Physiological effects of enteral and parenteral feeding on pancreaticobiliary secretion in humans

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OVER THE PAST 30 YEARS, great advances have been made in the nutritional support of hospitalized patients, such that there are few situations remaining where patients cannot be fed. Following Dudrick and Rhoads’ landmark studies (7) on beagle pups in the late 1960s showing that the intravenous feeding of a sterile solution of glucose, protein hydrolysate, and micronutrients (total parenteral nutrition [TPN]) allowed normal growth, TPN has been successfully used to sustain life and productivity in patients with gastrointestinal failure (26). However, TPN is associated with potentially serious side effects, particularly those associated with catheter-related sepsis, hyperglycemia, and venous thrombosis, and recent efforts have focused on new ways of using enteral access. For example, bypassing the stomach and infusing the diet in liquid form directly into the jejunum can often successfully feed critically ill patients with high gastric residues, nausea, and vomiting—which is a common indication for TPN. This has led to a profusion of interventional enteral feeding techniques, including fluoroscopic or endoscopic nasoenteric tube placement, percutaneous endoscopic, radiological or surgical gastrostomy with gastrojejunal extension, and direct surgical or endoscopic jejunostomy (41).

There is, however, concern that enteral and parenteral feeding may impair the normal process of pancreatic enzyme secretion, because the initial phases of pancreatic stimulation, i.e., the cephalic and the gastric phases, will be bypassed. Although it is generally assumed in clinical practice that intravenous feeding will avoid food-stimulated enzyme secretion, few systematic comparisons between enteral and parenteral feedings have been made. Published studies (22, 28) on mammalian physiology that are available have revealed contradictory results, with one study (20) in dogs concluding that intravenous amino acids and fat

O'Keefe, Stephen J. D., Ronzo B. Lee, Frank P. Anderson, Chris Gennings, Souheil Abou-Assi, John Clore, Douglas Heuman, and William Chey. Physiological effects of enteral and parenteral feeding on pancreaticobiliary secretion in humans. Am J Physiol Gastrointest Liver Physiol 284: G27–G36, 2003; 10.1152/ajpgi.00155.2002.—In the nutritional management of digestive disorders, it is important to know the relative secretory and metabolic responses to enteral and parenteral feeding. Twenty-seven healthy volunteers were studied while receiving either oral drinks or duodenal infusions of a complex formula diet, duodenal or intravenous infusions of elemental (protein as free amino acids, low fat) formulae, or saline. Pancreaticobiliary secretory responses were measured by nasoduodenal polyethylene glycol perfusion and aspiration, while monitoring blood hormone and nutrient levels. Diets were matched for protein (1.5 g·kg−1·d−1) and energy (40 kcal·kg−1·d−1). Compared with placebo, all oroenteral diets stimulated amylase, lipase, trypsin, and bile acid secretion and increased plasma concentrations of gastrin and cholecystokinin, whereas intravenous feeding did not. The complex formula produced a similar response whether given as drinks or duodenal infusions. Changing the duodenal formula to elemental reduced enzyme secretion by 50%, independently of CCK. Higher increases in plasma insulin, glucose, and amino acids were noted with intravenous feeding. Delivering food directly to the intestine by a feeding tube does not reduce pancreaticobiliary secretion. Enteral “elemental” formulae diminish, but only intravenous feeding avoids pancreatic stimulation. Intravenous administration impairs metabolic clearance.

pancreatic enzyme secretion; enteral and parenteral nutrition

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actually stimulate secretion. Knowledge of the secretory response to interventional feeding is important in the management of patients with high output intestinal fistulae and in acute pancreatitis where the production and secretion of digestive enzymes may exacerbate the disease process. On the other hand, bowel rest and a lack of pancreaticobiliary secretion can be harmful because it leads to stasis and bacterial overgrowth of the normally relatively sterile small intestine. There is clearly a need to understand how the different kinds of feeding techniques affect gastrointestinal physiology before further advances in the nutritional support of hospitalized patients can be made.

It is likely that much of the divergence in the conclusions of previous feeding studies in animals and humans can be explained by variations in the methods of nutrient delivery and enzyme recovery. Consequently, our objective is to systematically study what happens to pancreatic enzyme secretion during enteral and parenteral feeding as it is practiced in hospitals, using a standardized enzyme collection technique. The hypotheses to be tested will be 1) that tube feeding reduces the normal pancreatic secretory stimulus to eating, 2) that predigestion (e.g., an elemental diet) reduces the secretory stimulus, and 3) that intravenous feeding avoids pancreatic stimulation.

METHODS

Experimental Procedure

Twenty-five healthy adult volunteers were randomly divided into five dietary groups to compare the relative effects of various types of commonly used enteral and parenteral feeding techniques on pancreatic enzyme secretion. Individual follow-up studies were performed to assess variability of enzyme secretory rates during feeding. Informed, signed consent was obtained from all volunteers after reviewing the protocol and approval by the Institution Review Board.

