FURTHER STUDIES ON PROSTAGLANDIN E\textsubscript{1}-INDUCED JEJUNAL SECRETION OF WATER AND ELECTROLYTES IN MAN, WITH SPECIAL REFERENCE TO THE INFLUENCE OF ETHACRYNIC ACID, FUROSEMIDE, AND ASPIRIN

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Perfusion studies were performed in 35 healthy volunteers to investigate further the secretory effect of prostaglandin E\textsubscript{1} (PGE\textsubscript{1}), administered intraluminally, on the human jejunum. A perfusion system with a proximal occluding balloon and continuous aspiration of duodenal secretions was used. The influence of PGE\textsubscript{1} (0.9 \( \mu \)g per kg per min) on glucose, fluid, and ion transport was entirely reproducible throughout a 6-hr perfusion experiment and was fully reversible 60 min after the end of PGE\textsubscript{1} administration. The influence of ethacrynic acid (EA), aspirin (two agents previously reported to inhibit choleraic secretion), and furosemide was studied both on basal jejunal absorption and on PGE\textsubscript{1}-induced secretion of water and electrolytes. EA (2.5 mg per kg), administered in jejunal lumen, significantly reduced \((P < 0.001)\) the net secretory effect of intraluminal PGE\textsubscript{1}, and suppressed the PGE\textsubscript{1}-induced increase in plasma-to-lumen unidirectional flux of sodium. Intravenous or intraluminal aspirin (25 to 40 mg per kg) as well as intraluminal furosemide (1.5 mg per kg) did not modify the PGE\textsubscript{1}-induced secretion nor the basal absorption rates. Plasma immunoreactive levels of PGE\textsubscript{1}, calcitonin, and diverse gut hormones did not change significantly during PGE\textsubscript{1}-induced secretion. These results indicate that (1) aspirin, an inhibitor of prostaglandin synthesis, has no influence on the intestinal secretory effect of preformed PGE\textsubscript{1}; (2) EA, unlike furosemide, inhibits in man PGE\textsubscript{1}-induced jejunal secretion, an effect of EA similar to that observed in animals on cholera toxin- and cyclic AMP-mediated secretion.

Prostaglandins E\textsubscript{1} (PGE\textsubscript{1}), E\textsubscript{2} (PGE\textsubscript{2}), and F\textsubscript{2\alpha} (PGF\textsubscript{2\alpha}) have been shown to reverse net absorption of water and electrolytes into secretion both in the human\textsuperscript{5,6} and in animal\textsuperscript{7,8} small bowel. Several investigators have suggested that prostaglandins (PG's), cholera enterotoxin, and other bacterial agents may act upon a common intestinal secretory system, presumably the cyclic AMP-adenylate cyclase system.\textsuperscript{9,10} Recent studies have been concerned with the inhibitory effect of various drugs on some of these secretory stimuli: cycloheximide,\textsuperscript{11} amphotericin B,\textsuperscript{12} polymyxin,\textsuperscript{13} tenuazonic acid,\textsuperscript{14} ethacrynic acid (EA),\textsuperscript{15} or aspirin.\textsuperscript{16} Thus, EA, a natriuretic agent which may inhibit both Na-K-dependent adenosine triphosphatase (ATPase) and adenylate cyclase in several tissues,\textsuperscript{17-20} unlike furosemide reduces cholera toxin-induced intestinal fluid secretion in dogs,\textsuperscript{21} but it also reverses cyclic AMP-mediated secretion in isolated rabbit ileal mucosa.\textsuperscript{22} On the other hand, it has been shown that aspirin, an inhibitor of PG biosynthesis,\textsuperscript{23} antagonizes cholera toxin-induced secretion both in cat and rat intestine.\textsuperscript{24,25} The secretory effect of cholera toxin through endogenous PG release has been suggested,\textsuperscript{26} but this hypothesis is not supported by recent studies.\textsuperscript{14,15} Finally, the influence of aspirin on the intestinal action of preformed PG's has not been investigated in vivo.

