manifest. The problem of the appearance of hypercalciuria at relatively low serum-calcium levels while on treatment with dihydrotachysterol (Litvak *et al.*, 1958) has complicated his management. The second patient, critically ill with parathyroid poisoning, was cured by operation.

Possibly this association between parathyroid disorder and steroid-treated ulcerative colitis is purely fortuitous. Against this possibility is a previous report of the appearance of tetany in a patient with ulcerative colitis receiving steroid therapy (Moehlig and Steinbach, 1954). While the hypoparathyroidism might be explained by parathyroid involvement in a multisystem disease known to affect the skin, joints, eyes, liver, and kidneys as well as the bowel, the cause of the adenoma formation would remain obscure. Furthermore, one might expect that the steroid therapy which lessens the other manifestations of the disease might prevent parathyroid involvement, but in fact the opposite appeared to be the case.

A possible explanation for the association is that in severe long-standing ulcerative colitis calcium stores are reduced either through poor absorption or excessive excretion via the bowel. The use of steroids with their "anti-vitamin D" effect (Anderson *et al.*, 1954) might cause further embarrassment to the already depleted calcium stores. The effect of this might be a need for increased quantities of "para-thor-mone" resulting in either exhaustion, hypoparathyroidism, or adenoma formation.

Summary

Two patients with long-standing ulcerative colitis treated with steroids developed hypoparathyroidism and hyperparathyroidism respectively.

Both have fairly active arthritis, even though the first case has had a complete colectomy.

The tetany and cramps in the first case became more pronounced after colectomy and have persisted for four years. These symptoms respond to dihydrotachysterol, but he has a low renal threshold for calcium and a persistently positive Sulkowitch reaction in his urine. Furthermore, he has hyperthyroidism controlled by methylthiouracil.

The second case, one of hyperparathyroidism, presented with generalized weakness and a phlebotrombosis of his calf veins. He had had an episode of urolithiasis three months prior to admission. His condition deteriorated so rapidly after admission that he had to be subjected to an emergency operation for removal of a parathyroid adenoma, of chief-cell histology, with cure of his hyperparathyroidism.

The possible mechanism for this association of parathyroid dysfunction and ulcerative colitis is discussed.

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PHENYLBUTAZONE SUPPOSITORIES IN TREATMENT OF NON-SPECIFIC PROCTITIS

BY

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Recently the topical treatment of ulcerative colitis has come again into prominence. Truelove (1956, 1958). Schwartz *et al.* (1959), and others achieved a rapid clinical remission by local—that is, rectal—hydrocortisone. According to Truelove (1960) a better result is to be expected in moderate and mild cases from local treatment than from systemic prednisolone therapy. Local treatment has several advantages over systemic: (1) the active material acts directly on the diseased mucosa; (2) a greater local concentration can be attained; and (3) complicating side-effects are avoided.

We have successfully used local phenylbutazone treatment in ulcerative colitis (Hankiss and Keszthelyi, 1960; Hankiss, 1961). We tried this drug because of its excellent anti-inflammatory effect, and practical experience has supported our theoretical supposition. A rapid remission occurred in the responsive cases. This was similar to the results achieved by local hydrocortisone. The only essential difference was that, in contrast to Truelove's observations, the extent of involvement proved to be of decisive significance in the case of local phenylbutazone treatment. When the disease was limited to the distal part of the colon our results were good, whereas with diffuse colitis or with colitis involving mainly the right side of the colon local phenylbutazone was ineffective.

This treatment was given in the form of enemata which were excellently tolerated by the patients. It sometimes happened that the patients improved both subjectively and objectively but sigmoidoscopy still revealed a moderate hyperaemia above the anal ring. We thought that the enematas might maintain the inflammation here in a mechanical way and therefore we gave the phenylbutazone as suppositories. With this treatment the signs of inflammation soon disappeared.

At this time we began to be systematically engaged with the suppository treatment of non-specific proctitis.

Selection of Cases

The nature of non-specific proctitis is a debatable question. Some investigators (Thaysen, 1934; Brooke, 1953, 1954) consider it an independent unit, while others (Newell and Jones, 1958; Truelove, 1959) regard it as a concurrent phenomenon of ulcerative colitis. I hold to this second school of opinion, although in some cases of *primary proctitis* the process does not extend to the upper parts of the colon even after a long history. They show fewer general signs and are more benign *quoad sanationem*. We must bear in mind also the *secondary proctitis* which accompanies some other processes, as, for example, anal fissure, fistula-in-ano, haemorrhoids, perianal eczema, pruritus ani, helminthiasis, and post-radiation proctitis. These are usually mild forms of proctitis, without bleeding. Nevertheless they must be treated, because either they can exacerbate the underlying process—for example, perianal eczema or pruritus—or they may produce very unpleasant symptoms.

