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INTERNATIONAL CENTRE FOR
DIARRHOEAL DISEASE RESEARCH, BANGLADESH
DHAKA, BANGLADESH

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PREFACE

The **Specialized Bibliography Series** is part of the larger effort to facilitate exchange of information and to establish an information network in the field of diarrhoeal diseases -- an effort being carried out by the International Diarrhoeal Disease Information Service and Documentation Centre (DISC) of the ICDDR,B. The present issue, the tenth of the series, includes citations of 162 papers (124 abstracted) on antisecretory agents in the treatment of diarrhoeal diseases. This is a subject of high current importance, and the reason for selecting the topic is explained in the Introduction.

This is a selective bibliography on the topic. The bibliography was compiled from the resources available at the ICDDR,B Library/DISC, and it is possible that inadvertent omissions may have occurred.

We hope the present bibliography will contribute towards generating greater interest and awareness in this field, and will facilitate user access to existing knowledge. Copies of articles abstracted and cited in this bibliography are available from the DISC to interested persons/organizations. We will consider this attempt successful if the bibliography helps diarrhoeal disease researchers and practitioners' interest.

M Shamsul Islam Khan

Head, Library, Publication
and Communications
International Centre for Diarrhoeal
Disease Research, Bangladesh

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CONTENTS

INTRODUCTION

The recent advance in understanding the mechanism of intestinal secretion and absorption and the action of bacterial enterotoxins stimulated further studies on inhibiting secretion using pharmacologic agents. What has loosely been termed as the "antisecretory agents" include many drugs and chemicals which have been shown to be potent inhibitors of secretion in animals. Only a few of these agents including berberine, chlorpromazine and nicotinic acid have been shown to have clinical effects in man, though their mode of action is unknown.

If an effective and safe antisecretory drug could be developed it could serve as a useful adjuvant to oral rehydration therapy in reducing deaths from diarrhoea. The "ideal" antisecretory drug is being sought through further research by physiologists and clinicians all over the world. This bibliography is an effort towards assisting their research work. It is hoped that it will contribute to the development of a more simple therapy for diarrhoeal diseases.

G H Rabbani, MBBS, MSc, DPH

International Centre for Diarrhoeal
Disease Research, Bangladesh

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The **Specialized Bibliography Series** includes abstracts and citations of currently available literature from sources worldwide.

The bibliography is divided into subject and author sections. In the Subject Section, citations are arranged alphabetically by the first author under specific headings. The citation sometimes is followed by a sign (++), indicating that an abstract of the cited paper appears in the Author Section.

The Author Section contains citations arranged alphabetically by the first author and then by the title of paper. Co-authors' names also appear in alphabetical order along with a cross-reference to the first author (Abdo JA see Portnoy BL). This will facilitate a search by co-authors' names.

Efforts have been made to present abstracts with all available information regarding the study's nature and objective, methods used, and the major findings and conclusions.

The bibliography is in English. A title in parentheses indicates that the paper is in another language.

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VERAPAMIL

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AUTHOR SECTION

Abbey DM, Knoop FC. Effect of chlorpromazine on the secretory activity of Escherichia coli heat-stable enterotoxin. Infect Immun 1979 Dec;26(3):1000-3

The effect of chlorpromazine on the net intestinal fluid accumulation, induced by Escherichia coli heat-stable (ST) enterotoxin in an infant mouse model, was examined. Chlorpromazine, when administered with ST enterotoxin, caused a highly significant decrease in net intestinal fluid accumulation. The inhibition of ST enterotoxin activity was dose-dependent with various concentrations of chlorpromazine ($p<0.001$). A significant inhibition of toxic activity was also observed when chlorpromazine was administered before ($p<0.02$) or after ($p<0.05$) ST enterotoxin challenge. No significant differences in fluid accumulation were observed between control mice treated with buffer alone and those treated with only chlorpromazine. These data indicate that chlorpromazine markedly decreases the net intestinal fluid accumulation induced by E. coli ST enterotoxin. Further studies on the potential use of chlorpromazine in both the prophylaxis and the treatment of diarrhoeal diseases appear warranted. (Modified author's abstract).

Abdo JA see Portnoy BL

Abildgaard U see Stokholm KH

Ackerman PG see DuPont HL

Adaikan PG see Karim SMM

Ahrens FA, Zhu BL. Effects of epinephrine, clonidine, L-phenylephrine, and morphine on intestinal secretion mediated by Escherichia coli heat-stable enterotoxin in pig jejunum. Can J Physiol Pharmacol 1982 Dec;60(12):1680-5

Ahrens FA, Panichkriangkrai W. Effects of Escherichia coli heat-stable enterotoxin, atropine, clonidine, and morphine on chloride efflux from isolated enterocytes. Am J Vet Res 1985 Oct;46(10):2067-71

The effects of Escherichia coli heat-stable (ST) enterotoxin on chloride efflux rate were investigated in 3 fractions of enterocytes isolated in a villus-to-crypt gradient from porcine jejunum. There was no difference in chloride efflux rates between mature and immature cells from controls. ST enterotoxin significantly increased chloride efflux in all fractions. Morphine inhibited ST enterotoxin-augmented secretion in mature enterocytes. Atropine or clonidine had no effect. Calcium efflux rates and glucose or glutamic acid metabolism were not altered by ST enterotoxin. The results indicate that ST enterotoxin may stimulate chloride secretion in both villus and crypt cells and that opiates inhibit intestinal secretion by a direct action on villus epithelial cells. (Modified author's abstract)

Ahrens FA, Zhu B. Effects of indomethacin, acetazolamide, ethacrynate sodium, and atropine on intestinal secretion mediated by Escherichia coli heat-stable enterotoxin in pig jejunum. Can J Physiol Pharmacol 1982 Oct;60(10):1281-6

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Subcutaneous injection of cholera toxin in the dorsum of the rats' neck produced local inflammation. Between 1 and 100 mg/kg doses, the cholera toxin produced swelling which showed a fair dose-response relationship. It was maximal at about 27 h post-injection of cholera toxin and completely subsided over 4 days. The rat neck method in this paper compares well in sensitivity and temporal course of swelling with the classic rat paw model of earlier workers. In control experiments, heat-inactivated cholera toxin, Richardson's TRY medium, cholera vaccine or staphylococcal toxin proved ineffective. With the survived animals, the chronic immunological study was carried out. The method may be useful for the bioassay of cholera toxin batches. Berberine was found to effectively inhibit the local inflammation induced by cholera toxin, and the inhibition was dose-dependent. Berberine was more effective when injected at the inflammation site, but hydrocortisone and cyproheptadine did not inhibit this inflammation. Indomethacin inhibited swelling only in toxic doses. In the present method, carrageenin or formalin produced local swelling which was inhibited by cyproheptadine and indomethacin but not by berberine. Berberine was less effective than hydrocortisone in inhibiting chronic cotton pellet-induced granuloma. The results showed that berberine can not be considered as an anti-inflammatory agent. The inhibition of cholera toxin-induced inflammation by berberine is a selective antagonism.

Akhter MH, Sabir M, Bhide NK. Possible mechanism of antidiarrhoeal effect of berberine. Indian J Med Res 1979 Aug;70:233-41

Berberine, an alkaloid derived from the plant, Berberis aristata, is of a definite value in gastroenteritis. Some pertinent experiments were carried out to explain its mechanisms. Ipomoea turpethumrval, a purgative was used to induce purging in dogs. Berberine (0.06-20 mg/kg) given orally, prolonged the latent period and reduced frequency and severity of purging. Oral administration of 1.25-5 g/kg magnesium sulfate produced dose-dependent purging in adult rats. Berberine in 0.3-30 mg/kg doses did not reduce it between the two drugs. The results were unable to show any significant difference in the treatment of various chronic diarrhoeas between loperamide and codeine phosphate at this stage in the analysis.

Al-Awqati Q, Greenough WB, III. Prostaglandins inhibit intestinal sodium transport. Nature (New Biol) 1972 Jul 5;238(79):26-7

The effects of two prostaglandins (PGE and $PGF_2\alpha$) on intestinal ion transport in vitro were compared with theophylline, an agent that increases cyclic adenosine 3',5'-monophosphate by inhibiting its degradation. When 10^{-5} M PGE_1, $PGF_2\alpha$, or theophylline were added to the serosal reservoir, there was a rise in short-circuit current. The magnitude of the initial rise with maximal doses of PGE_1 (10^{-6} M) was 40±5 $\mu A/cm^2$ (baseline short-circuit current 62±7 μA), with $PGF_2\alpha$ (10^{-6} M) it was 46±5 $\mu A/cm^2$ (baseline short-circuit current 50±5), and with theophylline (10^{-2} M) it was 82±13 $\mu A/cm^2$ (baseline short-circuit current 80±5). Both PGE_1 and $PGF_2\alpha$ increased the short-circuit current when applied to the mucosal surface of the membrane. There was no significant difference between the short-circuit current of 10^{-5} M PGE_1 or $PGF_2\alpha$ and their respective controls. When 10^{-5} M PGE_1, 10^{-5} M $PGF_2\alpha$ and 10^{-2} M theophylline were added, there was a significant decrease in the net sodium movement. The chloride flux after PGE_1

was lower than the values found for the controls. The addition of theophylline resulted in the reversal of the direction of net chloride movement. The residual ion flux was not changed following the addition of PGE_1, $PGF_{2\alpha}$, or theophylline. Addition of glucose to the mucosal solution following the addition of theophylline, PGE_1, $PGF_{2\alpha}$, produced a rise in the short-circuit current. The results showed that both PGs and theophylline eliminated the net sodium absorption. It is concluded that PGs may produce diarrhoea not only by stimulating intestinal motility or mesenteric vascular changes, but also by inhibiting the absorption of sodium ion and possibly also by stimulating the secretion of chloride.

Alioto RL see Douglas GH

Alioto RL see Mir GN

Allen G, Watkinson G. A double-blind comparison of loperamide with codeine in the treatment of unremitting diarrhoea. In: Gough D, ed. The control of diarrhoea in clinical practice. London: The Royal Society of Medicine, 1978:35-40 (Royal Society of Medicine, International Congress and Symposium series, 5)

This study involves a double-blind comparison of loperamide with codeine in the treatment of unremitting diarrhoea. Twenty-three patients were given loperamide (2 mg) or codeine phosphate (30 mg) marked as drug A or drug B. Each patient recorded the time of defecation, their stool consistency and the time of ingestion of the drug A or drug B. During the investigation, some laboratory tests were carried out, such as peripheral hematology and regular inspection of blood urea, electrolytes, liver function tests at intervals of 0.4 and 9 weeks. There were only marginal differences between loperamide and codeine treatment. Though loperamide was more effective, the difference did not reach the required 95% level of probability. There was a correlation between the rating of severity of the diarrhoea by the patient and the objective measure of diarrhoea and also a significant and positive correlation between the number of capsules of drug taken and the severity of diarrhoea. There were no significant side-effects in either group. Neither objective measurement in the form of stool frequency and consistency nor the semi-quntitative linear analogue scale measurements were adequate to resolve the differences between the two drugs. The results were unable to show any significant difference in the treatment of various chronic diarrhoeas between loperamide and codeine phosphate at this stage in the analysis.

Amer MS see Leitch GJ

Ana CAS see Schiller LR

Anderson DS see McArthur KE

Andren B see Lonnroth I

Arndt WF, Jr., Burns JM. Use of Pepto-Bismol in diarrhea [letter]. J Pediatr 1982 May;100(5):839

Auyang K see Douglas GH

Avery GS see Heel RC

Awouters F, Niemegeers CJE, Janssen PAJ. Pharmacology of antidiarrheal drugs. Annu Rev Pharmacol Toxicol 1983;23:279-301

A pharmacological study of potential antidiarrhoeal drugs is based on the measurement of inhibition of diarrhoea in laboratory animals. The castor oil test in rats has been used for detecting and comparing the antidiarrhoeal activity of compounds. In this test, morphine-like antidiarrhoeals, and also various drugs of other pharmacological classes showed changes in their excretory pattern induced by castor oil. Most drugs were active in the castor oil test at a dose that exceeded the effective dose for their characteristic pharmacological action. For anticholinergics, aspirin-like drugs, clonidine-like drugs which had pronounced intestinal action, had low antidiarrhoeal specificity. Loperamide was found to have high antidiarrhoeal specificity. Loperamide and its metabolites are confined to an enterohepatic circuit in the organism. The local action of loperamide is partially mediated by opiate receptors and results in inhibition of both excessive propulsive- and secretory activity of the intestine. Loperamide was compared with several other antidiarrhoeal preparations in terms of their efficacy and modes of action in the gastrointestinal tract. The superiority of loperamide in controlling diarrhoea over a range of other opiate derivatives is shown.

Aye-Kyaw see Khin-Maung-U

Bardhan PK see Islam MR

Bardhan PK see Rabbani GH

Bardhan PK see Stoll BJ

Battisti L see Donowitz M

Beckers J see De Coster M

Bennet J. A review of antidiarrhoeal compounds. In: Gough D, ed. The control of diarrhoea in clinical practice. London: The Royal Society of Medicine, 1978:1-8 (Royal Society of Medicine International Congress and Symposium series, 5)

Bhide NK see Akhter MH

Bhide NK see Sabir M

Bianchi RG see Gullikson GW

Biddau P see Corda R

Binder HJ, Laurenson J, Dobbins JW. Mechanism of loperamide's anti-diarrheal action. Gastroenterology 1981 May;80(5, pt 2):1111

Loperamide is an effective non-opiate antidiarrhoeal drug. The mechanism of its action has been attributed to an effect on intestinal motility; however, recent studies have established that codeine, morphine and opioid peptides stimulate intestinal ion absorption which may represent an additional mechanism of action of antidiarrhoeal agents. These studies were designed to determine whether loperamide can stimulate water absorption or inhibit experimentally induced secretion. Luminal perfusion of the entire rat colon with a Ringer

solution containing ^{14}C-PEG as a non-absorbable marker was performed in vivo. The addition of 1 µM loperamide to the Ringer solution resulted in a significant increase in water absorption (31.2±9.3 vs 67.3±10.9 µl/min.g dry tissue weight; $p<0.01$; $n=8$). In contrast, in other experiments 1 M loperamide neither prevented nor reversed deoxycholic acid-induced fluid secretion. In studies of isolated rabbit ileal mucosa, 10µM loperamide increased J^{Na}_{net} (2.5±0.3 µEq/h.cm^2) and J^{Cl}_{net} (2.7±0.8 µEq/h.cm^3) in the presence, but not in the absence of naloxone. These results indicate that loperamide increases fluid and electrolyte absorption by a non-opiate process in both colon and ileum and provide evidence of an additional mechanism to explain loperamide's antidiarrhoeal action. (Author's abstract)

Bitar KN see Carter RF

Bloom SR, Christofides ND, Delamarter J, Buell G, Kawashima E, Polak JM. Diarrhoea in VIPoma patients associated with cosecretion of a second active peptide (peptide histidine isoleucine) explained by single coding gene. Lancet 1983 Nov 19;2(8360):1163-5

Peptide histidine isoleucine, first isolated from the pig intestine, is distributed identically to vasoactive intestinal peptide (VIP) in all mammals. Forty-two patients with high plasma VIP secondary to VIPoma also had very high plasma peptide histidine isoleucine-like immunoreactivity, in a constant ratio to VIP. None of the 125 patients with other endocrine tumors had high levels of either peptide. VIPoma tissue from 20 patients also contained peptide histidine isoleucine, shown by immunocytochemistry to be produced by the same cell as VIP. Messenger ribonucleic acid (mRNA) from one of these tumors contained the codes for VIP and a separate peptide histidine isoleucine-like sequence. Human peptide histidine isoleucine-like sequence differed from porcine peptide histidine isoleucine in only two amino acid residues. A single cell thus produced two separate regulatory peptides with apparently similar potencies but different spectra of activity. In normal tissue, the constant coproduction of two active neuropeptides by a single neuron provides further evidence against the doctrine of one neuron producing only one neurotransmitter. However, the discovery of two active peptides within a single cell is still open to question and needs further study. (Modified author's abstract).

Bockus HL see Pimparker BD

Bonorris G see Taub M

Bonorris GG see Coyne MJ

Broadhead R see Owens JR

Brock JH see Reiter B

Brogden RN see Heel RC

Brugmans J. Loperamide — a summary of clinicopharmacological studies. In: Gough D, ed. The control of diarrhoea in clinical practice. London: The Royal Society of Medicine, 1978:9-14 (Royal Society of Medicine International Congress and Symposium series, 5)

Buell G see Bloom SR

Bukhave K see Rask-Madsen J

Bukhave K see Steven K

Bunce KT see Spraggs CF

Bunjes R see Muhlendahl KE

Burke V, Gracey M. Effects of salicylate on intestinal absorption: in vitro and in vivo studies with enterotoxigenic micro-organisms. Gut 1980 Aug;21(8):683-8

Burns BJ see Douglas GH

Burns JM see Arndt WF, Jr.

Butler T, Rabbani G, Knight J, Sanyal S, Huq M. Antisecretory activity of berberine sulfate in acute cholera. Clin Res 1984 Apr;32(2):511A

The alkaloid berberine sulfate is used as antidiarrhoeal treatment in India. To test whether this drug could reduce diarrhoeal fluid output during acute cholera, 30 adult patients with Vibrio cholerae infection were treated with 400 mg of berberine sulfate, given as powder orally in a single dose. Thirty-one patients were concurrently randomized to an untreated control group stratified by purging rates. Stool volumes were measured 8-hourly in a graduated cylinder during a 8-h period before treatment and during 3 consecutive 8-h periods after treatment. Rehydration was carried out with intravenous fluid. The mean stool volumes ±SD in the 8-h pretreatment period were 4.62±1.96 L in the berberine sulfate-treated group and 4.49±1.79 L in the control group. In the second 8-h period after treatment, the mean stool volume in the berberine sulfate-treated group had declined to 2.22±1.11 L, which was significantly less than 2.79±1.06 L in the control group ($p<0.05$). During the third 8-h period, the difference between the groups persisted, but was not further increased. Stool cultures before and after berberine sulfate treatment showed persistence of viable vibrios, suggesting that berberine sulfate was not acting as an antimicrobial agent. These results indicate that berberine sulfate is an effective antidiarrhoeal drug in cholera and probably acts as an antisecretory agent on the small intestinal epithelium. (Modified author's abstract).

Butler T see Rabbani GH

Callahan DR see Steinhoff MC

Camp RC see Davis GR

Candy DCA see Sandhu B

Candy DCA see Sandhu BK

Cardamone A see Turjman N

Carpenter CCJ, Curlin GT, Greenough WB. Response of canine Thiry-Vella jejunal loops to cholera exotoxin and its modification by ethacrynic acid. J Infect Dis 1969 Sep;120(3):332-8

A series of studies were designed to show the response of canine Thiry-Vella jejunal loops to intraluminal challenge with crude cholera exotoxin and to study the effect of both intraluminal and intravenous ethacrynic acid on the response of the gut to cholera exotoxin. Mongrel dogs weighing 12-18 kg were included in the study. In all animals, the Thiry-Vella jejunal loops responded to intraluminal challenge with exotoxin by an outpouring of isotonic fluid. The production of isotonic fluid began during the second h after challenge with 2 g dose of exotoxin, reaching maximal rates during the third and the tenth h after challenge, and finally decreased very gradually during the remaining period of observation. Administration of ethacrynic acid (250-750 mg) by either the intravenous or intraluminal route resulted in a significant decrease in exotoxin-induced secretion of gut electrolytes. The maximal effect of ethacrynic acid was not observed until the second or third h after administration, and a detectable effect persisted for at least 7 h. The mechanism by which ethacrynic acid inhibits exotoxin-induced secretion of electrolytes in the gut has not yet been established. The observed effects of ethacrynic acid could be due either to enhanced absorption or decreased secretion of gut electrolytes. In the current study, the diuretic response to 750 mg of furosemide intravenously was similar to that caused by 750 mg ethacrynic acid, given intravenously with the exception that the urinary bicarbonate loss was greater during furosemide-induced diuresis. The inhibition of renal tubular carbonic anhydrase by furosemide explains the greater loss of bicarbonate in the furesemide-induced diuresis.

