Section of Proctology

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Meeting
January 13, 1960

A Comparative Trial of Salazopyrin,[1] Prednisone and Hydrocortisone Retention Enemata in the Out-Patient Treatment of Left-sided Colitis

Preliminary Report

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ENTHUSIASTIC reports have come from Sweden (Svartz, 1956) and America about the efficacy of Salazopyrin in the treatment of ulcerative colitis. Moertel and Bargen (1959) concluded that this drug benefited two-thirds of the patients to whom it was given and in one-third full remission was achieved; an improvement, they claim, comparable with the best results from corticosteroids. Cortisone is known to be an effective drug in the treatment of colitis (Truelove and Witts, 1955); Newell and Avery Jones (1958) reported that prednisone brought about remission in 2 out of 3 cases of active proctitis. Truelove (1958*a*) described similarly successful results using retention enemata of hydrocortisone hemisuccinate in mild or moderately severe cases of colitis. Both oral prednisone and hydrocortisone enemata have been shown by these authors to be much more effective than inert substances given as a control.

About one-third of the patients who improve initially relapse within the next few months, whichever treatment is given. Local hydrocortisone alone seems to be free of any undesirable side-effects; the potential dangers of oral corticosteroid therapy are well known. Salazopyrin also gives rise to unpleasant side-effects fairly often, including occasionally reversible hæmolytic anæmia (Spriggs *et al.*, 1958) and agranulocytosis (Moertel and Bargen, 1959).

The Present Trial

We have investigated by a direct comparative trial the relative effectiveness of these three remedies as out-patient treatment for left-sided colitis. Since controlled trials using a placebo have proved that two out of the three treatments are effective, we did not consider it necessary to treat a group of patients with an inert substance in this series. The criteria for including a patient in the trial were: (1) Each must be suffering from an exacerbation of left-sided colitis, proctosigmoiditis, or proctitis. (2) There must be no contraindication to the use of any of the three treatments.

After a patient had been deemed suitable for the trial, one of the three treatments was allocated according to a random scheme.

Salazopyrin was given in a dose of 4 g daily and the patient was instructed to reduce the dose if severe side-effects occurred. Prednisone, 60 mg daily, was given for the first week, 45 mg daily for the second week and 30 mg daily for the third week. The patients given hydrocortisone enemata made up a fresh solution each night of 100 mg of hydrocortisone (as hemisuccinate sodium) in 150 ml of normal saline and infused it into the rectum on going to bed, using a modified blood transfusion set (Truelove). Each patient who received this treatment was carefully instructed in the self-administration of the enema.

After treatment for three weeks patients were seen again and any change in symptoms or at sigmoidoscopy was noted. The sigmoidoscopic appearance was graded as follows:

Active disease: œdematous, friable mucosa.
Healing phase: drier, granular mucosa, only slightly friable.
Inactive disease: dry, granular mucosa, not friable, with or without vascular pattern.

When no apparent benefit resulted from the treatment in three weeks, it was considered a "failure" and the trial ended. A treatment beneficial during the first three weeks was continued in reduced dosage until full remission or maximum benefit was achieved, and then stopped. The results in these patients were assessed at three and six months after starting treatment and classed:

Success: remission began soon after starting treatment and maintained since.
Partial success: symptoms partially controlled or early improvement followed by a relapse.

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TABLE I.—COMPARABILITY OF THE THREE TREATMENT GROUPS

	No. of patients	Mean age	Males	Number in relapse	Symptoms		
					Diarrhœa, blood and mucus	No diarrhœa; blood and mucus	Diarrhœa only
Salazopyrin	20	38 (S.D. 16)	7	10	11	8	1
Prednisone	20	44 (S.D. 14)	8	12	13	7	0
Local hydrocortisone	20	45 (S.D. 17)	12	15	13	7	0