Our patients were selected after a very careful clinical examination. The cardinal complaints were the passage of mucus and blood per rectum and tenesmus. Mucus and blood were usually found on the surface of a formed stool. Diarrhoea was rare and the general health of the patients has usually remained good.

Besides digital examination, sigmoidoscopy, and examination of the stool, we carried out a barium-enema examination, made a helminthological examination, and excluded amoebiasis.

The classification of our patients into two groups of proctitis—proctosigmoiditis and ulcerative colitis—was made according to the extent of the alterations, the case history, and clinical findings. Here we deal only with those cases of ulcerative colitis in which the process was limited to the most distal part of the colon.

The effect of treatment was assessed by the bowel movements, the disappearance of bleeding and mucus, and especially by the sigmoidoscopic findings.

Method.—Three types of suppositories were used: (1) containing 200 mg. of phenylbutazone; (2) containing 200 mg. of phenylbutazone and 8 mg. of prednisolone; and (3) containing 200 mg. of phenylbutazone, 8 mg. of prednisolone, and 100 mg. of "protargol," incorporated in normal base.

Results

22 patients were treated with suppositories: brief individual details are given in the Table. At the beginning of the treatment we always used suppositories containing only phenylbutazone (Formula No. 1). At first the suppositories were used twice a day—one in the evening and the other in the morning, after defaecation. In a week or two the dose was reduced to one a day, and in two to three weeks, if the patient was then symptom-free, to one in two days, and later on to two a week.

If there was no improvement with phenylbutazone suppositories within 7 to 10 days, then, after discontinuing treatment for some days, we passed to the other types of suppositories. At first we used formula No. 2, but recently have preferred to employ the third one, the protargol of which adds to the anti-inflammatory activity and confers antibacterial properties, too.

Seven out of 11 patients with proctitis showed rapid and lasting remission. One improved on combined

suppositories only. In Case 4 a relatively good state could be maintained after relapse only by the administration of combined suppositories. Four of our patients did not require any treatment. In the case of the other improved patients the symptoms returned when we discontinued the 1–2 suppositories weekly, but the patients again became symptom-free when the suppositories were resumed.

The patients with ulcerative colitis did not respond satisfactorily. Only two out of seven are still symptom-free and even these were not really cases of ulcerative colitis. The refractory cases did not respond to combined suppositories either.

The secondary cases responded satisfactorily. Naturally, here the primary causes must be treated first—for example, helminthiasis was cured with the appropriate procedures; and pruritus ani due to eczema perianale got proper treatment. We began suppository treatment only if, after improvement of the primary cause, sigmoidoscopy still showed evidence of proctitis. In all but one case the treatment was followed by a subjective relief of symptoms, and the signs of inflammation disappeared. Here formulae 2 and 3 proved to be best. Prednisolone alone seems to be not so effective as when in combination with phenylbutazone. That is to say, the two drugs seem to potentiate each other's effectiveness.

In regard to effectiveness, two factors appear to be decisive: (1) the duration of the disease (Truelove, 1959)—old, chronic processes respond badly; and (2) the underlying cause. Naturally one can expect a relapse with a progressive ulcerative colitis much more than with pure proctitis. The secondary processes responded in a satisfactory manner only if the primary disease could be healed.

Discussion

In the treatment of chronic proctitis phenylbutazone has proved to be very efficient when used in the form of suppositories. Without doubt, in most part, proctitis cannot be considered an independent unit but is a form of ulcerative colitis (Goligher, 1953; Truelove, 1959). We know, however, that in the case of ulcerative colitis the lesion of the distal part of the colon is often the most serious one, and sometimes only this part is affected, the proximal colon being relatively intact. In

Clinical Details and Response to Phenylbutazone Suppository Treatment

Case	Sex and Age	Length of History	Diagnosis*	Response* to Treatment	Subsequent Course	Length of Observation
1	M 46	8 months	Proctitis	Remission	Symptom-free	2 years
2	M 35	1 month	"	"	"	3 months
3	M 54	4 years	"	Slight	No improvement on combined suppositories	6 "
4	M 36	7 months	"	Remission	Relapse. Improvement on combined suppositories	10 "
5	F 40	6 "	"	"	Symptom-free	5 "
6	M 46	1 month	"	"	"	7 "
7	M 29	3 months	"	"	"	8 "
8	F 34	1 year	"	"	"	4 "
9	M 47	6 years	"	No	No improvement on combined suppositories	7 "
10	M 46	16 months	"	Slight	Improved on combined suppositories	4 "
11	F 38	4 years	"	No	—	—
12	F 29	3 months	Ulc. colitis	Good	Relapsed	2 years
13	F 36	2 years	"	Slight	Requires constant treatment	14 months
14	F 34	2 "	Proctosigmoiditis	Remission	Symptom-free	5 "
15	M 48	10 months	"	"	"	7 "
16	F 60	10 years	Ulc. colitis	No	No improvement on combined suppositories	3 years
17	M 42	1 year	"	Slight	Relapse. Improved on combined suppositories	2 "
18	F 39	4 years	Proctosigmoiditis	No	—	—
19	F 18	2 "	Proctitis sec. Pruritus ani	Good	Symptom-free	16 months
20	F 36	2 "	"	Slight	Requires constant treatment	10 "
21	M 51	4 months	Proctitis sec. perianal eczema	"	Improved on combined suppositories	1 year
22	F 36	2 years	Sec. proctitis. Helminthiasis	Good	Symptom-free	4 months

* Clinical and sigmoidoscopic.

such cases Truelove (1959) achieved a good clinical remission in 14 out of 22 cases with hydrocortisone suppositories.

