PYLORIC REFLUX: A MODIFICATION OF THE TWO-COMPONENT HYPOTHESIS OF GASTRIC SECRETION

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SUMMARY

1. Gastric juice was obtained during continuous maximal stimulation with histamine diphosphate, 0.13 μmol h⁻¹ kg⁻¹ (0.04 mg h⁻¹ kg⁻¹) intravenously, in thirty-four control subjects, twenty-eight patients with duodenal ulcer, and eighteen with gastric ulcer. After correction for pyloric losses, the average rate of outputs of water, and of H⁺, Na⁺, K⁺ and Cl⁻ were determined.

2. The results were analysed in terms of the two-component theory of gastric secretion. The acid components in control subjects and duodenal ulcer patients were similar in composition, but that in gastric ulcer patients was by comparison hypotonic and less acid and contained more sodium ions.

3. Calculation of the volume and composition of the alkaline component gave reasonable results in the control and duodenal ulcer groups, but impossible results in the gastric ulcer group. The gastric juice of gastric ulcer patients could not be described in terms of classical two-component theory.

4. In all three groups, volume correlated quite well with Cl⁻ output alone, less well with H⁺ output, poorly with K⁺ output, and not at all with Na⁺ output. However, when volume was expressed as a function of the outputs of Cl⁻ and one other ion, K⁺ performed poorly, H⁺ well, and Na⁺ best of all.

5. Some features suggest that reflux of alkaline liquid from the duodenum is a better explanation of these results than back-diffusion of H⁺ in exchange for Na⁺ between the lumen and wall of the stomach.

6. If the refluxing liquid is assumed to be isotonic, its composition can be calculated. Hence, the volume of reflux in a sample of gastric juice can be deduced. Reflux appeared to be more important in the gastric ulcer patients than in the other two groups.

Key words: gastric juice, regurgitation, peptic ulcer, hydrochloric acid, gastric secretory rate, histamine.

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The electrolyte concentrations in gastric juice vary with the rate of secretion. Mathematical descriptions of the relationships between the outputs of water and electrolytes in gastric juice are of practical and theoretical interest. Their practical value lies in helping to pick out errors of collection or analysis in individual samples: for example, if we could describe gastric secretion sufficiently accurately, the volume-rate of secretion of a sample that had been half-lost by spilling might be deduced from the electrolyte concentrations that it contained. The theoretical significance is that greater accuracy of description should lead to better understanding of the physiology of gastric secretion.

Hobsley & Silen (1970) explored the two-component hypothesis during sub-maximal stimulation with histamine; they did not take pyloric losses into account. However, most gastric secretory studies are done with a maximal stimulus and so the present paper describes a different set of studies with maximal intravenous histamine; losses via the pylorus were measured. The possibility that a third component, pyloric reflux, accounts for deviations from the two-component pattern is considered with the aid of multiple regression analysis.

PATIENTS AND METHODS

Thirty-four control subjects, twenty-eight patients with duodenal ulcer, and eighteen patients with gastric ulcer were studied. The first two groups were described by Hassan & Hobsley (1971) with regard to their maximum secretion in relation to stature, and full details of these subjects can be found in that paper. The eighteen patients with gastric ulcer comprised twelve men and six women: their ages ranged from 39 to 70 years, with an average of 57-8 years (SD 8.3). Most of the studies were done as part of the clinical investigation of the patient's symptoms, but volunteers among the control subjects gave their informed consent and the approval of the Clinical Investigations Committee of The Middlesex Hospital was also obtained.

Each subject underwent a maximal histamine-infusion test (Lawrie, Smith & Forrest, 1964); the plateau of secretion evoked by 0.13 μmol (0.04 mg) of histamine diphosphate h⁻¹ kg⁻¹ body weight was collected by continuous aspiration and divided into 15 min collections. The Phenol Red marker was simultaneously installed into the upper part of the stomach by constant-infusion pump. The practical details, including the method of making the correction for pyloric losses, are described by Hobsley & Silen (1969). Correct positioning of the tube in the stomach was ensured (Hassan & Hobsley, 1970). The Phenol Red infusion added 1·2 ml of water, 18 mmol of Na⁺ and 5 mmol of HCO₃⁻ to the stomach contents each 15 min.