All subjects were admitted to the General Clinical Research Center the evening before the secretion study and were fasted from midnight. The study dietician took a 24-h dietary recall first thing in the morning, followed by measurement of nutritional composition by anthropometry and impedance plethysmography. Finally, basal metabolic rate was measured in a quiet private room. A double-lumen, duodenal perfusion/aspiration tube was then placed under fluoroscopy for the measurement of pancreatic enzyme secretion over a 4- to 6-h period during different dietary conditions. One group (n = 5) was given an intravenous and duodenal infusion of isotonic saline alone (placebo-saline group), and served as the control. The remaining four groups were all given diets providing 1.5 g of protein and 40 kcal energy·kg ideal body wt·day⁻¹. However, the mode of delivery of the diet and the composition varied as follows: 1) oral complex group (n = 5) received hourly drinks of a complex (polymeric) liquid formula diet (Ensure; Ross Abbott Laboratories, Chicago, IL); 2) duodenal complex group (n = 5) received continuous duodenal infusion of the same complex diet given to the oral group; 3) duodenal elemental group (n = 5) received continuous duodenal infusion of a liquid elemental formula diet (Vivonex; Novartis, Minneapolis, MN); and 4) intravenous group (n = 5) received continuous intravenous infusion of a 3-in-1 mixture of amino acids, glucose, and fat, synthesized in our pharmacy in proportions similar to the elemental diet and given into an antecubital vein.

Whereas the different diets were matched for protein and caloric content, the proportion of calories accounted for by fat was lower in the intravenous and elemental groups (i.e., 6% calories from fat) than in the oral and duodenal groups given the complex polymeric diet (22% calories from fat). The protein source in the elemental diet (Vivonex) was free amino acids and the energy source was maltodextrin, modified starch, and soybean oil, whereas the complex diet (Ensure) contained sodium and calcium caseinates, soy proteins, corn syrup, maltodextrin, sucrose, safflower oil, canola oil, and soy lecithin.

Nutritional Assessment

Body composition. Body mass index was calculated in kilograms per square meter from weight and height measurements. The proportion of body mass contributed by fat and lean body mass was calculated from the sum of triceps, biceps, and subcapsular and suprailiac skinfold thickness measurements measured using calipers (Lange Skinfold Calipers; Cambridge Scientific Industries, Cambridge MD) (8). Results were evaluated by comparison to percentage of body fat tables in Lange’s Skinfold Caliper Operators manual. Composition analysis was confirmed by bioelectrical imped ance measured with a bioelectrical impedance analyzer (model BIA-101, 1982; RJL Systems, Clinton Township, MI). Results were evaluated by comparison to the Body Comp II Program (DOS version 1.51h; c, 1988). Metabolic expenditure. Basal and resting metabolic rates were measured before and during the dietary infusion studies by indirect calorimetry (model 2900 metabolic cart; SensorMedics) under standard (resting, supine in a quiet room) conditions. Recordings were made after a steady state (at rest or a minimum of 10 min with a variance in VO₂ <10% and in resting energy expenditure (REE) of <5%) had been achieved.

Measurement of Pancreatic Enzyme and Bile Acid Secretion

The method was based on that previously described (25, 27, 28), using nutrients as secretagogues. Briefly, a 12-Fr double-lumen perfusion/aspiration tube (modified nasogastric decompression/jejunal feeding tube; Dobhoff Kangaroo, Kendall) was passed via the nose into the stomach and then guided by fluoroscopy into the duodenum, such that the perfusion port was adjacent to the ampulla of Vater and the aspiration tube at the ligament of Treitz. The tube consisted of an adjustable tube-within-a-tube that allowed final adjustment to the correct position with fluoroscopy before study commencement. All subjects then received a duodenal perfusion of normal saline containing 5 g/l polyethylene glycol (average molecular weight 5,500) at 300 ml/h and an infusion of saline at 80 ml/h iv. In the duodenal complex and duodenal elemental groups, the diet was added to the duodenal perfusate and the volume was made up with saline to maintain a perfusion rate of 300 ml/h. Throughout the study, mild suction (80 mmHg) was applied to the aspiration port. Aspired secretions were collected on ice and separated into 30-min fractions. One aliquot was taken for immediate measurement of trypsin concentration in the laboratory. Another
was stabilized with aprotinin and was frozen for amylase and lipase measurement. At the end of the 6-h infusions, an endoscopy was performed to check that tubes had remained in the correct position and to measure the volume of aspirated gastric contents.

In two further subjects, one given the elemental and one given the intravenous diet, aspirations were collected more frequently (every 10 min) to more accurately assess fluctuations in the secretory response.

Measurement of Plasma Gastopancreatic Hormones and Substrates

Venous blood samples were taken before the commencement of the secretion studies and again at 120 and 240 min during the studies to assess the relative effects of the different diets on gastrin, CCK, and insulin release. Blood glucose, free fatty acids, and amino acid concentrations were measured at the same time intervals. Heparinized plasma samples were frozen at −80°C to await analysis.