Carpenter CCJ, Jr. <u>see</u> Pierce NF

Carter RF, Zfass AM, Makhlouf GM. Inhibition by somatostatin of VIP-stimulated intestinal secretion. Clin Res 1977 Dec;25(5):309A

Somatostatin is known to inhibit endocrine and exocrine secretion in several digestive organs. The mechanism(s) by which this inhibition is mediated is unknown. The effect of somatostatin on colonic secretion, induced by vasoactive intestinal peptide (VIP) (10^{-8} M), theophylline (10^{-2} M) and dibutyryl-cyclic adenosine 3',5'-monophosphate (db-cAMP $2x10^{-3}$M), was examined. Secretion was measured in muscle-stripped everted colon sacs and expressed as the decrease in net absorptive flow rate (μl 30 min^{-1} mg^{-1} of dry weight). The secretory response to VIP (3.65±0.38) was maximal and equalled the responses to theophylline (3.65±0.31) and db-cAMP (4.31±0.33). Somatostatin (10^{-5} M) decreased significantly the secretory responses to VIP, theophylline and db-cAMP by 76 ($p<0.01$), 34 ($p<0.02$) and 37% ($p<0.01$) respectively. The decrease in response to VIP was significantly greater than the decrease in response to the two other agents. The inhibitory effect of somatostatin differed from that of the lactamimide RMI 12330A which abolished VIP-stimulated secretion and adenylate cyclase activity, but had no effect on theophylline or db-cAMP-stimulated secretion. Since somatostatin inhibited theophylline- and db-cAMP-stimulated secretion equally, one component of its effect was postulated to lie beyond the point of generation of intracellular cAMP and not to involve stimulation of phosphodiesterase activity. The greater inhibition of VIP-stimulated secretion suggests that another component of the action of somatostatin involves an early step in the generation of cAMP, such as inhibition of adenylate cyclase activity. This study clarifies the mechanism of inhibition of colonic secretion by somatostatin and shows that this peptide and the lactamimide are useful for the study of transport. (Modified author's abstract)

Carter RF, Bitar KN, Zfass AM, Makhlouf GM. Inhibition of VIP-stimulated intestinal secretion and cyclic AMP production by somatostatin in the rat. Gastroenterology 1978 Apr;74(4):726-30

The effect of somatostatin on colonic secretion, induced by 10^{-8} M vasoactive intestinal peptide (VIP), 10^{-2} M theophylline, and 2×10^{-3} M dibutyryl-cyclic adenosine 3',5'-monophosphate (db-cAMP), was studied in muscle-stripped everted open rat colon sacs. The secretory response to VIP measured as the decrease in net absorptive flow rate (microliters 30 min^{-1} mg^{-1} of dry weight), was maximal and equalled the responses to theophylline or db-cAMP. Somatostatin (10^{-5} M) blocked completely the secretory response to VIP, but only partially the secretory response to theophylline or db-cAMP. This difference in the extent of inhibition suggests that somatostatin exerts an inhibitory effect both before and after the point of generation of intracellular cAMP. To test the hypothesis that one component of the action of somatostatin involved inhibition of the production of cAMP, measurements of this nucleotide were made in isolated rat colon cells. Control levels of cAMP measured by radioimmunoassay (12.6 ± 1.6 pmol/10^6 cells) were not affected by 10^{-5}M somatostatin. VIP (5×10^{-8} M) increased cAMP levels 2-fold ($p<0.01$), and this increase was blocked by somatostatin. The results indicate that somatostatin inhibits secretion by exerting effects at two sites: one site lies at, and another beyond, the point of generation of intracellular cAMP. (Modified author's abstract)

Cash RA see Nalin DR

Cassuto J, Jodal M, Tuttle R, Lundgren O. The effect of lidocaine on the secretion induced by cholera toxin in the cat small intestine. Experientia 1979 Nov 15;35(11):1467-8

Castellion AW see Goldenberg MM

Cataland S see Dharmsathaphorn K

Chang-Chien S see LaCorte WSJ

Chapman J see LaCorte WSJ

Charney AN, Donowitz M. Prevention and reversal of cholera enterotoxin-induced intestinal secretion by methylprednisolone induction of Na^+-K^+-ATPase. J Clin Invest 1976 Jun;57(6):1590-9

The relationship of the mucosal enzyme systems Na^+-K^+-activated adenosine triphosphatase (Na-K-ATPase) and adenylate cyclase and their associated intestinal transport processes were studied in the rat ileum. Two ileal loops were constructed in each anesthetized rat; one loop was inoculated with saline, and the other loop with choleragen. Net transport of water and electrolytes was measured in vivo after which enzyme activity was measured in the mucosa of the perfused loops. All doses of choleragen between 5 and 150 g decreased water movement as early as 3½ h after inoculation. A linear relationship between the dose of choleragen and the level of net water and electrolyte secretion was observed when choleragen doses between 5 and 150 g were incubated in ileal loops for 4 h. Adenylate cyclase activity was always increased in secreting intestinal loops, whereas Na-K-ATPase was unaffected by choleragen. In animals pretreated with methylprednisolone acetate, 3 mg/100 g.day for 3 days before loop inoculation, saline loops had enhanced mucosal Na-K-ATPase activity and increased net water and electrolyte absorption; choleragen-exposed loops had increased adenylate cyclase and Na-K-ATPase activities, and net absorption of water and electrolytes 4 h after inoculation.

These effects of methylprednisolone acetate were still present 19½ h after inoculation. When a single injection of methylprednisolone acetate was given 3½ h after choleragen inoculation, both adenylate cyclase and Na-K-ATPase were activated, and net intestinal absorption of water and electrolytes was observed 19½ h after inoculation. These results suggest that methylprednisolone can prevent and reverse the secretory effects of choleragen by selectively stimulating a coexisting absorptive process. (Author's abstract)

Charney AN see Giannella RA

Chaudhuri K, Nandi R, Maiti M. Effect of berberine chloride binding on the structure of cholera phage Ø 2 DNA. Indian J Biochem Biophys 1983 Aug;20:188–92

Berberine chloride, a medically important alkaloid, is clinically useful in cholera, dermal leishmaniasis and amebiasis therapy. Therefore, berberine's binding with sonicated and non-sonicated Ø 2 deoxyribonucleic acid (DNA) was investigated. Its binding to Ø 2 DNA produced quenching and bathochromic shifts in the alkaloid's absorption spectrum. The spectra exhibited three sharp isosbestic points at 360, 385 and 450 nm, indicating an equilibrium between bound alkaloid and its free form. Spectrophotometric and spectrofluorimetric titration results of berberine with Ø 2 DNA were quantitated, and various binding parameters were evaluated. Berberine significantly stabilized Ø 2 DNA against thermal strand separation. Sonicated Ø 2 DNA's titration with berberine produced an increase in specific viscosity, indicating an increased helix length of sonicated rod-like Ø 2 DNA. The alkaloid's exceptionally high specificity to Ø 2 DNA may explain the inhibitory effect of Ø 2 phage production in host cells.

Chou BJ see Mir GN

Christofides ND see Bloom SR

Chung A see Coyne MJ

Chung A see Taub M

Cias J see Douglas GH

Conley D see Coyne MJ

Corbett C, Holdsworth D. The effect of loperamide in chronic diarrhoea: comparison with placebo, pilot comparison with other antidiarrhoeal agents, and effect on small bowel transit time. In: Gough D, ed. The control of diarrhoea in clinical practice. London: The Royal Society of Medicine, 1978:15–20. (Royal Society of Medicine International Congress and Symposium series, 5)

This two-part study was designed to assess the effectiveness of loperamide in chronic diarrhoea by a double-blind crossover comparison with placebo, and a pilot study was carried out comparing loperamide with codeine phosphate and diphenoxylate. The effect of loperamide on small bowel transit time was also studied. Patients with diarrhoea of more than three months' duration and requiring symptomatic treatment were entered to the trial. The 12 patients in the first part of the trial took loperamide as 2 mg capsules/twice daily, and this dose was gradually increased until control of diarrhoea was achieved. The

number of capsules taken until diarrhoea stopped was noted. Loperamide or a placebo of identical appearance were then given for 3 weeks each on a randomized double-blind crossover basis. In the second part of this study, patients were given codeine phosphate or diphenoxylate for 2 weeks each, the drugs being dispensed as identical capsules containing 30 mg of codeine phosphate or 2.5 mg of diphenoxylate. One to 3 capsules were given daily, and this dose was increased until diarrhoea stopped. Loperamide produced better control than 150-180 mg of codeine phosphate or 10-15 mg of diphenoxylate daily. Ease of control was not affected by the course of the diarrhoea. Mean small bowel transit time before treatment was 61.4±5.6 min and was prolonged by loperamide to 106.4±8.9 min ($p<0.001$). The patients in whom control of diarrhoea could not be achieved with other antidiarrhoeal agents was achieved with loperamide.

Corbett CL see Palmer KR

Corda R, Biddau P, Corrias A, Puxeddu E. Conalbumin in the treatment of acute enteritis in the infant. Int J Tissue React 1983;5(1):117-23

Conalbumin, a glycoprotein derived from eggwhite, has the property, like lactoferrin, of binding iron ions. An experimental study on acute enteritis in infants in the first year of life was undertaken. Forty infants with acute enteritis, not complicated by ionic imbalance or severe dehydration, were randomly allocated to two groups. The subjects of the first group were treated with the traditional dietetic therapy; those of the second were treated with the same diet plus conalbumin for periods ranging 6 to 10 days. General condition, the alvus and body weight trends were evaluated during and after the treatment period. Stool cultures were also carried out during treatment. In the group of children treated with conalbumin, the results were: excellent in 5 (25%), good in 13 (65%), fair in 1 (5%) and null in 1 (5%). The general status and the time needed to normalize the alvus were statistically significant ($p<0.001$) in favor of conalbumin. Body weight in the two groups showed no significant difference. Neither metabolic alterations nor intolerance phenomena were noted during treatment with conalbumin. In conclusion, conalbumin demonstrated therapeutic properties against acute enteritis in infants through the rapid normalization of the alvus. No side-effects were noted. It is concluded that conalbumin is a useful therapeutic agent which acts through a mechanism totally different from that of chemo-antibiotic agents. (Modified author's abstract)

Corrias A see Corda R

Coyne MJ, Bonorris GG, Chung A, Conley D, Schoenfield LJ. Propranolol inhibits bile acid and fatty acid stimulation of cyclic AMP in human colon. Gastroenterology 1977 Nov;73(5):971-4

Diarhoea resulting from the action on the colon of excess bile acids and fatty acids appears to be mediated by cyclic adenosine 3',5'-monophosphate (cAMP) in animal experiments. Propranolol, an adenylate cyclase inhibitor, prevents this colonic secretion in vivo. The aim is to determine in human colonic mucosa the effect on cAMP of bile acids, fatty acids, catecholamines, and propranolol. In normal colonic mucosa obtained at surgery, the effects of cAMP synthesis of deoxycholic acid, 10^{-5}M, cholic acid, 10^{-5}M, 9,10-hydroxystearic acid, 10^{-5} M, oleic acid, 10^{-5}M, epinephrine, 1^{-4}M, and norepinephrine, 10^{-4} M were studied in six experiments. Deoxycholic acid, 10^{-5}M, increased adenylate cyclase activity 203% ($p<0.01$) and 9,10-hydroxystearic acid, 10^{-5} M, increased adenylate cyclase

236% ($p<0.01$). No other agents stimulated adenylate cyclase. Propranolol, 10^{-6} M, decreased basal adenylate cyclase 43% ($p<0.01$), deoxycholic acid stimulated adenylate cyclase 46% ($p<0.01$), and hydrostearic acid stimulated adenylate cyclase 37% ($p<0.01$). Epinephrine, 10^{-4} M, or norepinephrine, 10^{-4} M, did not reverse these decreases. None of the agents studied affected phosphodiesterase. Deoxycholic acid and 9,10-hydroxystearic acid stimulate adenylate cyclase in human colonic musoca. Propranolol should be investigated as a possible treatment for these diarrhoeal conditions.

Coyne MJ see Taub M

Curlin GT see Carpenter CCJ

Dajani EZ see Gullikson GW

Darkes PR see Douglas GH

Darmansyah I see Wilmana PF

Davis GR, Camp RC, Raskin P, Krejs GJ. Effect of somatostatin infusion on jejunal water and electrolyte transport in a patient with secretory diarrhea due to malignant carcinoid syndrome. Gastroenterology 1980 Feb;78(2):346-9

The effect of intravenous somatostatin infusion was investigated in a patient with severe secretory diarrhoea due to malignant carcinoid syndrome. The patient underwent perfusion studies of the proximal and distal jejunum and colon. Continuous somatostatin infusion for 48 h (4 µg/kg.h) reduced stool volume from 2.2 to 0.7 liters/day. Somatostatin reduced urinary 5-HIAA to one-third of the amount excreted without somatostatin infusion. There were no changes in blood glucose and serum electrolyte levels nor any other side-effects during the 48 h of somatostatin administration. Intestinal perfusion studies before intravenous somatostatin infusion revealed decreased water and sodium absorption and jejunal chloride secretion. Somatostatin infusion for 2 h (8 µg/kg.h) reversed chloride secretion to absorption and markedly enhanced water and sodium absorption. These results suggest that somatostatin may have inhibited the secretory component of water and ion movement in the small bowel of the patient.

Davis GR see Schiller LR

De S, Sircar BK, De SP. Diphenoxylate hydrochloride (lomotil) in the management of cholera. Indian J Med Res 1975 Mar;63(3):469-74

Of the 85 adult cases of cholera, 65 were studied to compare the effectiveness of diphenoxylate with that of tetracycline. There were 21 cases treated with tetracycline, 20 cases with diphenoxylate and 24 cases with tetracycline and diphenoxylate combined together. The total stool output was 4.0±0.44 liters in the group of patients treated with tetracycline as opposed to 5.8±0.84 liters in the cases treated with diphenoxylate. The stool output in those treated with combined therapy was 3.4±0.56 liters -- an insignificant difference from the tetracycline-treated group. The total fluid requirement in the tetracycline-treated group was 5.0 ±0.38 liters, but in the diphenoxylate-treated group it was 6.8±0.69 liters; the difference was significant. In the combined therapy group, the fluid intake was 5.0± 0.57 liters — being not very different from the tetracycline-treated group. The duration of diarrhoea in the tetracycline-treated group was 20.3± 1.96 h,

whereas it was 26.8±2.14 h in the diphenoxylate-treated group — a difference which was significant. In the combined therapy group, the duration was 21.9± 2.02 h, and the difference with the tetracycline-treated group being insignificant. Tetracycline was a better drug in the treatment of cholera than diphenoxylate. (Modified author's abstract).

De SP see De S

De Campora E see Guandalini S

De Coster M, Kerremans R, Beckers J. A comparative double-blind study of two antidiarrhoeals, difenoxin and loperamide. Tijdschr Gastroenterol 1972;15:337-42

De Cree J see Verhaegen H

Debas H see Mulvihill S

Delamarter J see Bloom SR

Demeulenaere L, Verbeke S, Muls M, et al. Loperamide. An open multicentre trial and a double-blind cross-over comparison with placebo in patients with chronic diarrhoea. Curr Ther Res 1974;16:32-9

Desai AB, Shah KM, Shah DM. Berberine in treatment of diarrhoea. Indian Pediatr 1971 Sep;8(9):463-5

Berberine is shown to have antidiarrhoeal activity. In this paper, an attempt is made to find the effects of berberine in cases of acute diarrhoea in children. Three groups of patients were chosen for the experiment, e.g. i) those with mild diarrhoea, ii) those with moderate diarrhoea, and iii) those with severe diarrhoea of over 10 stools per day. Fifty mg of berberine was administered immediately and 25 mg at every 6 h until their diarrhoea stopped. Fluid therapy and symptomatic treatment was given to all as required. The response to treatment was considered good when the frequency of stools was reduced by 50% in severe cases within 24 h and complete control was achieved in 48-72 h. Half of the 42 cases did not grow any organism in their stool cultures. The mortality in this series was 14.4%. Berberine was effective in 35 cases. Berberine is recommended for use in the control of acute gastroenteritis caused by different organisms, including cases of cholera. It is available as a palatable liquid and can easily be administered to a child population; the treatment is short and economical.

Desjeux JF see Tai YH

Deventer GV see Mogard MH

Dharmsathaphorn K, Sherwin RS, Cataland S, Jaffe B, Dobbins J. Somatostatin inhibits diarrhea in the carcinoid syndrome. Ann Intern Med 1980 Jan;92(1):68-9

In this study, it is reported that somatostatin inhibits watery diarrhoea in a patient with the carcinoid syndrome. Blood sampling and stool and urine collections were taken during three consecutive 24-h periods before, during, and after somatostatin administration. Somatostatin was administered via continuous infusion pump (4 µg/min). No flushing was noted during infusion

although prolonged and severe flushing did develop immediately after somatostatin infusion. During somatostatin administration, stool frequency declined, and the stool became semisolid. The marked reduction in diarrhoea coincident with somatostatin administration and rapid return of symptoms upon somatostatin withdrawal may in part be accounted for by somatostatin inhibition of serotonin release, since urinary 5HIAA excretion was reduced. Serotonin blood levels were unaffected by somatostatin. Somatostatin may inhibit the action of serotonin on the intestine directly as well as affecting serotonin release by the tumor. An effect of somatostatin on intestinal motility may have contributed to its antidiarrhoeal effect. During the study, the effect of somatostatin was dramatic, but steatorrhea and hyperglycemia posed potential problems. More studies with long acting somatostatin analogues are needed to determine its usefulness in watery diarrhoea syndromes.