On each 15 min sample of plateau gastric juice, the following observations and measurements were made: volume, naked-eye inspection for the presence of bile, titratable acidity, and the concentrations of Na⁺, K⁺ and Cl⁻, and Phenol Red. The analytical methods were as described by Hobsley & Silen (1969).

Bile-staining implies regurgitation of alkaline duodenal contents into the stomach, and this must alter the relationships between concentrations of the various ions and the rate of secretion of the juice. Studies in which more than one of the plateau samples was bile-stained were carefully categorized, but in the first instance were included in the general analysis of results.

The statistical methods used were as described by Moore, Shirley & Edwards (1972).
RESULTS

The Phenol Red-corrected average results of all plateau samples in each subject, including volume (secretory rate) in ml/15 min, electrolyte outputs in mmol/15 min, and Phenol Red recovery as a percentage have been deposited as Clinical Science and Molecular Medicine Tables 74/5–7 with the Librarian, The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE; copies may be obtained from the Librarian on request.

These results are summarized in Table 1.

The duodenal ulcer group secreted significantly more gastric juice, with significantly greater outputs of $H^+$ and $Cl^-$, than the control group, while the gastric ulcer group secreted significantly smaller amounts of water and these two ions. With the unpaired $t$-test, all these differences were significant at the 95% level.

<table>
<thead>
<tr>
<th>Group</th>
<th>Volume (ml/15 min)</th>
<th>Electrolytes (mmol/15 min)</th>
<th>$Q_H$</th>
<th>$Q_{Cl}$</th>
<th>$Q_{Na}$</th>
<th>$Q_K$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>70.33 (22.86)</td>
<td>8.37 (3.40), 10.54 (3.84)</td>
<td>0.97</td>
<td>1.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>92.02 (29.39)</td>
<td>11.19 (4.41), 13.91 (4.80)</td>
<td>1.35</td>
<td>1.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>53.62 (19.93)</td>
<td>5.25 (2.47), 7.39 (2.99)</td>
<td>1.42</td>
<td>0.94</td>
<td>0.52</td>
<td>0.46</td>
</tr>
</tbody>
</table>

The average $K^+$ output in each group paralleled very closely the rate of secretion of water, in that $K^+$ concentration was similar in all three groups: 17.38 mmol/l in the controls, 17.72 mmol/l in the duodenal ulcer group, and 17.52 mmol/l in the gastric ulcer group. The duodenal ulcer group secreted more $Na^+$ than the control group, roughly in the same proportion as for water excretion; but the gastric ulcer group secreted an even greater average $Na^+$ output despite the smaller average of water secreted. The average $Na^+$ concentration was 13.7 mmol/l in the control group, 14.1 mmol/l in the duodenal ulcer patients, and 26.2 mmol/l in the gastric ulcer patients.

TWO-COMPONENT ANALYSIS

Details of this method of mathematical analysis of secretion data in terms of the two-component hypothesis of gastric secretion have been published previously (e.g. Hobsley & Silen, 1970).

Acid component

In the two-variable linear regression equations linking volume with the output in turn of
**TABLE 2. Two-variable regressions**

Data are Phenol Red-corrected.

