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Acute Undifferentiated Human Diarrhea in the Tropics

II. ALTERATIONS IN INTESTINAL FLUID AND ELECTROLYTE MOVEMENTS

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ABSTRACT The nature and magnitude of fluid and electrolyte loss into the small intestine were defined by the marker perfusion technique in patients with acute undifferentiated diarrhea (AUD) in the tropics. The patients were divided into two groups according to their small bowel bacteriologic findings, namely those with a predominant *Escherichia coli* flora and those with a mixed flora. 11 normal subjects served as controls. Net jejunal fluid secretion occurred into the lumen in four of seven patients with *E. coli* flora and three of seven with a mixed flora. The magnitude of secretion in the jejunum was greater in the *E. coli* flora patients than in those with a mixed flora. Four *E. coli* patients and one mixed flora patient had net fluid secretion in the ileum, although the magnitude of secretion in this area was less than in the jejunum. Intestinal fluid had higher bicarbonate concentration in the ileum than in the jejunum but was isotonic in both regions. It resembled in composition fluid from the same region of intestine in normal individuals. Recovery of normal fluid and electrolyte absorptive function was usually complete in both jejunum and ileum by 6–8 days after onset of the disease. Increase in unidirectional flux rates for H_2O and ^{24}Na occurred in acute *E. coli* flora diarrhea and returned to normal levels in recovery: increase in J_s (plasma to lumen flux) primarily accounted for the increase in fluid loss. Intestinal biopsy revealed no alterations in villous architecture.

A relationship between small bowel fluid production and the presence of toxigenic strains of *E. coli* within the small bowel has been found for *E. coli* flora patients. In many respects this disease resembles acute cholera. The mixed flora group represents a less defined entity which requires further study.

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INTRODUCTION

A preliminary investigation of patients with acute undifferentiated diarrhea (AUD) performed in Calcutta, India, during 1966–67, provided evidence for fluid and electrolyte secretion in the jejunum similar to that observed in acute cholera diarrhea (1). Gorbach, Banwell, Chatterjee, Jacobs, and Sack (2) in the preceding paper have characterized bacteriologically two subgroups of AUD[1]: (*a*) predominant *E. coli* intestinal microflora, and (*b*) mixed coliform intestinal microflora. In this facet of the study the pathogenesis of diarrhea in the two subgroups has been investigated. The purpose of this investigation was to define accurately the site, magnitude, and characteristics of fluid loss from the jejunum and ileum in the two forms of acute diarrhea, and to attempt to correlate changes in small intestinal microflora with net and unidirectional fluid and electrolyte transport rates using a marker perfusion technique (3).

METHODS

Studies of 17 patients admitted to the Infectious Disease Hospital, Calcutta, India, between November 1967 and November 1968 comprise the material for this report. They represent the identical patients reported in the previous paper of this series (2). Selection of patients and intubation techniques have been described (2, 3). The following parameters were investigated: (*a*) the electrolyte composition of intestinal fluid during acute diarrhea; (*b*) the net transmucosal movement of fluid and electrolytes in the jejunum and ileum at different stages in the disease; (*c*) unidirectional transmucosal fluxes of sodium and water in the acute period and during convalescence; and (*d*) the correlation between net transmucosal fluid movement and small intestinal bacterial flora. Patients were studied shortly after admission, during early convalescence (days 4–14) and during late con-

[1] *Abbreviations used in this paper:* AUD, acute undifferentiated diarrhea; J_s, flux from plasma to mucosa; J_a, mucosa to plasma flux.

valescence (21 days or more after admission). The marker perfusion technique used in these investigations was identical with that previously employed to study acute cholera diarrhea (3). The polyvinyl tube was swallowed 4–6 hr after admission when nausea and vomiting had subsided and acidosis had been corrected. Samples of fasting intestinal fluid were obtained for culture and analysis as the tube advanced to the ileum. Marker perfusion studies were then performed in the ileum, 18–24 hr after admission. The tube was then withdrawn and fluoroscopically positioned in the jejunum and jejunal perfusion study performed 4–6 hr later after equilibration as previously described. Two patients in recovery and three control subjects had jejunal perfusions performed on first entry of the tube into the jejunum and, again after the withdrawal procedure described, to ensure that significant telescoping of the bowel did not result in erroneous measurement of transmucosal transport rates. Values by both techniques proved to be essentially the same ($P > 0.1$). To measure unidirectional flux rates, ^{24}Na (3 μCi/liter) and H_2O (0.5 mCi/liter) were incorporated into the isotonic-electrolyte perfusion solutions.[2] Net transport rates were determined by standard methods; unidirectional fluxes were calculated by the modified formula of Curran and Solomon (4), derived by Soergel, Whalen, and Harris (5). This formulation assumes the existence of a steady-state two compartment system for analysis. Flux from plasma to mucosa (J_β) is derived from the net flux and mucosa to plasma flux (J_α) which are both measured directly. ($J_\beta = \text{net} + J_\alpha$). Intestinal biopsies were obtained with a Quinton hydraulic biopsy instrument (Quinton Instruments, Seattle, Wash.) or Crosby capsule.