Dharmsathaphorn K see McArthur KE

Diamond J see Douglas GH

Djupri L see Soeparto P

Dobbins J see Dharmsathaphorn K

Dobbins JW see Binder HJ

Dodge J. Chronic non-specific diarrhoea in children. In: Gough D, ed. The control of diarrhoea in clinical practice. London: The Royal Society of Medicine, 1978:31-4 (Royal Society of Medicine International Congress and Symposium series, 5)

This study describes a double-blind crossover trial of loperamide compared with placebo in their efficacy as antidiarrhoeal agents. Sixteen children with persistent diarrhoea were included in the study whose ages ranged from 6 to 56 months (median 22.5), and the duration of their diarrhoea ranged from 2 to 56 months (median 18). Initially, loperamide syrup, in a concentration 00.2 mg/ml, was given in increasing doses, until the control of diarrhoea was achieved or the predetermined maximum dose of 0.12 mg/kg was reached. After a five-day interval, loperamide hydrochloride syrup or a matching placebo was given at the previous dosage for five days. The alternative drug or placebo was given for a final five-day period. The stool frequency and character of the stools were recorded by the parents. The severity of diarrhoea was measured accordingly. The statistical analyses pertain only to the 12 patients whose records were complete for the three phases of the study. Three of the four withdrawal cases had a good response to loperamide. It was seen from the results that most marked effect was upon consistency of stools, although there was a decrease in the frequency with which they were passed. No side-effects were observed in those on loperamide, but one patient had a poor appetite while on placebo. Loperamide was thus found effective in children with chronic nonspecific diarrhoea.

Dodge JA see Hamdi I

Dodson SA see Douglas GH

Dom J, Leyman R, Schuermans V, et al. Loperamide (R 18 553), a novel type of antidiarrheal agent. Pt. 8. Clinical investigation. Use of flexible dosage schedule in a double-blind comparison of loperamide with diphenoxylate in 614 patients suffering from acute diarrhea. Arzneim Forsch/Drug Res 1974;24:1660-5

Donowitz M, Elta G, Battisti L, Fogel R, Label-Schwartz E. Effect of dopamine and bromocriptine on rat ileal and colonic transport: stimulation of absorption and reversal of chloera toxin-induced secretion. Gastroenterology 1983 Mar;84(3):516-23

Water and electrolyte transport was determined in rat ileum and colon using the single-pass perfusion technique. Intraperitoneal dopamine 5.2 µmol/250 g body weight caused prompt stimulation of both ileal and colonic water absorption. The dopamine effect was mediated by both specific dopamine and α_2-adrenergic receptors. Haloperidol, a specific dopamine antagonist, and yohimbine, an α_2-adrenergic antagonist, inhibited the effect of dopamine in ileal absorption; both antagonists alone had no effect on basal water transport. Bromocriptine (intravenous and intraluminal) stimulated ileal and colonic water absorption, which was inhibited by haloperidol and yohimbine, and reversed cholera toxin-induced ileal secretion. Magnitude and time-courses of the increased water absorption in ileal loops inoculated with cholera toxin were the same as in loops, inoculated with saline, suggesting that bromocriptine acted to reverse cholera toxin-induced secretion by stimulating absorption. Bromocriptine had no effect on the cyclic adenosine 3',5'-monophosphate increase caused by cholera toxin. It is concluded that (a) dopamine stimulates water absorption in vivo in rat ileum and colon; (b) this dopamine effect is via specific dopamine and α_2-receptors; (c) bromocriptine stimulates water absorption in ileum and colon and also acts by dopamine and α_2-receptors; and (d) bromocriptine reverses cholera toxin-induced secretion. (Modified author's abstract)

Donowitz M see Charney AN

Douglas GH, Diamond J, Studt WL, Mir GN, Alioto RL, Auyang K, Burns BJ, Cias J, Darkes PR, Dodson SA, O'Connor S, Santora NJ, Tsuei CT, Zalipsky JJ, Zimmerman HK. Antimotility and antisecretory action of some aryl substituted amidinoureas. Arzneim Forsch/Drug Res 1978;28(2):1435-41

A number of aryl-substituted amidinoureas have been prepared and examined for their gastrointestinal spasmolytic, antimotility, antidiarrhoeal and antisecretory effects. In general, antisecretory and antimotility effects have been found to be associated with each other in these compounds. The inhibition of gastric acid secretion in the pylorus-ligated rat was investigated by the Shay method. The Brodie's gastric emptying test was then performed. Charcoal motility in Swiss-Webster male mice was observed. The structure activity relationship found showed that substitution of the aromatic ring in positions other than 2 and 6 correlated poorly with potency. Potency of such compounds is low. But 2,6-disubstitution conferred high potency. The potency of 2,6-disubstituted compounds declined sharply with increasing weight of substitution of the amidinourea chain, with the important exception of the N-alkoxy amidinoureas. High potency in an amidinourea may be related to low basicity (or a high pKa value for its conjugate salt), but there are insufficient data to support this hypothesis fully. The actual tautomeric structure of an amidinourea probably affects its potency and this is discussed.

Douglas RJ, Jr. see Steinhoff MC

DuPont HL, Sullivan P, Pickering LK, Haynes G, Ackerman PB. Symptomatic treatment of diarrhea with bismuth subsalicylate among students attending a Mexican University. Gastroenterology 1977 Oct;73(4 pt. 1):715-8

DuPont HL see Ericsson CD

DuPont HL see Portnoy BL

Durbin TE see McArhtur KE

Dutta NK, Marker PH, Rao NR. Berberine in toxin-induced experimental cholera. Br J Pharmacol 1972 Jan;44(1):153-9

This study examines whether berberine is effective against toxin-induced diarrhoea. Choleraic diarrhoea was induced in baby rabbits by the administration of toxin prepared from cell-free culture filtrates of Vibrio cholerae 569 Inaba. Berberine significantly prolonged the life of these animals besides preventing death in 70% of the rabbits. There was no significant difference in the average survival time of controls given distilled water and those given saline. Administration of berberine was effective in prolonging the survival time and preventing death in three of the five treated animals when challenged with sonicate toxin. In each control group, all the animals died within 11-18 h as against the lowest of the mean survival time, 45.67 h, of the berberine-treated groups. Berberine is as effective as chloramphenicol or tetracycline in controlling experimental cholera in infant rabbits infected with cholera vibrios. The results showed that if treatment was begun 24 h before the administration of toxin, then a number of animals could be saved from death or the life of the remaining animals could be prolonged as compared to the untreated control animals.

Dutta NK, Panse MV. Usefulness of berberine (an alkaloid from Berberis aristata) in the treatment of cholera (experimental). Indian J Med Res 1962 Sep;50(5):732-6

The antibactericidal activity of extracts of the plant Berberis aristata and its alkaloid was carried out on Vibrio cholerae strains in vitro to ascertain whether the results would run parallel with those of the rabbit cholera method. Berberine has already demonstrated favorable effects among young rabbits suffering from diarrhoea. The drug may prove useful in human cases if the treatment is instituted early. Extracts from 8 medicinal plants were tested both for their vibriocidal property and their efficacy in curing experimental cholera. Although some of them were vibriocidal in nature yet almost all of them were ineffective against rabbit cholera. The mode of treatment has been divided into four classes. With the first group of rabbits, the treatment was begun 1 h before infection; to the second, 8 h after infection; to the third, 16 h after; and to the last — after onset of diarrhoea. Berberine prevented diarrhoea from appearing and saved all the animals when treatment began 1 h before infection. Berberine hydrochloride in a dose of 50 mg/100 g saved 7 out of 9 animals when treatment was initiated 8 h after infection and 3 out of 10 when given 16 h after infection. When disodium salt of berberine citrate was injected at 8 h after infection, 90% of the animals were saved. There was no relation between the vibriocidal property of the drug and their ability to cure cholera (rabbit). Berberine had no vibriocidal property. Berberine may also be useful in the treatment of cases of acute diarrhoea.

Dutta NK see Lahiri SC

Eash JR see Mir GN

Elashoff JD see Mogard MH

Elliot HL see Pierce NF

Elta G see Donowitz M

Ericsson CD, Evans DG, DuPont HL, Evans DJ, Jr., Pickering LK. Bismuth subsalicylate inhibits activity of crude toxins of Escherichia coli and Vibrio cholerae. J Infect Dis 1977 Nov;136(5):693-6

Estes MK see Graham DY

Evans DG see Ericsson CD

Evans DJ, Jr. see Ericsson CD

Farack UM, Kautz U, Loeschke K. Loperamide reduces the intestinal secretion but not the mucosal cAMP accumulation induced by cholera toxin. Naunyn Schmiedebergs Arch Pharmacol 1981 Sep;317(2):178-9

Feser JF see Tai YH

Fiasse R see Mainguet P

Field M, Sheerin HE, Henderson A, Smith PL. Catecholamine effects on cyclic AMP levels and ion secretion in rabbit ileal mucosa. Am J Physiol 1975 Jul;229(1):86-92

Effects of catecholamines on cyclic adenosine 3',5'-monophosphate (cAMP) levels and ion fluxes were examined in isolated rabbit ileal mucosa. The baseline cAMP level was unaffected by epinephrine, norepinephrine, and isoproterenol. The theophylline-augmented cAMP level was decreased slightly by epinephrine in one series of experiments but not in another. Propranolol did not enhance this effect. The increase in cAMP level produced by cholera toxin was almost completely reversed by addition of epinephrine or norepinephrine. This reversal was prevented by phenoxybenzamine. Epinephrine also partially reversed the increase in cAMP level produced by prostaglandin E_1. Effects of epinephrine on ion fluxes were determined following addition of secretagogues. Epinephrine significantly decreased theophylline-induced but not cAMP or cholera toxin-induced Cl secretion. A decrease in short-circuit current was nonetheless observed in the latter two instances. The observed discrepancies between α-adrenergic effects on cAMP levels and ion fluxes suggest the following possibilities: 1) ion transport-related cAMP is only a small fraction of total mucosal cAMP; 2) cAMP-induced active ion secretion is only slowly reversible, or 3) effects of α-adrenergic stimuli on ion transport are not due to inhibition of cAMP accumulation. Cholera toxin-induced secretion is not mediated by cAMP. (Modified author's abstract)

Field M, McColl I. Ion transport in rabbit ileal mucosa. III. Effects of catecholamines. Am J Physiol 1973 Oct;225(4):852-7

Effects of epinephrine and norepinephrine on ion transport in isolated rabbit ileal mucosa were studied in HCO_3-containing (25 mM HCO_3, 5% CO_2) and HCO_3-free (no HCO_3 or CO_2) Ringer solutions. In HCO_3-Ringer, epinephrine and norepinephrine (.05 mM) produced rapid and sustained decreases in short-circuit current of more than 100 $\mu a/cm^2$. In HCO_3-free Ringer (present on both sides of the mucosa or only on the luminal side), the decreases in short-circuit current produced by epinephrine and norepinephrine were much smaller. In both Ringer

solutions, norepinephrine reversed the increase in short-circuit current produced by theophylline, but not that produced by cyclic adenosine 3',5'-monophsphate or its dibutyryl analogue. These short-circuit current changes did not occur with isoproterenol, were unaffected by propranalol, and were partially reversed by phentolamine, suggesting that they are α-adrenergic in nature. Na and Cl flux measurements demonstrated the following effects of epinephrine and norepinephrine in HCO_3 -Ringer: an increase in net mucosa-to-serosa Na flux due to an increase in the mucosa-to-serosa unidirectional flux; an increase in net mucosa-to-serosa Cl flux due both to an increase in mucosa-to-serosa and a decrease in serosa-to-mucosa unidirectional fluxes; and disappearance of the residual ion flux (short-circuit current net Na flux + net Cl flux). Most of the short-circuit current change was due to the last of these effects. These effects were not seen in HCO_3-free Ringer. It is concluded that stimulation of α-adrenergic receptors in the ileal mucosa enhances active absorption of Na and Cl and reduces short-circuit current, probably by inhibiting net HCO_3 secretion. (Modified author's abstract)

Field M. Ion transport in rabbit ileal mucosa. II. Effects of cyclic 3',5'-AMP. Am J Physiol 1971 Oct;221(4):992-7

Addition of cyclic adenosine 3',5'-monophosphate (cAMP), dibutyryl- cAMP, or theophyline to the serosal side of isolated rabbit ileal mucosa rapidly increases short-circuit current. The maximal increment, 80 $\mu a/cm^2$, is the same for all three agents and is not exceeded by addition of more than one agent. The concentratioins giving half-maximal effects were $3x10^{-3}$ M, $8x10^{-5}$ M and $7x10^{-4}$ M respectively. Thirty to 60 min after addition of theophylline (10 mM) or cAMP (7.5 mM) to the short-circuited mucosa, the net mucosa-to-serosa Na flux had disappeared due to a decrease in mucosa-to-serosa unidirectional flux, and the net Cl flux has been reversed in direction from mucosa-to-serosa to serosa-to-mucosa due both to decrease in the mucosa-to-serosa and an increase in the serosa-to-mucosa unidirectional fluxes. Addition of glucose on the luminal side causes the same increment in short-circuit current in theophylline-treated as in control tissues, suggesting that cAMP does not inhibit glucose-coupled Na transport. Adenosine triphosphate, uridine 3',5'-triphosphate adenosine 3',5'-diphosphate, 5'-AMP, cyclic guanoside 3',5'-monophosphate, and pyrophosphate all increase short-circuit current when added on the serosal side. Prior addition of theophylline greatlly reduces these short-circuit current responses, suggesting a common mode of action. Several of these agents have been shown to inhibit phosphodiesterase in other tissues. It is concluded that cAMP stimulates an active secretory process in rabbit ileal mucosa which, under the short-circuit condition, is manifested by the appearance of a net serosa-to-mucosa Cl flux and the disappearance of an organic solute-independent net mucosa-to-serosa Na flux. (Modified author's abstract)

Field M see Frizzell RA

Field M see Kimberg DV

Field M see Powell DW

Field M see Schwartz CJ

Field M see Smith PL

Fogel R see Donowitz M

Fordtran JS see Schiller LR

Formal SB see Gianella RA

Formal SB see Gots RE

Fredman P see Stoll BJ

Frizzell RA, Field M, Schultz SG. Sodium-coupled chloride transport by epithelial tissues. Am J Physiol 1979;236(1):F1-8

There is compelling evidence that active Cl absorption by a variety of epithelia, widely distributed throughout the animal kingdom, is the result of an electrically neutral Na-coupled transport process at the luminal membrane and that the energy for transcellular Cl movement is derived from the Na gradient across that barrier. These co-transport processes are found predominantly in "leaky" or "moderately leaky" epithelia and permit these tissues to absorb Na and Cl with high degrees of efficacy. In addition, there is a growing body of evidence that cyclic adenosine 3',5'-monophsphate and Ca-induced electrogenic Cl secretion by a wide variety of epithelia may involve electrically neutral, Na-coupled Cl entry across the contraluminal membrane and that the energy for these secretory processes is derived from the Na-gradient across that barrier. (Author's abstract)

Froehlich JL see Sack RB

Fujimoto M, Okabayashi T. Proposed mechanisms of stimulation and inhibition of guanylate cyclase with reference to the actions of chlorpromazine, phospholipases and toxin X-100. Biochem Biophys Res Commun 1975 Dec 15;67(4):1332-6

Galambos JT, Hersh T, Schroder S, Wenger J. Loperamide: a new antidiarrheal agent in the treatment of chronic diarrhea. Gastroenterology 1976 Jun;70(6):1026-9

Twenty-seven patients (median age 44.5 years) with chronic diarrhoea due to Crohn's disease (8), ulcerative colitis (4), short bowel syndrome (3), and idiopathic (functional) causes (5) participated in a multiphase study (open, double-blind, and long-term open) of loperamide hydrochloride, a new single entity, oral antidiarrhoeal agent. In the open phase of the study, loperamide, a synthetic opium derivative, effectively relieved symptoms of diarrhoea in 21 of the 27 patients. The average number of stools dropped from eight in the initial relapse period to two stools after 1 month of treatment ($p=0.0001$). Efficacy was confirmed in the double-blind and long-term open phases of the study. Four patients who were not relieved while on therapy had discontinued the drug because of abdominal cramping. No other side-effects attributable to the drug were observed. Loperamide has been found to be a safe and effective agent for the treatment of chronic diarrhoea. (Modified author's abstract)

Gangal RN see Owens JR

Gentry LO see Graham DY

Gershon E see Kimberg DV

Giannella RA, Gots RE, Charney AN, Greenough WB, III, Formal SB. Pathogenesis of Salmonella-mediated intestinal fluid secretion: activation of adenylate cyclase and inhibition by indomethacin. Gastroenterology 1975 Dec;69(6):1238-45

Salmonella typhimurium, an organism that invades intestinal mucosa, but does not elaborate a traditional enterotoxin, evokes ileal secretion by causing alterations in active sodium and chloride transport mechanisms. To evaluate the possibility that these changes in transport may be related to the adenylate cyclase-cyclic adenosine 3',5'-monophosphate (cAMP) or Na^+ -K^+ -adenosine triphosphatase (ATPase) systems, mucosal adenylate cyclase, cAMP phosphodiesterase, Na^+ -K^+ and Mg^{++} ATPase activities, and cAMP concentrations were measured in rabbit ileal loops infected with two strains of S. typhimurium. Strain TML invades the mucosa and evokes fluid secretion, whereas strain SL 1027 invades, but does not evoke secretion. Cholera toxin-stimulated loops were also studied. When compared to control loops, TML-infected mucosa demonstrated a marked increase in adenylate cyclase activity in cAMP concentration, and no change in phosphodiesterase or ATPase activities. SL 1027-infected mucosa demonstrated no change in either adenylate cyclase of ATPase activities. Indomethacin pretreatment of TML-infected animals abolished both fluid secretion and adenylate cyclase activation. In contrast, indomethacin pretreatment of cholera toxin-exposed animals resulted in only a partial reduction of secretion while not altering the stimulation of adenylate cyclase. These results suggest that: (1) S. typhimurium causes ileal secretion by stimulating adenylate cyclase; (2) mucosal invasion alone (SL 1027) is not sufficient to activate adenylate cyclase, and (3) Na^+ -K^+-ATPase does not appear to be involved in Salmonella-induced secretion. The mechanism of Salmonella activation of adenylate cyclase is unclear, but apparently differs from that of cholera toxin in that it is inhibited by indomethacin. This could possibly be explained by the participation of prostaglandins in the Salmonella activation process. (Modified author's abstract)

Giannella RA see Gots RE

Glock RD see Lomax LG

Goldenberg MM, Honkamp LJ, Castellion AW. The antidiarrheal action of bismuth subsalicylate in the mouse and the rat. Am J Dig Dis 1975 Oct;20(10):955-60

Gots RE, Formal SB, Giannella RA. Indomethacin inhibition of Salmonella typhimurium, Shigella flexneri, and cholera-mediated rabbit ileal secretion. J Infect Dis 1974 Sep;130(3):280-4

Non-invasive, toxigenic Vibrio cholerae and the invasive enteropathogens, Shigella flexneri and Salmonella typhimurium, stimulate secretion of fluids in rabbit ileal loops. To assess similarities in secretory mechanisms and the possible involvement of prostaglandins (PG) in secretion, indomethacin (a rapid, intense inhibitor of PG synthesis) was used. Fluid secretion mediated by S. typhimurium was completely inhibited by treatment with indomethacin. Secretions stimulated by S. flexneri, V. cholerae, and cholera toxin were reduced by 40-60%. Indomethacin affected neither the local invasiveness of S. typhimurium or S. flexneri nor the peripheral dissemination of S. typhimurium. Therefore, indomethacin dissociated the invasive process from the secretory event. These data are consistent with the participation of PGs in these enteropathogen-stimulated secretory states. This conclusion must, however, be regarded as tentative in view of other possible mechanisms of indomethacin action. (Modified author's abstract)