Sample Analysis

**Pancreatic enzymes.** Trypsin concentrations were measured as previously described (25, 32), within 2 h of aspiration of duodenal juice by measuring hydrogen ion liberation after incubation with p-toluenesulfonyl-L-arginine methyl ester. Results were expressed in national formulary (NF) units. Amylase and lipase were measured by automated Vitros dry multilayered slide technique (Johnson and Johnson Clinical Diagnostics, Rochester, NY). The principle of the procedure for amylase involves conversion of dyed amylopectin into smaller dyed saccharides. The kinetic rate of change was measured by reflectance spectrophotometry at 2.3 and 5 min (36). Comparison to the reference potentriphenol method gave correlation coefficients of 0.989–0.999. For lipase, triacetylglucorol was hydrolyzed by lipase and colipase contained in the juice sample to diacetylglucorol, which in turn was hydrolyzed to glucorol by diacetinase. Glycerol kinase and glycerophosphate oxidase further catabolized the glucorol to yield dihydroxyacetone phosphate (DHAP) and hydrogen peroxide, which reacted with a leuco dye. The resultant change in reflectance density was measured after 3.85 and 5 min. Concentrated samples were diluted with 2% BSA. It should be noted that colipase activity is included in this measurement. Results were expressed as standard international units per liter. Duplicate samples were used to measure percentage of duodenal marker (PEG) concentration by turbidity/spectrophotometry (15).

**Bile acids.** Duplicate duodenal juice samples were processed for HPLC measurement of total and individual bile acid content as previously described (12).

**Amino acids.** Plasma was deproteinized for the measurement of amino acid profile by reverse-phase precolumn derivatization HPLC as previously described (25).

**Gastropancreatic hormones.** Plasma CCK concentrations were measured as previously described by specific radioimmunooassay on the basis of the antibodies developed from multiple immunizations of rabbits with pure porcine CCK (4). Gastrin and insulin were measured in the same samples by radioimmunooassay (34).

**Free fatty acids.** Nonesterified fatty acids were measured in serum with the use a commercial kit (NEFA C, ACS-ACOD Method; Wako Chemicals, Richmond, VA) on the basis of the enzymatic conversion to acyl-CoA and subsequent condensation to a colored product that can be measured colorimetrically at 550 nm.

**Calculations**

Rates of pancreateobiliary secretion were calculated by PEG marker correction using the equation

\[
\text{Pancreatic enzyme and bile acid secretion (U/hr)} = \frac{\text{conc (U/ml)} \times \text{PEGin (g/l)} \times \text{IR (ml/hr)}}{\text{PEGout (g/l)}}
\]

where conc is concentration, PEGin is the concentration of PEG in the perfusate, PEGout is the PEG concentration in the aspirated juice, and IR is the rate of infusion of perfusate.

**Statistical Analysis**

**Demographics and nutritional assessment.** To test for group differences across each variable, a Kruskal-Wallis test was used.

**Enzyme and bile secretion rates.** A one-way ANOVA model was used to test for differences among the diets for each of the three enzymes. The model assumed \( y_{ij} = \mu_i + \epsilon_{ij} \), where \( y_{ij} \) is the average response from the \( j \)th volunteer over the 6 h of measurements in the \( i \)th diet, \( \mu_i \) is the mean response in the \( i \)th diet group, and \( \epsilon_{ij} \) are unobserved random error terms, assumed to be normally distributed with mean 0 and variance \( \sigma^2_{ij} = \sigma^2/\omega_{ij} \). The method of weighted least squares was used to estimate test statistics with \( \omega_{ij} = 1/s^2_{ij} \) is the weight for the \( j \)th subject in the \( i \)th diet with sample variance, \( s^2 \). Hypotheses about the diet effects among the diet groups were tested with appropriate \( F \)-tests. A 5% significance level was used throughout. All residuals were tested for normality at the 1% significance level by the Kolmogorov-Smirnov test.

On completion of the studies, it was found that the standard deviations were different across the volunteers. Consequently, subsequent analyses were conducted as weighted analyses with weights calculated as the inverse of the sample variance estimate over time for each subject. Results for the amylase and lipase responses were normally distributed, but those for trypsin were not, necessitating log transformation. In all three resulting analyses, there was no indication of a departure from normality. Responses to feeding in the four dietary groups were initially evaluated by comparison to the placebo response. Differences in the responses to the different forms of feeding were then compared to determine whether 1) bypass of the cephalic phase reduced the response (i.e., oral complex vs. duodenal complex), 2) predigestion reduced the secretory response (i.e., elemental duodenal vs. complex duodenal), and 3) intravenous feeding avoids stimulation (i.e., intravenous vs. duodenal elemental).

**Plasma concentrations.** A mixed-effects analysis of variance model parameterized to include group, time, and group-by-time interactions was used to describe the changes from baseline at 120 and 240 min. Let \( y_{ijk} \) be the change from baseline response from the \( j \)th subject in the \( i \)th group at the \( k \)th time point, \( i = 1,2,3,4 \); \( j = 1,\ldots, n_i \); and \( k = 1,2 \). Then the model is given by

\[
y_{ijk} = \mu + \delta_i + \tau_j + (\delta\tau)_{ij} + \epsilon_{ijk} \tag{1}
\]

where \( \mu \) is the grand mean, \( \delta_i \) is the added effect due to the \( i \)th diet, \( \tau_j \) is the added effect due to the \( j \)th time point, and \((\delta\tau)_{ij}\) is the interaction effect due to the \( i \)th diet and the \( k \)th time point, \( \epsilon_{ijk} = [\epsilon_{i1} \epsilon_{i2}]' \) is the random error vector for the \( j \)th subject in the \( i \)th diet assumed to have a null mean and \( 2 \times 2 \) covariance matrix \( \Sigma \).