The present study reports the in vivo effect of EA, furosemide, and aspirin on basal and PGE\textsubscript{1}-induced movements of water and electrolytes in the human jejunum. Also studied were the time course and reproducibility of PGE\textsubscript{1} secretory action, as well as the effect of PGE\textsubscript{1} on plasma levels of various immunoreactive hormones known to be capable of inducing net intestinal secretion.
Methods

Experimental procedure. Studies were performed on 35 healthy male volunteers, ages 21 to 42, who gave informed consent. A technique of intestinal perfusion with a four-lumen tube including a proximal occluding balloon was used, as previously described,2 to prevent contamination by endogenous secretions and reflux of the infused solution above the infusion point. The test segment located immediately below the balloon was 25 cm long. The tube was swallowed by the subject 18 to 24 hr before the test, and the perfusion started when the infusion point, checked radiologically, was just beyond the ligament of Treitz. Each subject fasted for 12 hr before the experiment. Test solutions, warmed to 37°C, were infused at a constant rate of 10 ml per min by a Technicon infusion pump; at the beginning of the perfusion the balloon was inflated with 40 ml of air and its occluding effect was checked as previously indicated.3 For each period of measurement, three 10-min samples were recovered from the distal point of the test segment by siphonage or gentle suction, after an equilibration period of 30 to 45 min. The bowel proximal to the balloon was aspirated continuously. The perfusing solution was isotonic to plasma, and contained NaCl 130 mM, KCl 5 milliosmoles, before perfusion. In one of the experimental studies, a mannitol-saline solution was used, consisting of NaCl 90 mM, KCl 10 mM, mannitol 100 mM, and PEG 4000 g per liter.

Experimental design. Five sets of experiments were carried out. The total number of experiments was 75, i.e., an average of two per subject performed on separate days. In every PGEi period, study of PGEi was infused into the jejunal lumen at a rate of 0.9 µg per kg per min for 75 min (45 min of equilibration, and 30 min of sampling); this dosage has been previously shown to induce net secretion in the human jejunum.

In the first set of experiments, the duration and reversibility of PGEi effect on absorption were investigated in 10 subjects by prolonging collection of intestinal fluid during eight 10-min periods after cessation of PGEi administration. The reproducibility of PGEi effect on absorption throughout a 6-hr perfusion study was investigated in 19 subjects (fig. 1): results of transmucosal fluxes of glucose, water, and ions during an initial PGEi period of study were compared to those obtained in a second PGEi period starting 150 min after the end of the first period. Blood samples for radioimmunossay of diverse gastrointestinal hormones, and of calcitonin, PGEi, and PGEi, were obtained in 11 subjects, during control periods and at the end of the first 10-min collection of PGEi study periods.

In the second set of experiments, the effects of EA on basal and PGEi-induced net movements of glucose, water, and electrolytes were studied in 13 subjects, as shown in figure 1. During the first 15 min of two equilibration periods (EA and EA + PGEi), EA (total dose: 2.5 mg per kg) was delivered with the glucose-saline solution into the jejunal lumen. The experimental sequence in each subject consisted of the following periods: control, PGEi, control, EA, and EA + PGEi. We also investigated in 5 subjects the duration of the EA effect on absorption by prolonging intestinal fluid collections during set (in 10 min additional periods).

In the third experimental set, the furosemide effect on fluid transport (total dose: 1.5 mg per kg administered intraluminally) was studied in 7 subjects using the same protocol as for EA. Isotonic saline was used intravenously during both EA and furosemide studies to maintain a constant hydration (250 to 500 ml for 75 min); hematocrit and electrolyte plasma concentrations were determined immediately before and 1 hr after the administered EA or furosemide.

In the fourth set, using a similar experimental design, we studied the effect of a very water-soluble form of aspirin (lysine acetylsalicylate, Aspecig, Egric Laboratories, France) that was infused during 15 min either intraluminally (40 mg per kg, 7 subjects), or intravenously (25 mg per kg, 5 subjects). Peripheral blood samples were taken from each subject at 0, 30, 60, 90, and 120 min after aspirin infusion to measure total salicylate levels.