Gots RE see Giannella RA

Gotterer GS see Turjman N

Gotterer GS see Wald A

Gotzkowsky S see LaCorte WSJ

Gould RJ see Reynolds IJ

Goyal RK see Sharma R

Gracey M see Burke V

Graham DY, Estes MK, Gentry LO. Double-blind comparison of bismuth subsalicylate and placebo in the prevention and treatment of enterotoxigenic Escherichia coli-induced diarrhea in volunteers. Gastroenterology 1983 Nov;85(5):1017-22

Greenberg H see Steinhoff MC

Greenberg RN, Murad F, Guerrant RL. Lanthanum chloride inhibition of the secretory response to Escherichia coli heat-stable enterotoxin. Infect Immun 1982 Feb;35(2):483-8

Escherichia coli heat-stable (ST) enterotoxin appears to cause intestinal fluid secretion by activating intestinal particulate guanylate cyclase. Recent studies suggest that chlorpromazine and quinacrine reduce the intestinal secretory response to ST enterotoxin and activation of guanylate cyclase by ST enterotoxin. The purpose of this study is to examine the effects of lanthanum chloride, another agent that has been shown to inhibit calcium-dependent cellular processes, on the intestinal secretory response to ST enterotoxin and on the inhibition of ST enterotoxin by chlorpromazine and quinacrine. Lanthanum (2.5 to 10 umol per mouse) reduced ST enterotoxin-mediated intestinal fluid secretion in the suckling mouse assay by 40 to 56% respectively, but did not reduce basal fluid accumulation or ST enterotoxin activation of particulate guanylate cyclase. Intestinal fluid secretion in suckling mice, induced by 8-bromo-cyclic guanylate 3',5'-monophosphate (cGMP), was also reduced by lanthanum. When subeffective doses of lanthanum and chlorpromazine were combined, they blocked both ST enterotoxin-and 8-bromo-cGMP-mediated gut secretion in suckling mice. Likewise, the combination of subeffective doses of lanthanum and quinacrine reduced ST enterotoxin-mediated gut secretion in the suckling mice. However, 8-bromo-cGMP-induced secretion was not synergistically inhibited by lanthanum and quinacrine. These results suggest that lanthanum blocks ST enterotoxin-induced secretion after ST enterotoxin activation of guanylate cyclase. Additionally, lanthanum potentiates the inhibitory effects of quinacrine and chlorpromazine on ST enterotoxin and suggests that combination antisecretory therapy deserves further exploration. (Modified author's abstract)

Greenough WB see Carpenter CCJ

Greenough WB, III. Principles and prospects in the treatment of cholera and related dehydrating diarrheas. In: Ouchterlony O, Holmgren J, eds. Cholera and related diarrheas: molecular aspects of a global health problem. Basel: Karger, 1980:211-8. (43rd Nobel Symposium)

This paper is a review on the current diarrhoea treatment practices. Presently the therapeutic challenge is to teach families to use an appropriate oral rehydration solution for treating diarrhoea. In the treatment of cholera and the related diseases the rate of fluid loss needs to be diminished by an agent which is inexpensive, readily available, nontoxic and capable of easy measurement. The ability to rehydrate cholera patients by mouth decreases very rapidly as the rate of purging exceeds 100 ml/kg.24 h. Intravenous fluid therapy would be needed in such cases. An ideal oral solution should contain sodium and glucose. Sucrose is an acceptable substitute where glucose is expensive and not available. Several recent studies show that glucose is slightly better than other carbohydrates. Clinical trials should be carried out to examine whether rice or potato can be used as proteins and peptides. In the case of cane sugar, the advantage lies in the presence of potassium in it. The final oral fluid replacement contains table salt and sugar in water. Recently in Dhaka, Bangladesh, it was shown that oral rehydration replacement was successful, though in some cases, acidosis was associated. Basic studies to test the hypothesis that a receptor blockade would indeed prevent fluid loss are needed. To accomplish this goal, more information about the pathogenicity of Vibrio cholerae and their genetic loci are necessary. The inhibition of adenylate cyclase stimulation and interventions in ion transport have been discussed. A fundamental enquiry into the existing health beliefs and practices in the matrix of specific geocultural settings is essential to any application of current knowledge in the prevention or treatment of diarrhoea.

Greenough WB, III see Al-Awqati Q

Greenough WB, III see Giannella RA

Greenough WB, III see Pierce NF

Greenough WB, III see Rabbani GH

Greenough WB, III see Stoll BJ

Griffiths E, Humphreys J. Bacteriostatic effect of human milk and bovine colostrum on Escherichia coli: importance of bicarbonate. Infect Immun 1977 Feb;15(2):396-401

At pH 7.4 and in the presence of $NaHCO_3$, human milk and bovine colostrum inhibited the growth of Escherichia coli O111. Adding sufficient iron to saturate the iron-binding capacity of the lactoferrin present in the milk or colostrum prevented bacteriostasis. At pH 6.8, neither milk nor colostrum inhibited E. coli O111. Adjusting the pH to 7.4 with $NaHCO_3$ resulted in the development of bacteriostatic activity. Adjusting the pH to 7.4 with NaOH was ineffective. Dialyzed colostrum and milk inhibited bacterial growth at pH 6.8 in the absence of added $NaHCO_3$; addition of citrate or iron abolished bacteriostasis. The chromatographic elution profile of tyrosyl-transfer ribonucleic acid (tRNA) from iron-replete E. coli differed significantly from that of tyrosyl-tRNA from iron-deficient organisms. Examination of the elution profile of tyrosyl-tRNA from E. coli O111 growing in colostrum without added $NaHCO_3$ showed that such bacteria were fully replete in iron. The nature of the elution profile of tyrosyl-tRNA also showed that the iron was freely available to the bacteria when citrate was added to dialyzed colostrum but not available in its absence, even at pH 6.8. Results support the idea that the bacteriostatic action of milk and colostrum, due to the combined action of antibody and lactoferrin, depends on the addition of bicarbonate to counteract

the iron-mobilizing effect of the citrate normally present in these secretions. (Author's abstract).

Grill B see Gryboski JD

Gryboski JD, Hillemeier AC, Grill B, Kocoshis S. Bismuth subsalicylate in the treatment of chronic diarrhea of childhood. Am J Gastroenterol 1985 Nov;80(11):871-6

This study determines the value of Pepto-Bismol (bismuth subsalicylate) in the treatment of chronic diarrhoea of childhood and to establish an effective dosage for children and infants. Twenty-nine infants with chronic diarrhoea were admitted to a double-blind, parallel clinical trial. About 14% patients showed gastrointestinal allergy to milk and to soy proteins. Fourteen patients were assigned to the placebo formulation group and 15 to the bismuth subsalicylate formulation group. Stool transit times varied from 3-30 h and showed no consistent change to either therapeutic programs. Children in the bismuth subsalicylate group gained weight steadily during the study. The baseline number of stools was higher ($p<0.05$) in the bismuth subsalicylate group than placebo group. The stools became more firm following bismuth subsalicylate therapy than after placebo therapy ($p<0.01$). Bile acid excretion increased during therapy with both bismuth subsalicylate and placebo. The bismuth subsalicylate formulation gave better response ($p<0.01$) in the clinical treatment of diarrhoea. The stool cultures of the patients revealed no enteric pathogens. In the Schilling's test, the abnormal results in 20% of the patients suggest terminal ileal dysfunction and a choleretic mechanism for their diarrhoea. The dosages used in this study were safe as well as effective. The results suggest that bismuth subsalicylate in the dosage employed is useful in the therapy of chronic childhood diarrhoea.

Guandalini S, Migliavacca M, de Campora E, Rubino A. Cyclic guanosine monophosphate effects on nutrient and electrolyte transport in rabbit ileum. Gastroenterology 1982 Jul;83(1, pt 1):15-21

In cyclic adenosine 3,'5'-monophosphate (cAMP)-related diarrhoeas, the sodium-coupled absorptive processes for glucose and amino acids are intact, thus allowing oral use of nutrient-electrolyte solutions as a therapeutic tool. Not all bacterial enterotoxins, however, act by increasing cAMP: it is now known that some heat-stable (ST) enterotoxins act through cyclic guanosine 3',5'-monophosphate (cGMP). Although its effects on ion transport have been found similar to those of cAMP, nothing is known of its possible role on intestinal nutrient transport. The purpose of this study is to investigate the effects of the cyclic nucleotide analogue 8-bromo-cGMP (0.2 mM) on the influx (from the luminal solution into the epithelium) and on the transepithelial transport of several nutrients and of sodium in the ileal musoca of rabbits in vitro. Eight-bromo-cGMP completely blocked sodium chloride-coupled influx, while it did not affect the uptake of glucose, glutamic acid, lysine, phenylalanine, glycylphenylalanine, and glycylsarcosine. Also Escherichia coli ST heat-stable enterotoxin did not affect glucose influx measured at various substrate concentrations. Five mM glucose raised sodium uptake by an identical value both in the presence and in the absence of the cyclic nucleotide analog; also these increments were in good agreement with the uptake of glucose at 5 mM both in the absence and in the presence of ST enterotoxin, thus suggesting that the sodium glucose-coupled influx is intact. The effects of 8-bromo-cGMP on transepithelial transport of glucose, phenylalanine, and sodium across stripped, short-circuited ileal mucosa were also ivestigated. Although the

cyclic nucleotide analogue markedly shifted net sodium transport toward secretion, it did not alter the net absorption of either glucose or phenylalanine. It is concluded that cGMP, like cAMP: (a) inhibits sodium chloride-coupled influx and induces secretory changes on net sodium transport; (b) has no inhibitory effect on the 1:1 obligatory-coupled influx of glucose and sodium across the brush border; and (c) does not affect transport of glucose, amino acids, and dipeptides. These data support the oral use of nutrient-electrolyte solutions in the treatment of ST enterotoxin-induced diarrhoeas. (Modified author's abstract)

Guerrant RL see Greenberg RN

Gullikson GW, Dajani EZ, Bianchi RG. Inhibition of intestinal secretion in the dog: a new approach for the management of diarrheal states. J Pharmacol Exp Ther 1981;219(3):591-7

The purpose of this study is to investigate whether propranolol, chlorpromazine, verapamil, and lidamidine could block the deoxycholate-induced jejunal secretion in conscious Thiry-Vella dogs. Intestinal perfusion with a buffered deoxycholate solution (5 mM) markedly stimulated net water and electrolyte secretion. Lidamidine (1 and 4 mg/kg) showed a dose-dependent inhibition of intestinal electrolyte and fluid accumulation induced by deoxycholate. This effect appeared to be mediated by an inhibition of intestinal secretion, because lidamidine did not augment absorption of the buffered perfusate not containing deoxycholate. The antisecretory action of lidamidine (4 mg/kg) was also accompanied by evidence of attenuation of the mucosal damage produced by deoxycholate, reductions in the concentrations of calcium, lipid phosphorus and protein in the luminal fluid. These effects of lidamidine on deoxycholate-induced fluid and electrolyte secretion and mucosal membrane marker efflux were similar to those seen when the effects of deoxycholate were reversed by perfusion with control buffer. Chlorpromazine (5 mg/kg) produced a significant reduction in net fluid and electrolyte secretion, but was less active than lidamidine. Verapamil (1 and 5 mg/kg) and propranolol (5 and 10 mg/kg) failed to affect deoxycholate-induced secretion. It is concluded that lidamidine may be of clinical value in the managment of diarrhoea associated with bile acid malabsorption or exogenously administered bile acids. (Modified author's abstract)

Gupte S. Use of berberine in treatment of giardiasis. Am J Dis Child 1975 Jul;129(7):866

A study was carried out at the Postgraduate Institute of Medical Education and Research in Chandigarh, India, investigating various aspects of giardiasis. The study was later continued at the H.P. Medical College in Simla, India. Patients ranged in age from 5 months to 14 years with a mean age of 5 years who carried out the group-comparative trial. Berberine was administered orally in a dose of 10 mg/kg.day for 10 days, resulting in satisfactory parasitological cure, comparable to that obtained with other antigiardial drugs, e.g. quinacrine hydrochloride, furazolidone, metronidazole. A month later, however, a number of cases relapsed, and some of the patients became reinfected. It is concluded that berberine appears to be a useful therapeutic agent in the management of giardiasis. No side-effects and the convenience of administration make it acceptable to infants and children. It is suggested that more clinical trials, including cytochemical studies, are needed to confirm the above results.

Gyles CL, Zigler M. The effect of adsorbant and anti-inflammatory drugs on secretion in ligated segments of pig intestine infected with Escherichia coli. Can J Comp Med 1978 Jul;42(3):260-8

Hamdi I, Dodge JA. Toddler diarrhoea: observations on the effects of aspirin and loperamide. J Pediatr Gastroenterol Nutr 1985 Jun;4(3):362-5

This paper reports the effect of a prostaglandin (PG) synthetase inhibitor, aspirin, and an opiate analogue, loperamide, on the plasma concentrations of PGF_{α}, and the clinical response to treatment with these drugs. Twenty children with toddler diarrhoea, aged 9 to 35 months, were included in the study. The upper limits of normal values of plasma PGs in the laboratory were PGE_2 150 pg/ml and PGF_{α} 300 pg/ml. The patients studied showed a wide variation within and outside the normal range. Although aspirin reduced plasma levels of PGF_{α} after a week, loperamide had no effect on plasma PG concentrations. In the eight patients experiencing spontaneous remission of diarrhoea, plasma PGF_{α} levels were always lower at this time than during acute episodes. Clinically, stool frequency and/or consistency improved in six of the eight children given aspirin in whom the scoring system was used, while all 10 treated with loperamide responded well. The observations may support the concept of enhanced PG production in the small intestine rather than in the colon, and that the antisecretory action of loperamide is as important as its motility effects. Although a clinical remission of diarrhoea can be achieved consistently with loperamide and frequently with aspirin, no medication in view of side-effects and other factors were prescribed here.

Haqqani AH, Taqi S. Diphenoxylate hydrochloride in the diarrhoeal disease of children. Pakistan Pediatr J 1981 Dec;5(4):249-58

The effect of diphenoxylate hydrochloride (lomotil) with atropine as an antidiarrhoeal drug was studied in a trial from June to November 1980, at the National Institute of Child Health, Karachi, Pakistan. Two groups of children with diarrhoea were admitted into the study. None had blood or mucus in the stools or was thought to have Shigella or Salmonella infections. All had severe dehydration and were suffering from moderate to severe degrees of malnutrition. One group (77 patients) was randomly allocated to receive diphenoxylate, 0.25 mg/kg.day for 3 days. The other group (51 patients) received no drug. The drug was found to be effective in 78% of the children, i.e. the number of stools came down to 3 per 12 h in 3 days. Eighty-eight percent of the control group responded in the same way. The incidence of drowsiness was higher than in the control group, but the difference was not statistically significant. It is concluded that diphenoxylate can be prescribed provided dehydration is prevented early in the disease and caution taken not to prescribe to infants aged under 6 months.

Harries JT see Sandhu B

Harries JT see Sandhu BK

Haynes G see DuPont HL

Heel RC, Brogden RN, Speight TM, Avery GS. Loperamide: a review of its pharmacological properties and therapeutic efficacy in diarrhea. Drugs 1978;15:33-52

Henderson A see Field M

Henderson A see Kimberg DV

Hendrickse RG see Owens JR

Hendrix TR see Serebro HA

Hendrix TR see Turjman N

Hendrix TR see Wald A

Hersh T see Galambos JT

Herz A see Wuster M

Higgs NB see Hughes S

Higgs NB see McKay JS

Hillemeier AC see Gryboski JD

Hock CW. Relief of diarrhoea with diphenoxylate hydrochloride (lomotil). J Med Assoc Georgia 1961;50:485-8

Holdsworth CD see Palmer KR

Holdsworth D see Corbett C

Holmgren J, Lange S, Lonnroth I. Reversal of cyclic AMP-mediated intestinal secretion in mice by chlorpromazine. Gastroenterology 1978 Dec;75(6):1103-8

Chlorpromazine is known to inhibit hormonal stimulation of cyclic adenosine 3',5'-monophosphate (cAMP) formation in several cell types. Chlorpromazine was, therefore, investigated as a potential inhibitor of cAMP-mediated intestinal secretion in mice. Pretreatment with 4 μg of chlorpromazine per g of body weight given intramuscularly gave complete inhibition of the fluid response to large doses of cholera toxin, Escherichia coli heat-labile enterotoxin, prostaglandin E_1, as well as dibutyryl-cAMP. Submaximal cholera toxin doses were inhibited by <1 μg of chlorpromazine per g. Effective inhibition was also obtained by injecting chlorpromazine 1 or 2 h after the intestinal challenge with cholera toxin, at which times the secretion rate was maximal; the treatment reversed the intense net secretion into net absorption, consistent with the finding that intestinal net water uptake was not significantly affected by chlorpromazine. Studies with [^{35}S] chlorpromazine showed a rapid dose-proportional uptake of radiolabel into the membranes of both crypt and villus cells of the small intestine. Enzymatic analyses on intestinal mucosal membrane showed that cholera toxin stimulation of adenylate cyclase was totally inhibited in chlorpromazine-treated animals; fluoride activation of the enzyme was inhibited too, while the basal adenylate cylase activity was not significantly changed. However, the mucosal membrane-associated protein kinase activity was also strongly reduced, suggesting a multipoint effect. This might explain why chlorpromazine inhibited the intestinal secretion induced not only by various adenylate cyclase activators but also by dibutyryl-cAMP. (Modified author's abstract)

Holmgren J see Islam MR

Holmgren J see Lonnroth I

Holmgren J see Rabbani GH

Holmgren J see Stoll BJ

Honkomp LJ see Goldenberg MM

Hughes S, Higgs NB, Turnberg LA. Antidiarrhoeal activity of loperamide: studies of its influence on ion transport across rabbit ileal mucosa in vitro. Gut 1982 Nov;23(11):974-9

Loperamide is a well-established antidiarrhoeal agent having effects on gastrointestinal motility. It is demonstrated in this study that it also has antisecretory effects in the isolated rabbit ileum. In the isolated rabbit ileal mucosa, loperamide caused a dose-related fall in potential difference and short-circuit current and reduced the serosa-to-mucosa flux of chloride. The electrical effects were inhibited by naloxone (10^{-6}M) suggesting that they were mediated by opiate receptors. Loperamide (10^{-6}M) inhibited secretion provoked by heat-stable and heat-labile Escherichia coli toxins and by prostaglandin E_2. In the present study, loperamide did not influence net transport in unstimulated tissue, although it reduced serosa-to-mucosa chloride fluxes. It is concluded that loperamide is able to inhibit secretion mediated by cyclic adenosine 3',5'-monophosphate or cyclic guanosine 3',5'-monophosphate, and that this may be relevant to its antidiarrhoeal properties.

Hughes S, Higgs NB, Turnberg LA. Loperamide has antisecretory activity in the human jejunum in vivo. Gut 1984 Sep;25(9):931-5

This study reports the influence of loperamide on basal absorption of salt and water in the human jejunum in vivo and on secretion induced by prostaglandin (PG) E_2. Jejunal perfusion was carried out in 26 healthy volunteers by a triple lumen tube technique. Regarding the basal studies, all subjects absorbed water, Na, K, and Cl in the control period, and most subjects absorbed HCO_3. Mean transit time with bicarbonate-free perfusate was 7.53 min, and this was not changed significantly by loperamide. PGE_2-induced secretion was inhibited incompletely when loperamide was administered either before or after secretion had started. Loperamide caused a significantly greater fall in secretion than was observed spontaneously in the second of two PG perfusion periods. In three of the six subjects given loperamide, secretion had caused, and a small amount of absorption was observed. In these studies, PGE_2 shortened the transit time measured by the dye-dilution curve technique. The dose of loperamide used in these experiments was large compared with the usual therapeutic dose. The results suggest that loperamide may have some potential value in the treatment of secretory diarrhoea.

