The role of the colon in the pathogenesis of hyperchloraemic acidosis in ureterosigmoid anastomosis

J. B. McConnell, J. Murison and W. K. Stewart
The Renal Unit and Department of Medicine, Ninewells Hospital and Medical School, Dundee, Scotland, U.K.

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Summary
1. The composition of urine–faeces mixture in seven patients with ureterosigmoid anastomosis has been studied by a dialysis in vivo method using cellulose bags. Urine–faeces dialysate obtained from these patients contained much greater amounts of both bicarbonate and total ammonia than has been reported for faecal dialysate in normal subjects.
2. Total ammonia concentrations in urine–faeces specimens obtained by catheter suggest that urine excreted by the kidneys in these patients becomes increasingly acid with increasing systemic acidosis. The highly alkaline nature of urine–faeces mixtures, especially in acidic patients, indicates rapid alkalinization of the mixture in the colon. It appears that colonic secretion of bicarbonate is a direct consequence of the acidity of urine excreted by the kidney and draining into the colon.
3. The study suggests that the development of hyperchloraemic acidosis in patients with ureterosigmoid anastomosis is due to bicarbonate secretion by the colonic mucosa, with concomitant chloride absorption. With the development of metabolic acidosis, rapid alkalinization of the urine still occurs in the colon, but during further retention of the urine–faeces in the colon some reabsorption of bicarbonate occurs, probably in part by ionic diffusion since chloride concentration in the lumen increases.
4. Evidence suggestive of non-ionic diffusion of ammonia was found in only one patient. It seems probable that higher rates of urea breakdown in other patients mask the expected relationship between total ammonia and bicarbonate.

Key words: acidosis, ammonia, bicarbonate, colon, secretion, urea, ureterosigmoid anastomosis.

Introduction
Ureterosigmoid anastomosis is still used for urinary diversion though its popularity has declined in the past two decades. This followed reports of its biochemical complications, systemic acidosis, hyperchloraemia and hypokalaemia (Ferris & Odel, 1950), and the introduction of the ileal conduit as an alternative procedure (Bricker, 1950). Although these biochemical complications have caused the operation to fall from favour, they can usually be minimized with appropriate therapy (Fowler & Wilson, 1973; McConnell & Stewart, 1975). Oral therapy with alkali, 90–150 mmol/day, maintains these patients in normal acid–base balance.

In untreated patients, the incidence of hyperchloraemic acidosis has varied from series to series but usually has been reported at over 60% (Ferris & Odel, 1950; Jacobs & Stirling, 1952; Jacobs, 1967) and has even been reported in 100% of patients in one series (Megalli & Lattimer, 1973). Patients with minor degrees of acidosis may remain asymptomatic, but are liable to develop severe acidosis with hypokalaemia, usually during an intercurrent infection.
The pathogenesis of the hyperchloraemic acidosis remains uncertain. Several mechanisms have been proposed, and these can basically be divided into those which consider the primary factor to be either (a) renal tubular dysfunction or (b) intestinal absorption of ions from the urine–faeces mixture.

The rate of development and severity of acidosis in experimental animals is related to the area of colonic mucosa exposed to urine (Irvine, Allan & Webster, 1956; Hayward, Wakim, Remine & Grindlay, 1961a). This is supported in man by the infrequency of electrolyte disturbances in patients with rectosigmoid bladders (Ghoneim, 1970). The infrequency of electrolyte disturbances in patients with anal incontinence. Unless renal function is greatly impaired, the kidney itself does not seem to contribute to the imbalance of electrolytes (Hayward, Wakim, Remine & Grindlay, 1961b). Accordingly the inference from circumstantial evidence is that colonic function is of prime importance in the development of hyperchloraemic acidosis. Selective intestinal absorption of chloride and urea was originally suggested by Ferris & Odel (1950) as being the main factor. However, understanding of intestinal mucosal physiology has advanced considerably since then.

The technique of dialysis in vivo of stool juice, with cellulose bags containing an oncotic solution (Wrong, Metcalfe-Gibson, Morrison, Ng & Howard, 1965), has clarified some features of colonic function. These include confirmation of passive non-ionic diffusion of ammonia, which is facilitated by colonic secretion of bicarbonate (Down, Agostini, Murison & Wrong, 1972). With this method we have examined bicarbonate, chloride, ammonia and urea concentrations in the urine–faeces mixture of patients with ureterosigmoid anastomosis.