Besides reducing PGEi-induced secretion, EA was also observed to promote per se a net secretion of water and ions. Therefore, a fifth set of experiments was undertaken, in order to determine whether the inhibition of PGEi-mediated secretion by previous EA administration was merely due to the fact that the jejunum was already in a secretory state; for this purpose, we studied in 9 subjects the secretory effect of PGEi with a mannitol-saline solution which, in normal basal conditions, induces a net water and sodium secretion.

Chemical analysis. Sodium and potassium were measured by flame photometry; glucose and chloride were analyzed on a Technicon AutoAnalyzer. PEG was determined in duplicate by the method of Hyden,42 and Na was counted on a gamma counter (Picker X-Ray Corp., White Plains, N. Y.). Plasma levels of diverse gastrointestinal hormones,27 i.e., glucagon, vasoactive intestinal peptide (VIP), secretin, motilin, and gastrin, and of calcitonin,27 PGEi,27 and PGEi,42 were measured by radioimmunosassay. Total serum salicylate was measured according to a colorimetric method.46 Albumin in the intestinal fluid was determined according to the immunodiffusion method of Mancini et al.,41 using an anti-human albumin antiserum (obtained from Behrinwerke, AG, Marburg, Germany); the absence of pancreatic trypsin and chymotrypsin activity in the fluid (collected below the occluding balloon) was checked in 10 subjects.

Calculation of results. Net movements of water and electrolytes were calculated as previously indicated.4 Unidirectional fluxes of sodium were determined according to the method of Visscher et al.44 For net movements, a minus sign
indicates absorption from the lumen, and a plus sign indicates secretion into the lumen. The term insorption refers to unidirectional flux from lumen to blood, and the term exsorption refers to the opposite flux. Data are presented as the mean ± SEM. Statistical analysis was performed by block design method for each set of experiments, because each subject acted as his own control. Neumann-Karls methods and Tukey's t-test were used for multiple comparisons within each set of experiments. Student's t-test using residual variance obtained in block design analysis allowed comparisons between several sets of experiments.

Results

Effect of PGE₁ on Water, Electrolyte, Glucose, and Albumin Transintestinal Movements

Glucose-saline solution. In all of the subjects tested, PGE₁ reversed the net absorption of sodium (figs. 2 and 3), water, chloride, and potassium (table 1) into a profuse net secretion (P < 0.001), and reduced the glucose absorption by an average of 20% (P < 0.001). Sodium exsorption was strikingly increased (P < 0.001) while the reverse flux decreased (P < 0.001) (table 2). Albumin output into the lumen (506 ± 101 µg per min per 25 cm) increased, as compared to control levels (179 ± 44 µg per min per 25 cm) by an average of 290% (P < 0.01). The rate of fluid recovery from the jejunal lumen proximal to the occluding balloon was similar (P > 0.70, n = 25) during PGE₁ (18 ± 6 ml per 30 min) and control (27 ± 6 ml per 30 min) periods of study.

Mannitol-saline solution. PGE₁ induced a large increase in net water and electrolyte secretion (P < 0.001), as compared to control levels (table 1). Secretion rates of water and sodium during mannitol-saline-PGE₁ perfusions were significantly (P < 0.001) higher than with glucose-saline-PGE₁, but the change in sodium and water transport (net secretory effect) induced by PGE₁ was slightly less with the former than with the latter solution (fig. 4).

Duration and Reproducibility of PGE₁ Effect on Fluid and Electrolyte Absorption

Results concerning the time course of the secretory effect of PGE₁ are shown in figure 3 for net sodium and water movements. After the end of PGE₁ infusion, net secretion declined in 30 min, and movements of fluid and solutes including glucose and albumin returned to control levels by 60 min.

The effect of PGE₁ on fluid, ion, and glucose absorption was entirely reproducible throughout the duration of the perfusion experiments, as shown in figure 2 for sodium; in the 19 subjects tested, the mean variability of results between the first and the second PGE₁ period of study was less than 5%.