TABLE II.—PRELIMINARY RESULTS AT THREE AND SIX MONTHS

	3 months				6 months			
	Success	Partial success	Failure	Total	Success	Partial success	Failure	Total
Salazopyrin	8	5	5	18	6	4	5	15
Prednisone	6	5	4	15	5	5	4	14
Local hydrocortisone	2	3	12	17	1	1	11	13

The Patients in this Series (Table I)

60 consecutive patients who attended the Out-Patient Department at St. Mark's Hospital fulfilled the criteria described and have been admitted to the trial. They were divided into groups of 20 patients, each treated with one of the three remedies. Patients have been included in the trial once only. All were living normal lives and experienced little or no constitutional upset from their disease. We did not consider it justifiable to perform a new barium enema specially to define the extent of the disease at the time of the trial. Those patients who were seen for the first time had a barium enema when admitted to the trial; others had previously had a barium enema showing left-sided colitis.

Most complained of diarrhœa with the passage of blood and mucus, some had normal or constipated bowel actions but with blood and mucus, and one had diarrhœa only. Patients with these different symptoms were distributed evenly between the three groups (Table I).

The difference in age and sex distribution between the groups was small. In the hydrocortisone group more patients were treated for a relapse rather than for the first attack, than in the other two groups.

Results

At the moment we can only report preliminary results because the trial is still in progress and in some patients the data at three or six months are incomplete.

After three weeks' treatment the greatest proportion of patients free of symptoms was in the prednisone group and the lowest in the local hydrocortisone group (Fig. 1). The difference between these groups is such as would have occurred by chance only once in fifty times. 7 out of the 15 patients who told us that they

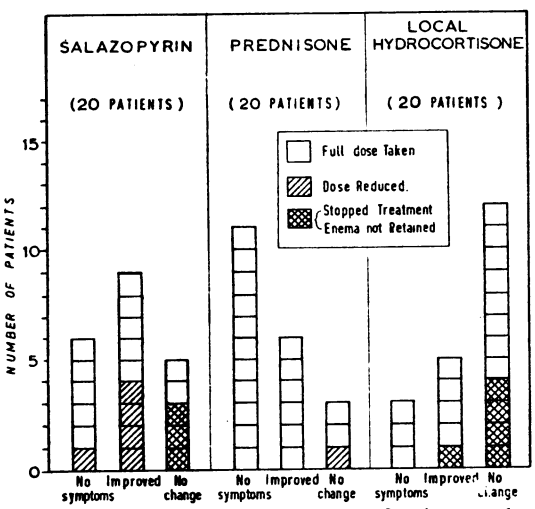

FIG. 1.—Symptoms after treatment for three weeks. There is a significant difference between the results in the prednisone and local hydrocortisone groups ($\chi^2_c = 7{\cdot}8$, n = 2, P = 0·02).

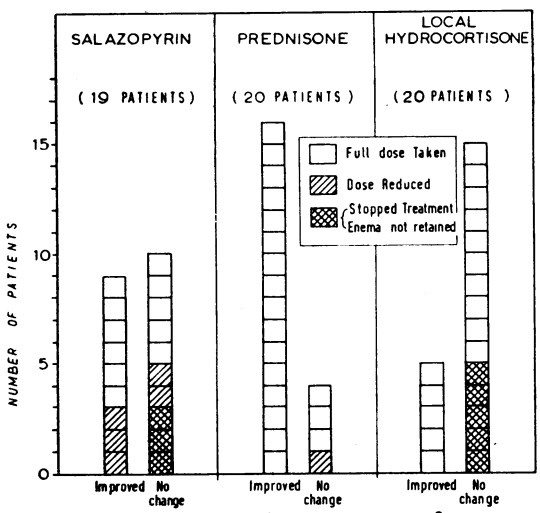

FIG. 2.—Sigmoidoscopic appearances after treatment for three weeks. There is a significant difference between the results in the prednisone and local hydrocortisone groups ($\chi^2_c = 10{\cdot}0$, n = 1, P = <0·01).

retained the hydrocortisone solution in the rectum more than two hours improved during the treatment. Objective assessment by sigmoidoscopy bears out the symptomatic changes (Fig. 2). Again, the best results followed prednisone and the worst local hydrocortisone; the difference between them would only have occurred by chance once in 100 times.