Methods

Patients and clinical methods

Seven patients (ages 21–80 years), who had undergone ureterosigmoid anastomosis between 1 and 38 years before testing, agreed after full explanation to participate in the investigation. Two patients had hyperchloraemic acidosis (plasma bicarbonate < 20 mmol/l), one never had received alkali therapy, and the other omitted his usual therapy for 4 days before testing. These patients have been termed acidic (patients not taking alkali orally, plasma bicarbonate < 20 mmol/l and plasma chloride > 108 mmol/l). A third patient, also acidic, was investigated while receiving a broad-spectrum mixture of antibiotics (benzylpenicillin, lincomycin and gentamicin) for pyelonephritis. This patient (after stopping all antibiotics for 1 month), one of the first two patients and four others were also tested when receiving regular alkali therapy and in normal acid–base balance. These have been termed treated patients. Specimens from the patients were obtained in two ways.

(a) Dialysate bags containing 10% dextran were prepared as described by Wrong et al. (1965). Those for testing in vivo were enclosed in gelatin capsules, and each patient took 10–20 orally over a 48 h period. The bags were recovered by immediate examination of all urine–faeces mixture passed. Patients evacuated their colon as frequently as they needed. The time interval between the previous bowel action and the voiding in which the bag was recovered was recorded and referred to as the retention time. It has been assumed that when expelled the dialysate bag contents had equilibrated with the accumulating urine–faeces mixture held in the colon during this period. These samples have been termed ‘retention’ specimens.

(b) Six patients (two acidotic, four treated) also provided ‘catheter’ specimens, obtained by passing a rectal catheter immediately after a bowel action, and collecting under oil in a closed system the first 30–50 ml of mixture passed through the catheter. Dialysate bags were added immediately, allowed to equilibrate in vitro at room temperature with the mixture and removed at various intervals from 1 h to 30 h. Since Wrong et al. (1965) found that equilibration in vitro between bag contents and the surrounding medium occurs in 1 h, bags removed 1–4 h after immersion (‘early catheter’ specimens) were considered to reflect, though not equate with, the diffusible solute content of the urine–faeces obtained by catheter, which had passed over the lower colonic mucosa but not been retained.

On recovery or removal of dialysate bags from the urine–faeces they were immediately opened under oil and pH, total CO₂, ammonia, chloride and urea concentrations measured.

Analytical methods

Urea and ammonia concentrations of dialysis bag fluid were estimated by a micro-diffusion method (Conway, 1962), pH was measured by glass electrode under anaerobic conditions at 37°C. Total CO₂ content was estimated by using
the Harlem CO₂ apparatus, based on the Van Slyke CO₂ determination. When compared directly with the Van Slyke method, this consistently underestimated the total CO₂ content by 11.0 ± 3.4% (mean ± SD). Bicarbonate concentration and CO₂ tension were calculated from measured total CO₂ content by the Henderson–Hasselbalch equation. Chloride was measured by a titrimetric method with mercuric nitrate (Schales & Schales, 1941). Blood gases were measured by using the IL 313 pH/Blood Gas Analyser.

Calculations

The composition of retained specimens with retention times of 1–4 h has been compared in acidic and treated patients, as have ‘early catheter’ specimens in these two patient groups. ‘Early catheter’ and ‘retention’ specimens with retention times of 1–4 h have also been compared, since both types of specimens had been in contact with urine–faeces for similar periods. ‘Early catheter’ specimens had only briefly been in contact with the colonic mucosa and ‘retention’ specimens had been in contact for the total period. The higher incubation temperature in the colon was expected to increase bicarbonate and total ammonia concentrations in ‘retention’ specimens by increased urea hydrolysis, so that differences not explicable by the different incubation conditions have been related to changes effected by the colonic mucosa during retention. ‘Retention’ specimens with retention times of more than 45 min have been included in all other statistical assessments not involving comparison with ‘early catheter’ specimens, since bags passing with the intestinal contents would have been equilibrating gradually during their passage along the intestine and so would require less equilibration time in the distal colon. Urea breakdown was estimated by subtracting the measured urea content of ‘retention’ specimens from the maximum urea concentration of ‘early catheter’ specimens.

Group results have been expressed as means ± 1 SD and intergroup comparisons were made by using Student’s t-test. Correlations were calculated by linear regression with the method of least squares.

Results

Dialysate bags were recovered between 36 h and 7 days after being taken orally. However, bag contents on collection reflected only the solute composition of the urine–faeces accumulating in the colon since the previous voiding, i.e. during the retention time. Retention times varied between 45 min and 5 h.

