Electrical potentials of the sigmoid colon and rectum in irritable bowel syndrome and ulcerative colitis

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SUMMARY Using a simple and rapid method, electrical potential differences across rectal and colonic mucosa have been measured at routine sigmoidoscopy in patients with irritable bowel syndrome and ulcerative colitis. In patients with irritable bowel syndrome, all of whom had diarrhoea, the mucosa was charged negatively on the luminal side and potential differences were not significantly different from those of normal subjects. In acute exacerbations of ulcerative colitis, the potential difference was reversed, the luminal side being positive. This characteristic change was seen even in mild attacks. The potential difference was usually restored to normal within a few weeks of commencing treatment. In some cases, however, it was persistently abnormal for months and failed to show the normal response to stimulation by the mineralocorticoid, fludrocortisone. The way in which measurements of potential difference can be useful in diagnosis, prognosis, and as a guide to treatment is discussed.

The mucosal epithelium of human rectum and colon is electrically polarized, the lumen of the gut being charged negatively with respect to the serosal side in the normal condition (Edmonds and Godfrey, 1969; Geall, Spencer, and Phillips, 1969). Animal studies have indicated that the potential difference is generated mainly by the active transport of sodium ions from the luminal to the serosal side of the epithelium (Cooperstein and Hogben, 1959; Cofré and Crabbé, 1967; Edmonds and Marriott, 1968). This property represents what is probably the principal activity of the epithelium, since water absorption appears to depend on the active sodium absorption, and conservation of sodium and water is the most important function of the colon. It seemed likely, therefore, that measurement of the potential difference generated by colonic mucosa could prove a useful index of the functional integrity of the tissue. We recently introduced a method which allowed rapid measurement of the potential difference of the sigmoid colon and rectum to be made at routine sigmoidoscopy (Edmonds and

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Godfrey, 1969 and 1970), and the present paper reports the results obtained using the method to measure potential difference of the colon in patients with the irritable bowel syndrome or with ulcerative colitis.

Methods

Ten patients with diarrhoea and diagnosed as having irritable bowel syndrome and 18 patients having ulcerative colitis were studied. Diagnosis was based on the history and the results of stool examination, sigmoidoscopy, barium enema, and in many patients a rectal biopsy. The experimental nature of the procedure for measuring potential difference was explained to all subjects when permission was obtained for the test.

PROCEDURE OF MEASUREMENT

The technique for measuring potential difference was essentially similar to that described previously

(Edmonds and Godfrey, 1970) except that a portable transistorized millivoltmeter was used instead of a high input impedance electrometer, and the reference electrode modified. The reference electrode was strapped to the forearm after the skin had been cleaned with spirit and moistened with NaCl 150 mM. Sigmoidoscopy was done in the left lateral position and the appearances graded in the way described by Baron, Connell, and Lennard-Jones (1964). Grade I denoted normal appearances, grade II a non-friable mucosa without vascular pattern, grade III a friable mucosa which bled on contact, and grade IV denoted a mucosa which bled spontaneously. To measure potential difference the probe electrode (a Perspex tube about 30 cm long and 0.5 cm in diameter with a tip containing a silver screw coated with AgCl and embedded in NaCl 150 mM-agar 3%) was placed alternately on the perianal skin (skin potential difference) and on the mucosa (mucosal potential difference). What is referred to in the present paper as the rectal or colonic potential difference was given by:

Rectal (colonic) potential difference = mucosal potential difference—skin potential difference.

As the perianal skin is charged to the extent of a few mV, the present method slightly underestimates the true transmucosal potential difference.

The convention adopted in referring to mucosal charge is to give the polarity of the probe electrode. For example, in the normal state when the probe electrode is moved from the perianal skin to the mucosa, it becomes more negative and thus by the present convention the colonic potential difference of the normal subject is negative.

