*Brit. J. Psychiat.* (1975), 127, 144–8

# The Potential Difference Across the Rectal Mucosa During Depressive Illness and Lithium Therapy

By MALCOLM PEET

**Summary.** The potential difference across the rectal mucosa (rectal p.d.) is generated by the active transport of sodium across the mucosa, and it is sensitive to the action of aldosterone. The rectal p.d. values of depressive patients on no treatment, tested whilst depressed or after recovery, were found to be similar to those of control subjects, indicating that sodium transport across the rectal mucosa and the activity of aldosterone were normal in these patients. This contrasts with previous reports of abnormalities of sodium transport and of aldosterone levels in manic-depressive patients. Manic-depressive patients taking lithium carbonate as a prophylactic agent were found to have significantly elevated rectal p.d. values when normothymic. Patients who had become depressed whilst taking lithium, and in whom prophylaxis had therefore failed, were found to have normal rectal p.d. values. Lack of elevation of rectal p.d. in response to lithium administration may be a characteristic of patients who fail to respond to lithium prophylaxis.

## Introduction

There is evidence of reduced sodium transport across certain membranes in patients with depressive illness. Thus, there are reports of diminished transport of sodium from blood to cerebrospinal fluid (Coppen, 1960; Carroll, 1972) and across parotid gland duct walls (Glen *et al.*, 1968) in depressive patients. An increase in erythrocyte Na-K ATPase on recovery from depression has also been reported (Naylor *et al.*, 1973).

Lithium salts are effective in the treatment of mania (Stokes *et al.*, 1971) and in the prophylaxis of recurrent affective illness (Coppen *et al.*, 1971). They may also have an antidepressant effect (Mendels *et al.*, 1972). There is evidence that lithium increases sodium transport across erythrocyte membranes *in vitro* (Glen *et al.*, 1972) and across the rectal mucosa *in vivo* (Rask-Madsen *et al.*, 1972).

The human rectal mucosa is normally polarized, the luminal side being negative with respect to the serosal side. The rectal transmucosal potential difference (rectal p.d.) is generated by the active transport of sodium from the lumen to the blood (Archampong and Edmonds, 1972). Measurement of the rectal p.d. thus provides a convenient method of assessing sodium transport in this organ.

In the present investigation the rectal p.d. of patients with depressive illness and of lithium-treated patients is compared with that of a group of control subjects.

## Subjects

1. *Depressive patients*

Patients with depressive illness characterized by such features as depression, diurnal variation of mood, loss of appetite and libido, early morning waking, self-blame, and diminished energy, interest and concentration, were tested following admission to hospital. Patients in hospital who had recovered from depressive illness were also tested. No patient was taking drugs other than night sedation (nitrazepam 5–10 mg. or ethchlorvynol 250–500 mg.) at the time

of testing. The degree of depression was assessed using the self-rating depression inventory (D.I.) devised by Beck *et al.*, (1961).

2. *Lithium-treated patients*

Patients with recurrent affective illness who were taking lithium carbonate (Priadel, Delandale Laboratories) as a prophylactic agent were also tested. The patients, who were all in good physical health, had a history of at least two previous episodes of depression or mania, and had been taking lithium for at least one month. Six patients were also taking night sedation (ethchlorvynol 250–500 mg. or nitrazepam 5–10 mg.), two patients were taking diazepam 5 mg. thrice daily, and one patient was taking thyroxine in a replacement dose. Subjects taking other medication were excluded. The measurements were usually made during a routine visit to a lithium clinic, at which time plasma lithium levels were also determined. A small number of patients were tested following admission to hospital. No patient was manic when tested. The degree of depression was rated on the D.I., and by a psychiatrist's clinical rating on a 0–3 scale as normal, mildly depressed, moderately depressed or severely depressed. The patients were divided into a depressed group (D.I. $>10$ and/or clinical rating $>1$) and a normothymic group.

3. *Control subjects*

The control subjects were surgical in-patients and out-patients who had no history of psychiatric illness and who were taking no drugs. The subjects had no organic bowel disease or other physical illness likely to affect rectal p.d.

Informed consent was obtained in all cases prior to testing.

## Methods

The method used to construct the electrodes and to measure the rectal p.d. was based on that described by Edmonds and his colleagues (Edmonds and Godfrey, 1970; Archampong and Edmonds, 1972).