11 healthy Indian male subjects (aged 16–60 yr) served as controls. All were asymptomatic and denied gastrointestinal symptoms. None had steatorrhea although three had low *d*-xylose excretion and four had nonspecific changes in their jejunal biopsies. These features are frequently encountered in normal individuals from this tropical region (6).

RESULTS

The severity of the clinical state on admission is shown in Table I. Dehydration, hypotension, and metabolic acidosis of moderate severity were present in most patients. Diarrhea had ceased by the time of admission in one patient in the *E. coli* flora group and four patients in the mixed flora group. Considered as a group, the patients with an *E. coli* flora had a more severe illness which brought them to the hospital earlier. They also had a higher plasma-specific gravity, pulse rate, and respiration rate than patients with a mixed flora. Furthermore, mean stooling rates in the initial 10–14 hr were significantly higher in the *E. coli* group than in the mixed flora group ($P = < 0.02$).

Intestinal fluid composition. Stool and small bowel fluid from both groups of patients with diarrhea were essentially isotonic, with an osmolality similar to an ultrafiltrate of plasma (Table II). Jejunal and ileal bicarbonate concentrations were similar in the two groups of diarrhea patients and the control subjects. However, bicarbonate concentrations were significantly lower in jejunum than in the ileum in all patients for each group ($P = < 0.001$). The electrolyte composition of intestinal fluid in the patients with *E. coli* or mixed flora diarrhea showed no significant difference (except in relation to the jejunal bicarbonate concentration) from our previous studies of intestinal fluid obtained during cholera diarrhea (3).

TABLE I

*Summary of Admission, Clinical, and Laboratory Data for 17 Patients with Acute Undifferentiated Diarrhea**

	E. coli flora	Mixed flora
	(eight patients)	(nine patients)
Weight, *kg*	42 ±7	42 ±7
Systolic blood pressure, *mm Hg*	69 ±17	68 ±31
Pulse, *per min*	114 ±14	96 ±15
Respiration, *per min*	32 ±11	26 ±5
Arterial pH	7.33‡	7.30 ±0.05
Plasma-specific gravity	1.036 ±0.042	1.032 ±0.059
Serum osmolality§, *m Osm*	275	284
Serum HCO_3, *mM/liter*	16 ±3	18 ±5
Rice water stool	6/8	3/9
‖Stool output (10–14 hr before initial acute perfusion study), *ml/hr*	95 ±96	5 ±6
Mean duration of symptoms (from onset to admission), *hr*	8.6 (4½–15)	14.8 (5½–45)
Mean duration of diarrhea (admission to cessation of stooling), *hr*	16.7	14.6

* Mean ±SD.
‡ Value from two patients.
§ Value from three patients.
‖ Significantly different from corresponding study ($P = < 0.02$).

Net transmucosal fluid transport (Tables III and IV)

Acute studies. In the *E. coli* group, four of seven patients demonstrated net fluid secretion into the jejunal lumen (+ 0.27 to + 5.95 ml/hr per cm) and in the mixed flora group, three of seven patients were secreting (+ 0.18 to + 1.88 ml/hr per cm) (Figs. 1 and 2). The mean jejunal fluid transport rate was significantly greater in *E. coli* diarrhea than in mixed flora diarrhea (+ 1.65 ml/hr per cm vs. − 1.03 ml/hr per cm) ($P = < 0.05$).

All four acute ileal perfusion studies in the *E. coli* group demonstrated net fluid secretion (+ 0.01 to + 7.78

[2] Perfusion solutions: Jejunum, Na, 145 mmoles; K, 5 mmoles; Cl, 140 mmoles; HCO_3, 10 mmoles. Ileum, Na, 140 mmoles; K, 10 mmoles; Cl, 120 mmoles; HCO_3, 30 mmoles per liter.