Humphreys J see Griffiths E

Huq I see Stoll BJ

Huq M see Butler T

Iber FL see Serebro HA

Islam A see Rabbani GH

Islam MR, Sack DA, Holmgren J, Bardhan PK, Rabbani GH. Use of chlorpromazine in the treatment of cholera and other severe acute watery diarrhoeal diseases. Gastroenterology 1982 Jun;82(6):1335-40

In some previous controlled, nonblinded studies, chlorpromazine administered orally or intramuscularly in doses from 1 to 4 mg/kg significantly reduced the purging rates in adult cholera patients who received intravenous (i.v.) fluids, but no antibiotics. This encouraged further investigation, and as such, 410 patients with severe watery diarrhoea, including 316 patients with cholera, were studied in a double-blind, randomized, placebo-controlled trial to determine if chlorpromazine (1 mg/kg) would be useful in the management of such patients. Patients, aged over 2 years, were selected from those admitted to the International Centre for Diarrhoeal Disease Research, Bangladesh. All patients were at least 7.5% dehydrated on admission into the study; all received i.v. fluids followed by oral rehydration solution, and all received tetracycline. In addition, one-half of the patients received chlorpromazine, 1 mg/kg orally as a single dose 2 h after admission. The effectiveness of chlorpromazine was determined by comparing oral therapy failure rates, purging rates, vomiting rates, i.v. fluid requirements and hospitalization time in groups of the patients receiving and not receiving the drug. In children with severe cholera characterized by shock on admission or at very high purging rates, chlorpromazine lowered the oral therapy failure rate by about 50%. However, children with less severe cholera, adults with cholera, and patients of all ages with non-cholera diarrhoea, could not be demonstrated to benefit significantly from the drug. This was different from the previous studies where the benefit of the drug in such patients was demonstrated, and may be explained by the several differences in the study design. The implications from the results of the present study are that chlorpromazine may be of value in the treatment of children with severe cholera when used in addition to standard hydration and antibiotic therapy, but is not helpful in patients with non-cholera watery diarrhoea.

Isolauri E see Vesikari T

Jacoby HI, Marshall CH. Antagonism of cholera enterotoxin by anti-inflammatory agents in the rat. Nature (Lond) 1972 Jan 21;235(5334):163-4

Although the process of treatment of cholera by fluids and electrolytes is effective and well established, but during large-scale outbreaks, this may not be a workable mode of epidemic control. A drug which could be given orally to reverse the loss of fluid and electrolytes by antagonizing the effect of cholera enterotoxin on secretory mechanisms of the small intestine has been suggested. To find the appropriate drug for controlling epidemics, several anti-inflammatory agents were examined for their nature and extent of anti-cholera activity. Drugs tested include: aspirin, indomethacin, phenylbutazone, sodium salicylate, dexamethasone, prednisolone, and ethacrynic acid. These drugs were either administered orally 30 min before ligation or subcutaneously at the time of ligation. Anti-inflammatory compounds inhibited cholera toxin-induced fluid accumulation and when given in higher doses decreased the gut weight in rats given only saline; both effects were dose-related. Dexamethasone and prednisolone were effective at relatively high doses only. Indomethacin was the most active, showing activity at doses as low as 0.06 mg/kg when given subcutaneously. Aspirin, indomethacin and phenylbutazone were also active when given orally. Ethacrynic acid was active against cholera toxin at a dose of 32 mg/kg given subcutaneously, but was not active orally. Locating a drug of choice for use in epidemics may be effective

specially when the available manpower and equipment to fight the outbreak are insufficient or at a bare minimum.

Jaffe B see Dharmsathaphorn K

Jaffe BM. Prostaglandins and serotonin: nonpeptide diarrhoeagenic hormones. World J Surg 1979;3(5):565-77

Prostaglandins (PG) and serotonin are vasoactive compounds with profound effects on the gastrointestinal tract. Both are known to cause inhibition of gastric acid secretion (although serotonin stimulates gastric pepsin secretion), stimulation of intestinal motility, and conversion of small intestinal mucosa from absorption to secretion of water and electrolytes. Their effects on pancreatic and biliary function are still not clear. Although PGs appear to elicit their effects primarily by a paracrine mode of action, and serotonin is primarily a neurotransmitter (neurocrine), it is clear that even under normal conditions both can function as humoral agents. Studies have shown that serotonin plays a physiologic role as a humoral inhibitor of gastric acid secretion. However, the effects of these agents became more pronounced in patients with humorally mediated diarrhoeagenic syndromes. Serotonin (and related indoles, particularly 5-hydroxytryptophan) has been firmly implicated as a cause of diarrhoea in patients with carcinoid syndrome. Recent studies suggest that the diagnosis can be more effective by measuring circulating immunoreactive serotonin concentrations rather than urinary excretion of 5-IIIAA. It has also been found that some circulating serotonins escape hepatic inactivation, and thus, large intestinal tumors can cause carcinoid syndrome in the absence of hepatic metastases, and that large amounts of serotonin are produced by some noncarcinoid diarrhoeagenic tumors. A large number of tumors of probable moral crest origin, including medullary thyroid carcinoma, carcinoids, and tumors associated with the watery diarrhoea, hypokalemia, achlorhydria syndrome, secrete large amounts of PGs, particularly PGE_2. The clinical response of at least some of the patients harboring these tumors to inhibitors of PG synthesis (particularly indomethacin) suggests that PGs play a role in the etiology of these diarrhoeagenic syndromes. (Modified author's abstract)

Janssen PAJ see Awouters F

Janssen PAJ see Niemegeers CJE

Jaswal OP see Owens JR

Jennische E, Lonnroth I. Effects of chlorpromazine on fluid transport across the intestinal mucosa of the rat. Acta Pharmacol Toxicol 1982;50:305-9

The effect of chlorpromazine on net fluid transport in the small intestine of the rat was studied, using a ligated-loop model. Given intramuscularly at 5 mg/kg, chlorpromazine induced a 50%-increase of net fluid absorption in jejunum, but showed no effects in the ileum. Similarly, the drug decreased net fluid accumulation induced by dibutyryl-cyclic adenosine 3',5'-monophosphate (cAMP) in jejunum, but did not influence net fluid accumulation in ileum. In contrast, net fluid accumulation induced by cholera toxin was decreased by chlorpromazine in both jejunum and ileum. Inhibition of cAMP - which probably mediates the hypersecretion by the toxin - was also noted. These results suggest that chlorpromazine reverses fluid transport during cholera in two ways: by a cAMP-independent enhancement of fluid absorption in jejunum and by

inhibition of the toxin-induced cAMP production in jejunum as well as ileum. Each of these processes may be independently affected by pharmacological substances and subjected to neural and hormonal regulation. (Modified author's abstract)

Jennische E see Lonnroth I

Jodal M see Cassuto J

Johnson J see Kimberg DV

Joshi CK see Sharma R

Josse M, Schoenaers F, Kaeckenbeek A. Inhibition del'action de I'enterotoxine thermostable d'Escherichia coli par la sous-salicylate de bismuth. Ann Med Vet 1979;123:481-3

Justus PG see Leibach JR

Kaeckenbeek A see Josse M

Kahn E, Stein H, Wayburne S. Antidiarrhoeal effect of antibiotics. Lancet 1963 Oct 5;2(7310):703-6

An attempt was made to elaborate a "diarrhoea index" which would correlate with stool volume, and thus to provide an easier but accurate means of assessing antibiotic efficacy in future trials. Studied were 3 groups of children, 70 in each group, at the pediatric emergency center of the Baragwanath Hospital in Johannesburg in 1961-1962. Urine output, stool weight, and change of body weight as a percentage of food intake were marked within 72 h of admission to the hospital. Shigella and Salmonella species were identified from the rectal swabs of all patients. Chloramphenicol and paromomycin produced beneficial effects compared to the placebo. Paromomycin emerged as a better antibiotic than chloramphenicol in the treatment of severe gastroenteritis in children. The correlation between diarrhoea index and stool volume was too poor to permit accurate prediction of stool volume in individual cases, but diarrhoea index in the whole group confirmed the better results obtained with paromomycin as compared with chloramphenicol.

Kane MG, O'Dorisio TM, Krejs GJ. Production of secretory diarrhea by intravenous infusion of vasoactive intestinal polypeptide. N Engl J Med 1983 Dec 15;309(24):1482-5

Attempt was made to reproduce the diarrhoea of pancreatic cholera syndrome with prolonged (10-h) administration of vasoactive intestinal polypeptide (VIP) in five healthy nonfasting subjects. The polypeptide was given as a continuous intravenous infusion at a rate of 400 pmol/kg body weight.h. By 2 h, the plasma VIP concentration had risen from a normal basal value of 15.3± 0.2 (mean±SEM) to 129 ± 40 pmol/l — within the range found in patients with pancreatic cholera syndrome. In each subject, profuse watery diarrhoea developed within 4.3±0.8 h (range, 2.0 to 6.3), and the mean stool weight at 10 h was 2441±600 g (normal 24-h stool weight, <200 to 250 g). The results of stool analysis were consistent with secretory diarrhoea. Between the first and last stools, there were significant increases in fecal sodium and bicarbonate concentrations and in pH. The large fecal bicarbonate loss induced hyperchloremic metabolic acidosis, which is characteristic in patients with

pancreatic cholera syndrome. This study suggests that VIP is not merely a marker of pancreatic cholera, but is the mediator of watery diarrhoea in this syndrome. (Modified author's abstract)

Karim SMM, Adaikan PG. The effect of loperamide on prostaglandin induced diarrhoea in rat and man. Prostaglandins 1977 Feb;13(2):321-31

This study describes the effect of loperamide on the stimulating effect of prostaglandin (PG) on the gastrointestinal smooth muscle and its effect on PG-induced diarrhoea in rat and man. Wistar rats were treated orally with both PG and loperamide separately. After 30 min of each dose the animals were killed. The effect of loperamide on PG-induced diarrhoea was studied in five men. Loperamide (0.4-3.2 µg/ml) markedly antagonised the smooth muscle stimulating action of PGE_2 and $PGF_{2\alpha}$ in the guinea pig ileum, guinea pig colon, gerbil colon, hamster and rat fundus. Contractions produced by acetylcholine and histamine were also antagonised by loperamide. On the rabbit jejunum, loperamide inhibited the activity and contractions produced by PGE_2, $PGF_{2\alpha}$ and acetylcholine. Oral administration of 0.1 to 2.0 mg/kg PGE_2 produced a dose-dependent increase in the volume of intestinal content of rats. Loperamide (1 mg/kg) orally given before PGE_2 reduced the increase in fluid accumulation in the small intestine by 50-80%. In experiments with PGE_2 0.5 mg/kg and varying doses of loperamide (0.25, 0.5 and 1.0 mg/kg), the inhibition of diarrhoea and the duration of action of loperamide was dose-dependent. The antidiarrhoeal effect of loperamide in healthy male volunteers was noted. After an oral dosage of 4 mg of loperamide in four patients watery diarrhoea stopped which was induced by administration of 5 mg PGE_2. The mechanism of PG-induced diarrhoea may be due to a direct effect on gut motility or due to an effect on intestinal electrolytes. Loperamide may act by interfering with both mechanisms also.

Kassem AS, Madkour AA-S, Massoud BZ, Mehanna ZM. Loperamide in acute childhood diarrhoea: a double blind controlled trial. J Diarrhoeal Dis Res 1983 Mar;1(1):10-6

The aim of this study is to evaluate the role of loperamide hydrochloride, an opiate agonist, in acute diarrhoea of early childhood. A double-blind controlled trial was conducted in two comparable groups of children aged under 2. The drug was given in a dose of 0.24 mg/kg.day in 3 equally spaced daily doses, until the termination of the diarrhoeal episode and for a minimal period of 2 days. No other drugs were given, and oral rehydration solution was allowed ad libitum. A record was kept of the intakes and the stool output. The loperamide group did not show any statistically significant differences as compared to the controls, with regard to the diarrhoeal stool output, the amount of rehydration fluid, the time required for initial rehydration, as well as the weight gain after rehydration. However, after the initial high output diarrhoea phase was over, loperamide improved the consistency of stool, probably through its antimotility effect. (Author's abstract)

Kato R see Nakaki T

Kauffman GL, Jr. see Mogard MH

Kautz U see Farack UM

Kawashima E see Bloom SR

Kawashima K see Sohji Y

Kerremans R see De Coster M

Khin-Maung-U, Myo-Khin, Nyunt-Nyunt-Wai, Aye-Kyaw, Tin-U. Clinical trial of berberine in acute watery diarrhoea. Br Med J 1985 Dec 7;291(6509):1601-5

A randomized, double-blind, placebo-controlled clinical trial of berberine, tetracycline, and tetracycline plus berberine was undertaken to examine the antisecretory and vibriostatic effects of berberine. Four hundred adults, hospitalized in Rangoon, Burma with acute watery diarrhoea, were studied; 185 patients had cholera and 215 had non-cholera diarrhoea. Among patients with cholera, tetracycline significantly reduced the number of motions ($p<0.05$), duration of diarrhoea in hospital ($p<0.001$), and volume of required intravenous ($p<0.001$) and oral ($p<0.001$) fluids. Patients given both berberine and tetracycline also showed reduction in these variables. Berberine did not produce an antisecretory effect. Analysis by factorial design equations, however, showed a reduction in diarrhoeal stools by one liter and a reduction in cyclic adenosine 3',5'-monophosphate concentrations in stools by 77% in the groups given berberine. After 24 h, significantly fewer patients with cholera treated with tetracycline ($p<0.01$) or tetracycline with berberine ($p<0.05$) excreted Vibrio cholerae in their stools compared with patients treated with placebo or berberine alone; none of these patients continued to excrete V. cholerae in their stools at 48 h. Neither tetracycline nor berberine had any benefit over placebo in patients with non-cholera diarrhoea.

Kimberg DV, Field M, Johnson J, Henderson A, Gershon E. Stimulation of intestinal mucosal adenyl cyclase by cholera enterotoxin and prostaglandins. J Clin Invest 1971 Jun;50(6):1218-30

The effects of several prostaglandins (PG) and a highly purified preparation of cholera enterotoxin on intestinal mucosal adenyl cyclase activity and the effect of cholera enterotoxin on intestinal mucosal cyclic adenosine 3',5'-monophosphate (cAMP) concentration were determined in guinea pig and rabbit small intestine and were correlated with the effects of the same agents on ion transport. Adenylate cyclase activity, measured in a crude membrane fraction of the mucosa, was found at all levels of the small intestine with the highest activity per milligram protein in the duodenum. The PGs when added directly to the assay, increased adenylate cyclase activity; the greatest effect (2-fold increase) was obtained with PGE_1 (maximal effect at 0.03 mM) and PGE_2. The PGs also increased short-circuit current in isolated guinea pig ileal mucosa, with PGE_1 and PGE_2 again giving the greatest effects. The prior addition of theophylline (10 mM) reduced the subsequent short-circuit current response to PGE_1 and vice versa. It was concluded that the short-circuit current response to PGE_1, like the response to theophylline, represented active Cl secretion. Cholera enterotoxin increased adenylate cyclase activity in guinea pig and rabbit ileal mucosa when preincubated with the mucosa from 1 to 2.5 h in vitro or for 2.5 h in vivo, but not when added directly to the assay. The increments in activity caused by PGE_1 and NaF were the same in cholera enterotoxin-treated and control mucosa. cAMP concentration in rabbit ileal mucosa was increased 3.5-fold after a 2-h preincubation with cholera enterotoxin in vitro. Phosphodiesterase activity in the crude membrane fraction of the mucosa was unaffected by either cholera enterotoxin or PGE_1. A variety of other agents including insulin, glucagon, parathormone, thyroid-stimulating hormone, L-thyroxine, thyrocalcitonin, vasopressin, and epinephrine all failed to change adenylate cyclase activity. It is further

concluded that cholera enterotoxin and certain PGs produce small intestinal fluid secretion by increasing mucosal adenylate cyclase activity, thereby stimulating an active secretory process. (Modified author's abstract)

Kimberg DV see Schwartz CJ

Kirkwood B see Rabbani GH

Knight J see Butler T

Knoop FC see Abbey DM

Knoop FC see Madsen GL

Knoop FC see Thomas DD

Kocoshis S see Gryboski JD

Kovacs T see Mogard MH

Krebs JB see Mir GN

Krejs GJ see Davis GR

Krejs GJ see Kane MG

Krienke EG see von Muhlandahl KE

Krishnan MN see Mandangopal N

Kumar A, Sharma VD. Inhibitory effect of garlic (Allium sativum Linn.) on enterotoxigenic Escherichia coli. Indian J Med Res 1982 Dec;76(Suppl):66-70

The effect of fresh aqueous garlic extract (Allium sativum Linn.) on the growth and enterotoxigenicity of enterotoxigenic Escherichia coli (ETEC) was examined. Garlic extract completely inhibited the growth of ETEC strains in 1:10 dilution, while in 1:20 dilution, the viable cell count of one ETEC strain was 10 times less than the control. When ETEC strain 14 (LT^+/ST^+) was grown in presence of 1:40 or lower dilutions of garlic extract, its cell-free filtrate did not cause any rabbit gut loop dilatation. Garlic extract in 1:5 dilution significantly ($p<0.01$) reduced fluid accumulation in rabbit gut loop when given with whole-cell cultures and saline cell suspension of ETEC strain 14 (LT^+/ST^+), suggesting that the extract minimized the enterotoxigenic effects of these in vivo. Further, the dilatation index of the same strain's cell-free culture was significantly ($p<0.01$) less when garlic extract in 1:10 dilution was injected in rabbit gut loop 15 min prior to challenge. This suggests that garlic also can be used as a prophylactic agent against ETEC-induced diarrhoea and that its prophylactic dose appears to be less than its anti-enterotoxigenic dose.

Label-Schwartz E see Donowitz M

LaCorte WSJ, McMurtrey JJ, Chapman J, Gotzkowsky S, Chang-Chien S, Ryan JR, McMahon FG. A simple controlled method for the clinical evaluation of antidiarrheal drugs. Clin Pharmacol Ther 1982 Jun;31(6):766-9

A castor oil model of induced diarrhoea was used to evaluate dose regimens of the standard antidiarrhoeal polycarbophil. The study population consisted of 100 healthy volunteers, divided into five groups of 20 each, in whom diarrhoea was induced by 120 ml flavored 36.4% castor oil. The polycarbophil dose regimens evaluated were 1, 1.5, 2, or 3 g at 30-min intervals after castor oil to total the usual prescribed dose of 6 g/day. One g taken every 30 min for six doses lowered the number of bowel movements and also induced the least number of cramps and lowest cramp severity rating (reported by subjects). The same total dose over a different-dosing interval was no more effective than placebo. (Modified author's abstract)

Lahiri SC, Dutta NK. Berberine and chloramphenicol in the treatment of cholera and severe diarrhoea. J Indian Med Assoc 1967 Jan 1;48(1):1-11

Berberine has been used in clinical cases of cholera for two successive epidemics which occurred in 1964 and 1965 in Calcutta, India. The total number of cases treated with berberine was 356 and with chloramphenicol, with which it was compared, was 264. Berberine has been proved to be an effective remedy both in bacteriologically positive and negative patients. It reduced the mortality rate, volume and duration of diarrhoea, period of hydration, intake of intravenous fluid and the convalescence period. Berberine was found to be better than chloramphenicol in certain respects. Within the doses tried, it showed no side-effects or toxicity. It is not an antimicrobial drug and is free from the hazards of antibiotic treatment. Its use as an adjunct to isotonic saline and electrolyte replacement therapy in acute cholera is recommended.