The probe electrode consisted of a narrow perspex tube, the tip of which was filled with agar (4 per cent in normal saline) in contact with a silver screw coated with silver chloride. The reference electrode was a cylinder of perspex, 2·5 cm. in diameter and 1 cm. deep, with a hole through the centre which was also filled with agar in contact with a silver screw coated with silver chloride.

With the subject lying on his side, 10 c.c. of normal saline was introduced into the rectum, using narrow polythene tubing connected to a syringe. The saline facilitated electrical contact between the mucosa and the probe electrode. Normal saline was then injected intradermally into the uppermost thigh, to raise a bleb. This procedure abolishes the small p.d. normally present across the skin and thus renders the skin surface equipotential with the serosa (Archampong and Edmonds, 1972).

The reference electrode was strapped to the thigh over the injection site, and the probe electrode was introduced 8 cm. into the rectum. The electrodes were connected to a portable battery-operated millivoltmeter (Comark Electronics Limited, Littlehampton, England). When the reading was stable it was recorded and the probe electrode was removed. Three readings of rectal p.d. were made on each occasion and the mean taken. Between measurements the electrodes were kept moist with normal saline. Before each measurement, the electrodes were placed together in a beaker of normal saline and the asymmetrical potential difference was recorded. The observed value of the rectal p.d. was corrected for this.

## Results

The characteristics of the patients are shown in Table I, and the rectal p.d. values for each group are shown in Fig. 1. The control subjects

Table I

*Sex, age, and D.I.'scores of depressive and lithium-treated patients and control subjects*

| Group | N | Sex | | Age (yrs.) | | Beck D.I. | |
|---|---|---|---|---|---|---|---|
| | | M | F | Mean | S.E. | Mean | S.E. |
| Controls .. .. .. | 11 | 7 | 4 | 48·6 | 3·6 | — | — |
| Depressed patients .. .. | 16 | 2 | 14 | 57·2 | 3·7 | 21·8 | 1·9 |
| Recovered depressives .. | 7 | 2 | 5 | 49·7 | 4·2 | 4·14 | 1·10 |
| Lithium-treated patients (normothymic) .. .. | 22 | 5 | 17 | 52·2 | 1·8 | 2·7 | 0·6 |
| Lithium-treated patients (depressed) .. .. | 9 | 3 | 6 | 52·4 | 2·4 | 14·2 | 2·0 |

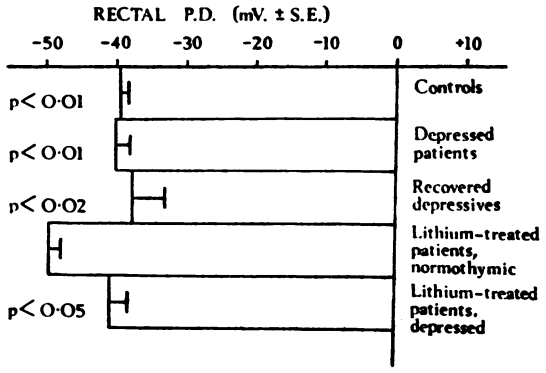


FIG. 1.—Rectal p.d. values for each group of patients. Probability values refer to the differences between each group and the normothymic lithium-treated patients.

are somewhat younger than the psychiatric patients, but the difference in age does not reach statistical significance. The rectal p.d. of the control subjects was 39±5 (S.D.) mV. This is comparable with the value of 40±7 mV reported by Archampong and Edmonds (1972). The patients tested during a depressive episode, the recovered depressives, and the control subjects all have similar rectal p.d. values.

The normothymic lithium-treated patients have a significantly higher mean rectal p.d. than the control subjects, the depressed patients and the recovered depressives. However, the mean rectal p.d. of the depressed lithium-treated patients does not significantly differ from that of the control subjects and is significantly lower than that of the normothymic group of lithium-treated patients.

The mean plasma lithium level of the normothymic lithium-treated patients (0·84 mEq./l.) does not significantly differ from that of the depressed lithium-treated patients (0·85 mEq./l.).

## DISCUSSION

The rectal p.d. of the untreated depressive patients, tested whilst depressed or after recovery, was similar to that of the normal control subjects. The results do not indicate any abnormality in sodium transport across the rectal mucosa in patients with depressive illness. This finding contrasts with the reduction in sodium transport which has been reported in other organs of depressive patients (Glen *et al.*, 1968; Coppen, 1960; Carroll, 1972).