Influence of EA, Furosemide, and Aspirin on Basal and PGE₁-Induced Movements of Water and Electrolytes

EA studies. As shown in figure 4 and table 1, EA itself induced net secretion of water and ions, and reduced
The net effect of PGE, on transport rates, as evaluated during administration of PGE, alone (fig. 4, table 1); the net secretion of water, sodium, and other ions decreased significantly \((P < 0.01)\) as compared to that observed during administration of PGE, alone (fig. 4, table 1); the rate of secretion was also much lower \((P < 0.001)\) than that induced by PGE, with the mannitol-saline solution. The net effect of PGE, on transport rates, as evaluated from the differences in flux rates between EA + PGE, (or PGE,) and EA (or control) periods of study, was reduced \((P < 0.001)\) after EA administration by an average of 78% for sodium and 75% for water. In spite of this, the combination of EA and PGE, resulted in a further decrease in glucose absorption (41% of control levels), as compared to the decrease induced by PGE, (20%) or EA (23%) alone. In the EA + PGE, period no increase in sodium exsorption was observed (table 2). After EA administration, the subjects exhibited increased urinary output within 40 min; the maximum diuretic effect was observed 30 to 90 min after EA, with a mean urinary output of 15 ml per min during this time period. One hour after EA administration, hematocrit and electrolyte plasma concentrations did not differ significantly from control levels.

**Furosemide studies.** Administration of furosemide did not result in any significant changes \((P > 0.50)\) in glucose, water, and electrolyte absorption rates, nor in PGE,,-induced net secretion (fig. 4, table 1). All subjects

### Table 1. Effects of EA, furosemide, and aspirin on net basal absorption of glucose, water, and electrolytes, and on PGE,,-induced jejunal secretion (mannitol-saline solution), and effect of PGE, on net water and ion transport from a mannitol-saline solution

<table>
<thead>
<tr>
<th>Studies</th>
<th>Water</th>
<th>Chloride</th>
<th>Potassium</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-saline solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA control (1st period)</td>
<td>-3.0 ± 0.30</td>
<td>-382 ± 42</td>
<td>-6 ± 2</td>
<td>-284 ± 5</td>
</tr>
<tr>
<td>PGE,</td>
<td>3.43 ± 0.43</td>
<td>523 ± 73</td>
<td>30 ± 3</td>
<td>-237 ± 10</td>
</tr>
<tr>
<td>EA control (2nd period)</td>
<td>-2.92 ± 0.27</td>
<td>-388 ± 45</td>
<td>-2 ± 2</td>
<td>-279 ± 6</td>
</tr>
<tr>
<td>EA</td>
<td>0.62 ± 0.25</td>
<td>120 ± 36</td>
<td>16 ± 3</td>
<td>-222 ± 12</td>
</tr>
<tr>
<td>EA + PGE,</td>
<td>1.22 ± 0.30</td>
<td>232 ± 46</td>
<td>17 ± 2</td>
<td>-169 ± 11</td>
</tr>
<tr>
<td>Furosemide studies (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (1st period)</td>
<td>-3.14 ± 0.38</td>
<td>-414 ± 65</td>
<td>8 ± 2</td>
<td>-278 ± 9</td>
</tr>
<tr>
<td>PGE,</td>
<td>3.42 ± 0.43</td>
<td>517 ± 75</td>
<td>27 ± 3</td>
<td>-241 ± 11</td>
</tr>
<tr>
<td>Control (2nd period)</td>
<td>-3.18 ± 0.26</td>
<td>-428 ± 45</td>
<td>-10 ± 2</td>
<td>-293 ± 8</td>
</tr>
<tr>
<td>Furosemide</td>
<td>-3.28 ± 0.27</td>
<td>-438 ± 44</td>
<td>-9 ± 2</td>
<td>-298 ± 5</td>
</tr>
<tr>
<td>Furosemide + PGE,</td>
<td>3.32 ± 0.44</td>
<td>509 ± 54</td>
<td>25 ± 2</td>
<td>-248 ± 8</td>
</tr>
<tr>
<td>Aspirin studies (n = 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (1st period)</td>
<td>-2.81 ± 0.35</td>
<td>-353 ± 60</td>
<td>3 ± 2</td>
<td>-280 ± 5</td>
</tr>
<tr>
<td>PGE,</td>
<td>2.69 ± 0.35</td>
<td>435 ± 52</td>
<td>25 ± 3</td>
<td>-222 ± 10</td>
</tr>
<tr>
<td>Control (2nd period)</td>
<td>-2.70 ± 0.16</td>
<td>-360 ± 35</td>
<td>3 ± 1</td>
<td>-283 ± 5</td>
</tr>
<tr>
<td>Aspirin</td>
<td>-2.91 ± 0.29</td>
<td>-341 ± 32</td>
<td>-3 ± 2</td>
<td>-284 ± 6</td>
</tr>
<tr>
<td>Aspirin + PGE,</td>
<td>2.71 ± 0.30</td>
<td>437 ± 56</td>
<td>26 ± 4</td>
<td>-223 ± 13</td>
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<tr>
<td>Mannitol-saline solution (n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.06 ± 0.24</td>
<td>106 ± 40</td>
<td>-32 ± 4</td>
<td>0</td>
</tr>
<tr>
<td>PGE,</td>
<td>5.84 ± 0.36</td>
<td>754 ± 60</td>
<td>0 ± 4</td>
<td>0</td>
</tr>
</tbody>
</table>