Phenylbutazone is known to possess several actions, such as anti-inflammatory (Wilhelmi, 1949; Belart, 1949), reduction of capillary permeability (Wilhelmi, 1949, 1950), and antihistaminic (Domenjoz, 1952). Its local effect is also proved (Heilmeyer *et al.*, 1953) and we have previously used it with success for the local treatment of ulcerative colitis. The drug gets into the deeper layers of the mucosa, too, as was demonstrated by Hawkins and Fawns (1959), who investigated its absorption from the rectum. In our above-mentioned observations we pointed out that the direct contact of the drug with the diseased area is the decisive factor influencing its effectiveness. Our present observations also support this view.

The severity of the inflammatory process does not seem to determine the success of treatment. The decisive factor is the localization of the process. We could achieve success even with a lesion reaching the sigmoid colon if the enemata described above were given for some days before suppository treatment.

Phenylbutazone, by reducing inflammation and capillary permeability, as well as by its antihistamine effect, is beneficial to the inflamed mucosa. Phenylbutazone and prednisolone used in combination seem to potentiate each other's effect (Wilhelmi and Domenjoz, 1951; Kuipers, 1959; Châtel, 1960). They may have a different mechanism of action; this is supported by the fact that in some cases only the one drug, in other cases only the other, is effective.

We have never encountered the ulcerogenic side-effects of phenylbutazone either in suppository form or in enemata. On the contrary, its use in cases of ulcerative colitis and proctitis has resulted in rapid improvement of ulcers and in stopping bleeding.

It should be noted that all treatments of this kind must be preceded by thorough-going proctological examinations to establish the diagnosis and to exclude lesions such as carcinoma.

Summary

Phenylbutazone is well known to be an anti-inflammatory agent, and this property applies to its local use.

Suppositories containing 200 mg. of phenylbutazone have been found to produce clinical remission and sigmoidoscopic improvement in a large proportion of patients with proctitis, either primary non-specific or secondary. In the case of secondary proctitis, the primary disease was given appropriate treatment before employing suppositories for the proctitis.

Even better results were obtained with "combined" suppositories in which prednisolone and (in some cases) "protargol" were also included. Such "combined" suppositories brought about improvement in some patients who failed to improve with suppositories containing phenylbutazone alone.

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ACUTE ARSENICAL POISONING DUE TO ACETARSOL PESSARIES

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Packing the vagina with acetarsol pessaries is sometimes recommended for resistant cases of trichomonal vaginitis. The danger of this method is illustrated by the following case (reported briefly in the *British Medical Journal* of July 16, 1960, p. 242).

A healthy married woman of 28 complained of vaginal discharge due to infection with *Trichomonas vaginalis*. She had not been pregnant, nor had she any serious illness. In January and February, 1958, she was treated for eight weeks with acetarsol 4-gr. (0.26-g.) pessaries, one night and morning for four weeks and then two each night for four weeks. Because the infection persisted and she complained of some local irritation, "penotrane" and then nystatin pessaries were given with lactic-acid douches. Nine months later (April, 1959) she returned to hospital and was treated with penotrane pessaries for a month and acetarsol 4-gr. (0.26-g.) pessaries two nightly for four months. In January, 1960, she was again treated, with "pruvagol" pessaries, but without improvement.

She was admitted to hospital, and on April 6 her vagina was packed, under general anaesthesia, with 18 acetarsol pessaries (total dose 72 gr.—4.67 g.). The next day she complained of nausea and vomited several times. As this was thought to be due to the anaesthetic she was given chlorpromazine hydrochloride ("largactil") 25 mg. On April 8 12 acetarsol pessaries (48 gr.—3.1 g.) were inserted into the vagina without anaesthesia. Nausea persisted and her temperature was 99° F. (37.2° C.). On April 9 she was restless and at midday had a generalized epileptiform fit, after which she was drowsy and disorientated. She appeared dehydrated; her pulse was 116 a minute, blood-pressure 110/70 mm. Hg. and temperature 100° F. (37.8° C.). There were no abnormal physical signs in the central nervous system: she was able to move all her limbs, the pupils reacted to light, and the fundi appeared normal; her jerks