The covariance structure for the within-subject responses was of the form

\[
\begin{bmatrix}
\Sigma_{ij} & \Sigma_{i+} \\
\Sigma_{+j} & \Sigma_{++}
\end{bmatrix}
\]

\( \Sigma_{ij} \) is the covariance matrix for the \( i \)th diet and the \( j \)th subject, \( \Sigma_{i+} \) is the covariance vector for the \( i \)th diet, \( \Sigma_{+j} \) is the covariance vector for the \( j \)th subject, and \( \Sigma_{++} \) is the covariance matrix for the \( i \)th diet and the \( j \)th subject. \( \Sigma_{ij} \) is then estimated sequentially as:

\[
\Sigma_{ij} = \frac{1}{n_i} \sum_{j=1}^{n_i} \hat{\epsilon}_{ijk} \hat{\epsilon}_{ijk}'
\]

where \( \hat{\epsilon}_{ijk} \) is the estimated residual for the \( j \)th subject in the \( i \)th diet at the \( k \)th time point.

On completion of the studies, it was found that the standard deviations were different across the volunteers. Consequently, subsequent analyses were conducted as weighted analyses with weights calculated as the inverse of the sample variance estimate over time for each subject. Results for the amylase and lipase responses were normally distributed, but those for trypsin were not, necessitating log transformation. In all three resulting analyses, there was no indication of a departure from normality. Responses to feeding in the four dietary groups were initially evaluated by comparison to the placebo response. Differences in the responses to the different forms of feeding were then compared to determine whether 1) bypass of the cephalic phase reduced the response (i.e., oral complex vs. duodenal complex), 2) predigestion reduced the secretory response (i.e., elemental duodenal vs. complex duodenal), and 3) intravenous feeding avoids stimulation (i.e., intravenous vs. duodenal elemental).
In general, it is of interest to determine which diet results in higher peptide levels and whether this changes over time. The usual null hypotheses ($H_0$) for interaction and main effects in the model in equation 1 are given as follows: hypothesis of no interaction ($H_1$) $H_0: (\delta_{iak} = 0$ for all $i,k$ vs. $H_1$: an inequality exists); hypothesis of no diet effect ($H_2$) $H_0: \delta_i = 0$ for all $i$ vs. $H_1$: an inequality exists; and (H3) $H_0: \tau_k = 0$ for all $k$ vs. $H_1$: an inequality exists.

Tests for interaction and main effects were on the basis of the usual $F$-test statistic.

RESULTS

Demographics and Nutritional Assessment

Table 1 summarizes the physical and nutritional characteristics of the five study groups. There were no significant baseline differences in the group mean values for age, sex, nutritional status, previous dietary consumption, and metabolic rates. Dietary intake rates for protein and energy were similar for all the fed subgroups. Body fat content measured by anthropometry, 23.9 ± 1.8%, was similar to, and closely ($P < 0.0001$) correlated with the measurement by impedance plethysmography of 25.7 ± 2.0%.

Enzyme Secretion

The PEG recovered was similar among the different dietary groups: 16% for oral, 18% for duodenal complex, 31% for elemental, 27% for intravenous, and 20% for placebo-saline. Similarly, the mean volumes of gastric juice remaining at the termination of the studies was similar for the oroenteral groups, i.e., 69 ml for the oral group, 70 ml for the duodenal complex, and 51 ml for the elemental group.

Secretion rates were shown to vary considerably from one 30-min collection to another. Figure 1 shows the detailed secretory pancreatic enzyme and bile acid secretion patterns in the two subjects receiving the elemental (enteral) and intravenous (parenteral) diet whose secretions were sampled every 10 min for 6 h. A similar cyclical secretory wave pattern in response to enteral feeding was identified in all three pancreatic enzymes and in bile acids. Using the definitions of waves proposed by Holtmann et al. (14), we noted that the waves occurred approximately every 40 min, with amplitudes of 30–50% of the medium response. Because secretion rates were considerably lower during parenteral feeding, no clear pattern could be detected.

Comparison of results when expressed as rates per whole body, per kilogram body weight, and per kilocalorie metabolic rate (i.e., REE; see Table 1) showed that the significances of the differences among the groups were accentuated by correction for body mass and metabolic expenditure. For this reason, and because diets were given in relationship to body weight, secretion rates are quoted in per kilogram body weight.

Secretory Response to Feeding

Table 2 compares the relative pancreatic enzyme secretory responses induced by the various forms of enteral and parenteral feeding to the baseline rates observed during placebo saline infusions. Although the magnitude of the response varied, all three oroenteral diets stimulated secretion in contrast to intravenous feeding that did not, as we had hypothesized. In fact, amylase secretion during intravenous feeding was lower ($P = 0.001$) than placebo (Fig. 2).