REFERENCE ELECTRODE AND MILLIVOLTMETER

Since the portable millivoltmeter was without 'backing-off' facility, the reference electrode differed from that previously used. It consisted of a silver screw coated with AgCl embedded in a jelly of NaCl 150 mM-agar 3% and contained in a small Perspex chamber. Thus the reversible electrode systems of the probe and reference electrode were similar and there was little asymmetry potential difference between them. A portable battery operated millivoltmeter was built for the present work as described by Edmonds and Cronquist (1970). It weighed only 1.1 kg and was considerably more convenient for use in out-patient clinics and wards than the valve-operated electrometer employed previously.

EFFECT OF FLUDROCORTISONE

In several patients, a test of the response to fludrocortisone acetate was made, 1 mg being given six-hourly for four doses, measurements of potential difference being made four to six hours after the last dose.

Results

IRRITABLE BOWEL SYNDROME

This group comprised six men and four women with an age range from 20 to 58 years. The condition had been present for between six months and a year in three patients and for between two and 12 years in the other seven. All these patients presented with episodes of diarrhoea generally lasting several months, the frequency of bowel action being from two to three times daily up to eight to 10 times daily. Usually the stools were simply unformed but four of the patients said that they often passed motions which were fluid. One patient had suffered repeated attacks of diarrhoea since having bacillary dysentery 12 years previously and at the time of examination passed fluid or unformed stools four to five times daily. Three patients noticed that mucus was usually passed with the stools and two had seen blood occasionally. Investigations showed an absence of known pathogens in the stools and no abnormality was seen on barium enema. Sigmoidoscopy showed no significant abnormality of the mucosa in any patient but in two some mucus and fluid were seen. The results of measurements of potential difference are shown in Figure 1. In

Fig. 1 Measurements of potential difference in 10 patients with irritable bowel syndrome (●) and in six patients during an acute exacerbation of ulcerative colitis (×). The values in the former patients are similar to those of normal subjects while in all patients with acute ulcerative colitis the potential difference is reversed, the luminal side being positive.

all patients the lumen was negatively charged and the range of values of potential difference (Table) was like that found in normal subjects by this method. Thus in this group of patients with diarrhoea, there was no evidence of any disturbance in the function of the mucosal epithelium at least as revealed by its electrical charge.

Condition	No. of Patients	Distance from Anus (cm)					
		12	10	8	6	4	2
No bowel disease ¹	28	22 ± 1.0	24 ± 1.2	27 ± 1.7	25 ± 1.7	26 ± 1.6	—
Irritable bowel syndrome	9	20 ± 2.3	23 ± 3.5	21 ± 3.4	21 ± 2.8	20 ± 3.3	22 ± 2.8
Ulcerative colitis (in remission)	4	19 ± 4.3	21 ± 4.4	19 ± 4.2	21 ± 5.1	21 ± 5.2	21 ± 5.6

Table Mean value of potential difference (mV) at various distances from the anus in patients with irritable bowel syndrome and ulcerative colitis in remission²

¹From data in Edmonds and Godfrey (1970).

²Results are given as means ± 1 standard error.

ULCERATIVE COLITIS

Patients with acute disease

Six patients were seen during a severe exacerbation, all being hospital inpatients. With the exception of one patient who was seen before treatment commenced, all were being treated with oral prednisolone and often with prednisolone enemas in addition at the time of examination. There was systemic disturbance with pyrexia and weight loss in all patients, and the disease affected the colon beyond the rectum. Sigmoidoscopy showed blood in the rectum, usually with some faecal material, and consequently measurements were limited. The appearances were grade IV (spontaneous mucosal bleeding; Baron *et al*, 1964). The potential difference measurements were all markedly abnormal. The polarity was reversed from the normal (Fig. 1), the mucosa being charged positively on its luminal side over the range + 8 to + 20 mV.

With remission of the disease, the potential difference usually reverted within two to five weeks to values similar to those found in normal subjects, the mucosa being negatively charged on the luminal side. The course will be illustrated by the events in one patient.