All patients whether acidotic or not passed highly alkaline urine–faeces (Table 1). This was true for specimens in contact with colonic mucosa for short periods (‘early catheter’ specimens) and those retained for some hours in the colon (‘retention’ specimens). The ‘early catheter’ specimens obtained from acidic patients contained significantly more bicarbonate than those from patients in normal acid–base balance (P < 0.001) (Table 1). Similarly total ammonia content was significantly greater in ‘early catheter’ specimens from acidic patients than in those from patients with normal acid–base balance (P < 0.001).

Acidotic patients’ ‘early catheter’ specimens contained significantly more bicarbonate (P < 0.01) and total ammonia (P < 0.02) than ‘retention’ specimens, whereas in patients in normal acid–base balance the converse was true, ‘retention’ specimens containing significantly more bicarbonate (P < 0.001) and total ammonia (P < 0.02) than ‘early catheter’ specimens (Table 1). In all ‘early catheter’ specimens taken together there was a significant negative correlation between plasma bicarbonate and bicarbonate content of the urine–faeces (r = −0.87, P < 0.001) (Fig. 1). A similar negative correlation existed between urine–faeces total ammonia and plasma bicarbonate in these samples (r = −0.92, P < 0.001) (not shown).

Calculated carbon dioxide tensions were less than those recorded in faecal dialysate from normal subjects (Down et al., 1972). Although values were greater in ‘retention’ specimens from acidic patients than from those on treatment, this difference did not reach statistical significance.

Chloride content was significantly greater in ‘retention’ specimens from acidic subjects than in samples obtained by catheter (P < 0.05) (Table 1), whereas for patients in normal acid–base balance ‘catheter’ specimens contained more chloride than ‘retention’ specimens (P < 0.05). ‘Retention’ specimens from acidic patients contained more chloride than similar specimens from treated patients but for ‘catheter’ specimens the converse was true (Table 1).

In ‘catheter’ specimens kept in vitro at room temperature there were positive correlations between bicarbonate and total ammonia concentrations (r = 0.95, P < 0.001) as well as between pH
**TABLE 1.** Median pH and total CO$_2$, bicarbonate, total ammonia and chloride concentrations and $P_{CO_2}$ of urine–faeces mixtures for groups of ureterosigmoid anastomosis patients

<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Acidotic</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>'Retention'</td>
<td>'Early catheter'</td>
</tr>
<tr>
<td></td>
<td>$n = 4, s = 8$</td>
<td>$n = 4, s = 8$</td>
</tr>
<tr>
<td>pH</td>
<td>8.68</td>
<td>8.48</td>
</tr>
<tr>
<td>Total CO$_2$ (mmol/l)</td>
<td>70.5 ± 14.9</td>
<td>44.1 ± 5.9</td>
</tr>
<tr>
<td>HCO$_3$ (mmol/l)</td>
<td>70.3 ± 14.9</td>
<td>43.7 ± 6.2</td>
</tr>
<tr>
<td>Total ammonia (mmol/l)</td>
<td>62.5 ± 21.4</td>
<td>33.5 ± 16.4</td>
</tr>
<tr>
<td>$P_{CO_2}$ (mmHg)</td>
<td>6.5 ± 1.5</td>
<td>11.6 ± 1.4</td>
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<tr>
<td>Cl$^-$ (mmol/l)</td>
<td>46.1 ± 22.2</td>
<td>67.7 ± 16.3</td>
</tr>
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Mean values ± SD are shown. $n$, Number of subjects; $s$, total number of specimens.

**Significant differences**

<table>
<thead>
<tr>
<th>Bicarbonate and total ammonia</th>
<th>Total CO$_2$ and HCO$_3$</th>
<th>Total ammonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated retention &gt; treated catheter</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.02$</td>
</tr>
<tr>
<td>Acidotic catheter &gt; acidotic retention</td>
<td>$P &lt; 0.01$</td>
<td>$P &lt; 0.02$</td>
</tr>
<tr>
<td>Acidotic catheter &gt; treated catheter</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
</tr>
</tbody>
</table>

Chloride

| Treated catheter > treated retention | $P < 0.05$ |
| Acidotic retention > treated retention | $P < 0.05$ |
| Acidotic retention > acidotic catheter | $P < 0.05$ |
| Treated catheter > acidotic catheter | $P < 0.05$ |

Fig. 1. 'Early catheter' specimens. Correlation of urine–faeces bicarbonate with plasma bicarbonate concentration. Observations in six patients.

and bicarbonate concentration ($r = 0.59, P < 0.01$) and pH and total ammonia concentration ($r = 0.69, P < 0.001$) (not shown). Positive correlations also existed for retained specimens between pH and bicarbonate concentration ($r = 0.62, P < 0.001$) and pH and total ammonia ($r = 0.50, P < 0.02$) (neither shown). The correlation between bicarbonate and total ammonia in these specimens ($r = 0.70, P < 0.001$) (Fig. 2) showed ammonia concentration to change less in relation to changes in bicarbonate concentration (0.77 mmol of ammonia/mmol of bicarbonate) than that found in catheter specimens (1.41 mmol of ammonia/mmol of bicarbonate) or the theoretical rate for urea hydrolysis (2.00 mmol of ammonia/mmol of bicarbonate).