At three and six months our results so far show approximately equal results in the Salazopyrin and prednisone groups (Table II). This is because some of the patients, symptom free after three weeks' treatment with prednisone, have now relapsed. The relapse sometimes occurred as the dose of the drug was reduced and sometimes soon after stopping the treatment.

There is no doubt that most patients prefer prednisone to Salazopyrin. 6 of our patients given prednisone experienced mild side-effects and 1 reduced the dose on account of syncopal attacks. 1 patient complained of colic after the retention enemata. With Salazopyrin over half our patients complained of side-effects, usually anorexia, nausea or malaise. 3 patients (accounting for 3 out of the 5 failures) could not take the drug even in small doses, 5 others could take only a reduced amount (Fig. 1). Side-effects were more frequent among these patients than in most reported series, possibly due to the fact that our patients were feeling well and were thus conscious of mild malaise or digestive upsets. One on Salazopyrin developed a skin rash; we have not observed any hæmatological complications.

Discussion

The results presented support the contention that Salazopyrin is an effective remedy in ulcerative colitis. The response is slower than that to prednisone but at three and six months after starting treatment there is little to choose between them. Prednisone is the most effective for the immediate relief of symptoms but the relapse rate is high and corticosteroids are potentially dangerous. Salazopyrin frequently gives rise to unpleasant side-effects but dangerous complications are rare.

The elegant controlled trials of Truelove (1958*b*) and Watkinson (1958) have proved conclusively that local hydrocortisone enemata can be an effective remedy in the type of case we have treated. We do not think that our disappointing results can be attributed to the number treated in relapse, because the treatment failed in 4 out of 5 patients treated during a first attack (4 of whom retained the solution in the rectum all night). Neither can the failure be attributed to the extent of the disease, because in half the cases given this treatment a barium enema was normal or showed only minimal changes at the time of the treatment, and in 3 an upper limit to the disease could be seen on sigmoidoscopy. We think it most likely that the treatment often failed because a rather complex and inconvenient mode of administration was used under ordinary out-patient conditions. Our "failures" include 1 patient who did not give himself the treatment because of emotional aversion to it and 3 patients who completely failed to retain the enemata. Nearly half the patients who told us that they were able to retain the solution in the rectum for longer than two hours improved during the treatment.

Both Truelove and Watkinson took great care in demonstrating the technique of self-administration of the enemata to their patients; the latter admitted his patients to hospital for two to three days for this purpose. Our results suggest that out-patient explanation is not enough and that a practical demonstration, possibly in hospital, is needed for success. We think that retention enema treatment using a more convenient technique and a more stable drug, such as prednisolone 21-phosphate, is likely to give good results under out-patient conditions.

We suggest the following *out-patient regime for patients with left-sided colitis.* We emphasize that we are not including ill patients in hospital but only patients having little constitutional upset and living normal lives.

A. *Disease Extending Above the Rectum*

(1) Begin with *Salazopyrin* (convenient, moderately effective and safe).

(2) If this fails, use *local treatment* (retention enemata of hydrocortisone hemisuccinate or prednisolone 21-phosphate).

(3) If other treatments fail or a prompt response is specially needed use *prednisone* (the most effective drug of the three for rapid relief but potentially the most dangerous).

B. *Disease Confined to the Rectum*

Begin with suppositories of prednisolone 21-phosphate (Truelove, 1959; Lennard-Jones *et al.*, unpublished data).

Acknowledgment.—We wish to thank Glaxo Laboratories for supplying the hydrocortisone hemisuccinate sodium used in this trial.