A 24-year old man had a history of intermittent attacks of weakness and diarrhoea with bleeding for 10 years. He had received several courses of systemic and topical steroids. He was first seen during an acute episode which had been present for about one week, and at this time was passing six to eight bloody motions daily. Barium enema revealed a total colitis sparing only the caecum. On sigmoidoscopy the rectum was seen to contain blood, and the mucosa was very friable and oozing blood (grade IV). The electrical polarity

was reversed, the potential differences being positive on the luminal side (Fig. 2). The patient was treated with oral prednisolone and prednisolone enemas twice daily. One week later, appearances at sigmoidoscopy had improved; the mucosa appeared granular and less fragile. The changes coincided with clinical improvement, bowel frequency being less (about 4-5 per day) and accompanied by less blood. Measurements of potential difference did not, however, show any significant change, the mucosa retaining the reversed polarity. However, over the next two weeks further clinical improvement was associated with gradual reversion of the potential differences to normal. By the twelfth week, about a month after discharge from hospital, he was well, passing formed motions two to three times daily without bleeding. He was still receiving oral prednisolone (20 mg daily) and prednisolone enemas once daily. Sigmoidoscopy showed a granular mucosa which was not fragile (grade II) and the measurements of potential difference were between 25 and 35 mV with the lumen negative.

In two patients, both with extensive involvement of the colon, the potential differences did not return to normal. One of these patients improved enough to be discharged after three weeks' admission. One month later, however, although he was fairly fit, the potential differences still remained reversed. Within eight months he suffered a severe relapse and died. The other patient showed no improvement with treatment, potential differences were persistently reversed, and colectomy was eventually performed about four weeks after the onset of the acute attack.

Patients examined after a recent acute episode

In eight patients measurements were made within a few weeks of the onset of an acute episode although not at the beginning of the attack. Thus when they were first investigated clinical improvement had already begun. Five of the patients were being treated with prednisolone by enema and by mouth, while two were having Salazopyrin only. Four of the patients were outpatients and, at the time that the measurements were first made, all their symptoms were mild. Most of the patients complained of increased frequency of bowel habit and softness of the stool though generally without macroscopic bleeding. Sigmoidoscopy showed grade II or grade III changes. In only two of these patients were potential difference measurements within the normal limit (Fig. 3). One of these had suffered a mild exacerbation, treated only by increasing the maintenance dose of Salazopyrin that she was taking from 2.0 to 4.0 g daily. She improved rapidly but was still passing unformed stools with a little blood occasionally at the time of examination. The measurements of potential difference were within the normal range but were low varying from - 2 to - 14 mV. The other patient in this group with normal values had also had only a mild acute attack three weeks earlier

Fig. 2 Recovery of potential difference after an acute exacerbation of ulcerative colitis. The first measurements were made during the second week of the acute attack, while the patient was taking oral prednisolone (initially 40 mg daily and by the twelfth week the dose had only been reduced to 20 mg daily). Prednisolone retention enemas twice daily were started during the fourth week and subsequently reduced to once daily. In these and in Figures 4 and 5, the measurements are given at intervals of 2 cm between 12 and 4 cm from the anus, the results being plotted from left to right.

Fig. 3 Measurements of potential difference in 12 patients with ulcerative colitis, including patients clinically in complete remission and at least four months after an acute attack (○) and patients who had suffered a recent acute exacerbation (×). Note that only two of the latter had a potential difference of normal polarity and that these two had almost fully recovered from mild attacks when the measurements were made.

and had been treated as an outpatient with prednisolone enemas and Salazopyrin. He had fully recovered by the time of examination and was passing two formed motions daily. Measurements of potential difference ranged from -12 to -20 mV and so were within the normal range but again lower than the average. In the other six patients the potential difference was reversed, the luminal side of the mucosa being positively charged (Fig. 3). The reversal of potential difference did not appear to depend on the severity of the initial episode, for in two patients the preceding attack was only mild yet the potential differences were reversed at the time of examination. Although the potential difference was usually found to become normal within a few weeks of commencing treatment, this was not invariably so. In two of the patients the potential difference remained reversed for a long period although they had only minor symptoms. This is illustrated by the course of one of these patients followed for over a year.