TABLE II

*Intestinal Fluid Composition in Acute Undifferentiated Diarrhea and Normal Control Subjects**

	No. of subjects	Electrolytes				Osmolality
		Na	K	Cl	HCO_3	
	n	*mmoles/liter*	*mmoles/liter*	*mmoles/liter*	*mmoles/liter*	*mOsm/liter*
E. coli flora						
Jejunum	8	136 ±6	5.7 ±1.1	125 ±14	10.1 ±3.4	301§
Ileum	5	128 ±2	6.4 ±0.4	123 ±9	24 ±13	310§
Stool	3	128	10.2	86	37.7 ±10	290§
Mixed flora						
Jejunum	9	132 ±17	7.0 ±2.3	125 ±13	5.4 ±4.3	
Ileum	6	134 ±7	5.9 ±1.4	110 ±20	45.8 ±14.0	283 ±21‖
Stool	10	132 ±11	15.9 ±5.4	85 ±16	39 ±95	288 ±16
Normal subjects						
Jejunum	7	142 ±7	4.8 ±0.5	135 ±8	8.2 ±5	285 ±10
Ileum	9	140 ±6	4.9 ±1.5	125 ±12	30 ±11	292 ±12
Acute cholera¶						
Jejunum	13	147 ±6	5.6 ±0.7	138 ±5	15 ±4	292 ±8
Ileum	9	140 ±4	5.7 ±0.9	122 ±8	41 ±5	290 ±12

* Mean ±SD.

‡ Composition of stool from a group of patients with acute undifferentiated diarrhea.

§ (n = 2)

‖ (n = 3)

¶ Data from Banwell et al. (3)

TABLE III

Stool Output and Net Jejunal Fluid and Electrolyte Transport Rates for Acute Undifferentiated Diarrhea

	Patient	Stool output*	Net transmucosal transport rate, jejunum				
			H_2O	Na	K	Cl	HCO_3
		ml/hr	*ml/hr per cm*	*μmoles/hr per cm*	*μmoles/hr per cm*	*μmoles/hr per cm*	*μmoles/hr per cm*
E. coli flora	924	83	+2.53	+403	+5	+493	—
	928	61	+0.47	+58	+5	+25	−43
	931	21	+4.69	+697	+19	+615	+83
	936	125	+5.95	+913	−48	+330	+87
	966	8	−0.08	−19	−1	−11	−18
	969	254	−0.67	−74	−8	−59	−30
	79	15	−1.13	−151	−8	−190	−23
	89	0	No Perfusion Study				
Mixed flora	912	0	+1.88	+318	+10	+256	+15
	914	0	−4.59	−681	−50	−532	−69
	916	8	No Perfusion Study				
	927	17	+0.83	+147	0	+224	
	934	0	−2.57	−372	−9	−418	−19
	941	8	No Perfusion Study				
	945	0	−1.61	−215	−7	−163	−46
	85	0	+0.18	+105	+7	+449	+74
	86	0	−1.34	−273	−5	−108	−43

* Measured stool output 10–14 hr before initial acute perfusion study.

‡ (+) = Net secretion into intestinal lumen; (−) = Net absorption from lumen.

TABLE IV

Stool Output and Net Ileal Fluid and Electrolyte Transport Rates for Acute Undifferentiated Diarrhea

	Patient	Stool output*	Net transmucosal transport rate, Ileum				
			H_2O	Na	K	Cl	HCO_3
		ml/hr	*ml/hr per cm*	*μmoles/hr per cm*	*μmoles/hr per cm*	*μmoles/hr per cm*	*μmoles/hr per cm*
E. coli flora	924	83	+0.01	−21	−7	−11	—
	928	61			No Perfusion Study		
	931	21	+1.25	+190	+16	+188	+65
	936	125	+0.68	+131	+7	+64	+52
	966	8	+7.78	+1021	+64	+753	+472
	969	254			No Perfusion Study		
	79	15			No Perfusion Study		
	89	0			No Perfusion Study		
Mixed flora	912	0	+0.20	+24	+3	+103	+69
	914	0	−1.11	−188	−16	−146	−26
	916	8	−2.23	−295	−33	−363	+11
	927	17	−2.79	−396	−35	−371	+15
	934	0			No Perfusion Study		
	941	8	−1.56	−458	−38	−86	−135
	945	0	−1.40	−189	−22	−106	+20
	85	0			No Perfusion Study		
	86	0			No Perfusion Study		

* Measured stool output 10–14 hr before initial acute perfusion study.

‡ (+) = Net secretion into intestinal lumen; (−) = Net absorption from lumen.

ml/hr, cm) whereas only one of six patients with a mixed flora were secreting in this region (Figs. 1 and 2). Mean ileal fluid transport rates in the *E. coli* group exceeded that of the mixed flora group but did not reach statistical significance ($P = > 0.05$, $P < 0.01$).

Jejunal fluid output was usually greater than ileal fluid output although the ileal study was performed before the jejunal study in all cases. The mean time which elapsed between admission and the onset of the perfusion study was similar for both groups of patients (25.2 and 25.6 hr). At the onset of perfusion for the measurement of net transmucosal fluid transport, five of eight *E. coli* patients and two of nine mixed flora patients continued to have diarrhea.