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DISCUSSION

Dr. S. G. Flavell Matts (Bristol): I was interested that Dr. Lennard-Jones found the method of slow intrarectal infusion of hydrocortisone cumbersome and time consuming, and not very portable. It can also be difficult and time consuming to explain to the patient the method of setting up and administering it. In our experience of this therapy we have had satisfactory results, but have noted the drawbacks.

In view of these I have been trying to develop a simpler administration of intrarectal therapeutic solutions. A trial has just been completed of an alternative method of local therapy for ulcerative colitis.

This consists of a solution of a soluble prednisolone (prednisolone 21-phosphate) given in the form of a small retention enema, from a disposable plastic bag.

The patient gives this to himself every night on retiring to bed, the time taken being about five minutes. The solution is usually retained all night, and so far no technical difficulties have been encountered.

It is a method which particularly lends itself to out-patient work as the bags are portable and easy to dispense. The method of use can be explained to the patient in a few seconds.

The trial has been conducted in two parts: (1) A double blind trial employing sequential analysis to establish the value of the method. (2) Assessment on a larger number of patients. All had acute or relapsing ulcerative colitis, and were mainly out-patients. Admission to hospital was unnecessary in most cases.

The results were encouraging. Improvement was obtained in over 90%, sometimes rapidly and dramatically. If therapy is continued from four to eight weeks, a remission can usually be expected. The patients who responded best were those with fairly acute left-sided ulcerative colitis, but surprisingly good results have been obtained in the generalized disease.

The advantages of this method are numerous, particularly its simplicity, the time saved to patient and doctor and its ease for out-patient work; in suitable cases it may easily be combined with systemic therapy. The detailed results are published in the *Lancet*, together with an account of the technique (Matts, 1960).

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Irradiation Damage to the Bowel

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IRRADIATION damage to the bowel was the subject of a Hunterian Lecture in 1938 by Professor T. F. Todd of Manchester, but it does not appear to have been discussed at a meeting of this Section. Although it is a relatively uncommon lesion it can present the proctologist with a difficult problem.

The usual cause of irradiation damage to the bowel is treatment of carcinoma of the cervix by the conventional Stockholm radium method, but any external irradiation can act in a similar manner. Brick (1955) recorded damage to the stomach, small intestine and colon following supervoltage therapy to the abdomen. Bloom (1959) commented on the obvious advantages of supervoltage therapy for treating deep-seated tumours, but also spoke of the damage it can produce to other structures.

Conventionally, carcinoma of the cervix is treated by the insertion of a tube of radium into the uterus and packages of radium placed in the vaginal fornices. The dose is controlled by the time factor to give about 6,000 mg hours of irradiation, and may be followed by external irradiation to the parametria. If the radium slips or is in a bad position, an unexpected "high spot" of irradiation can occur to the rectum causing a localized area of overdosage.

All authors agree that there is a great deal of variation in the sensitivity of individual tissues to irradiation. Nevertheless, attempts to cure tumours by high dosage may achieve their object at the expense of damage to other structures.

At the Royal Marsden Hospital the insertion of the radium in these cases is checked by means of a scintillation probe dosimeter, which measures irradiation being received by the bladder and rectum. If a high dose of irradiation is given to the rectum the radium packages are readjusted. This control requires the support of a physics department; unfortunately few hospitals possess these facilities.

It is difficult to assess the incidence of rectal reactions, which must vary with techniques, stage of disease and age of the patient. Strickland (1954) recorded rectal damage in 2·4% of 501 cases treated in the years 1947 to 1952. Requarth and Roberts (1956) reported a similar incidence of 2·1% in the University of Illinois, but with a subsequent mortality of 33·3%; Wigby (1943) of Houston found that a colostomy was required in 7·9% of his cases.

Irradiation on the tissues produces initial œdema and congestion, with necrosis or hyaline degeneration. Endarteritis of the small vessels is a prominent feature, and necrosis, ulceration, fibrosis and stenosis of the bowel wall occur in varying degree, leading to fibrosis and stricture.

Todd (1938) classified the rectal reactions into