'Catheter' specimens, 'early' and 'late' (bags removed after equilibrating for more than 4 h) from four patients in normal acid–base balance, when kept under oil at room temperature outside the patients, showed increasing amounts of bicarbonate (3.6 mmol h$^{-1}$ l$^{-1}; P < 0.001$) (Fig. 3). Total ammonia in the same specimens increased at a rate of 4.8 mmol h$^{-1}$ l$^{-1}$ ($P < 0.001$) (not shown). This relationship between time and both bicarbonate and total ammonia concentration was also true for the two acidotic patients though the correlations here were not statistically significant. Simultaneously the
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The urea concentration of these 'catheter' specimens decreased (2.3 mmol h⁻¹ l⁻¹).

'Retention' specimens on the other hand showed an even greater rate of increase of bicarbonate (9.8 mmol h⁻¹ l⁻¹; $P < 0.05$) (Fig. 3). Total ammonia content in these samples showed an increase but did not correlate significantly with retention time, and varied widely from patient to patient. Samples from one patient showed an inverse relationship between total ammonia and bicarbonate, with ammonia decreasing as bicarbonate increased. Urea disappearance in this particular patient was estimated at 8.3 mmol h⁻¹ l⁻¹. Three other samples did not show such a relationship and in these patients urea disappearance in 'retention' specimens was estimated to be greater than 15 mmol h⁻¹ l⁻¹ (Table 2).

The one patient receiving broad-spectrum antibiotics, although acidotic, passed a mixture which was less alkaline than expected. Both bicarbonate and total ammonia content in it were much less than any other samples. These constituents markedly increased after stopping all antibiotics.

Discussion

In this study the dialysis technique in vivo provided specimens, largely free from bacterial contamination, which reflected the solute content of the urine–faeces mixture with which the dialysate bags had been in contact. Since bacterial activity continued in the urine–faeces after voiding, the dialysate is likely to have reflected retained urine–faeces composition better than direct measurement,
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**Fig. 4.** Diagrammatic representation of suggested scheme of colonic mucosal transport of ions in early and late post-anastomosis states.

as has been shown to be the case for faeces (Vince, Down, Murison, Twigg & Wrong, 1976). In 'catheter' specimens any advantage of the technique was probably minimal since urine–faeces composition changed, presumably due to bacterial action, during equilibration of the bags with the urine–faeces stored outside the patient. The nature of the study did not allow the use of a volume marker to identify any contribution of movement of water to differences in ion concentrations between 'early catheter' and 'retention' specimens. However, the differences in bicarbonate and total ammonia concentrations, between the two types of specimens, in both acidic and treated patients were the converse of the chloride concentration difference (Table 1), and the differences in all three were opposite in acidic and treated patients. This suggests that real movements of ions did occur during retention of urine–faeces and changes in volume had limited influence on the concentration differences found.

The present results show that patients with ureterosigmoid anastomosis pass a highly alkaline urine–faeces with greater concentrations of both bicarbonate and total ammonia than have been reported for normal faecal dialysate (Wrong et al., 1965; Wilson, Ing, Metcalfe-Gibson & Wrong, 1968). The most alkaline mixtures with the largest amounts of bicarbonate and total ammonia were found in 'early catheter' specimens from acidic patients. 'Early catheter' specimens from treated patients, although also alkaline, contained significantly less bicarbonate and total ammonia. The marked alkalinity of 'early catheter' specimens suggests that either the urine excreted by the kidney is alkaline or that secretion of bicarbonate occurs rapidly during its passage over the distal colonic mucosa. The high total ammonia content of 'early catheter' specimens and its increase with increasing systemic acidosis suggest that urine excreted by the kidneys in these patients is acid and becomes increasingly so with systemic acidosis. This is against any renal tubular acidification defect and implies bicarbonate secretion by the colonic mucosa.