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- * indicates net absorption, + indicates net secretion.
- \( P < 0.01 \) compared to control periods.
- \( P < 0.05 \) compared to control periods.
- \( P < 0.50 \) compared to EA.

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**Table 2. Effect of PGE, EA, and EA + PGE, on sodium unidirectional fluxes (7 subjects)**

<table>
<thead>
<tr>
<th>Periods of study</th>
<th>Insorption (lumen to plasma)</th>
<th>Exsorption (plasma to lumen)</th>
<th>( \mu \text{Eq} / \text{min} / 25 \text{ cm} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st control period</td>
<td>1107 ± 75</td>
<td>801 ± 55</td>
<td>107 ± 55</td>
</tr>
<tr>
<td>PGE,</td>
<td>576 ± 100</td>
<td>1124 ± 100</td>
<td>76 ± 55</td>
</tr>
<tr>
<td>2nd control period</td>
<td>1020 ± 58</td>
<td>768 ± 64</td>
<td>76 ± 64</td>
</tr>
<tr>
<td>EA</td>
<td>650 ± 53</td>
<td>746 ± 69</td>
<td>65 ± 69</td>
</tr>
<tr>
<td>EA + PGE,</td>
<td>425 ± 40</td>
<td>706 ± 69</td>
<td>42 ± 69</td>
</tr>
</tbody>
</table>

- \( P < 0.01 \) compared to control periods.
- \( P < 0.05 \) compared to EA.
- \( P < 0.001 \) compared to control periods.

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* Glucose absorption by an average of 25%; the rate of fluid secretion was significantly lower \((P < 0.001)\) than that induced by PGE, alone. In the EA period, sodium insorption was decreased \((P < 0.01)\), but exsorption was unchanged (table 2). In the 5 subjects in whom fluid collection was prolonged during 70 min after the initial EA collection period, net secretion of water and sodium was still present in the last three 10-min periods, although 25% lower \((P < 0.05)\) than during the initial EA study period. In the EA + PGE, period of study, net secretion of water, sodium, and other ions decreased significantly \((P < 0.01)\) as compared to that observed during administration of PGE, alone (fig. 4, table 1); the rate of secretion was also much lower \((P < 0.001)\) than that induced by PGE, with the mannitol-saline solution. The net effect of PGE, on transport rates, as evaluated from the differences in flux rates between EA + PGE, (or PGE,) and EA (or control) periods of study, was reduced \((P < 0.001)\) after EA administration by an average of 78% for sodium and 75% for water. In spite of this, the combination of EA and PGE, resulted in a further decrease in glucose absorption (41% of control levels), as compared to the decrease induced by PGE, (20%) or EA (23%) alone. In the EA + PGE, period no increase in sodium exsorption was observed (table 2). After EA administration, the subjects exhibited increased urinary output within 40 min; the maximum diuretic effect was observed 30 to 90 min after EA, with a mean urinary output of 15 ml per min during this time period. One hour after EA administration, hematocrit and electrolyte plasma concentrations did not differ significantly from control levels.
exhibited increased urinary output within 60 min. The maximum diuretic effect was observed 40 to 90 min after furosemide, the mean urinary output being 10 ml per min during this time period. During furosemide studies, no significant changes in hematocrit or electrolyte plasma levels were observed in any of the 7 subjects tested.