<table>
<thead>
<tr>
<th>Group</th>
<th>Regression equation</th>
<th>Index of determination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( Q_H )</td>
<td>( 0.134V - 1.04 )</td>
<td>0.82</td>
</tr>
<tr>
<td>( Q_{Cl} )</td>
<td>( 0.160V - 0.72 )</td>
<td>0.91</td>
</tr>
<tr>
<td>( Q_{Na} )</td>
<td>( 0.006V + 0.55 )</td>
<td>0.08</td>
</tr>
<tr>
<td>( Q_K )</td>
<td>( 0.017V + 0.02 )</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Duodenal ulcer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( Q_H )</td>
<td>( 0.135V - 1.21 )</td>
<td>0.81</td>
</tr>
<tr>
<td>( Q_{Cl} )</td>
<td>( 0.158V - 0.64 )</td>
<td>0.93</td>
</tr>
<tr>
<td>( Q_{Na} )</td>
<td>( 0.013V + 0.16 )</td>
<td>0.15</td>
</tr>
<tr>
<td>( Q_K )</td>
<td>( 0.019V - 0.13 )</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Gastric ulcer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( Q_H )</td>
<td>( 0.112V - 0.76 )</td>
<td>0.82</td>
</tr>
<tr>
<td>( Q_{Cl} )</td>
<td>( 0.147V - 0.51 )</td>
<td>0.96</td>
</tr>
<tr>
<td>( Q_{Na} )</td>
<td>( 0.015V + 0.62 )</td>
<td>0.34</td>
</tr>
<tr>
<td>( Q_K )</td>
<td>( 0.022V - 0.23 )</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Fig. 1. Regression lines indicate that the relationships between output of \( H^+ \) and volume-rate of gastric secretion are the same in normal subjects (---) and duodenal ulcer patients (-- --), but different in gastric ulcer patients (- - - -). The points (●) plotted are the actual data from the gastric ulcer patients.
Pyloric reflux modifying gastric secretion

Each electrolyte (Table 2), the concentration of each electrolyte in the acid component is represented by the coefficient of the volume-term. Thus for $H^+$ in the control group,

$$Q_H = 0.134V - 1.04$$

and since $Q_H$ is expressed as mmol, $V$ as ml, the $H^+$ concentration is 0.134 mmol/ml or 134 mmol/l. Fig. 1 shows the regression lines for $H^+$ output against volume in the three groups of subjects: the normal subjects and the patients with duodenal ulcer were similar to each other, but apparently different from the patients with gastric ulcer. The actual data for the gastric ulcer patients are indicated.

The following deductions can be made from the coefficients of $V$ in Table 2:

(a) All electrolyte concentrations in the acid component of control subjects were very similar to those in patients with duodenal ulcer. The single discrepancy was for $Na^+$: 6 mmol/l in the control subjects, 13 mmol/l in the duodenal ulcer group.

(b) The sum of the concentrations of the cations ($H^+, Na^+, K^+$) tallied well with the $Cl^-$ concentration. Again, the single exception was provided by the duodenal ulcer group: the total cation concentration was 167 mmol/l, $Cl^-$ concentration only 158 mmol/l.

(c) $K^+$ concentration was virtually identical in the acid components of all three groups, about 19 mmol/l.

(d) The acid component in patients with gastric ulcer was definitely hypotonic (in terms of ionic constituents) compared with that in the other two groups. In the gastric ulcer group, the amount by which the $Cl^-$ concentration fell short of that in the control subjects was exceeded by the discrepancy in the corresponding $H^+$ concentrations: the resultant gap in the cation concentrations was made good by an increased concentration of $Na^+$.

None of the above results, including the slopes and intercepts of the regression equations, was significantly altered by excluding the studies in which visible contamination with bile occurred.

The indices of determination quoted in Table 2 are discussed later.

**Apparent alkaline component**

This term is used here to indicate the mixture of true alkaline component secreted by the stomach plus swallowed saliva (Hobsley & Silen, 1970). Gardham & Hobsley (1970) collected alkaline secretions from the stomachs mainly of individuals with pernicious anaemia, i.e. samples in which the acid component was missing. The means and ranges of volumes and electrolyte concentrations in their studies were as follows: $V$, 5.9 (3.4–21) ml/15 min; $Na^+$, 80 (48–146) mmol/l; $K^+$, 17 (11–27) mmol/l; $Cl^-$, 92 (56–147) mmol/l; $HCO_3^-$, 8, (3–18) mmol/l.