Contrary to our first hypothesis, the secretory response to oral feeding was not greater than that induced by infusion of the same diet directly into the

Table 1. Baseline and demographic summary statistics across diet and placebo groups. The corresponding $P$ values are based on a Kruskal-Wallis test comparing across the groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diet Group</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duodenal Complex</td>
<td>Duodenal Elemental</td>
<td>IV</td>
<td>Oral Complex</td>
<td>Placebo-Saline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>3:2</td>
<td>3:2</td>
<td>3:2</td>
<td>3:2</td>
<td>3:2</td>
<td>0.843</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>35.4 ± 11.8</td>
<td>28.2 ± 8.3</td>
<td>31.6 ± 10.2</td>
<td>34.4 ± 12.1</td>
<td>33.4 ± 13.6</td>
<td>0.998</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.3 ± 19.1</td>
<td>77.1 ± 17.3</td>
<td>76.3 ± 17.4</td>
<td>75.9 ± 15.5</td>
<td>78.6 ± 14.2</td>
<td>0.986</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.1 ± 6.1</td>
<td>25.0 ± 3.6</td>
<td>25.8 ± 4.3</td>
<td>24.5 ± 3.0</td>
<td>25.5 ± 4.2</td>
<td>0.592</td>
<td></td>
</tr>
<tr>
<td>%Lean body mass</td>
<td>76.4 ± 11.4</td>
<td>74.8 ± 5.5</td>
<td>73.4 ± 8.0</td>
<td>76.0 ± 5.9</td>
<td>74.0 ± 16.5</td>
<td>0.393</td>
<td></td>
</tr>
<tr>
<td>REE, kcal/d</td>
<td>1484.8 ± 211.7</td>
<td>1678.6 ± 448.6</td>
<td>1771.8 ± 371.2</td>
<td>1532.0 ± 326.3</td>
<td>1694.0 ± 309.6</td>
<td>0.352</td>
<td></td>
</tr>
<tr>
<td>24-h dietary analysis</td>
<td>2375.8 ± 658.3</td>
<td>1594.0 ± 122.0</td>
<td>2076.2 ± 872.7</td>
<td>1689.2 ± 723.9</td>
<td>2285.6 ± 921.2</td>
<td>0.684</td>
<td></td>
</tr>
<tr>
<td>Protein, g/d</td>
<td>112.3 ± 43.2</td>
<td>65.9 ± 6.9</td>
<td>81.5 ± 25.9</td>
<td>74.7 ± 40.2</td>
<td>83.8 ± 31.0</td>
<td>0.352</td>
<td></td>
</tr>
<tr>
<td>Fat, g/d</td>
<td>70.6 ± 31.2</td>
<td>46.6 ± 19.1</td>
<td>52.4 ± 48.8</td>
<td>54.4 ± 30.0</td>
<td>62.8 ± 24.6</td>
<td>0.393</td>
<td></td>
</tr>
<tr>
<td>Study intake, kcal·h⁻¹</td>
<td>1.5 ± 0.34</td>
<td>1.4 ± 0.22</td>
<td>1.4 ± 0.37</td>
<td>1.6 ± 0.15</td>
<td>0.037 ± 0.008</td>
<td>0.010 ± 0.001</td>
<td>0.010 ± 0.001</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n = 5$ volunteers per group. Dietary analysis (24-h) represents the usual prestudy intake of participants calculated by dietary recall. The study intakes of protein and energy were similar in all 4 dietary groups, and the dietary composition was similar in the oral and duodenal groups, in the elemental and iv groups. BMI, body mass index. REE, resting energy expenditure during the studies. $P$ values are based on a Kruskal-Wallis test comparing across the groups.

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duodenum; in fact, the trypsin response was lower \((P = 0.02)\). However, in keeping with our second hypothesis, changing the composition from complex to elemental reduced the overall secretory response to duodenal infusion by \(-50\%\) (amylase was reduced 52\%; \(P = 0.04\); trypsin was reduced 44\%; \(P = 0.03\); lipase was reduced 38\%).

Figure 3 shows the different patterns of total bile salt secretion during placebo-saline or nutrient infusion. Secretion rates were similar for all oroenteral diets and higher than in the intravenous \((P < 0.0001)\) and placebo saline \((P < 0.0001)\) infusions. However, the pattern of response was different to pancreatic enzyme secretion, with higher secretion with duodenal feeding of both polymeric and elemental formulae compared with oral drinks. There was no difference between placebo and intravenous groups \((P = 0.3)\). Analysis of the different bile acid composition of juice showed no differences among the groups and no change during the course of the infusions (data not shown).

### Blood Concentrations

No significant group differences in baseline preinfusion gastrin, CCK, glucose, insulin, amino acid, and free fatty acid concentrations were found. Figure 4 illustrates the group changes in gastrin concentrations at 120 and 240 min of nutrient infusion. Levels increased significantly in the three oroenteral groups, whereas there was no significant change in the intravenous and placebo groups. Consequently, levels achieved in the oroenteral groups were higher than in the intravenous group \((P = 0.007)\). Whereas plasma concentrations were highest in the orally fed group and continued to increase with time, the differences in overall responses were no different from the two tube-fed groups.

Figure 5 illustrates that all three oroenteral groups developed increases in plasma CCK concentrations during nutrient infusion, with no differences among the groups.