Lange P see Steven K

Lange S see Holmgren J

Lange S see Lonnroth I

Laurenson J see Binder HJ

Leibach JR, Sninsky CA, Justus PG, Riley RL, Mathias JR. Lidamidine HCL (WHR-1142A): a new drug for the treatment of diarrheal disorders. Gastroenterology 1981 May;80(5, pt 2):1207

This study investigates the efficacy and safety of lidamidine hydrochloride in ambulatory inpatients treated for a 14-day period. Lidamidine hydrochloride is a new experimental drug under investigation for treatment of diarrhoeal disorders. The drug causes smooth muscle relaxation and has been shown to be extremely effective in the acute control of certain disease states with fulminant diarrhoea. Doses greater than 30 mg/24 h, however, have resulted in a fall in systemic blood pressure and hyperglycemia in some subjects. Nine subjects with chronic diarrhoea from inflammatory bowel disease were investigated at the Clinical Research Center of the University of Florida. The stool frequencies fell from 10.8 to 5.0 after lidamidine was given to the study patients. It is concluded that lidamidine hydrochloride is an effective antidiarrhoeal agent for the control of chronic diarrhoea. The drug when administered to ambulatory subjects in doses less than 30 mg/24 h did not cause significant changes in blood pressure, blood chemistries, or hemogram and there was no central nervous system stimulation or depression commonly found with narcotic antidiarrhoeal agents. (Modified author's abstract)

Leitch GJ, Amer MS. Lanthanum inhibition of Vibrio cholerae and Escherichia coli enterotoxin-induced enterosorption and its effects on intestinal mucosa cyclic adenosine 3',5'-monophosphate and cyclic guanosine 3',5'-monophosphate levels. Infect Immun 1975 May;11(5):1038-44

Several trivalent cations, including lanthanum, inhibited the secretion (enterosorption) induced by the enterotoxins of Vibrio cholerae and Escherichia coli in the rabbit ileum in vivo. High concentrations (>10 mM) of lanthanum were required to inhibit cholera enterotoxin-induced enterosorption, probably because of the adsorption of the lanthanum to mucus and its precipitation by HCO_3. Exposure to lower concentrations of lanthanum often potentiated the cholera enterotoxin-induced enterosorption. If luminal lanthanum exposure followed cholera enterotoxin exposure, some recovery of the enterosorptive response was observed. The longer the lag between the cholera enterotoxin exposure and the lanthanum exposure, the greater was the recovery of the enterosorptive response. Lanthanum inhibited HCO_3 secretion more than Cl secretion. By altering the luminal fluid pH at the time of lanthanum exposure, it was found that lanthanum was adsorbed to negatively charged luminal sites, having an apparent pK between 2.5 and 3.0. Although lanthanum antagonized the enterosorptive response to cholera enterotoxin, it mimicked rather than antagonized the cyclic adenosine 3',5'-monophosphate (cAMP) elevation and cyclic guanosine 3',5'-monophosphate (cGMP) depression induced by the toxin. It is, therefore, concluded that the lanthanum inhibition of the cholera enterotoxin-induced enterosorption must have occurred at a site following the generation of the cyclic nucleotides. Cholera enterotoxin caused complex time-dependent changes in the mucosal cAMP and cGMP levels, as revealed by studying tissue cAMP/cGMP ratios. The possible roles these two cyclic nucleotides may play in the pathogenesis of the cholera diarrhoea are discussed. (Modified author's abstract)

Lenaerts FM see Niemegeers CJE

Levine MM see Robins-Browne RM

Leyman R see Dom J

Linaker BD see McKay JS

Loeschke K see Farack UM

Lonnroth I, Holmgren J, Lange S. Chlorpromazine inhibits cholera toxin-induced hypersecretion. Med Biol (Helsinki) 1977;55:126-9

Lonnroth I, Andren B, Lange S, Martinsson K, Holmgren J. Chlorpromazine reverses diarrhea in piglets caused by enterotoxigenic Escherichia coli. Infect Immun 1979 Jun;24(3):900-5

The effect of chlorpromazine on diarrhoea caused by enterotoxigenic Escherichia coli (ETEC) was tested in piglets since chlorpromazine has been shown to be a potent antagonist to enterotoxins in vitro in a cell system and in vivo in a mouse model. Experimental diarrhoea was induced in three litters of newborn piglets which were infected by mouth with $2x10^9$ E. coli bacteria, which produce heat-labile (LT) and heat-stable enterotoxins. Treatment with chlorpromazine, given intramuscularly 1 h after the onset of diarhoea, reversed fluid secretion in small intestine as well as dehydration, as judged by clinical criteria. A dose of 5 mg of chlorpromazine per kg of body weight completely normalized the

intestinal fluid content measured 4 h after diarrhoea developed, whereas 1 to 2 mg of chlorpromazine per kg of body weight was somewhat less effective, but still caused significant reduction of fluid ($p<0.001$). Studies with radioactive [^{35}S] chlorpromazine showed preferential and dose-dependent uptake of ^{35}S in the intestinal mucosa, the radioactivity being evenly distributed in the membranes of both crypt and villus cells. The enzyme adenylate cyclase, which probably mediates the cellular effects of LT enterotoxin, was shown to have two- to three-fold higher activity in the infected than in the uninfected animals. This activation was reduced about 50% by the chlorpromazine treatment (2 mg/kg of body weight). In a preliminary field trial, the effect of chlorpromazine was tested in a spontaneous outbreak of diarrhoea in piglets due to ETEC. The animals were treated either with oral electrolyte solution and standard antimicrobial agents only (controls) or with 1 mg of chlorpromazine per kg of body weight intramuscularly in addition to this treatment. The mean duration of diarrhoea in chlorpromazine-treated animals was significantly shorter, 4.1 h ($n=23$), than that in controls, 7.2 h ($p<0.05$). (Author's abstract)

Lonnroth I, Munck BG. Effect of chlorpromazine on ion transport by cholera toxin, cyclic AMP and cyclic GMP in isolated mucosa from hen intestine. Acta Pharmacol Toxicol 1980;47:190-4

The isolated short-circuit mucosa of chicken colon was established as an *in vitro* model for studies of the pathophysiology of diarrhoea and the mechanism of action of antidiarrhoeic drugs. Cholera toxin, 10^{-7}M, added to the mucosal side of the preparation, caused in a delayed eaction, a pronounced increase of short-circuit current. Cyclic adenosine 3',5'-monophosphate (cAMP), which mediates the effect of cholera toxin (when added serosal) induced an immediate rise of short-circuit current. Half maximal reaction was achieved at 3 mM cAMP and maximal at 7 mM. The increase of short-circuit current corresponded to the increase in the flux of chloride from serosa-to-mucosa. Unlike cAMP, cyclic guanosine 3',5'-monophosphate (cGMP) almost equally stimulated sodium and chloride transport from serosa-to-mucosa, while the effect on short-circuit current of the two nucleotides was additive. Chlorpromazine, which effectively reverses diarrhoea in cholera patients, totally normalized short-circuit current after treatment with either cholera toxin, cAMP or cGMP. This reduction was achieved by a specific stimulation of transport of chloride from mucosa-to-serosa. The effect occurred also without previous treatment of the tissue with secretagogues (cholera toxin, cyclic nucleotides). No change in mucosal resistance was induced by chlorpromazine or cGMP, while it was reduced by cAMP. (Modified author's abstract)

Lonnroth I, Lange S, Holmgren J. Effect of phenothiazines, thioxanthens and related drugs on experimental cholera. In: Usdin E, Eckerts H, Forrst JS, eds. Phenothiazines and structurally related drugs: basic and clinical studies. New York: Elsevier, 1980:303-6

Lonnroth I, Jennische E. Reversal of enterotoxic diarrhoea by anaesthetic and membrane-stabilizing aents. Acta Pharmacol Toxicol 1982;51:330-5

The effect of membrane-stabilizing and sedative drugs on enterotoxic diarrhoea was studied in mice. Fluid secretion was induced in ligated loops of the small intestine by challenge with cholera toxin, heat-labile (LT) enterotoxin from *Escherichia coli* or dibutryl-cyclic adenosine 3',5'-monophosphate (db-cAMP). Chlorpromazine, melperone, diazepam, mebumal, ketamine, and ethanol all inhibited cholera toxin-induced hypersecretion, ED_{50} being 1.5, 4, 4, 35, 70

and 1500 mg/kg respectively. The drugs also blocked cholera toxin-stimulation of adenylate cyclase, which mediates the action of cholera toxin. Concomitant with the antisecretory effect, a sedative effect was induced, as judged by the motility and righting reflex of the animals. Hypersecretion by E. coli and LT enterotoxin was also totally blocked by chlorpromazine, diazepam, ketamine, and ethanol. In contrast, the secretion by db-cAMP which by-passes adenylate cyclase in its action, was not affected by diazepam and was only partly reversed by chlorpromazine, ketamine, and ethanol. The reversal of db-cAMP-secretion is probably due to enhanced absorption rather than inhibition of adenylate cyclase. The use of membrane-stabilizing drugs may represent a new principle for pharmacological treatment of diarrhoea. (Modified author's abstract)

Lonnroth I see Holmgren J

Lonnroth I see Jennische E

Lonnroth I see Rabbani GH

Loperamide - what does it block? [editorial]. Lancet 1981 Nov 14;2(8255):1088-9

Most drugs used to treat diarrhoea work as inhibitors of gut motility, the principal group being the opiate derivatives. Loperamide, an opiate analogue of the piperidine class, is effective in reducing acute or chronic diarrhoea of varying etiologies. The reported side-effects are few and mild. Loperamide inhibits the diarrhoea induced by cholera toxin and prostaglandin E_2, but has no effect on the raised adenylate cyclase activity. The effect of loperamide was found to be blocked by the opiate antagonist naloxone which was independent of adenylate cyclase. These findings suggest that loperamide may act via opiate receptors either distal to or separate from the adenylate cyclase/cyclic adenosine 3',5'-monophosphate pathway in the secretory process. The recommended dose of loperamide in an adult is 2-4 mg. Presumably loperamide exerts its antidiarrhoeal effect by two mechanisms, one predominating at low and the other at high doses. Comparison of the antisecretory and antimotility effects of all the opiate analogues over a wide dose range could clarify this. As supportive evidence for antisecretory opiate receptors in gut mucosa becomes available through further research, a clearer understanding, both of drug action and of the mechanisms underlying diarrhoea, can be gained.

Lundgren O see Cassuto J

McArthur KE, Anderson DS, Durbin TE, Orloff MJ, Dharmsathaphorn K. Clonidine and lidamidine to inhibit watery diarrhea in a patient with lung cancer. Ann Intern Med 1982 Mar;96(3):323-5

A patient with watery diarrhoea syndrome secondary to bronchogenic carcinoma responded to treatment with clonidine and lidamidine. Stool weight decreased to 43 and 53% of control on two separate trials of clonidine. Stool weight decreased to 35% of control during a trial of lidamidine. Both clonidine and lidamidine increased sodium and chloride absorption in vitro in human intestine. Clonidine, lidamidine, or drugs that are structurally similar may become therapeutic choices for secretory diarrhoea. (Author's abstract)

McColl I see Field M

McKay JS, Linaker BD, Higgs NB, Turnberg LA. Studies of the antisecretory activity of morphine in rabbit ileum in vitro. Gastroenterology 1982 Feb;82(2):243-7

This study examines whether morphine influences intestinal secretion by simply enhancing absorption or by inhibiting the secretory mechanism or through a combination of both. For these investigations, secretion was provoked by prostaglandin (PG) E_2, acetylcholine, or cholera toxin. In rabbit ileal mucosa in vitro morphine (10^{-4}M) did not influence the electrical response to the subsequent administration of PGE_2 or of acetylcholine, but did inhibit the net secretion of chloride provoked by both agents and prevented the reduction of sodium absorption induced by the PG. Morphine reduced the peak electrical response to cholera toxin and reduced toxin-induced net chloride secretion. Results revealed that morphine inhibits secretion by more than one mechanism. Firstly, it enhances absorption, and secondly, it inhibits secretogogue-induced ion transport responses either by inhibiting these transport responses directly or by interfering with production or activity, of one or more of the intracellular mediators of secretion, such as cyclic adenosine 3',5'-monophosphate or calmodulin.

McMahon FG see LaCorte WSJ

McMurtrey JJ see LaCorte WSJ

Madkour AA-S see Kassem AS

Madsen GL, Knoop FC. Inhibition of the secretory activity of Eshcerichia coli heat-stable enterotoxin by indomethacin. Infect Immun 1978 Oct;22(1):143-7

The effect of indomethacin on the net intestinal fluid accumulation, induced by Escherichia coli heat-stable (ST) enterotoxin in the infant mouse model, was examined. The E. coli strain PB-122-B1 was used, and a toxin preparation was made and assayed for toxic activity by the infant mouse model. Indomethacin, when administered with ST enterotoxin, caused a striking decrease in net intestinal fluid accumulation. This inhibition of ST enterotoxin activity was dose-dependent with various concentrations of indomethacin ($p<0.01$). A significant inhibition of toxicity was also observed when indomethacin was given before ($p<0.01$) or after ($p<0.02$) ST enterotoxin challenge. No significant differences in fluid accumulation were observed between control mice treated with buffer alone and those challenged with only indomethacin. These data indicate that indomethacin markedly decreases the net intestinal fluid accumulation induced by E. coli ST enterotoxin. A dose-dependent titration curve was required. The mechanism of inhibition of intestinal fluid accumulation by indomethacin is unknown. Further investigations are required to define the inhibitory mechanism of indomethacin in prophylaxis and in the therapy of diarrhoeal diseases.

Mainguet P, Fiasse R. Double-blind placebo-controlled study of loperamide (imodium) in chronic diarrhoea caused by ileocolic disease or resection. Gut 1977 Jul;18(7):575-9

Loperamide was compared with a placebo in a double-blind crossover study of 21 patients with chronic diarrhoea caused by ileocolic disease or resection. Eighteen of the 21 patients completed the trial. Each patient was treated with loperamide or placebo and then switched to the alternate medication in the subsequent treatment period. The median duration of loperamide treatment

period was 37 days and of placebo 16.5 days ($p<0.001$). The frequency, consistency, and weight of the stools were superior during loperamide treatment as compared with the placebo. The median dose of loperamide was 6 mg. Carmine transit time was found to be longer during administration of loperamide. Eight patients reported side-effects (nausea, vomiting, abdominal pain, and distension). Alleviation of diarrhoea was more effective with loperamide than with the placebo. Gastrointestinal side-effects were few and comparable during both treatment periods. As the effect of loperamide in the patients was to prolong the reduced transit time acquired by diarrhoea, the drug should prove to be useful in patients with intestinal resections or with extensive regional enteritis.

Maiti M see Chaudhuri K

Makhlouf GM see Carter RF

Maki M see Vesikari T

Mandangopal N, Krishnan MN, Srinivasan G, Subramaniam R. Pilot trial with diphenoxylate hydrochloride (lomotil) in diarrhoeal diseases. Curr Med Pract 1972;16:185-90

Marker RH see Dutta NK

Marnane WG see Tai YH

Marshall CH see Jacoby HI

Martinsson K see Lonnroth I

Massoud BZ see Kassem AS

Mathias JR see Leibach JR

Maxwell V see Mogard MH

Mehanna ZM see Kassem AS

Merlo M. The effect of diphenoxylate hydrochloride on diarrhoea. Am J Gastroenterol 1960;34:625-30

Migliavacca M see Guandalini S

Milla PJ see Sandhu BK

Mir GN, Sperow JW, Krebs JB, Eash JR, Rowles GS, Yelnosky J. Mechanism of action studies of lidamidine hydrochloride (WHR-1142A), a novel antidiarrheal agent. Arzneim Forsch/Drug Res 1978;28(8a):1454-61

This paper describes studies that attempt to determine the mechanism of action of 1-(2'6-Dimethylphenyl)-3-methylamidinourea hydrochloride (WHR-1142A, lidamidine hydrochloride), a novel antidiarrhoeal agent, which inhibited contractile activity in isolated guinea pig ileum stimulated by acetylcholine, histamine, serotonin, dimethylphenyl piperazinium, prostaglandin E, $BaCl_2$ and KCl. WHR-1142A also blocked spontaneous and stimulated contractile activity measured with extraluminal strain gauges in the duodenum, ileum and colon of

dogs. Studies on the automatic effects of WHR-1142A indicated little, if any, peripheral adrenergic stimulatory or cholinergic blocking activity. Inhibition of intestinal motility by WHR-1142A was not antagonized by naloxone. WHR-1142A also showed no morphine-like analgesic effects and was devoid of any H -antihistamine activity. WHR-1142A appears to be a pharmacologically unique antidiarrhoeal agent.

Mir GN, Sperow JW, Riley RL, Alioto RL, Nuss GW, Chou BJ, Yelnosky J. Pharmacological properties of lidamidine hydrochloride (WHR-1142A), a novel antidiarrheal agent. Arzneim Forsch/Drug Res 1978;28(8a):1466-71

1-(2,6-Dimethylphenyl)-3-amidinourea hydrochloride (WHR-1142A, lidamidine hydrochloride), a potent, unique antidiarrhoeal agent, was tested for other pharmacological properties. Two separate tests with WHR-1142A on gastric acid secretion in the pylorus-ligated rat were run on different days. The WHR-1142A test caused a dose-related inhibition of gastric acid secretion in both 4-h and 22-h pylorus-ligated rats and reduced mortality and gastric ulcer severity in the latter test. The mechanism for this effect is not known. WHR-1142A was proved to be an effective anti-ulcer agent, preventing both ulceration and mortality. WHR-1142A also exhibited local anesthetic activity in the rabbit corneal reflex and guinea pig intradermal wheat tests and reversibly blocked conduction in isolated frog nerves. Low doses of WHR-1442A increased plasma glucose concentration in fasted mice and rats and prolonged the hyperglycemia in response to a glucose meal. WHR-1142A showed mild diuretic activity, but had no anti-inflammatory or anti-bacterial activity. The acute oral LD_{50} of WHR-1142A was 260 (208,328) mg/kg in male mice, 267 (212,336) mg/kg in male rats and 160 (130,197) mg/kg in female rats.