**Control group.** Correction of the regression equations of Table 2 for the presence of 1.2 ml of Phenol Red and its alkali and $Na^+$ content yielded the equations (1a)–(1d).

$$Q_H = 0.134V - 0.829 \quad (1a)$$
$$Q_{Cl} = 0.160V - 0.528 \quad (1b)$$
$$Q_{Na} = 0.006V + 0.539 \quad (1c)$$
$$Q_K = 0.017V + 0.037 \quad (1d)$$

Granted that the alkaline component must be alkaline (i.e. titratable alkalinity >0), eqn. (1a) shows that its volume $V < 0.829/0.134 = 6.18$ ml. If the alkaline component contains chloride ($Q_{Cl} > 0$), then (1b) shows that $V > 0.528/0.160 = 3.3$ ml.
Exploring the electrolyte outputs for values of $V$ between 4 ml and 6 ml/15 min yields results in which the cation concentrations always total much more than the $\text{HCO}_3^-$ plus $\text{Cl}^-$. Since gastric juice contains no ions in appreciable quantities other than $\text{Na}^+$, $\text{K}^+$, $\text{H}^+$ (or $\text{HCO}_3^-$) and $\text{Cl}^-$, the sum of the anions must always equal the sum of the cations. It follows that the two-component hypothesis apparently cannot explain these results.

In view of the considerable evidence that favours the two-component hypothesis, the above conclusion does not seem likely. The difficulty appears to be the high constant term, 0.539, in the $\text{Na}^+$ regression eqn. (1c): the magnitude of this figure seems to be primarily responsible for the fact that the sum of the cations always exceeds the sum of the anions. It must be emphasized that while the regression equations of $\text{H}^+$, $\text{Cl}^-$ and $\text{K}^+$ have fairly high indices of determination, the corresponding index for the $\text{Na}^+$ regression is very low (0.08; see Table 2). Therefore while the eqns. (1a), (1b) and (1d) are probably excellent estimates of the true relationships, (1c) may easily be in some error. In the acid component itself, the only anion is $\text{Cl}^-$ and so the sum of the $\text{H}^+$, $\text{Na}^+$ and $\text{K}^+$ concentrations should be 160, the concentration of $\text{Na}^+$ $160-(134+17)=9$ mmol/l and the true slope of the eqn. (1c) should be 0.009. This hypothesis has been explored mathematically: this mathematical analysis is lodged (see above) with the Librarian, Royal Society of Medicine, as Clinical Science and Molecular Medicine, Table 74/8, and results in estimates of the true and apparent alkaline components that fit quite well the data of Gardham & Hobsley (1970).

To summarize these calculations, the two-component hypothesis fits the data of the control group quite well, provided that one accepts that the very shallow slope of the $\text{Na}^+$ regression line may be in error by 3 mmol/l, and leads to the conclusions that: (1) 15 min samples of maximally stimulated gastric juice contain 3.5 ml of saliva, 2.5 ml of pure alkaline component; (2) this 6 ml of apparent alkaline component contains 0.432 mmol of $\text{Cl}^-$, 0.070 mmol of $\text{HCO}_3^-$, 0.387 mmol of $\text{Na}^+$ and 0.142 mmol of $\text{K}^+$; (3) the remainder of the 15 min volume contains pure acid component of concentration of $\text{H}^+$, 134 mmol/l, $\text{Cl}^-$, 150 mmol/l, $\text{Na}^+$, 9 mmol/l, and $\text{K}^+$ 17 mmol/l.