A significant negative correlation also existed between urine–faeces bicarbonate and plasma bicarbonate (Fig. 1). It thus seems probable that the acidity of the urine entering the colon is the primary stimulus to mucosal bicarbonate secretion. The more marked the acidity of the urine the more rapid the rate of bicarbonate secretion. In conditions of excess bicarbonate secretion a marked increase in pH will result, thus accounting for the high pH of urine–faeces in these patients. Bicarbonate secretion is further supported by the decrease in chloride concentration concomitant with the increase in bicarbonate concentration when 'retention' specimens in treated patients are compared with 'early catheter' specimens. This inverse relationship is in keeping with bicarbonate–chloride exchange across the colonic mucosa. However, increased urea hydrolysis due to the higher incubation temperature of retained mixtures probably makes a major contribution to the observed differences in bicarbonate concentrations. In retained specimens the lower rate of increase in total ammonia concentration (0.77 mmol/mmol of bicarbonate: Fig. 2) than expected from urea hydrolysis is in keeping with mucosal secretion of bicarbonate.

'Retention' specimens of acidic patients contained significantly less bicarbonate and total ammonia than 'early catheter' specimens, despite the higher incubation temperature of retained urine–faeces. This suggests that during retention of urine–faeces in these patients absorption of bicar-
Carbonate and ammonia occurs. Chloride concentrations were significantly greater in 'retention' compared with 'early catheter' specimens in acidic patients. The inverse relationship between chloride and bicarbonate suggests that in these patients bicarbonate reabsorption occurs after initial rapid bicarbonate secretion, and does so by ionic as well as non-ionic (as CO₂) diffusion. Such ionic diffusion would be favoured by the large gradient between colonic and plasma bicarbonate concentrations in acidic patients. This reabsorption of bicarbonate may explain why untreated patients usually stabilize postoperatively in a mildly acidotic state rather than deteriorating inexorably to severe acidosis. In treated patients the relatively low bicarbonate and total ammonia concentration in 'early catheter' specimens are in keeping with the inflow of neutral or mildly acid urine associated with little bicarbonate secretion. Higher bicarbonate and ammonia concentrations in 'retention' specimens probably result from continuing urea hydrolysis during retention.

Thus the present results support the concept of acid urine excreted by the kidneys in untreated ureterosigmoid anastomosis patients (Parsons, Pyrah, Powell, Reed & Spiers, 1952). Together with alkaline urine--faeces as voided this implies alkalinization of urine during its transit through the colon. Alkalinization of colonic contents is well documented in man (Annis & Alexander, 1952; Bown, Sladen, Rousseau, Gibson, Clark & Dawson, 1972). It has also been shown in dogs that colonic loops containing saline and sodium bicarbonate equilibrate towards a total CO₂ concentration of 76 mmol/l (Swallow & Code, 1976), similar to the total CO₂ concentrations found in our investigations (Table 1).

Our results indicate that in patients with ureterosigmoid anastomosis there is reciprocal coupling of the movements of bicarbonate and chloride as in normal individuals (Devroede & Phillips, 1969) and that this anion exchange may occur in either direction across the mucosa (Holmberg, Perheentupa & Launiala, 1975). Our results are in keeping with bicarbonate secretion being an active process (Swallow & Code, 1967; Devroede & Phillips, 1969) and probably the prime mover in bicarbonate--chloride exchange. Thus the hyperchloremia of ureterosigmoid anastomosis is not the result of any selective absorption of chloride, as suggested initially by Ferris & Odel (1950), but the concomitant of bicarbonate secretion by the colon (Fig. 4). The amount of alkali usually required by these patients to maintain acid--base balance (90–150 mmol of bicarbonate/day) correlates well with our measurements of bicarbonate loss in the urine--faeces (70 mmol/l), in keeping with losses of 100–150 mmol of bicarbonate/day, as daily volumes of urine--faeces in these patients were 1–2 l.

This study suggests that intraluminal urea disappears more rapidly than reported rates of hydrolysis of circulating urea (2.3–4.8 mmol of urea/h) (Varcoe, Halliday, Carson, Richards & Tavill, 1975). This is probably due to the greater exposure of urea to bacterial ureases in ureterosigmoid patients. Various rates of urea breakdown in individual patients presumably reflect differing amounts of bacterial urease and differing rates of absorption of the reaction products of urea hydrolysis. The latter may indicate that absorption of ammonia and/or bicarbonate across the mucosa is rate-limited, so that when urea breakdown is especially rapid mucosal exchange cannot keep pace and consequently total ammonia and bicarbonate both increase in the urine--faeces. This would mask the inverse relationship between total ammonia and bicarbonate concentrations suggestive of non-ionic diffusion of ammonia, which was only apparent in one patient with the slowest rate of urea breakdown.

References