Convalescent studies

Jejunum. Repeat perfusion studies were performed during early or late convalescence in the jejunum of nine patients (six *E. coli* and three mixed flora) who had evidence of net secretion during the acute jejunal study. Eight of nine had returned to net fluid absorption during early convalescence (days 4–14); the final patient was absorbing when restudied on day 28 (Fig. 3a). There was no apparent difference in the rates of recovery of patients with *E. coli* and mixed flora diarrhea. Furthermore, net jejunal fluid absorption was similar during convalescence to that of the control subjects. The mean net transport rates for fluid and Na, K, Cl, and HCO_3 in the jejunum and ileum are shown in Table V.

Ileum. Four patients with an *E. coli* flora and one with mixed flora diarrhea had repeat ileal perfusions during convalescence (Fig. 3b). Two continued to demonstrate net ileal secretion on days 4 and 6 respectively, although the other three patients returned to a net absorptive state. In the latter subjects, ileal absorption rates were similar to control subjects.

Unidirectional flux rates

An increase of 3- to 4-fold in J_α and J_β for ^{24}Na and H_2O above normal levels was encountered in the acute disease, the increased net flux resulting from the greater increase in J_β flux (Fig. 4). Sodium flux values were 3–4 times larger than net sodium movement and water 8–10 times greater than net water movement. Net, J_α (lumen to plasma) and J_β (plasma to lumen flux) for sodium and water in the acute studies significantly differed from the corresponding value in convalescence ($P = < 0.001$) and from values obtained in six control subjects. Values for unidirectional ^{24}Na and H_2O fluxes in convalescence and in the Indian control subjects were similar in magnitude to those obtained by Soergel et al. (5) for control subjects using a similar perfusion technique.

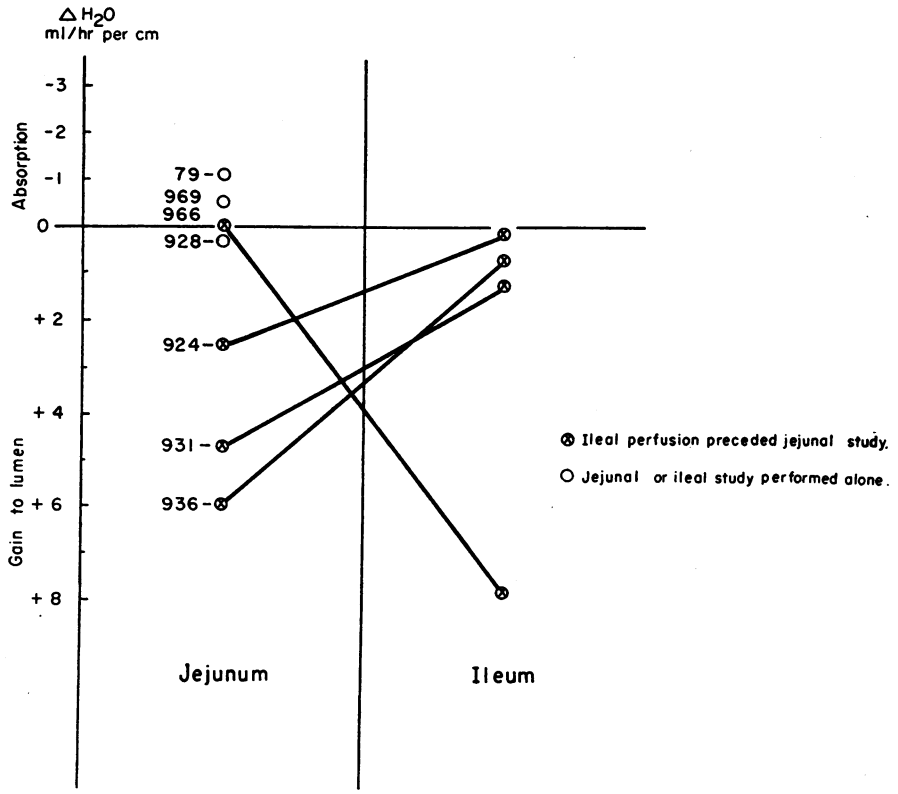

FIGURE 1 Net fluid transport rates in jejunum and ileum for patients with acute *E. coli* flora. (Jejunal net fluid secretion significantly exceeded ileal secretion [$P = <0.05$]) The concentration of toxigenic coliforms in the small intestine for each patient prior to measurement of fluid secretion is shown below.

Patient	Concentration of toxigenic coliforms in the jejunum and ileum
	(*organisms/ml*
924	10^4–10^5
928	10^3–10^8
931	10^5–10^6
936	$<10^6$–10^7*
966	$<10^8$*‡
969	10^2–10^3
79	0§
89	10^3–10^6

* Signifies that other nontoxigenic coliform organisms were also present in the small intestine to contribute to this figure. Concentration represents the over-all concentration of coliform organisms.
‡ In midileum only.
§ Toxigenic strain (06) only present in colon).