**Duodenal ulcer group.** Corrections of the regression equations of Table 2 for the presence of Phenol Red results in equations (2a)–(2d).

\[
\begin{align*}
Q_H &= 0.135V - 1.05 \\
Q_{\text{Cl}} &= 0.158V - 0.55 \\
Q_{\text{Na}} &= 0.013V + 0.15 \\
Q_K &= 0.019V - 0.11 
\end{align*}
\]

Attempts to determine an alkaline component consistent with these equations meet with the same difficulty as in the control group—the value of the constant in the $\text{Na}^+$ regression equation, but for the opposite reason, namely that the value is too small. The assumption that the $\text{Na}^+$ concentration in the acid component is 0.009 mmol/ml, the same as in the control group, gives quite a good fit, but the best fit is given by a slope of 0.008 mmol/ml, and the corresponding volume of the apparent alkaline component is 7 ml/15 min.

In other words, the two-component hypothesis can explain the duodenal ulcer data, in terms of an apparent alkaline component very similar in volume and ionic concentrations to that deduced in the control group, but only if a sodium concentration is accepted for the acid component that leads to a slight imbalance between the anions and cations.

**Gastric ulcer group.** Correction of the regression equations of Table 2 for the presence of
Phenol Red and adjustment of the coefficient of volume in the Na\(^+\) regression to 0.013 results in equations (3a)–(3d).

\[
\begin{align*}
Q_H &= 0.112V - 0.59 & (3a) \\
Q_{Cl} &= 0.147V - 0.32 & (3b) \\
Q_{Na} &= 0.013V + 0.71 & (3c) \\
Q_K &= 0.022V - 0.21 & (3d)
\end{align*}
\]

These equations result in impossible conditions for the alkaline component. Thus: only when \(Q_H < 0\), i.e. when \(V < 5.25\) ml, is the non-acid component alkaline; only when \(Q_{Cl} > 0\), i.e. when \(V > 2.18\) ml, does the non-acid component contain \(Cl^-\); only when \(Q_K > 0\), i.e. when \(V > 9.5\) ml, does the non-acid component contain \(K^+\). These conditions cannot be simultaneously satisfied. It follows that the two-component hypothesis cannot explain the results in the gastric ulcer group.

**MULTIPLE REGRESSION ANALYSIS**

It is, of course, possible that the two-component theory is not an accurate description of the gastric juice in patients with gastric ulcer. However, it seemed reasonable to seek a modification of the theory, i.e. some factor responsible for the apparent alteration in ionic concentrations in the acid component. Hobsley & Silen (1970) pointed out that a closer correlation could be obtained between secretory rate of gastric juice and concentrations of \(H^+\) and \(Cl^-\) by the technique of multiple regression analysis: volume is expressed as the sum of a number of terms, each of which is proportional to one of the electrolyte concentrations, plus a constant term. This procedure has been applied to the present data. All the results quoted are for Phenol Red-corrected data; the results are not significantly different with uncorrected data. If all four measured electrolytes are taken into account, equations of the form

\[
V = aQ_H + bQ_{Cl} + cQ_{Na} + dQ_K + e
\]

are obtained, where \(a\), \(b\), \(c\), \(d\) and \(e\) are constants, \(V\) is the output of water and \(Q_A\) the output of electrolyte \(A\) in 15 min. However, fewer than four electrolyte outputs can be used.

An index of determination can be derived for each regression equation, and inspection of these allows the importance or otherwise of the contribution of any given electrolyte to the relationship with volume to be assessed. The values of \(a\), \(b\), \(c\) and \(d\) in all degrees of the multiple regression analysis are given in *Clinical Science and Molecular Medicine* Table 74/9 deposited with the Librarian of the Royal Society of Medicine, as detailed above. Table 3 gives the index of determination of all the multiple regressions, including any two and any three as well as all four electrolyte outputs, for Phenol Red-corrected data. Corresponding regression equations for uncorrected data were very similar. For ease of reference, the corresponding indices of determination for the simple regressions of volume against each individual electrolyte output are repeated in this table.