Aspirin studies. Levels of total serum salicylate obtained after intravenous and intraluminal administration are shown in figure 5. Whatever the route of administration, aspirin did not promote any significant change ($P > 0.70$) in glucose, water, and ion absorption nor in PGE$_1$-mediated secretion of fluid and electrolytes; results of intravenous and intraluminal aspirin studies were combined (fig. 4, table 1).

Effect of PGE$_1$ on Plasma Immunoreactive Levels of PGs, Calcitonin, and Diverse Gut Hormones

During PGE$_1$ infusion, no significant changes in plasma levels of calcitonin, VIP, secretin, motilin, gastrin, total, and pancreatic glucagon were observed, as compared to control levels. PGE$_1$ and PGF$_2a$ plasma levels increased from $74 \pm 29$ to $249 \pm 130$ pg per ml, and from $18 \pm 5$ to $39 \pm 12$ pg per ml, respectively, but differences did not reach significance ($P = 0.10$).

Clinical Effects of PGE$_1$, Jejunal Infusion

No significant changes in systemic blood pressure or heart rate were noted during or after PGE$_1$ administration in any of the subjects tested. In 59% of the subjects a usually moderate watery diarrhea was observed within 6 hr after the end of the perfusion; i.e., in 5 of the 13 subjects who underwent PGE$_1$, EA, and EA + PGE$_1$ studies, 8 of the 12 subjects who underwent PGE$_1$, aspirin, and aspirin + PGE$_1$ studies, and 13 of the 19 subjects who received PGE$_1$ alone twice during the same perfusion experiment.

Discussion

The present data show that EA inhibits the secretory response in human jejunum to PGE$_1$. It is unlikely that this EA effect was mediated by the diuretic action of the drug or by systemic changes in water and electrolyte balance, because (1) furosemide, another potent diuretic agent, did not result in any modification in PGE$_1$-induced fluid secretion; (2) during EA and furosemide studies, urinary losses were compensated by intravenous saline infusion, and no significant variations in hematocrit or electrolyte plasma concentrations were observed throughout the studies. The possible role of mesenteric
and/or mucosal blood flow changes cannot be excluded from this study; however, it is noteworthy that a reduction up to 70% of the superior mesenteric artery blood flow does not modify significantly the response of canine jejunum to a secretory stimulus such as cholera toxin.28 In the present work, the EA and EA + PGE, periods of study were not randomized because of the prolonged action of EA on absorption; but it can be reasonably assumed that the EA effect on PGE,-induced secretion would not be influenced by the perfusion sequence, since there existed an excellent reproducibility of basal and PGE,-mediated flux rates throughout the perfusion experiment in the same subject.

These findings clearly suggest that the inhibitory effect of EA upon PGE,-mediated net secretion is not due to the stimulation of an absorptive process such as glucose-dependent water and sodium transport: (1) EA promoted by itself a slight net secretion of fluid and electrolytes together with a 25% reduction in fluid absorption; (2) EA combined to PGE, induced a further decrease in glucose absorption (40% of control values) and in lumen-to-plasma sodium unidirectional flux, while markedly decreasing PGE,-induced net secretion. An attractive hypothesis would be that EA, which is known to inhibit active transport processes (ouabainsensitive17, 34 and -insensitive16, 27) in several extradigestive tissues, would also inhibit an active intestinal secretory process. Although the physiological meaning of unidirectional fluxes as measured during in vivo perfusion studies is not entirely clear, it is of interest that EA completely suppressed the PGE,-induced increase in plasma-to-lumen unidirectional flux of sodium. However, the antiserotactatory effect of EA on PGE,-, cholera toxin-, and cyclic AMP-mediated secretion does not promise to be of therapeutic value because of its diuretic effect. As previously suggested,28 investigation of nonabsorbable EA derivatives on intestinal transport should be profitable. On the other hand, the inhibitory effect of EA, reported herein in vivo in man, is of special theoretical interest because EA has been previously shown to reverse cholera toxin- and cyclic AMP-mediated intestinal secretion in vitro,32 and to reduce, unlike furosemide, the response of dog jejunal mucosa to cholera toxin in vivo.18 Whether the drug acts on basal movements through inhibition of Na-K-dependent ATPase as in several other tissues,18, 33 and on PGE,-induced secretion through interaction with intestinal adenylate cyclase, remains to be determined; in a previous study, EA has been reported to inhibit mucosal adenylate cyclase activity both in control and in cholera toxin-treated rabbit intestine,28 whereas in another study it did not significantly affect cyclic AMP levels in isolated ileal mucosa.29