A 21-year-old man had noticed that for about two years blood and mucus were often passed with his stools. This had been attributed to haemorrhoids and it was not until he came to a

general medical clinic with symptoms of severe anaemia that ulcerative colitis was diagnosed. On treatment with prednisolone enemas for one month and Salazopyrin 4 g daily he improved considerably and rectal bleeding ceased. When he was first seen for measurements of potential difference four months later he said that he usually passed a formed stool once or twice a day but sometimes the stools were soft and occasionally he passed a little fluid with some mucus. His general health was excellent and no other bowel symptoms occurred during 1969; he continued to take Salazopyrin (1 g four times daily). Sigmoidoscopy at various times showed a moist mucosa without visible vascular pattern. The mucosa was not fragile and no blood was present although there was always a little fluid and some mucus in the rectum. All the measurements made in 1969 showed persistent reversal of the potential difference, the lumen being between 10 and 20 mV positive when compared with perianal skin (Fig. 4). In December 1969 he had a further course of prednisolone enemas, one being given and retained well each night. The measurements made at the end of the course showed that the electrical polarity of the mucosa had been restored to

Fig. 4 Prolonged reversal of potential difference in a patient with ulcerative colitis taking Salazopyrin (4 g daily) and with minor bowel symptoms. Potential difference did not revert to normal until he received a four-week course of prednisolone retention enemas (during weeks 55 to 58).

normal although the potential differences were low. There was some change in sigmoidoscopic appearance in that the mucosa now appeared dry. Further follow-up two months and four months after the course of enemas had finished showed that the potential differences were still of correct polarity.

The other patient, who had a 23-year history of ulcerative colitis affecting most of the colon, had suffered a fairly mild acute attack which was initially treated with prednisolone. When first seen for measurements, she was having Salazopyrin only. Throughout the period of follow up over several months, the potential difference remained persistently reversed although her general condition was good and bowel symptoms mild. This patient eventually had a total colectomy.

Patients with inactive disease

Four patients were studied when they were fit and claimed to be symptom free. All were taking maintenance Salazopyrin at the time of examination but no other therapy. In most of these patients bowel function appeared to be normal, and sigmoidoscopic appearances were either practically normal or showed only mild changes (grade II). Measurements of potential difference were within the normal range (Fig. 4) and there was no significant difference between the mean values of potential difference of normal subjects (previously studied), of the patients with irritable bowel syndrome, and of those having ulcerative colitis but apparently in complete clinical remis-

sion (Table). One of these patients subsequently suffered an acute exacerbation of ulcerative colitis and measurements were then completely abnormal, the polarity being reversed with the luminal side positive. The course in this patient is detailed in the next section.

Effect of fludrocortisone

In subjects with normal bowel, aldosterone administration produces a considerable rise in the colonic potential difference and fludrocortisone has a similar effect (Edmonds and Godfrey, 1969). It was of interest, therefore, to see whether a similar response was demonstrable in patients with disease of the colon, and some preliminary investigations were carried out in the course of the present study. Two of the patients with irritable bowel syndrome were given fludrocortisone and both responded in a manner similar to that of normal subjects, potential difference rising to values of between 50 and 60 mV. Four of the patients with ulcerative colitis were also given fludrocortisone. In two of these patients the potential differences were initially reversed, that is, the lumen was positive, although both had only minor symptoms and sigmoidoscopic changes at the time of the test. In both of these subjects fludrocortisone was completely without effect, no change in potential difference being observed at all. In the other two patients, both of whom had inactive disease and potential differences initially within the normal range, fludrocortisone produced a rise in potential difference to between 40 and

Fig. 5 Effect of fludrocortisone while a patient with ulcerative colitis was in complete remission and during and following an acute exacerbation. He was taking Salazopyrin throughout and had a short course of oral prednisolone and prednisolone enemas at the time of the acute attack. This patient was first examined in remission. The zero of the time scale corresponds to his previous acute attack.

50 mV. One of these patients was studied on several occasions both when he was in complete clinical remission and during an acute exacerbation.