In general, the correction for Phenol Red made little difference to the indices of determination, although the correction possibly slightly improved the correlations where these were low (e.g. against \(Q_{Na}\) and \(Q_K\), individually and in combination). In subsequent paragraphs, the data for the whole study are used as illustrations except where otherwise specified. All probability values quoted were obtained by a standard analysis of variance.
Volume was tied more closely to the amount of Cl⁻ secreted ($r^2 = 0.94$) than to any of the other ions individually. Na⁺ output alone was the worst predictor ($r^2 = 0.11$), with practically no power of prediction except in patients with gastric ulcer ($r^2 = 0.34$); yet Na⁺ output significantly ($P < 0.01$) improved the prediction ($r^2 = 0.97$) from Cl⁻ alone. Output of H⁺ was definitely ($P < 0.05$), though slightly ($r^2 = 0.86$), less good at predicting volume than Cl⁻, but again the addition of Na⁺ data to the H⁺ data significantly ($P < 0.01$) improved the prediction ($r^2 = 0.94$). Output of K⁺ alone gave some measure of prediction ($r^2 = 0.67$), and this was not significantly improved by Na⁺ ($r^2 = 0.68$, $P > 0.05$).

This ability of $Q_{Na}$ to improve the predictions from $Q_{Cl}$ alone and $Q_{H}$ alone, although it did not itself have much power of prediction, suggests that $Q_{Na}$ is strongly tied to $Q_{H}$ and $Q_{Cl}$ in a way that $Q_{K}$ is not.

### Table 3. Multiple regression analysis: indices of determination

Data are Phenol Red-corrected.

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th>$Q_H$</th>
<th>$Q_{Cl}$</th>
<th>$Q_{Na}$</th>
<th>$Q_{K}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>0.97</td>
<td>0.93</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>0.97</td>
<td>0.93</td>
<td>0.97</td>
<td>0.98</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>0.97</td>
<td>0.93</td>
<td>0.97</td>
<td>0.98</td>
</tr>
<tr>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>0.96</td>
<td>0.92</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>+</td>
<td>0.95</td>
<td>0.92</td>
<td>0.94</td>
<td>0.97</td>
</tr>
<tr>
<td>+</td>
<td>0.94</td>
<td>0.91</td>
<td>0.93</td>
<td>0.96</td>
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<tr>
<td>+</td>
<td>0.94</td>
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<td>0.94</td>
<td>0.98</td>
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<td>0.94</td>
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<td>+</td>
<td>0.89</td>
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<td>0.95</td>
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<td>0.81</td>
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<tr>
<td>+</td>
<td>0.68</td>
<td>0.39</td>
<td>0.81</td>
<td>0.90</td>
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<tr>
<td>+</td>
<td>0.67</td>
<td>0.39</td>
<td>0.79</td>
<td>0.90</td>
</tr>
<tr>
<td>+</td>
<td>0.11</td>
<td>0.08</td>
<td>0.15</td>
<td>0.34</td>
</tr>
</tbody>
</table>

### DISCUSSION

The success of the two-component hypothesis in explaining the results of the control and duodenal ulcer series requires the following comments.

1. The apparent alkaline component has an electrolyte composition that is practically identical in both groups and is secreted at about the same rate. Moreover, both composition and secretion rate are compatible with the findings of Gardham & Hobsley (1970) in an acid samples of gastric juice. After allowing for the presence of saliva, the composition of true alkaline component in these data is very similar to that described by Makhlouf, McManus & Card (1966). However, these results have only been achieved by arbitrarily assigning a sodium concentration of 8 or 9 mmol/l to the acid component.
(2) The acid component in both groups has a total ionic concentration of 316–320 mmol/l, i.e. it is about isotonic with plasma. This result seems reasonable.