Correlation between net transmucosal fluid movement and small bowel bacterial flora

There was a distinct correlation in the *E. coli* group between bacteriological findings and small bowel fluid transport as measured by the perfusion technique. In general, as shown in Fig. 1, patients with toxigenic strains of *E. coli* in the small intestine had abnormal fluid secretion into the lumen.

Patient 969 was normally absorbing in the jejunum but had only low concentrations of these organisms in the jejunum i.e., 10^2–10^3/ml. Patient 966 was also absorbing in the jejunum but coliforms were not present

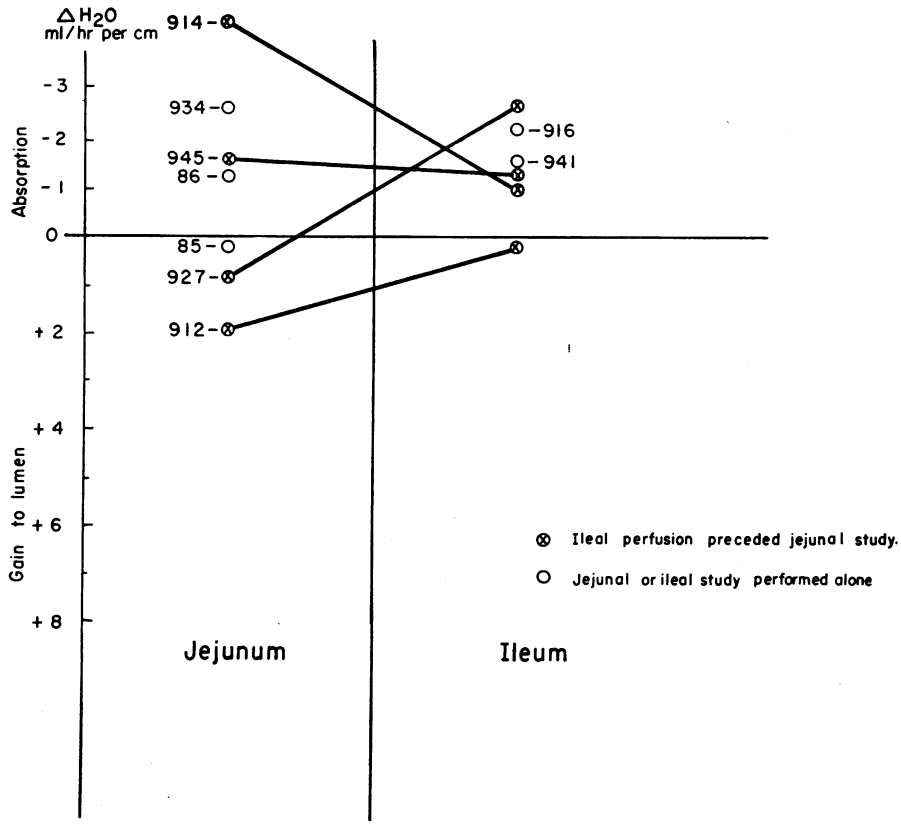

FIGURE 2 Net fluid transport rates in jejunum and ileum for patients with mixed flora. No toxigenic coliform organisms were detected in the small intestine: coliforms in small intestine were nontoxigenic strains.

in this area. On the other hand, the ileum displayed net secretion and *E. coli* were present in concentrations of approximately 10^7/ml. In patient 79, net absorption was found in the jejunum. However, as noted in the first paper of this series (2), the *E. coli* serotype (0115) in the small bowel was only found in the feces. In the mixed flora group, the correlation was less definitive. Net fluid secretion of a mild degree was noted in three patients.

Intestinal biopsies

Biopsies were obtained from the jejunum and ileum of two patients with an *E. coli* flora on a day 2 (No. 969) and day 6 (No. 936) of their illness, and one patient (No. 948) with a mixed flora on day 4. Specimens from the jejunum and ileum of all patients were similar, showing moderate chronic inflammatory infiltration of the lamina propria and slight blunting of villi. Mitotic figures were evident in the crypts, but there was no evidence of acute inflammation or epithelial cell damage. These nonspecific changes have been described previously in patients with acute diarrheal disease as well as in normal subjects from this region of the tropics (7).

Sigmoidoscopy was performed on the day of admission in three patients with an *E. coli* flora and four with mixed flora. In no instance was abnormal rectal mucosa, ulcerations, friability, or bleeding detected. A rectal biopsy in one patient with a mixed flora (No. 914) revealed normal mucosa.

DISCUSSION

The patients with AUD were similar in all respects to previous reports of this type of disease from Asia (8–10). However, although the clinical disorder resembles cholera diarrhea (10) it is usually milder and of shorter duration.