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### Table 2. Pancreatic enzyme secretory responses relative to various forms of enteral and parenteral feeding compared to placebo

<table>
<thead>
<tr>
<th>Dietary group</th>
<th>Amylase, IU·kg(^{-1})·h(^{-1})</th>
<th>(P) Value</th>
<th>Lipase, IU·kg(^{-1})·h(^{-1})</th>
<th>(P) Value</th>
<th>Trypsin, NPU·kg(^{-1})·h(^{-1})</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-saline</td>
<td>35.8 ± 13.1</td>
<td></td>
<td>954 ± 323</td>
<td></td>
<td>3.088 ± 0.554</td>
<td></td>
</tr>
<tr>
<td>Oral complex</td>
<td>229.9 ± 74.6</td>
<td>0.001</td>
<td>9225 ± 2571</td>
<td>0.006</td>
<td>5.659 ± 1.456</td>
<td>0.218</td>
</tr>
<tr>
<td>Duodenal complex</td>
<td>220.5 ± 32.7</td>
<td>0.002</td>
<td>10920 ± 2755</td>
<td>0.001</td>
<td>10.961 ± 1.927</td>
<td>0.001</td>
</tr>
<tr>
<td>Duodenal elemental</td>
<td>105.7 ± 16</td>
<td>0.208</td>
<td>6719 ± 1801</td>
<td>0.033</td>
<td>6.479 ± 1.328</td>
<td>0.103</td>
</tr>
<tr>
<td>Intravenous</td>
<td>26.6 ± 13.1</td>
<td>0.001</td>
<td>989 ± 432</td>
<td>0.990</td>
<td>4.380 ± 1.516</td>
<td>0.530</td>
</tr>
</tbody>
</table>

Values are means ± SD; \(n = 5\) volunteers per group. In comparison to placebo saline infusions, all 3 oroenteral diets were associated with higher secretion rates, whereas intravenous feeding produced lower amylase secretion (see \(P\) values). Between group comparisons showed that amylase \((P = 0.04)\) and lipase \((P = 0.03)\) secretion was lower with duodenal elemental diet infusions than duodenal complex polymeric diet infusions. Evaluation of differences was by 1-way ANOVA.
their individual responses. In contrast, there was no change in levels in the intravenous and placebo groups. Once again, levels were higher in the oroenteral groups than in the intravenous \((P = 0.004)\) and placebo \((P = 0.007)\) groups.

Figure 6 shows that all four dietary groups developed increases in blood glucose concentrations during the infusions. Furthermore, unlike the changes in gastrin and CCK, there was a time effect with levels peaking at 120 min. The glycemic responses were higher \((P = 0.001)\) in the intravenous group than all three oroenteral groups. No significant change was noted in the placebo-saline group. Consequently, glucose responses to both intravenous \((P < 0.0001)\) and enteral feeding \((P = 0.008)\) were higher than placebo responses. The pattern of insulin responses to enteral and parenteral feeding (Fig. 7) almost exactly followed the glucose responses. Concentrations during intravenous feeding were higher than during placebo-saline infusions \((P = 0.005)\).

Amino acid concentrations remained constant in the oroenterally fed subjects, but total amino acids, glycine, and alanine all increased in the intravenous group. For example, total amino acid concentrations increased from \(1,740 \pm 114\) to \(2,402 \pm 263\) \((P < 0.001)\), glycine from \(354 \pm 40\) to \(540 \pm 61\) \((P < 0.001)\), and alanine from \(243 \pm 35\) to \(354 \pm 46\) nmol/ml \((all \ P < 0.01)\).

Free fatty acid concentrations decreased \((P < 0.001)\) at 120 and 240 min in all the fed groups in contrast to the fasted placebo group where they remained constant (Fig. 8).

**DISCUSSION**

In the series of studies reported, we have demonstrated clinically relevant differences in the pancreatic secretory responses to various forms of enteral and parenteral feeding commonly used for the nutritional support of hospitalized patients. It is important to recognize that the method we used is on the basis of the physiological response to feeding and therefore, does not simply test pancreatic exocrine function, as in the conventional intravenous CCK stimulation test, but also tests intestinal function, triggering the physiolog-

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**Fig. 2.** Amylase secretion in response to enteral and parenteral nutrition. Relative amylase secretory responses to enteral and parenteral feeding, illustrating no difference between oral and duodenal feeding of a complex diet, an intermediate response to duodenal elemental diet feeding, and no stimulatory effect of intravenous feeding compared with placebo saline.

**Fig. 3.** Total bile acid secretion in response to enteral and parenteral feeding. Total bile salt secretion in response to the different forms of feeding, illustrating suppression \((P < 0.0001)\) by intravenous feeding compared with oroenteral feeding.

**Fig. 4.** Gastrin response to enteral and parenteral feeding. Illustration of the changes in plasma gastrin given as group means ± SE, showing \((P = 0.007\), mixed-effects ANOVA\) increases during oral and duodenal feeding, but not during intravenous or placebo saline infusions.

**Fig. 5.** CCK response to enteral and parenteral feeding. Plasma CCK responses to feeding, displayed as group means ± SE, showing divergent changes after enteral and parenteral nutrition. Whereas baseline levels were similar, oroenteral feeding increased \((P = 0.002)\), and intravenous feeding had no effect on plasma concentrations.
ical release of endogenous pancreatic stimulants from the mucosa, such as gastrin, CCK, and cholinergic mediators. Furthermore, the method permits the simultaneous measurement of the absorption and metabolism of the products of digestion of ingested nutrients. Our observation that the initial 2 h of secretion strongly predicts the 6-h secretory response suggests that a more tolerable and practical 2-h physiological test of digestive function could be developed.