(3) The Na⁺ concentration of the acid component is not directly assessable from the present data because of the low correlation between Na⁺ output and volume. The inference from the concentrations of the other electrolytes in the acid component that the Na⁺ concentration is in fact 0.009 mmol/ml may not be accurate, but there is some supporting evidence that this is a reasonable figure. On average, the duodenal ulcer series secreted 22 ml/15 min more than the control series and on the two-component hypothesis the increased volume must have consisted of pure acid component; so the fact that the gastric juice Na⁺ concentration averaged almost exactly the same figure in both series (0.014 and 0.015 mmol/ml) implies that the Na⁺ concentration of the acid component could not be far different from the 0.014 mmol/ml of the control series gastric juice. This problem of the true value of the Na⁺ concentration in the acid component can only be resolved by the accumulation of further data.

The findings by multiple regression analysis may now be examined in the light of possible factors that might reduce the acidity of the acid component of gastric juice. There seem to be two possible candidates for this factor: back-diffusion of H⁺ in exchange for Na⁺ (Davenport, 1968) and reflux through the pylorus of alkaline duodenal contents (Du Plessis, 1965). Back-diffusion of H⁺ through the mucosa of the stomach wall could explain the lowered H⁺ and raised Na⁺ concentration, but less well the lowered Cl⁻ and certainly not the higher K⁺ concentration in the acid component of gastric ulcer patients relative to controls. In the first instance, therefore, the problem will be approached from the viewpoint of reflux, and, where the data might be expected to discriminate between the two possibilities, attention will be drawn to the weakness of back-diffusion as the explanation.

The possibility that reflux is the disturbing factor is supported by the multiple regression analysis. Thus the relationship in the whole series between \( V \), \( Q_H \) and \( Q_{Cl} \) is given by

\[
V = -3.96Q_H + 9.38Q_{Cl} + \text{constant}
\]

The negative value of the coefficient of \( Q_H \) indicates that the smaller \( Q_H \) the greater the volume \( V \). This is readily explained by reflux of alkaline liquid containing bicarbonate: the \( \text{HCO}_3^- \) remove an equivalent number of H⁺ from the solution and the volume of reflux is increased by the volume of the refluxing liquid. Back-diffusion of H⁺ in exchange for Na⁺ does not fit the mathematical data so well, because there would not appear to be any necessity for volume to increase as the H⁺ concentration falls if back-diffusion is responsible.

The indices of determination in Table 3 can be interpreted in the light of possible reflux as follows. (a) \( Q_{Cl} \) alone is an excellent determinant of volume. This suggests that the refluxing liquid has a Cl⁻ concentration not too far different from gastric juice. (b) The addition of \( Q_H \) to \( Q_{Cl} \) greatly improves the prediction because it takes into account the fall in H⁺ concentration produced by reflux. (c) The addition of \( Q_{Na} \) produces an even greater increase in accuracy of prediction than does \( Q_H \). The reason that \( Q_{Na} \) is superior to \( Q_H \) is not clear; in terms of back-diffusion of one H⁺ in exchange for one Na⁺, Na⁺ and H⁺ outputs should theoretically be of equal importance. In terms of reflux, it is possible that the alkalinity of the duodenal contents is much more variable than its Na⁺ concentration. Pancreatic secretion varies in its \( \text{HCO}_3^- \) concentration between 25 and 150 mmol/l, and intermittent injections of bile, with its rather lower alkalinity, into the duodenum must produce marked variations in the \( \text{HCO}_3^- \) concentration of the duodenal contents. In all these circumstances, however, there
is no necessity for the $Na^+$ concentration to vary from its average 143 mmol/l. (d) No further improvement in accuracy of prediction can be obtained by considering $Q_H$ and/or $Q_K$ in addition to the combination of $Q_{Na}$ and $Q_{Cl}$. This implies that $K^+$ concentration is much the same in the refluxing liquid as in gastric juice. This result is in line with the data on the two-variable correlation between $Q_K$ and $V$: such regression lines have a zero intercept on $x$ and $y$ axes, indicating that $K^+$ concentration must be fairly similar in all components of the aspirated juice. (e) Output of $Na^+$ is in general of no predictive value because in true gastric juice it is mainly confined to the fixed output of apparent alkaline component: the $Na^+$ concentration of acid component is very small. However, its presence in reflux increases its predictive value in gastric ulcer patients. This latter result is also inexplicable in terms of a one for one exchange of $H^+$ for $Na^+$ by back-diffusion in the gastric ulcer group: back-diffusion should not affect volume.