Previous investigations have shown that transmucosal fluid and electrolyte transport rates can be accurately measured by a marker perfusion technique in normal human subjects (11–14) and in patients with acute cholera diarrhea (3). Through application of the same technique to study AUD alterations in fluid and electrolytes were found which were similar to acute cholera. Net fluid secretion was demonstrated in the jejunum and

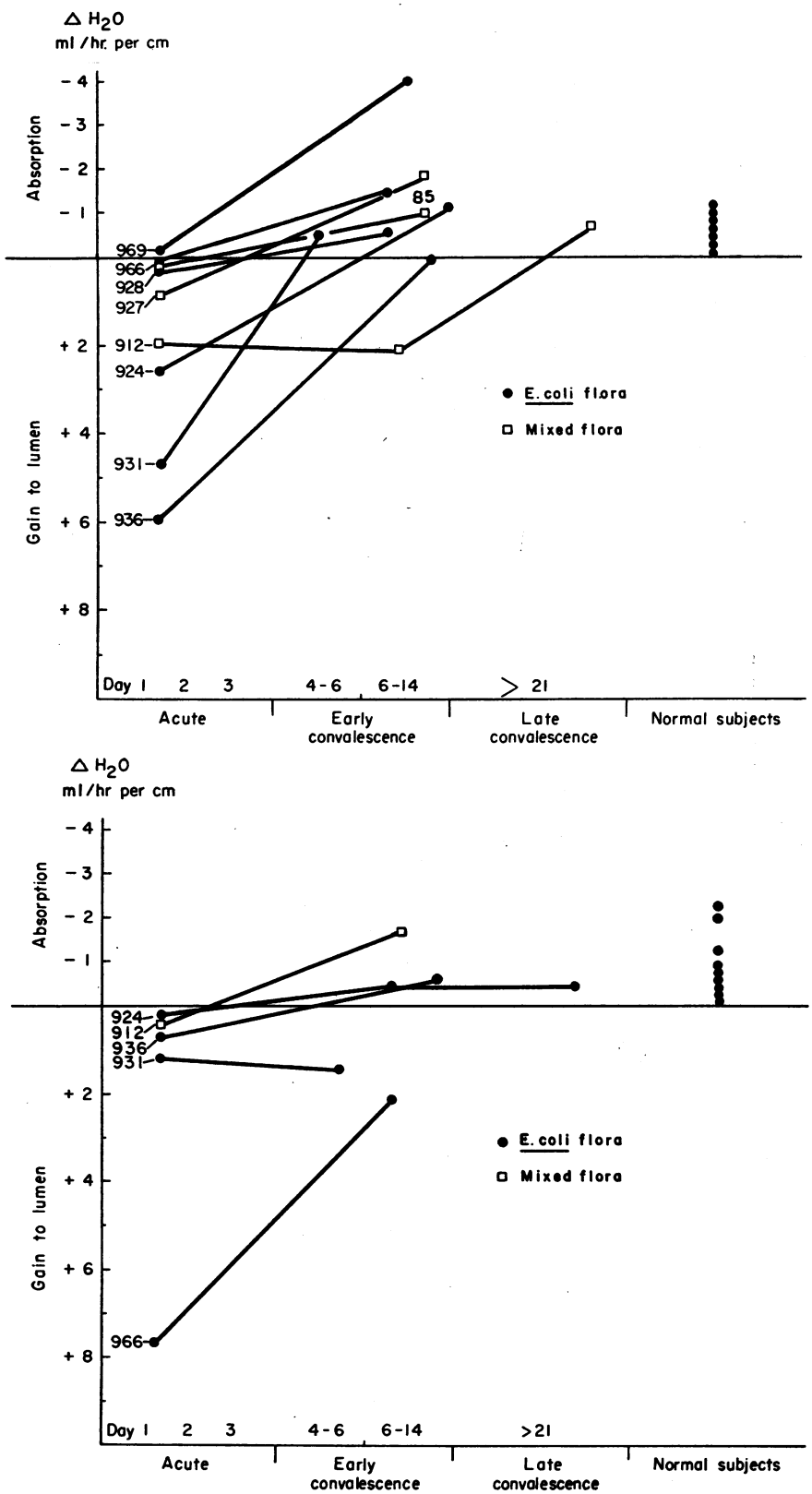

FIGURE 3 The recovery of net fluid absorption in (*a*) the jejunum (top) and (*b*) ileum (bottom) for *E. coli* flora and mixed flora patients in convalescence contrasted with control subjects.