A postgraduate student of 26 years was first investigated 14 months after an attack of ulcerative colitis. This episode had responded rapidly to a four-week course of oral prednisolone and when first seen for measurements he had been symptom-free for more than one year maintained on Salazopyrin (2 g daily). Measurements of potential difference made initially and six months later were normal and fludrocortisone produced a rise in potential difference (Fig. 5). Thirteen months after the first measurements, he had an episode with acute onset of diarrhoea. He passed soft stools with some mucus but no blood three to four times daily. When he presented five days after the onset, sigmoidoscopy showed a rectum containing a little fluid with mucus but no blood; the mucosa was moist but not fragile. The potential difference was reversed over the whole region examined and fludrocortisone now produced no change (Fig. 5). He was given oral prednisolone (40 mg daily) but the diarrhoea worsened at first and he began to pass some blood. However, this state continued for less than two days and he then improved rapidly. One week after the initial set of measurements taken during this attack, he was passing a semisolid stool once or twice daily. The potential difference was, however, still reversed, though to a somewhat lesser extent. Oral prednisolone dosage was reduced and prednisolone retention enemas were given. Ten days later the potential differences had reverted to low normal level but there was still no evidence of a rise in potential difference after fludrocortisone was given. These observations suggest that impairment of the response to fludrocortisone may be present even when the unstimulated potential difference is within the normal range, probably indicating persisting damage to the epithelial cells.

Discussion

The method of measuring the rectal and sigmoid potential differences employed in the present study has the advantages of simplicity and rapidity, yet the discomfort to the patient is not greater than that of sigmoidoscopy alone. The technique can, therefore, be used easily in a clinic involved in the routine follow up of patients. It has the disadvantage that the true transmucosal potential difference is slightly underestimated owing to the small charge present across perianal skin (Edmonds and Godfrey, 1970). To measure true transmucosal potential difference the placing of a reference electrode intravenously is probably the best practicable method since this has been shown to be equivalent to placing the reference electrode directly on the serosal side of the epithelium

(Edmonds, 1967; Geall, Code, McIlrath, and Summerskill, 1970). Such a procedure does, however, complicate and prolong the measurements and is considerably more uncomfortable for the patient. It is doubtful whether it could be developed as a routine procedure and, since colonic potential differences are relatively large, the small contribution due to the perianal skin charge is of little importance in the practical clinical situation.

Considerable changes in potential difference were observed in some patients in the present study and the question arises as to what such changes mean. As outlined in the introduction, the potential difference of the colon appears to be generated mainly by active transport of sodium ions from the lumen towards the blood side of the epithelium. It can be regarded as largely resulting from the flow of electric current (ionic movements) through an electrical resistance (membranes having limited ionic permeability). Changes in potential difference could reflect changes either in active transport of ions or in permeability. Thus the reversed potential difference seen in some colitics may mean either that the epithelial cells have lost the ability to transport sodium actively or that the membranes have become so permeable that active ion transport produces little effect on the potential difference. Possibly both factors are involved. The fact that the potential difference actually reverses rather than becomes zero may in part at least be a consequence of the technique. There is a small electrical charge on the perianal skin, the skin surface being negative with respect to the subcutaneous tissue (Edmonds and Godfrey, 1970). This means that when there is zero charge on the mucosa, with the present method the probe would indicate about 5 to 15 mV positive.

The potential differences measured in patients with irritable bowel syndrome were similar to those found in normal subjects, presumably indicating normal epithelial function as regards sodium transport. Several of these patients had quite severe diarrhoea so that it seems that diarrhoea itself is not responsible for a fall in potential difference. The loss of the normal potential difference in active ulcerative colitis, when there is much spontaneous bleeding and loss of epithelium, is not surprising. In many patients, however, the potential difference was reversed even when there was no bleeding or fragility and when the epithelium must, therefore, have been intact. In these patients this presumably indicated that the epithelial cells were damaged in some way by the disease process so as to lose their ability to transport sodium actively. This would be consistent with evidence obtained from perfusion studies indicating that sodium absorption is reduced when the bowel is affected by the disease (Duthie, Watts, de Dombal, and Goligher, 1964; Harris and Shields, 1970). Damage to the sodium absorption mechanism impairs water absorption and so is probably an important factor