### Table 4. Calculation of reflux

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Vol. of reflux in 15 min sample $V_R$ (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Na^+$</td>
<td>$7.47Q_{Na} - 0.067V - 2.48$</td>
</tr>
<tr>
<td>$H^+$</td>
<td>$0.580V - 4.34Q_H - 3.78$</td>
</tr>
<tr>
<td>$Cl^+$</td>
<td>$0.718V - 4.49Q_{Cl} - 2.37$</td>
</tr>
</tbody>
</table>

The possibility that reflux accounts for the differences in the gastric ulcer group can be explored mathematically in the manner described in *Clinical Science and Molecular Medicine* Table 74/8. The principles of the technique are:

(a) $K^+$ concentration in reflux is assumed as a first approximation to be identical with that in the acid and the apparent alkaline components [but see paragraphs (d) and (e) above].

(b) The refluxing liquid is probably isotonic.

(c) At a fixed secretion rate ($V$), the multiple regression equations allow the effect of a given reduction in $H^+$ output (by neutralization by the alkaline reflux) upon the outputs of the other electrolytes to be calculated. The ideal relationship for the situation of no reflux must be assumed, since it is the variation from the ideal relationship that allows reflux to be calculated. Clearly without direct measurement of the reflux it is not possible to be certain of the ideal relationship. It has been arbitrarily assumed for the purpose of this paper that there was no reflux in the control group. Any calculations of reflux in the duodenal ulcer and gastric ulcer groups thus represent volumes of reflux in excess of those occurring normally in the control group, rather than absolute values.

The results of the mathematical analysis in Table 4 give the equations for calculating the volume of reflux in a 15 min sample of gastric juice, based on the individual output of $Na^+$ or $H^+$ or $Cl^-$. The estimate from $Na^+$ should be the most reliable, as discussed above. The concentrations of electrolytes in the hypothetical reflux that would result in the observed multivariate regression relationships are $Cl^- 63, HCO_3^- 97, Na^+ 143, K^+ 17$ mmol/l. These
values would do well for moderately stimulated pancreatic secretion. This result is in accord with the finding of Tankel, Lester, Richman & Hollander (1957) that histamine stimulates pancreatic as well as gastric secretion.

It must be emphasized that the mathematical analysis is merely a description of how a purely hypothetical reflux of duodenal contents into the stomach might account for the observed deviations in behaviour of patients with gastric ulcer from those in the control group. Back-diffusion of H\(^+\) in stomachs with a gastric ulcer could explain the observations almost as well, and the data in the present paper do not allow one to make a definite choice between these two hypotheses although the multiple regression relations favour reflux. Further work is in progress to attempt to measure reflux more directly.

The slight difficulty in fitting the data from duodenal ulcer patients into the same two-component analysis that suits the control series could be explained by the presence in the duodenal ulcer series of a small amount of reflux. This would explain why, despite the greater average rate of secretion in the duodenal ulcer group compared with the controls, the average Na\(^+\) concentration was no smaller. One would expect the larger volume of acid component with its small (9 mmol/l) Na\(^+\) concentration to reduce the overall Na\(^+\) concentration, but this effect would be cancelled by the presence of some Na\(^+\)-rich reflux.

Finally, it should be emphasized that if the rate of secretion and the Na\(^+\) concentration of a sample of gastric juice are measured, the volume of duodenal reflux in the sample can be estimated.

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REFERENCES