TABLE V

*Mean Values for Stool Output and Net Fluid and Electrolyte Transport Rates in Acute Undifferentiated Diarrhea Patients and Control Subjects**

Small intestine: region of study	Number of studies	Stool output	Net fluid and electrolyte transport rates				
			H_2O	Na	K	Cl	HCO_3
		ml/hr	*ml/hr per cm*	*μmoles per cm*	*μmoles per cm*	*μmoles per cm*	*μmoles per cm*
JEJUNUM							
E. coli flora	7	95 ±96	+1.65 ±2.78	+261 ±416	+8 ±19	+175 ±305	+9 ±5
Mixed flora	7	5 ±6	−1.03 ±2.2	−32 ±370	−8 ±20	−99 ±300	−8 ±50
Control	7	—	−0.58 ±0.48	68 ±56	−5 ±5	−64 ±59	−34 ±24
ILEUM							
E. coli flora	4	95 ±96	+2.43 ±3.60	+283 ±523	+20 ±3	+224 ±373	+196 ±238
Mixed flora	6	5 ±6	−1.48 ±1.02	−250 ±173	−23 ±10	−196 ±134	−7 ±69
Control subjects	9	—	−0.77 ±1.22	−87 ±71	−3 ±9	−110 ±135	+18 ±61

* Mean ±SD.

\+ = Net secretion into intestinal lumen; − = Net absorption from lumen.

ileum during the acute disease in the absence of significant histological damage to the epithelium and this finding was more common in patients with a predominant *E. coli* flora and less frequent in those with a mixed microflora. Furthermore, net fluid transport in the jejunum often exceeded that in the ileum; recovery of net fluid absorption occurring within 6–8 days.

These findings, and the relationship between toxigenic *E. coli* strains in the small intestine and fluid secretion, suggest that the human small bowel may secrete fluid

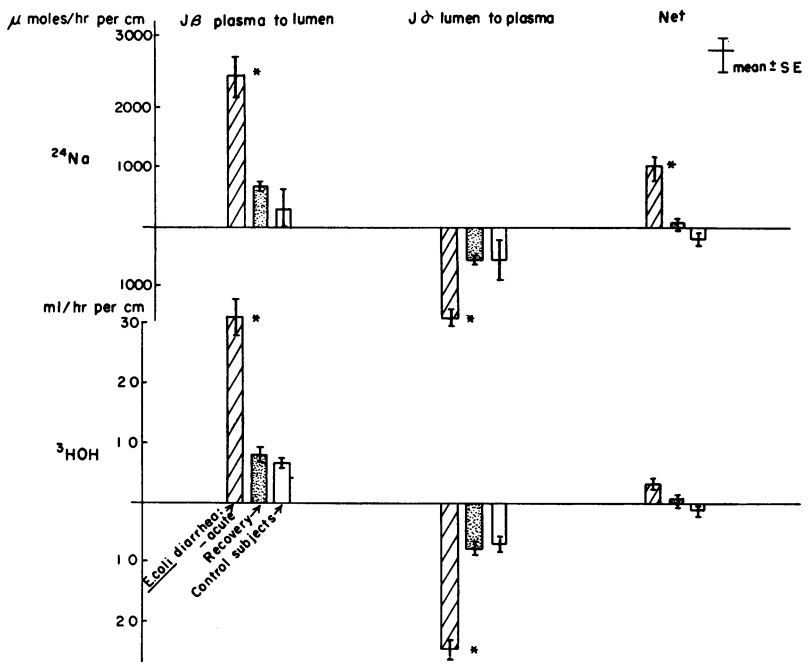

FIGURE 4 J_β (plasma to lumen), J_α (lumen to plasma) and net fluxes for ^{24}Na and H_2O in *E. coli* flora diarrhea (n = 3) on admission and during recovery compared to control subjects (n = 6). The flux rate for tritiated water (^3HOH) was calculated and has not been corrected for the lower diffusion coefficient of ^3HOH compared with H_2O. * indicates a significant difference between the acute and convalescent study ($P = < 0.001$).

in response to colonization with specific toxigenic strains of *E. coli* in a similar manner to that following exposure to *Vibrio cholerae* or its exotoxin (15). Mixed flora diarrhea may also originate in the same way but owing to the lesser magnitude of diarrhea and probably shorter duration of fluid secretion, this could not be demonstrated: perfusion studies were usually completed towards the end of the diarrheal illness and indeed, only four of nine mixed flora patients had diarrhea at the time of the perfusion study.

In at least two *E. coli* patients (Nos. 931 and 966), net fluid secretion was still occurring in the small intestine at a time when diarrhea had almost ceased. However, in this disease, it is probable that the colon, as in cholera diarrhea (15), retained its normal reabsorptive function and prevented small intestinal fluid accumulation leading to diarrhea. Normal colonic reabsorptive capacity alone can account for reabsorption of up to 100 ml/hr of fluid from the lumen in human subjects (16).