The rectal p.d. is aldosterone-sensitive. Thus, there is a strong positive correlation between rectal p.d. and plasma levels of endogenous or intravenously administered aldosterone (Beevers, 1973; Efstratopoulos *et al.*, 1974). Measurement of the rectal p.d. has been suggested as a screening test for hyperaldosteronism, in which the rectal p.d. is often greater than −60 mV (Edmonds and Richards, 1970; *Lancet*, 1973). Also, Edmonds (1974) found that administration of the aldosterone antagonist spironolactone in a dose of 300 mg. daily for six weeks resulted in a mean fall in rectal p.d. of 8 mV, in a group of 21 hypertensive patients with previously normal rectal p.d. values. Falls in rectal p.d. of 5–10 mV were also recorded in three normal subjects following the administration of spironolactone (Edmonds, 1974).

There are reports of marked fluctuations in urinary aldosterone excretion (Jenner *et al.*, 1967) and aldosterone production rate (Allsopp *et al.*, 1972) associated with mood change in patients with short-cycle bipolar affective illness. However, the present finding of a normal rectal p.d. in depressive patients indicates that there was no significant abnormality of aldosterone activity in these patients.

The elevation of rectal p.d. in the normothymic lithium-treated patients is similar to that reported by Rask-Madsen *et al.* (1972). The present finding that the rectal p.d. of the normothymic lithium-treated patients was significantly higher than that of the recovered depressives on no treatment demonstrates that the elevation of rectal p.d. is an effect of lithium rather than a characteristic of patients who have recovered from an affective illness.

The mechanism by which lithium produces an elevated rectal p.d. is not clear. Increased urinary aldosterone excretion occurs at the start of lithium therapy (Murphy *et al.*, 1969). This appears to fall back to normal within seven days. Since the present group of patients had been taking lithium for at least one month, it is unlikely that the elevation of rectal p.d. was mediated by aldosterone. Vasopressin reduces sodium and water transport by the human colon

(Levitan and Mauer, 1968). Vasopressin-resistant polyuria is a recognized side-effect of lithium (Forrest *et al.*, 1974). It is therefore possible that lithium could inhibit the action of vasopressin on the colon, leading to increased sodium transport across the colonic mucosa. It has also been reported that erythrocyte Na-K ATPase activity is raised following the administration of lithium (Naylor *et al.*, 1974) and this could reflect a similar process in the rectal mucosa.

The depressed lithium-treated patients did not have elevated rectal p.d. values. These patients had all become depressed whilst taking lithium, and a normal affective state as assessed by the D.I. and the psychiatrist's rating had been recorded on previous visits to the lithium clinic. Lithium prophylaxis had therefore failed in these patients. It is possible that the rectal p.d. of these patients was raised by lithium before they became depressed, and that the onset of a depressive episode resulted in a reduction of rectal p.d. However, we have seen in the untreated patient that depression in itself is not associated with a reduction in rectal p.d. It is therefore unlikely that the occurrence of a depressive episode would lead to such a marked reduction of rectal p.d. in the lithium-treated patients. It seems more likely that lithium had failed to raise the rectal p.d. of these patients even before they became depressed. Lack of elevation of rectal p.d. in response to lithium administration may thus be a characteristic of patients who fail to respond to lithium prophylaxis.

### Acknowledgements

This work was carried out whilst the author was employed in the M.R.C. Neuropsychiatry Unit, West Park Hospital, Epsom, Surrey. Thanks are due to Dr. A. Coppen, who suggested the study, Dr. C. J. Edmonds for providing electrodes and advice on the method of measuring rectal p.d., and Mr. R. S. Taylor and Mr. J. A. Southam for allowing control measurements to be made on patients under their care.

### References

Allsopp, M. N. E., Levell, M. J., Stitch, S. R. & Hullin, R. P. (1972) Aldosterone production rates in manic-depressive psychosis. *British Journal of Psychiatry*, **120**, 399–404.

Archampong, E. Q. & Edmonds, C. J. (1972) Effect of luminal ions on the transepithelial electrical potential difference of human colon. *Gut*, **13**, 559–65.

