared to the zero time. In addition, there was no observed clinical evidence of a hyperadrenocortical state during the administration of the steroid.

The levels of plasma cortisol after a saline enema in patient L.D. are similar to those obtained after the cortisol enema. The levels in both instances are above the normal values for our laboratory (7-15 μg/100 ml)(3). It is possible that the zero-hour value of 28.5 μg/100 ml may be a reflection of the effect of the disease on the adrenal cortex, since patients with a variety of serious diseases may have abnormally high levels of cortisol (unpublished data).

The plasma cortisol concentration in normal patients reaches a peak 2 hours after the administration of 200 mg of oral cortisol; a plateau is obtained between 2 and 4 hours after intramuscular cortisol(4). Patients with ulcerative colitis who received 200 mg of rectal cortisol did not demonstrate any significant peak.

Within the first hour the plasma contained conjugated steroids derived from the cortisol given by rectum, but the concentration of these conjugates fell rapidly to non-detectable limits within 4 hours. This indicates that whatever cortisol is absorbed is rapidly metabolized by the liver into the reduced glucuronisides of cortisol, and subsequently excreted in the urine. An increased twenty-four hour excretion of 17-hydroxycorticosteroids and 17-ketosteroids after cortisol enemas has been demonstrated by Nabarro *et al.* (6).

Present knowledge does not permit the statement that the levels of plasma cortisol observed after therapeutic enema are pharmacologically ineffective; however, this was suggested clinically in our study. Complete metabolic balance studies are being conducted which may lend support to our clinical impression that this method of administration is relatively devoid of any of the known side effects of steroid therapy and may therefore

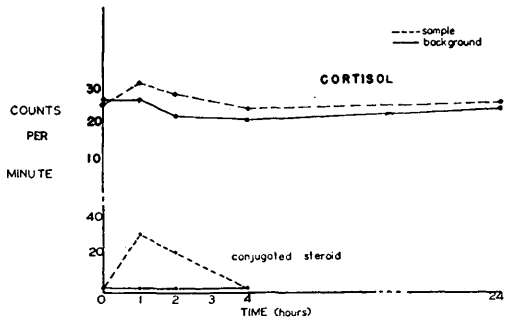

FIG. 2. Plasma steroid radioactivity concentrations after rectal administration of cortisol-4-C^{14}.

be particularly useful in the treatment of acute early ulcerative colitis.

Summary. Rectal cortisol has been used in treatment of chronic ulcerative colitis with good results. Following administration of 200 mg of the steroid dissolved in 100 cc of normal saline, there was no significant increase in blood levels of cortisol. This was confirmed by absence in the plasma cortisol fraction of any appreciable radioactivity following instillation of cortisol-4-C^{14}. By implication, our data suggest that the good clinical results obtained were probably the result of a local effect of the cortisol on the rectal mucosa.

1. Truelove, S. C., *Brit. Med. J.*, 1957, v1, 1437.

2. Allodi, A., Muratori, F., *Gastroenterologia,* 1956, v86, 697.

3. Bondy, P. K., Abelson, D., Scheuer, J., Tseu, J. K. L., Upton, G. V., *J. Biol. Chem.*, 1957, v224, 47.

4. Bondy, P. K., Upton, G. V., PROC. SOC. EXP. BIOL. AND MED., 1957, v94, 585.

5. Peterson, R. E., Wyngaarden, J. B., Guerra, S. L., Brodie, B. B., Bunim, J. J., *J. Clin. Invest.*, 1955, v34, 1779.

6. Nabarro, J. D. N., Moxham, A., Walker, G., Slater, J. D. H., *Brit. Med. J.*, 1957, v2, 272.

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Fluoride Content of Urinary and Biliary Tract Calculi.* (23835)

I. ZIPKIN, W. A. LEE AND N. C. LEONE† (Introduced by G. M. Briggs)
National Institute of Dental Research, N.I.H., P.H.S., U. S. Dept. of Health, Bethesda, Md.

In connection with an extensive survey of the fluoride content of human skeletal tissues (1,2), it was of interest to assess the relation of water-borne fluoride to the fluoride content of urinary and biliary tract calculi. With the exception of the recent duplicate reports‡ by Herman(3) and Spira(4), no data are available on the fluoride content of urinary tract calculi. Murray(5) reported that kidney stones contained fluoride, but no data were given. Data on the fluoride content of biliary calculi appear to be limited to the recent report of Spira(6). In the present study, the fluoride content of urinary and biliary tract calculi was also compared with that of bone obtained from individuals residing in low (0.0-0.6 ppm in the drinking water) and high fluoride areas (2.6 ppm in the drinking water).

Methods and materials. Thirty-three urinary and 9 biliary tract calculi obtained from individuals with verified histories of fluoride exposure were dried overnight at 105°C and pulverized. They were then extracted with alcohol for 8 hours and with ether for 4 hours, ashed at 550°C for 3 hours and analyzed for calcium(7), phosphorus(8) and fluoride(9,10,11). Samples of dry, fat-free urinary tract calculi were submitted for X-ray diffraction analysis to determine if calculi with strong apatite patterns showed higher concentrations of fluoride. A pooled sample of bile from four individuals who had resided in Washington, D.C. (1 ppm F in the drinking water) was also analyzed for fluoride. The fluoride content of urinary and biliary tract calculi was compared with that of some 35 bones taken at autopsy from individuals residing in low fluoride areas (0.1-0.4 ppm) and in a high fluoride area (2.6 ppm F). Data on the fluoride content of bones from individuals drinking water containing 0.1-4.0 ppm F will be presented elsewhere(1).

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† Present address, Nat. Cancer Inst. N.I.H., Bethesda, Md.

‡ Since the fluoride data are identical in both reports, these studies do not appear to be independent investigations.