Perfusion studies were only performed in jejunum and ileum and it is not possible to entirely preclude the duodenum, pancreatic and biliary system from contributing to the diarrheal fluid loss. However, in a random group of fasting patients with AUD, the intestinal flow rates (13) in the upper jejunum (4.3 ±1.2 ml/min) were only slightly increased above normal (2.2 ±1.3 ml/min)[3] making this an unlikely source of fluid loss. Also, Koya, Kosakai, and Fukasawa (17) have shown in human volunteers that the colon is unresponsive to instillation of enteropathogenic *E. coli* organisms and this is corraborated by the normal findings of sigmoidoscopy and rectal biopsy in our patients.

Small bowel intraluminal fluid composition was similar in patients with AUD acute cholera and in normal subjects, indicating that the small intestine retains its normal ability to elaborate an isotonic fluid and to maintain concentration gradients between plasma and intraluminal fluid with respect to chloride and bicarbonate, during the course of a variety of acute diarrheal illnesses. The jejunal bicarbonate concentration was slightly higher in cholera than in AUD and normal subjects, but this observation requires confirmation before its significance can be assessed.

Unidirectional flux measurements provide some understanding of how net fluid secretion into the bowel lumen may have occurred. Both plasma to lumen (J_β flux) and lumen to plasma (J_α flux) were increased in acute *E. coli* diarrhea, although the greater increase of J_β compared with J_α flux primarily accounted for the change in net sodium and water movement from absorption to secretion. In the absence of a significant change in active sodium absorption, an assumption which is valid for mucosa exposed to cholera exotoxin (15, 18–20), the alterations in unidirectional sodium fluxes probably represent both (*a*) an increase in passive diffusion across the mucosa between solutions of similar sodium concentration and (*b*) an increase in J_β attributable to an increase in passive convective (presumably hydrostatic pressure) or active convective forces (cellular metabolic work) (21). A similar increase in plasma to lumen flux for H_2O and ^{22}Na occurs in the dog and rabbit in vivo jejunal loop on exposure to cholera toxin (22, 23), and also in human cholera diarrhea (24) suggesting that a similar process may be involved in the fluid secretion of cholera to that found in the *E. coli* flora patients.

Torres-Pinedo, Rivera, Fernandez, and Maldonado (25), using a similar perfusion technique demonstrated that glucose absorption was impaired in the proximal jejunum of infants with enteropathogenic *E. coli* diarrhea. In the presence of a perfused glucose load the defect in glucose absorption resulted in a reduction in net absorption of fluid and electrolytes from the small intestine and an accumulation of osmotically active products in the lumen which induced fluid secretion. However, when glucose was not included in the isotonic electrolyte solution, net absorption of water and sodium occurred in both patients and control subjects. This latter observation is contrary to our findings. Although the infants had liquid stool when selected for study, the perfusion study may have been performed after net fluid absorption had been regained. Alternatively the diarrheal disease due to enteropathogenic *E. coli* (in infants) may have different characteristics from that of the adult *E. coli* flora patients. However, production of osmotically active organic acids from the intraluminal bacterial degradation of unabsorbed carbohydrate in infants with gastroenteritis, has no similar counterpart in our adult AUD patients. Adult stool specimens in *E. coli* flora diarrhea were isotonic (not hypertonic) to plasma and the total measured ionic content (Na^+, K^+, Cl^-, HCO_3) of the stool almost entirely accounted for the measured tonicity. In addition, in both jejunum and ileum, fluid was isotonic and of a composition similar to that found in normal subjects. Although acquired disaccharidase deficiences may follow adult AUD (26) and ingestion of carbohydrate in the form of poly- or disaccharides will, under these conditions, cause fluid secretion through the intraluminal accumulation of osmotically active organic acids (27), diarrhea from this cause can only occur after oral intake of carbohydrate which was not possible in fasting patients. Moreover, such a mechanism cannot explain the acute onset of either enteropathogenic *E. coli* diarrhea in infants or adult *E. coli* flora diarrhea, which have both been associated with bac-

[3] Banwell, J. Unpublished observations.

terial overgrowth in the small intestine by toxigenic *E. coli* strains (28, 2).

The characteristics of intestinal fluid and electrolyte transport of *E. coli* flora patients indicate many similarities between this form of AUD and cholera diarrhea. The sites of fluid production, electrolyte composition of intestinal fluid and stool, the nature of the secretion, without significant pathological change in the intestinal mucosa, all suggest that a distinct enterotoxic material may be causing fluid secretion by an effect on the mucosal epithelium similar to that induced by "cholera-toxin." Such an enterotoxin has been described in diarrhea associated with classic enteropathogenic *E. coli* in children (29, 30) and in the pig (31), and evidence for the production of a similar type of enterotoxin by some of the *E. coli* strains isolated from our patients has already been referred to by Gorbach et al. (2). Although the diarrhea of mixed flora patients may have a similar pathogenesis and represent the "end stage" of *E. coli* flora diarrhea after toxigenic strains of *E. coli* have been cleared from the bowel (2), the etiology of these forms of AUD remain to be defined.

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