in diarrhoea production. With treatment, the potential difference usually returned towards normal, some times within two weeks of the onset of the acute episode. However, it was evident that many patients still had no return of potential difference even after several weeks of treatment and despite considerable clinical improvement. When the potential difference was reversed, the attempt to stimulate sodium transport by fludrocortisone was unsuccessful, although when the colitis had been in prolonged remission and the mucosa was normally charged, the response to fludrocortisone was restored.

The present results suggested several ways in which measurements of potential difference could be helpful. The method provides in the first place an objective index to add to the subjective visual impression obtained at sigmoidoscopy. It seems likely that loss or reversal of potential difference, although possibly not specific for ulcerative colitis, does indicate the presence of an active process damaging the epithelium. This could be of diagnostic value and could also assist in the assessment of the efficacy of treatment. For example, the persistent reversal of potential difference, or possibly a low potential difference with poor response to fludrocortisone, indicates continuing activity and hence probably the need to use treatment more effective than Salazopyrin alone. The present results also suggested that the combination of extensive colitis with persistent reversal of potential difference despite full treatment was particularly ominous. Of the three patients who had this combination, two came to colectomy and one died.

In conclusion, using a simple technique it is possible to show that in ulcerative colitis considerable alterations occur in the electrical charge on the bowel wall. The present results show that measurement of mucosal potential difference is possible as a routine procedure and may be of

value in diagnosis, prognosis, and as a guide to treatment.

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References

- Baron, J. H., Connell, A. M., and Lennard-Jones, J. E. (1964). Variation between observers in describing mucosal appearances in proctocolitis. *Brit. med. J.*, **1**, 89-93.
- Cofré, G., and Crabbé, J. (1967). Active sodium transport by the colon of *Bufo marinus*: stimulation by aldosterone and antidiuretic hormone. *J. Physiol. (Lond.)*, **188**, 177-190.
- Cooperstein, I. L., and Hogben, C. A. M. (1959). Ionic transfer across the isolated frog large intestine. *J. gen. Physiol.*, **42**, 461-473.
- Duthie, H. L., Watts, J. M., de Dombal, F. T., and Goligher, J. C. (1964). Serum electrolytes and colonic transfer of water and electrolytes in chronic ulcerative colitis. *Gastroenterology*, **47**, 525-530.
- Edmonds, C. J. (1967). The gradient of electrical potential difference and of sodium and potassium of the gut contents along the caecum and colon of normal and sodium-depleted rats. *J. Physiol. (Lond.)*, **193**, 571-588.
- Edmonds, C. J., and Cronquist, A. (1970). A simple millivoltmeter and electrodes for measurement of rectal electrical potential in man. *Med. Biol. Engng.* (In press.)
- Edmonds, C. J., and Godfrey, R. (1969). Transmucosal electrical potentials of human rectum and pelvic colon. *Gut*, **10**, 1044.
- Edmonds, C. J., and Godfrey, R. (1970). Measurement of electrical potentials of human rectum and pelvic colon in normal and aldosterone treated subjects. *Gut*, **11**, 330-337.
- Edmonds, C. J., and Marriott, J. (1968). Electrical potential and short circuit current of an in vitro preparation of rat colon mucosa. *J. Physiol. (Lond.)*, **194**, 479-494.
- Geall, M. G., Code, C. F., McIlrath, D. C., and Summerskill, W. H. J. (1970). Measurement of gastrointestinal transmural electrical potential difference in man. *Gut*, **11**, 34-37.
- Geall, M. G., Spencer, R. J., and Phillips, S. F. (1969). Transmural electrical potential difference of the human colon. *Gut*, **10**, 921-923.
- Harris, J., and Shields, R. (1970). Absorption and secretion of water and electrolytes by the intact human colon in diffuse untreated proctocolitis. *Gut*, **11**, 27-33.