Bennett has suggested that PGs might mediate the cholera toxin effects on intestinal secretion.22 But a number of recent observations indicates that PGs do not provide an essential link in the activation of adenylate cyclase by cholera enterotoxin.14, 24 The latter studies do not firmly exclude, however, a cyclic AMP-independent, PG-mediated effect of the toxin in vivo, because aspirin and several other antiinflammatory agents have been reported to reduce cholera toxin-mediated fluid accumulation in animals.16, 22 Whether these drugs act only by depressing the endogenous biosynthesis of PGs or by preventing the action of PGs already formed is not entirely clear. The present data show that aspirin does not influence the secretory response of human jejunum to preformed PGE,.

Up to now there was little information on the in vivo influence of renal drugs on intestinal absorption. In vitro studies have shown that EA inhibits the absorption of water,26 sodium,41 aminoacids, sugars,42 and pyrimidine41 in hamster, rabbit, or rat small intestine. The present results confirm in man similar EA effects on water and ion fluxes. However, the intimate mechanism of EA inhibitory action on glucose and sodium intestinal transport cannot be elucidated from these data; Chez et al.71 have shown from in vitro studies that EA impairs the ability of intestinal tissue to maintain a low intracellular sodium concentration and a high intracellular potassium concentration, and therefore have suggested that EA might exert an inhibitory effect on a sodium extrusion mechanism within the epithelial cell. Conversely, the present data on furosemide action on mucosal transport are at variance with those reported by Mackenzie et al.,42 who have shown that intravenous furosemide reduces net absorption of water and ions in man. This discrepancy might be explained in terms of dosage and route of administration, but a very recent work indicates that furosemide does not influence fluid and electrolyte output in the human distal duodenum.

The present study also brings out some new information on the characteristics of PGE,-induced jejunal secretion in man. Under the experimental conditions described, the secretory effect of PGE, was entirely reproducible within the duration of the perfusion experiments, and was fully reversible by 60 min after cessation of PGE, administration. The absence of changes in systemic blood levels of diverse immunoreactive hormones suggests that PGE, does not act through release of hormones capable of inducing intestinal secretion. The observation that PGE, did not increase the fluid recovery rate above the inflated balloon is in agreement with a local mucosal effect of the drug, as previously suggested.5, 3 Data on protein movements indicate that PGE, increases albumin output toward the lumen; a similar increase in total protein content of intestinal fluid has been reported in dog jejunal mucosa exposed to PGE,26.4 It is unlikely that these findings are a result of gross structural damage, because of the rapid reversibility and short-term reproducibility of PGE, action on fluid movements. In contrast, whether the increased protein loss indicates that PGs enhance permeability of mucosal capillaries or induce a subtle change in membrane structure is unknown.

PGs have been reported to be present in intestinal contents of some animal species,24 but to our knowledge, in man no data are available. Because the local tissue concentration of PGE, was unknown, it cannot be stated from the present data whether PGE, plays a physiological role in water and electrolyte movements across human small bowel mucosa.48 Nevertheless, several of
the characteristics of PGE\textsubscript{1} action as shown in this paper (i.e., magnitude, rapid onset and reversibility, reproducibility) indicate that PGE\textsubscript{1}, when administered intraluminally, is one of the most convenient tools for studying intestinal secretory processes in vivo in man and for investigating the influence of antisecretory drugs.

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