Our chief findings were that 1) bypassing the cephalic phase of pancreatic secretion by intestinal tube feeding did not reduce the pancreatic secretory response; 2) conversion of a complex formula diet to an elemental one reduced the secretory response to tube-feeding; and 3) only intravenous feeding avoided pancreatic stimulation. We were surprised to find that there was no major difference in the stimulatory effect of a complex liquid formula diet given in the form of hourly drinks or a postpyloric infusion. Because the stimulation of pancreatic enzyme secretion has been classically divided into cephalic, gastric, and intestinal phases, we expected in our first hypothesis that oral drinks would produce greater stimulation than duodenal tube infusions. Furthermore, recent studies have concluded that the cephalic phase can account for as much as 50% of the total feeding stimulus (17). The most likely explanation is that the cephalic and intestinal phases are not additive, but rather, are complimentary. Clearly, there is no physiological need for prestimulation of the pancreas when the diet is given as a liquid duodenal infusion, because it only takes just >1 min for the discharge of zymogen stores from the acinar cell into the intestine (31).

Our finding of a lower secretory response to the elemental, compared with the complex formula, could be attributed to both the elemental nature of the nitrogen source, i.e., amino acids rather than a mixture of milk and plant proteins, and the lower fat content, i.e., 4 vs. 20%. Although it would have been ideal to control for the fat content and thus allow specific assessment of the role of an elemental nitrogen source, our experimental design focused on testing the responses to commercially available, and therefore commonly used, diets. All commercial elemental formulae are low in fat to aid digestibility. Vidon and colleagues (38) ran into the same problem when comparing the relative secretory responses to complex (crushed food homogenate) and elemental formula (the same commercial formula we used) fed into the jejunum. Like us, they found a lower secretory response to the elemental diet, but the protein content was also lower, leading them to conclude that the difference was due to the nitrogen content. However, taken in conjunction with our results where diets were isonitrogenous, a more likely explanation was the considerably lower fat content of 1.5 g/l, compared with 29 g/l. Experimental evidence from rats and cats suggest that the higher secretory stimulus induced by complex protein [complex protein, unlike free amino acids, binds luminal trypsin and thereby prevents the degradation of CCK-releasing peptides, thus potentiating further secretion (40)] and fat are mediated by CCK release from the duodenal mucosa.
However, in our studies, (29, 39) plasma CCK levels were, if anything, lower during complex protein and high-fat diet feeding, supporting the accumulating evidence that in humans there is a weak association between secretion and CCK. This is consistent with the observation of Vu et al. (39) that distal jejunal feeding stimulated CCK release but not enzyme secretion, endorsing the current view that the final control of secretion is cholinergic (2). On the other hand, association with bile secretion was stronger where the higher CCK responses to the elemental diet than the oral complex diet were associated with higher bile acid secretion.

Much of the confusion regarding the secretory effects of feeding can be attributed to differences in mammalian physiology, and the extrapolation of observations from one species to another. Results in dogs are particularly misleading. For example, Ragins et al. (30) found that the same elemental diet we used had no stimulatory effect in dogs when given as an intraduodenal infusion. Secondly, Konturek et al. (20) showed, that in contrast to our studies in humans intravenous amino acids and fat stimulated enzyme secretion. Furthermore, feedback control of enzyme secretion appears to be absent, or under secretin control, in dogs (16, 32). These differences can be compounded by variations in experimental conditions. For example, the basal studies in dogs reported by Ragins et al. (30) were conducted under conditions of constant secretin infusion, whereas those of Guan et al. (11) in rats, comparing the secretory effects of elemental and complex diets, were measured during continuous intraportal infusion of atropine to “suppress the high basal interdigestive pancreatic protein and fluid secretion that is peculiar to rats.” It is clearly important to confirm the conclusions derived from animal experiments in humans before applying them to the human condition.

Our observations support the mounting evidence that intravenous nutrition, given in the composition and quantities typically used in clinical practice, does not stimulate pancreatic exocrine secretion in humans and that intravenous nutrition can be safely used in situations where pancreatic rest or bowel rest is required. Bowel rest and pancreatic rest are commonly used in the conservative management of high-output intestinal and pancreatic fistulae, in pancreatic ascites, and in acute pancreatitis to reduce the volume and proteolytic properties of intestinal secretions. Earlier studies of ours (28) in healthy volunteers showed that CCK-stimulated amylase and trypsin secretion was inhibited by intravenous infusions of glucose. Furthermore, amino acid infusions suppressed the synthesis of trypsin supporting the suggestion that the end products of protein and carbohydrate digestion exert negative feedback control (5), as has been claimed for absorbed glucose and amylase synthesis (22). However, our results were on the basis of a background infusion of CCK, and it remained possible that intravenous infusions of nutrients during basal unstimulated conditions would increase secretion, as proposed by Konturek et al. (20) from their studies on dogs. Hence the need for the follow-up studies in humans presently reported. Based on anecdotal case reports (21, 24), there has also been concern that intravenous fat may stimulate pancreatic secretion and exacerbate acute pancreatitis. However, our results indicate that low concentrations have no stimulatory effect, and there is no hard evidence that moderate rates of infusion (i.e., <500 ml 10% lipid emulsion over 24 h) are harmful (9) in the absence of an underlying metabolic abnormality that impairs plasma clearance.