Beck, A. J., Ward, C. H., Mendelson, M., Mock, J. & Erbaugh, J. (1961) An inventory for measuring depression. *Archives of General Psychiatry*, **4**, 561–71.

Beevers, D. G. (1973) Mineralocorticoids and rectal potential difference. *Lancet*, *ii*, 682–3.

Carroll, B. J. (1972) Sodium and potassium transfer to cerebrospinal fluid in severe depression. In *Depressive Illness* (eds. Brian Davies, Bernard J. Carroll, and Robert M. Mowbray), pp. 247–57.

Coppen, A. J. (1960) Abnormality of the blood-cerebro-spinal fluid barrier of patients suffering from a depressive illness. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 156–61.

Coppen, A., Noguera, R., Bailey, J., Burns, B. H., Swani, M. S., Hare, E. H., Gardner, R. & Maggs, R. (1971) Prophylactic lithium in affective disorders. *Lancet*, *ii*, 275–9.

Edmonds, C. J. & Godfrey, R. C. (1970) Measurement of electrical potentials of the human rectum and pelvic colon in normal and aldosterone-treated patients. *Gut*, **11**, 330–7.

—— & Richards, P. (1970) Measurement of rectal electrical potential difference as an instant screening test for hyperaldosteronism. *Lancet*, *ii*, 624–7.

—— (1974) Personal communication.

Efstratopoulos, A. D., Peart, W. S. & Wilson, G. A. (1974) The effect of aldosterone on colonic potential difference and renal electrolyte excretion in normal man. *Clinical Science and Molecular Medicine*, **46**, 489–99.

Forrest, J. N., Cohen, A. D., Torretti, J., Himmelhoch, J. M. & Epstein, F. H. (1974) On the mechanism of lithium-induced diabetes insipidus in man and rat. *Journal of Clinical Investigation*, **53**, 1115–23.

Glen, A. I. M., Bradbury, M. N. B. & Wilson, J. (1972) Stimulation of the sodium pump in the red blood cell by lithium and potassium. *Nature* (*London*), **239**, 339–401.

—— Ongley, G. C. & Robinson, K. (1968) Diminished membrane transport in manic-depressive psychosis and recurrent depression. *Lancet*, *ii*, 241–3.

Jenner, F., Gjessing, L., Cox, J., Davies-Jones, A., Hullin, R. P. & Hanna, S. (1967) A manic-depressive psychotic with a persistent forty-eight hour cycle. *British Journal of Psychiatry*, **113**, 895–910.

Lancet (1973) Leading article. Potential difference of gut epithelia. *ii*, 424–5.

Levitan, R. & Mauer, I. (1968) Effect of intravenous antidiuretic hormone administration on salt and water absorption from the human colon. *Journal of Laboratory and Clinical Medicine*, **72**, 739–46.

Mendels, J., Secunda, S. K. & Dyson, W. L. (1972) A controlled study of the antidepressant effects of lithium carbonate. *Archives of General Psychiatry*, **26**, 154–7.

Murphy, D. L., Goodwin, F. K. & Bunney, W. E. (1969) Aldosterone and sodium response to lithium administration in man. *Lancet*, *ii*, 458–61.

NAYLOR, G. J., DICK, D. A. T., DICK, E. G., LE POIDEVIN, D. & WHYTE, S. F. (1973) Erythrocyte membrane cation carrier in depressive illness. *Psychological Medicine*, **3**, 502–8.

—— —— —— & MOODY, J. P. (1974) Lithium therapy and erythrocyte membrane cation carrier. *Psychopharmacologia* (Berlin), **37**, 81–6.

RASK-MADSEN, J., BAASTRUP, P. C. & SCHWARTZ, M. (1972) Lithium-induced hyperpolarisation of the human rectum *in vivo*. *British Medical Journal*, *i*, 496–7.

STOKES, P. E., STOLL, P. M., SHAMOIAN, C. A. & PATTON, M. J. (1971) Efficacy of lithium as acute treatment of manic-depressive illness. *Lancet*, *i*, 1319–25.

Malcolm Peet, M.B., Ch.B., B.Sc., M.R.C.Psych., *Senior Registrar, Royal Dundee Liff Hospital, by Dundee Scotland; Honorary Lecturer in Clinical Psychiatry, University of Dundee*

(*Received 23 October 1974*)