Mir GN see Douglas GH

Modak MJ see Modak S

Modak S, Modak MJ, Venkataraman A. Mechanism of action of berberine on Vibrio cholerae and Vibrio cholerae biotype eltor. Indian J Med Res 1970 Nov;58(11): 1510-22

Berberine was found to possess antidiarrhoeal effects. This paper reports on the mechanism of the action of berberine on cholera-causing organisms. After ingestion, in the initial static period there was a leakage of the intracellular constituents probably due to membrane damage. The cell-free preparations (crude toxin) made from berberine-treated vibrios failed to produce choleraic symptoms in the infant rabbit model, suggesting that the toxin was either inactivated or neutralized. The uptake of precursors of protein and nucleic aids was restricted in the static period of the two Vibrio cholerae strains. The V. cholerae biotype El Tor seemed to be more resistant to berberine action. This could be explained on the basis of differential absorption of berberine by the two strains. The pattern of intracellular distribution of berberine was the same for both the strains, major portions being associated with the lipids. The drug caused a static period during which there was an inhibition of the synthesis of all the macromolecules, e.g. nucleic acids. Once the growth was resumed, the synthesis of the different components started, and by the end of the growth period, the nucleic acid synthesis reached almost the same level as the normal untreated cells. The synthesis of all the ribonucleic acid subfractions was inhibited more or less to the same extent. The proteins and lipid synthesis were stimulated very much, to an extent of 2 to 2½ times more than that of the control.

Mogard MH, Maxwell V, Kovacs T, Deventer GV, Elashoff JD, Yamada T, Kauffman GL, Jr., Walsh JH. Somatostatin inhibits gastric acid secretion after gastric mucosal prostaglandin synthesis inhibition by indomethacin in man. Gut 1985 Nov;26(11):1189-91

The present study examines the hypothesis that protaglandins (PG) mediate the inhibitory effects of somatostatin on gastric acid secretion, in humans as well. Five male volunteers without history of gastrointestinal disorders were studied. The effect of PG synthesis inhibition on somatostatin-induced supression of food-stimulated acid secretion was tested. The gastric acid secretory responses to the glucose meal were 3.0±0.5 (1.6-4.6), 2.6 ± 0.9 (0.7-6.0) and 3.7±1.0 (0.2-6.7) mmol/15 min in the control, the somatostatin heated and the indomethacin-somatostatin groups respectively. The peptone meal significantly stimulated acid output similarly in all groups. In the control group, acid output remained at a plateau level throughout the experiment. The 200, 400 and 800 pmol/kg.h doses of somatostatin each significantly reduced the acid output to 3.0±0.3 (2.0-4.0), 0.7±0.2 (0-0.1) and 0±0.0 (0-0.1) mmol/15 min respectively. There was no significant effect of indomethacin on glucose, or peptone-stimulated acid secretion on somato-induced reduction of acid output. Indomethacin treatment significantly reduced the PGE_2 generative capacity of antral and corpus gastric mucusol tissue amounting to 91 and 90% inhibition respectively. PG synthesis inhibition by indomethacin failed to affect the inhibitory action of somatostatin in man in the present study. At the cellular level, the mechanism of somatostatin action is not understood.

Morawski SG see Schiller LR

Moritz M, Womelsdorf AH. Rabbit cholera: inhibitory effect of tenuazonic acid on cholera-induced secretion of water and electrolytes. Gastroenterology 1973 Aug;65(2):259-64

This communication reports that tenuazonic acid, an inhibitor of protein synthesis, has qualitatively similar inhibitory effect on cholera toxin response as that of cycloheximide. Acute experiments were performed in male rabbits weighing 2.5 to 3.0 kg. The tenuazonic acid's effect on cholera-induced secretion was studied in rabbit jejunum in vivo. Tenuazonic acid inhibited significantly net water and ion secretion induced by cholera toxin. The overall inhibition of net ion flux was 72%; of the total reduction in net anion flux, 57% was due to a decrease in Cl and 43% to a decrease in HCO_3. The drug had no significant effect on the net absorption of H_2O, Na, Cl, and K, or net secretion of HCO_3 in jejunal loops not incubated with purified cholera toxin, nor did it alter the linear relationship between net fluxes of Na and H_2O observed during absorption or secretion. It is suggested that the effect of tenuazonic acid may be directed toward either the cell membrane or enzymes. (Modified author's abstract)

Morris SM see Powell DW

Moylan FMB. Aluminum hydroxide in the symptomatic treatment of infants with chronic diarrhea. J Pediatr Gastroenterol Nutr 1983 May;2(2):295-8

Muls M see Demeulenaere L

Mulvihill S, Passaro E, Jr., Debas H, Yamada T. Severe diarrhea after colonic pseudo-obstruction: treatment with somatostatin [letter]. N Engl J Med 1984 Feb 16;310(7):467-8

The successful use of somatostatin, a cyclic tetradecapeptide, to control diarrhoea and resultant hypokalemia in a patient with acute colonic-pseudo-obstruction was reported in this study. Somatostatin was infused on four occasions for 6 to 12 h each. Stools of the patient were collected. Plasma somatostatin-like immunoreactivity was measured by antibody 1001.9. Somatostatin infusion was effective in controlling diarrhoea at a dose of 500 µg/h. The effect of somatostatin was mainly on volume, e.g. stool output fell from 78-15 ml/h in the first infusion, but no substantial alteration was seen in stool electrolyte or protein concentrations. After four courses of somatostatin treatment, the serum potassium level stood at 4.1 mmol/l. The plasma concentration of vasoactive intestinal polypeptide was 12 pg/ml (normal). The cause of this patient's secretory diarrhoea remains unclear. It is possible that the colonic distention was sufficient to cause a similar mucosal injury and secretory dysfunction. Somatostatin proved to be a useful adjunct in the patient's care.

Munck BG see Lonnroth I

Murad F see Greenberg RN

Myo-Khin see Khin-Maung-U

Nakadate T see Nakaki T

Nakaki T, Nakadate T, Yamamoto S, Kato R. Alpha$_2$-adrenergic inhibition of intestinal secretion induced by prostaglandin E_1, vasoactive intestinal peptide and dibutyryl cyclic AMP in rat jejunum. J Pharmacol Exp Ther 1982 Mar;220(3):637-41

Nakamura H see Sohji Y

Nalin DR, Cash RA. Kaolin and cholera. J Pak Med Assoc 1970 Jun;20(6):177-82

In preliminary studies in dogs, culture filtrate of Vibrio cholerae was used to produce diarrhoea in intestinal Thiry-Vella loops in dogs. Kaolin mixed with culture filtrate or put into loops before culture filtrate protected the loops against the diarrhoeagenic action of the filtrate. Kaolin did not prevent diarrhoea if instilled after putting the culture filtrate into the loops. A study was then carried out in cholera patients to determine whether kaolin could shorten the duration or volume of diarrhoea by adsorbing diarrhoeagenic toxin in gut luminal fluid. All patients were given intravenous replacement for their fluid and electrolyte losses. One group received oral kaolin suspension in water and another received kaolin suspension and tetracycline. The differences in stool volumes after 24 h were not significant. (Modified author's abstract)

Nandi R see Chaudhuri K

Niemegeers CJE, Lenaerts FM, Janssen PAJ. Loperamide (R 18 553), a novel type of antidiarrheal agent. Pt. 1. In vivo oral pharmacology and acute toxicity. Comparison with morphine, codeine, diphenoxylate and difenoxin. Arzneim Forsch/Drug Res 1974;24:1633-6

Niemegeers CJE see Awouters F

Noerasid H see Soeparto P

Nuss GW see Mir GN

Nyunt-Nyunt-Wai see Khin-Maung-U

O'Connor S see Douglas GH

O'Dorisio TM see Kane MG

Okabayashi T see Fujimoto M

Orloff MJ see McArthur KE

Owens JR, Broadhead R, Hendrickse RG, Jaswal OP, Gangal RN. Loperamide in the treatment of acute gastroenteritis in early childhood. Report of a two centre, double-blind, controlled clinical trial. Ann Trop Paediatr 1981 Sep;1(3):135-41

Loperamide at a dose of 0.2 mg/kg.day was compared with a placebo in the treatment of acute infantile gastroenteritis in hospital-based double-blind clinical trials carried out in parallel in Liverpool, England and in Benghazi, Libya in 1980. Fifty patients, aged one month to four years, entered the study in each center. Rotavirus was the predominant pathogen isolated at both centers. Pathogenic Escherichia coli was cultured from five children in the Liverpool study. No statistically significant differences were observed in the duration of diarrhoea, length of stay in hospital or weight gain during the first 48 h after admission, between loperamide and placebo groups at either center. No toxic effects of loperamide were also observed. Loperamide, in the dosage used in this study, appears to have no significant effect on the course of acute gastroenteritis in early childhood.

Palmer KR, Corbett CL, Holdsworth CD. Double-blind cross-over study comparing loperamide, codeine and diphenoxylate in the treatment of chronic diarrhea. Gastroenterology 1980 Dec;79(6):1272-5

A double-blind crossover trial in 30 individuals with chronic diarrhoea was carried out to compare the relative efficacies of loperamide, codeine phosphate and diphenoxylate in their treatment. Each underwent three randomized treatment periods of 4 weeks' duration. Patients were instructed to increase the daily dose gradually until control was achieved or side-effects became intolerable. Stool frequency, consistency, urgency, and incontinence were then compared when a stable dose was reached. Though 2.3 capsules (4.6 mg) of loperamide, 2.3 capsules (103.5 mg) of codeine and 2.5 capsules (12.5 mg) of diphenoxylate all reduced stool frequency to the same extent, diphenoxylate was significantly less effective in producing a solid stool. Before treatment, 95% of patients experienced urgency, sometimes associated with fecal incontinence, often as their major disability. Loperamide and codeine were more effective in relieving this than was diphenoxylate. Side-effects, particularly central nervous effects, were greatest with diphenoxylate and least with loperamide. Approximately equal numbers discontinued each preparation; poor control and central nervous system side-effects were the usual reasons for stopping diphenoxylate and codeine, and abdominal pain and constipation for stopping loperamide. It is concluded that both loperamide and codeine phosphate are superior to diphenoxylate in the symptomatic treatment of chronic diarrhoea. (Modified author's abstract)

Panichkriangkrai W see Ahrens FA

Panse MV see Dutta NK

Passaro E, Jr. see Mulvihill S

Paustian FF see Pimparker BD

Pelemans W, Vantrappen G. A double blind crossover comparison of loperamide with diphenoxylate in the symptomatic treatment of chronic diarrhea. Gastroenterology 1976 Jun;70(6):1030-4

Loperamide was compared with diphenoxylate in a double-blind crossover study of 23 patients (12 males and 11 females), with chronic diarrhoea of various etiologies. Loperamide and diphenoxylate were supplied in identical opaque capsules, each containing either 2 mg of loperamide or 5 mg of diphenoxylate plus 0.05 mg of atropine sulfate (i.e. twice the marketed dose strength). Both antidiarrhoeal agents were found to be capable of controlling or greatly reducing chronic diarrhoea. Loperamide was superior to diphenoxylate in its ability to decrease the frequency and improve the consistency of the stools, even at a 2.5-fold lower dose level. (Modified author's abstract)

Pickering LK see DuPont HL

Pickering LK see Ericsson CD

Pierce NF, Carpenter CCJ, Jr., Elliot HL, Greenough WB, III. Effects of prostaglandins, theophylline, and cholera exotoxin upon transmucosal water and electrolyte movement in the canine jejunum. Gastroenterology 1971 Jan;60(1):22-32

Piercey MF, Ruwart MJ. Naloxone inhibits the anti-diarrhoeal activity of loperamide. Br J Pharmacol 1979 Jul;66(3):373-5

This study shows that the antidiarrhoeal activity of loperamide, presumed to be due to its effects on smooth muscle contraction, may be mediated through opiate receptors. Sixty male Upjohn rats (200 to 220 g) were divided into 6 equal groups. Groups 1, 2, and 5 were given vehicle and groups 3, 4 and 6 given naloxone (0.5 mg/kg) by subcutanous injection. Subsequently, groups 5 and 6 were given loperamide (1 mg/kg) and groups 1-4 were injected with vehicle. Subcutanous prostaglandin (PG) E_2 (2.5 mg/kg) was administered to groups 2,4,5,6, while the remaining had vehicle. For a group of 10 rats, the maximum score indicating severe diarrhoea was 20. A score of 0 indicated the absence of diarrhoea. Group 1 rats who did not have diarrhoea received only vehicle injections. Group 2 treated with PG produced a maximum score of 20. Naloxone did not alleviate this diarrhoea (group 4) nor did it produce diarrhoea when given to rats not receiving PGE_2 (group 3). Loperamide was very effective against PG-induced diarrhoea, reducing the activity score from 20 to 1 (group 5). However, pretreatment with naloxone completely inhibited the beneficial effect of loperamide (group 6). Since naloxone by itself does not cause diarrhoea, its antagonism of the antidiarrhoeal actions of loperamide possibly occurs due to opiate receptor-mediated blockage.

Pimparker BD, Paustian FF, Roth JLA, Bockus HL. Effect of polycarbophil on diarrhea and constipation. Gastroenterology 1961 Feb;40(2, pt.2):397-404

Polak JM see Bloom SR

Portnoy BL, DuPont HL, Pruitt D, Abdo JA, Rodriguez JT. Antidiarrheal agents in the treatment of acute diarrhea in children. JAMA 1976 Aug 16;236(7):844-6

To evaluate the efficacy of antidiarrhoeal agents, a study was conducted with Guatemalan children with acute diarrhoea. Eighty patients, aged 3 to 11 years, were hospitalized and treated for two days with one of five agents: kaolin-pectin suspension concentrate, kaolin suspension, pectin suspension, diphenoxylate-atropine liquid (lomotil), or placebo. Although the patients receiving kaolin-pectin produced stools that tended to be more formed than those of the placebo-treated group, the study did not demonstrate any effect by any of the tested agents in influencing the frequency of bowel movement, the water content of the stools, or the weight of stools. Kaolin-pectin suspension and diphenoxylate-atropine liquid do not appear to be useful in the relief of acute nonspecific diarrhoea in children. (Modified author's abstract)

Powell DW, Tapper EJ, Morris SM. Aspirin-stimulated intestinal electrolyte transport in rabbit ileum in vitro. Gastroenterology 1979 Jun;76(6):1429-37

Because aspirin and the heavy metal salts of related anions have effects on intestinal ion transport and on diarrhoeal states, the effect of aspirin on the in vitro rabbit ileum was studied in an attempt to understand its mechanism of action. Ten mM of aspirin increased the conductance of rabbit ileum by 10-50%, but did not change the permselectivity of the shunt path as determined by measurement of diffusion potentials. In Cl-free and HCO_3 -free solutions, aspirin reduced both Na absorption and the short-circuit current, which suggests an effect on electrogenic Na transport. Such an effect was not unexpected, since aspirin interferes with adenosine 3',5'-triphosphatase production. However, in Ringer solution, aspirin in concentrations as little as 1 mM in the serosal solution reduced the short-circuit current as before, but also stimulated Na and Cl absorption and reduced possibly the HCO_3 secretion to zero. Aspirin had no effect on Na transport in the absence of Cl and no effect on Cl transport in the absence of Na, which suggests that aspirin stimulated a coupled-transport process. Although these effects of aspirin resemble those of α-adrenergic agents, aspirin's effect was not blocked by α-adrenergic blockers, such as phentolamine or phenoxybenzamine. The exact mechanism of aspirin-stimulated NaCl absorption remains to be determined. (Modified author's abstract)

Powell DW. Muscle or mucosa: the site of action of antidiarrheal opiates? [editorial]. Gastroenterology 1981 Feb;80(2):406-8

Powell DW, Field M. Pharmacological approaches to treatment of secretory diarrhea. In: Field M, Fordtran JR, Schultz SG, eds. Secretory diarrhea. Bethesda, Md.: American Physiological Society, 1980:187-209

Pruitt D see Portnoy BL

Purohit KR, Rao KS. Neomycin compound with berberine. Trial in infantile diarrhoea. Antiseptic 1969;66:855-63

Puxeddu E see Corda R

Rabbani G see Butler T

Rabbani GH, Butler T. Berberine inhibits fluid-loss in non-cholera diarrhoea. In: Proceedings of the 25th Interscience Conference on Antimicrobial Agents & Chemotherapy, Minneapolis, 30 Sep 1985:138

Berberine sulfate has earlier been reported to reduce fluid loss in cholera. To test whether this drug also reduces stool in non-cholera watery diarrhoea, 26 adult patients were treated with 400 mg of berberine powder orally in a single dose. Twenty-eight patients were concurrently randomized to an untreated group. All received intravenous fluid but no antibiotics. Stool volumes were measured in ml per 8 h before treatment and during three consecutive 8-h periods after treatment. The mean stool volume ±SD before treatment was 2,019±813 ml in the berberine-treated group and 1,915±1,014 ml in the control group. In the first 8-h period after treatment, the mean stool volume in the berberine-treated group had declined to 663±468 ml as compared to 1,096±1,031 ml in the controls ($p<0.05$). In the second 8-h period, the berberine-treated group also had a lower mean stool volume (354 ± 345 ml vs 532±516 ml, $p>0.05$). In the third 8-h period, the mean stool volume in the berberine-treated group was less than the control group (192±261 ml vs 452 ± 479 ml, $p<0.01$). By 24 h, more berberine-treated patients had stopped diarrhoea as compared to controls (46% vs 20% $p<0.05$). No side-effects of berberine sulfate were noted other than having a bitter taste. These results indicate that berberine sulfate is an effective and safe treatment of non-cholera watery diarrhoea. (Modified author's abstract)

Rabbani GH, Greenough WB, III, Holmgren J, Lonnroth I. Chlorpromazine reduces fluid-loss in cholera. Lancet 1979 Feb 24;1(8113):410-2

Chlorpromazine is known to inhibit cholera toxin-stimulated intestinal adenylate cyclase and fluid secretion in laboratory animals, thus its ability to reduce fluid loss in human cholera was investigated. Eleven cholera patients with severe purging (360-1340 ml/h) were studied. Eight were given chlorpromazine intramuscularly (1 mg/kg or 4 mg/kg), and three were given a dose of 1 mg/kg by mouth. In the 32 h after treatment, there was an overall reduction in stool output of 66 ± 5% in the chlorpromazine-treated patients. This decrease was significantly larger than the 26±9% reduction in stool output seen in patients not receiving the drug, who were observed at the same time in the course of their illness. The decrease in nausea and the mild sedation produced by chlorpromazine added to the patients' comfort. No hypotension was seen in these well-hydrated patients. (Modified author's abstract)

Rabbani GH. Chlorpromazine as a therapeutic antisecretory agent in cholera and related diarrhoeas. Dhaka: International Centre for Diarrhoeal Disease Research, Bangladesh, 1980. 65 p. (Thesis and dissertation, 1)

Rabbani GH, Greenough WB, III, Holmgren J, Kirkwood B. Controlled trial of chlorpromazine as antisecretory agent in patients with cholera hydrated intravenously. Br Med J 1982 May 8;284(6326):1361-4

To investigate the ability of chlorpromazine to reduce intestinal secretion in cholera, a randomized, controlled trial was conducted in 46 male adults with cholera, selected from the patients referred to the International Centre for Diarrhoeal Disease Research, Bangladesh. Chlorpromazine had reduced the loss of intestinal fluid in animals with diarrhoea induced by cholera toxin, and in a preliminary study, the drug had reduced purging in patients with cholera. Of the 46 patients, 34 were treated with chlorpromazine (1 mg/kg or 4 mg/kg either by mouth or intramuscularly) and 12 served as controls. After treatment with the drug, there was a significantly greater reduction in the rate of fluid loss in the treated patients than in the controls during the first ($p<0.005$), second ($p<0.005$), and fourth ($p>0.01$) 8-h periods, but not during the third 8-h period; the dose of 4 mg/kg was only marginally more effective than 1 mg/kg.