Wide variability of measurements of enzyme secretion in the same individual with time is well recognized. In the present study, we detected 40-min cyclical variations in trypsin, amylase, and lipase secretion of ~40% during enteral, but not during parenteral feeding. DiMagno and colleagues (6, 19) have closely investigated this concern and, on the basis of simultaneous collection of pancreatic duct secretions and recordings of intestinal motility, have concluded that there is incontrovertible evidence that the variations originate from the pancreas and not from problems with duodenal sampling. Most of this variation, particularly during fasting, has been attributed to bursts of secretion associated with the interdigestive migrating motor complexes, which pass down the bowel every 60–90 min (37). Although feeding disrupts the interdigestive pattern, Holtmann et al. (14) provided evidence that enteral feeding at the rate we used (i.e., 1.75 kcal/min) and above (≥2.8 kcal/min) did not abolish, but rather modulated the cycle characteristics. It was interesting to observe that after the initial high rate of bile acid secretion presumably related to gall bladder contraction, bile flow also conformed to the same cyclical pattern, suggesting that hepatic secretion may also be phasic. The apparent loss of cycling in the three enzymes and bile acids during intravenous feeding could be explained by the suppressive effect of parenteral nutrition on gut motility.

There is also concern that the results of secretion rates quoted by different workers often vary considerably, despite the recent preferred use of international standards of measure. For this reason, it was important for us to include a control placebo-saline infusion group to allow internal comparison and evaluation of the relative stimulatory effects of the different feeding techniques.

There is convincing evidence from human studies that the secretory response to both elemental and polymeric diets gradually decreases the further down the intestine they are infused. Although there seems to be little difference between duodenal and proximal jejunal infusions, a recent study (39) showed that the infusion of a mixed polymeric liquid diet at normal tube feeding rates (i.e., 1.6 kcal/min; similar to ours) into the jejunum 60 cm below the ligament of Trietz produced 50% less pancreatic stimulation than proximal jejunal infusions and that the secretion rate was similar to basal levels. Consequently, it should be possible to provide enteral feeding without stimulating pancreatic enzyme secretion, but it would then be important to use an elemental formula to prevent maldi-
gestion and malabsorption. The problem with distal jejunal feeding is, however, that it is difficult to achieve in practice and is therefore rarely used. Most commercial jejunal feeding tubes, including silks, Stayputrs, and Dobhohs, are relatively short in length and terminate at the level of the ligament of Treitz or, at best, the proximal jejunum, and therefore, differ little from the duodenal feeding used in our studies.

There was a clear difference in the CCK and gastrin responses to oroenteral and intravenous feeding. All three oroenteral diets stimulated the release of gastrin and CCK into the bloodstream during the course of the 6-h studies, whereas levels progressively decreased in the group given intravenous nutrition in a similar fashion to the group given placebo-saline infusions. This confirms the view that mucosal contact with nutrients is required for the release of gut peptides rather than changes in the surrounding blood or tissue levels. The lack of difference in gastrin release between oral and enteral feeding was unexpected, and suggests that gastrin release is sensitive to the minor levels of duodenogastric reflux we noted.

Our measurements of blood levels during the nutrient infusions indicate that for a given quantity of carbohydrate, the increase of blood glucose concentrations was greater if a carbohydrate is given intravenously than enterally. This could have been anticipated, because the normal first-pass control mechanisms of the pancreas and liver were bypassed by intravenous feeding. However, we have no explanation, other than an insulin resistance for the higher insulin levels, because gut peptides, such as GLP-1 and GIP, normally augment insulin release. Our comparative measurements of the glycemic response to enteral and parenteral feeding help explain why one of the chief complications of TPN is hyperglycemia (1). The higher plasma levels of glucose and amino acids may also reflect lower metabolic clearance and help explain why the efficiency of utilization of nutrients is greater if the more physiological enteral route is used.

The other serious complication of intravenous feeding is septicemia (1). In addition to its role in the digestion and absorption of food, the gut is a lymphoid organ capable of converting highly contaminated food into a sterile solution of metabolic substrates. Thus it is understandable that bypass will increase the risk of systemic infection. An additional explanation is the detrimental effect of bowel rest on mucosal integrity and function. Lack of topical nutrients results in mucosal atrophy, decreased intestinal motility, stasis, and an increased risk of bacterial overgrowth. Bacterial proliferation is further enhanced by the lack of bile salts and proteolytic enzymes, which together inhibit bacterial growth and adhesion (13). Although the evidence for bacterial translocation in this setting is chiefly drawn from animal studies, TPN-associated septicemias commonly involve gut bacteria and cholestasis is well associated with translocation (35). Furthermore, bacterial overgrowth may partly explain the enhanced endotoxemia-associated cytokine production and protein catabolism (10, 42), as well as the cholestatic liver dysfunction (3) that commonly accompanies prolonged TPN use.

In summary, our results provide some of the physiological reasons why tube feeding may be well or poorly tolerated by patients, and why enteral feeding is safer and more effective than intravenous feeding. Further effort is required to develop practical techniques for the placement of distal jejunal feeding tubes for the management of secretory disorders.

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