The antisecretory effect of chlorpromazine was strikingly biphasic, with one peak in the first 8 h and another 24-32 h after administration. It was assumed that the first peak reflects a toxin-antagonizing effect of chlorpromazine, whereas the second might be due to the generation of some metabolite of the drug having an antisecretory activity. To explain the antisecretory effect of chlorpromazine, a number of hypotheses were advanced, the exact mechanism of action being unknown. Chlorpromazine also significantly reduced the duration of diarrhoea, frequency of vomiting, and amount of intravenous fluid required. The drug induced mild sedation, but no hypotension in these well-hydrated patients. These findings confirm the effectiveness of chlorpromazine in reducing fluid loss in cholera. A sedative effect, however, especially in children, may limit its usefulness and requires further study.

Rabbani GH, Butler T. Indomethacin and chloroquine fail to inhibit fluid loss in cholera. Gastroenterology 1985 Nov; 89(5):1035-7

The efficacy of indomethacin and chloroquine in reducing intestinal secretion was investigated in a randomized, controlled trial in 29 adults hospitalized with cholera at the International Centre for Diarrhoeal Disease Research, Bangladesh. All patients received intravenous infusion to restore fluid balance, but no antibiotics were given. Indomethacin was given in capsule form to 9 patients in 2 doses (150 mg followed by 50 mg) 8 h apart. Chloroquine phosphate tablets were given to patients in 2 doses (1000 mg followed by 500 mg) 8 h apart. Patients treated with these 2 drugs did not show significantly different stool outputs than untreated controls during the five 8-h post-treatment periods (40 h). Although animal studies indicated that indomethacin and chloroquine to be effective against cholera, both drugs, at comparable doses, failed to reduce fluid secretion in actively purging patients in this trial.

Rabbani GH, Butler T, Bardhan PK, Islam A. Reduction of fluid-loss in cholera by nicotinic acid: a randomised controlled trial. Lancet 1983 Dec 24/31;2(8365/6):1439-42

A randomized, controlled clinical trial at the International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka during May-November 1982, investigated the ability of nicotinic acid to reduce intestinal fluid loss in patients with severe cholera. Sixty-two adults with (a) history of watery diarrhoea of less than 48 h, (b) Vibrio cholerae in their stools, (c) severe dehydration, and (d) no history of current antibiotic use, were studied. Of these, 29 received either 1 or 2 g of nicotinic acid given orally in divided doses, and 33 served as controls. Patients receiving the 2-g dose had less fluid loss than did the controls during the first ($p<0.01$) and second ($p<0.05$) 8-h post-treatment periods, with an overall drug-specific reduction in stool volume of 31.47% during the first 16 h after treatment. Peak inhibition occurred in the second 8-h post-treatment period. The effect of the 2-g dose was significantly better than that of the 1-g dose. Patients receiving the 1-g dose had lower purging rates than did the controls, but not significantly so. During the third and fourth 8-h periods, these rates continued to be lower for both treatment groups, but again the differences were not significant. The drug was well tolerated, the only side-effect being transient flushing of the body in one patient. The need for further studies on the drug's effect on intravenous fluid requirements and on duration of diarrhoeal illness, as well as on its usefulness in childhood diarrhoea and Escherichia coli, is indicated.

Rabbani GH see Islam MR

Rajendra GR see Wald A

Rao KS see Purohit KR

Rao NR see Dutta NK

Raskin P see Davis GR

Rask-Madsen J, Bukhave K. Prostaglandins and chronic diarrhoea: clinical aspects. Scand J Gastroenterol 1979;14(Suppl 53):73-8

Rask-Madsen J see Steven K

Reiter B, Brock JH, Steel ED. Inhibition of Escherichia coli by bovine colostrum and post-colostral milk. II. The bacteriostatic effect of lactoferrin on a serum susceptible and serum resistant strain of E. coli. Immunology 1975 Jan;28(1):83-95

Two strains of Escherichia coli were inhibited by complement-inactivated cow serum and to lesser extent by precolostral calf serum devoid of specific antibodies. They were not inhibited by undiluted colostral whey or milk, but colostral whey became bacteriostatic after dialysis or dilution in Kolmer saline and addition of precolostral calf serum or lactoferrin. The inhibition in all these fluids was due to iron-binding proteins (transferrin or lactoferrin). Undiluted dialysed milk was not inhibitory because of its low content of lactoferrin, but became inhibitory after addition of 1 mg/ml of lactoferrin. The lack of inhibition in undiluted whey is due to the high concentration of citrate in colostral whey (and milk), and it is suggested that citrate competes with the iron-binding proteins for iron and makes it available to the bacteria. Addition of bicarbonate, which is required for the binding of iron by transferrin and lactoferrin, can overcome the effect of citrate; hence, the bacteriostatic effect of cow serum and precolostral calf serum is due to the presence of both transferrin and bicarbonate as well as the low level of citrate. (Author's abstract)

Reynolds IJ, Gould RJ, Snyder SH. Loperamide: blockade of calcium channels as a mechanism for antidiarrheal effects. J Pharmacol Exp Ther 1984;231(3):628-32

Popular antidiarrhoeal opiates, such as loperamide, fluperamide, diphenoxylate and fetoxylate, are known to inhibit binding of [^{3}H]nitrendipine to membranes from guinea pig cerebral cortex with K_i values of 0.5 μM. Loperamide and fluperamide reversed the tiapamil elicited lowering of [^{3}H]nitrendipine binding with IC_{50} values of 0.2 to 0.5 μM, indicating a verapamil-like action of these drugs. An oral dose of 1 mg/kg of loperamide reduced gastrointestinal motility and gave concentrations of 0.45 ± 0.19, 0.38 ± 0.22 and 0.49 ± 0.25 μM in the duodenum, jejunum and ileum respectively. The apparent K_i for loperamide in preventing calcium-induced contractions of guinea pig ileum depolarized with 80 μM potassium was 0.10 μM. It is suggested that calcium channel antagonism may be responsible at least in part for the antidiarrhoeal actions of loperamide and related agents. Evidence includes the calcium antagonist actions of loperamide at antidiarrhoeal doses, the constipating effects of certain calcium antagonists and the failure of opiate antagonists to prevent some intestinal effects of loperamide. (Modified author's abstract)

Riley RL see Leibach JR

Riley RL see Mir GN

Robins-Browne RM, Levine MM. Effect of chlorpromazine on intestinal secretion mediated by Escherichia coli heat-stable enterotoxin and 8-Br-cyclic GMP in infant mice. Gastroenterology 1981 Feb;80(2):321-6

Subcutaneously administered chlorpromazine reduced intestinal fluid accumulation induced by Escherichia coli heat-stable (ST) enterotoxin in infant mice. The antisecretory effect of chlorpromazine, although dose-related, was, even with high doses, less than that observed with respect to cholera toxin. Whereas, 100 µg of chlorpromazine abolished cholera toxin-induced intestinal secretion almost completely, 500 µg of chlorpromazine (equivalent to 200 µg/g of body weight) lowered secretion induced by (ST) enterotoxin by only 41%. The effect of chlorpromazine on intestinal secretion was quantitatively similar regardless of whether (ST) enterotoxin or the cyclic guanosine 3',5'-monophosphate (cGMP) analogue, 8-Br-cGMP, was the secretagogue. This finding, which suggested that the inhibitory effect of chlorpromazine on ST enterotoxin was independent of guanylate cyclase, was confirmed by assaying this enzyme in intestinal homogenates from mice that had been inoculated with chlorpromazine, and also in experiments in which chlorpromazine was added to guanylate cyclase assay mixtures in vitro. Caution is advised before chlorpromazine is routinely adopted for the treatment of all syndromes of watery diarrhoea. (Modified author's abstract)

Rodriguez JT see Portnoy BL

Rodriguez L. The use of loperamide in acute non specific diarrhea. Gastroenterology 1975 Apr;68(4):974

In this study, 27 patients with acute nonspecific diarrhoea [4 or more unformed stools (B.M)/24-h period] were given a double-blind trial of 4 mg loperamide (2 capsules) versus placebo as a single dose. After the 3-h waiting period, patients were given lomotil (diphenoxilate 2.5 mg and atropine sulfate .025 mg) one tablet per loose stool. Thirteen patients receiving the placebo had 32 loose stools in the subsequent 48 h for a mean of 1.23 loose B.M./patient.24 h. The 14 patients receiving loperamide had only 8 loose stools in the same period of time for a mean of 0.29 loose B.M./patient.24 h. In the placebo group, loose stools were experienced by 9 and 5 cases on the first and second day respectively. Only 3 patients in the loperamide group had diarrhoea on the first day of therapy and none on the second day. Lomotil had to be used by 6 patients in the placebo (17 tablets) on the first day, for only 2 (7 tablets) in the loperamide group and 4 in the placebo group, as they had no more diarrhoea. These results suggest that a single dose of loperamide is effective in controlling acute nonspecific diarrhoea.

Roth JLA see Pimparker BD

Rowles GS see Mir GN

Rubino A see Guandalini S

Ruwart MJ see Piercey MF

Ryan JR see LaCorte WSJ

Sabir M, Akhter MH, Bhide NK. Antagonism of cholera toxin by berberine in the gastrointestinal tract of adult rats. Indian J Med Res 1977 Mar;65(3):305-13

Berberine has been found to be effective against cholera toxin in adult rats in a number of experiments. In this study, berberine inhibited cholera toxin-induced fluid accumulation in the gastrointestinal tract, in the ligated intestinal loop of adult rats. Berberine at 10 mg/kg prolonged the latent period and significantly reduced incidence and severity of diarrhoea induced by 2 and 4 g/kg cholera toxin. Berberine (10 mg/kg) reduced the levels of water and electrolytes in the gastrointestinal tract of rats killed within 4 h of the oral feeding of cholera toxin. In the ligated intestinal loop (30 cm long) preparation, 30 and 10 mg of cholera toxin provoked fluid accumulation over 5 h which was significantly inhibited by 5 mg of berberine. "Raswat", a traditional crude dried preparation of Berberis aristata, at a dose of 1.2 g/kg inhibited cholera toxin-induced diarrhoea and fluid accumulation in the gastrointestinal tract. The study thus supports the traditional use of berberine as an adjuvant in clinical cholera.

Sabir M see Akhter MH

Sack DA see Islam MR

Sack RB, Froehlich JL. Berberine inhibits intestinal secretory response of Vibrio cholerae and Escherichia coli enterotoxins. Infect Immun 1982 Feb;35(2):471-5

Berberine has been found to have an antidiarrhoeal property. In this study, it is reported that berberine significantly (i) inhibited the secretory response of both Vibrio cholerae and Escherichia coli heat-labile enterotoxins in the rabbit-ligated intestinal loop model even when administered after the enterotoxin had bound to intestinal mucosa, and (ii) also inhibited the secretory response of the heat-stable (ST) enterotoxin of E. coli in the infant mouse model. The drug was effective when given either before or after enterotoxin binding and when given either intraluminally or parenterally; it did not inhibit the stimulation of adenylate cyclase by cholera enterotoxin and caused no histological damage to intestinal mucosa. Berberine also markedly inhibited the secretory response of E. coli ST enterotoxin in the infant mouse model. Although the mechanism of action of the drug is not yet known, the data provide a rationale for its apparent clinical usefulness in healing acute diarrhoeal disease.

Sack RB, Froehlich JL, Yardley JH. Berberine inhibits secretory response of cholera enterotoxin and E. coli heat-labile enterotoxin. Clin Res 1980 Apr;28(2):514A

Berberine, used in India as an antidiarrhoeal medication, has been shown, in some animal models, to inhibit cholera enterotoxin when administered prior to cholera enterotoxin. The adult rabbit-ligated intestinal loop model was used to study the effects of berberine sulfate, given at different time intervals, on the secretory responses elicited by cholera enterotoxin and Escherichia coli heat-labile (LT) and heat-stable (ST) enterotoxins. The effect of increasing concentrations of berberine (0.01 mg to 30 mg/loop) on the dose-related secretory response produced by cholera enterotoxin (0.25 - 2.0 mg/loop of cholera enterotoxin, NIH 001 Lot) by sacrificing the animals at 4, 7, and 18 h after cholera enterotoxin administration, was examined. Berberine injected into intestinal loops inhibited the secretory effects of cholera enterotoxin by

60-70% ($p<0.01$); maximum inhibition occurred at berberine concentration of 10 mg/loop and occurred when berberine was given a) immediately before, b) 15 min following, or c) 4 h following the injection of cholera enterotoxin into the loops. Berberine had no inhibitory effects when administered into loops adjacent to cholera enterotoxin-injected loops, or when given intraperitoneally (20 mg/kg). Berberine produced no histologic damage to intestinal mucosa, and did not inhibit cholera toxin-mediated stimulation of cyclic adenosine 3',5'-monophosphate (cAMP). Identical inhibition of LT-mediated secretion was found. By way of contrast, berberine did not inhibit ST-mediated secretory responses in rabbit loops or in infant mice. Because of the marked antisecretory effect of berberine which occurred after cholera enterotoxin and LT enterotoxin were bound to intestinal mucosa, the author feels that further studies on the mechanism of action of berberine and its potential therapeutic usefulness are warranted. (Modified author's abstract)

Sack RB, Froehlich JL, Yardley JH. Berberine inhibits secretory response of cholera enterotoxin and Escherichia coli heat-labile enterotoxin. In: Holme T, Holmgren J, Merson MH, Mollby R, eds. Acute enteric infections in children: new prospects for treatment and prevention. Amsterdam: Elsevier, 1981:355-60

Berberine has demonstrated antidiarrhoeal activity. In this study, it was investigated whether berberine might also exert an antitoxic effect when given after cholera toxin had already bound to intestinal mucosa. The studies done primarily in the rabbit-ligated intestinal loop model have extended these observations; berberine inhibits the secretory response of both cholera enterotoxin and the heat-labile enterotoxin of Escherichia coli by about 60-70% when given either before or after (as long as 4 h) the enterotoxins. Berberine has no inhibitory effect when administered into loops adjacent to the enterotoxin-injected loops, but does inhibit secretion when given intraperitoneally. Berberine produces no histologic damage to intestinal mucosa and does not inhibit the stimulation of cyclic adenosine 3',5°-monophosphate by cholera enterotoxin. Berberine, however, does not inhibit intestinal secretion induced by the E. coli heat-stable enterotoxin, either in infant mice or rabbit intestinal loops. Because of the marked antisecretory effects of berberine, it is felt that further studies of its mechanism of action and potential therapeutic usefulness are warranted.

Said SI see Schwartz CJ

Sandhu B, Tripp JH, Candy DCA, Harries JT. Loperamide inhibits cholera toxin-induced small-intestinal secretion [letter]. Lancet 1979 Sep 29;2(8144):689-90

Loperamide, an opiate analogue, is an effective antidiarrhoeal agent. The effects of loperamide on cholera toxin-induced secretion of water and electrolytes in the rat jejunum using an in vitro steady-state perfusion technique was investigated. The perfusion rate was 0.46 ml/min; after a 30-min equilibration period 10 min collections were done. Net absorption rates were calculated, and the results were expressed as the mean of the three collection periods in units/min.g wet weight of jejunum. There was net absorption of water and electrolytes, and it was seen that a significant difference between these values and cholera toxin had no significant effect on glucose absorption. Loperamide reversed cholera toxin-induced secretion of water, sodium, and chloride to absorption, and reduced potassium secretion. The results clearly indicate that loperamide possesses potent antisecretory properties, with cholera toxin as a secretory stimulant. The precise mechanism requires further

study. It is concluded that the beneficial effects of loperamide in patients with diarrhoeal states may be related not only to its known effect on intestinal motility but also to its antisecretory properties.

Sandhu BK, Tripp JH, Candy DCA, Harries JT. Loperamide: studies on its mechanism of action. Gut 1981 Aug;22(8):658-62

The effects of loperamide on net solute and water absorption, and prostaglandin (PG) E_2 and cholera toxin-induced secretion were studied in the rat jejunum using an in vivo steady-state perfusion technique. Loperamide stimulated absorption of fluid, electrolytes, and glucose and reversed PGE_2 and cholera toxin-induced secretion to absorption; this opiate analogue had no effect on cholera toxin stimulation of adenylate cyclase activity or the rise of tissue cyclic adenosine 3',5'-monophosphate (cAMP) concentrations. The opiate antagonist, naloxone, reduced the antisecretory effects of loperamide without affecting tissue levels of cAMP. These results indicate that loperamide inhibits PGE_2 and cholera toxin-induced secretion, and that this phenomenon is independent of any direct effect that cholera toxin has on the adenylate cyclase system. The action of naloxone suggests, but does not prove, that loperamide exerts its effect via opiate receptors. (Author's abstract)

Sandhu BK, Milla PJ, Harries JT. Mechanisms of action of loperamide. Scand J Gastroenterol 1983;18(Suppl 84):85-92

The benefits of large doses of loperamide in some infants with severe diarrhoea indicate that loperamide has an antisecretory action. Using a steady-state perfusion technique in rat jejunum it is shown that loperamide inhibits cholera toxin-induced secretion of water, sodium and chloride ($p<0.001$). This antisecretory action was blocked by naloxone and not mediated via an effect on tissue cyclic adenosine 3',5'-monophosphate (cAMP) level or adenylate cyclase activity. Observations suggest that loperamide may act via opiate receptors, either distal to or separate from the adenylate cyclase/cAMP pathway. Osmotic secretion induced by luminal hypertonic mannitol was not affected by loperamide, whereas prostaglandins E_2 and deoxycholic acid-induced secretion was reversed to absorption. Loperamide thus has an effect on specific transport systems, as opposed to nonspecific passive diffusional processes.

Santora NJ see Douglas GH

Sanyal SC see Butler T

Schiller LR, Davis GR, Ana CAS, Morawski SG, Fordtran JS. Studies of the mechanism of the antidiarrheal effect of codeine. J Clin Invest 1982 Nov;70(5):999-1008

In this study the effects of therapeutic doses of codeine on experimental diarrhoea and on the rate of intestinal absorption of water and electrolytes in normal human subjects are discussed. The results showed that codeine markedly reduced stool volume during experimental diarrhoea, induced by rapid intragastric infusion of a balanced electrolyte solution. There was no evidence that codeine stimulated the rate of intestinal absorption in the gut as a whole or in any segment of the gastrointestinal tract, either in the basal state or when absorption rates were reduced by intravenous infusion of vasoactive intestinal polypeptides. The segmental transit times to determine whether and where codeine delayed the passage of fluid through the intestine were measured. Codeine caused a marked slowing of fluid movement through the

jejunum, but had no effect on the movement of fluid through the ileum or colon. The conclusions were that therapeutic doses of codeine increase the net intestinal absorption (and thereby reduce stool volume) by increasing the contact time of luminal fluid with mucosal cells and that endogenous opiates do not regulate intestinal absorption in humans.

Schoenaers F see Ericsson CD

Schoenfield LJ see Coyne MJ

Schoenfield LJ see Taub M

Schroder S see Galambos JT

Schuermans V see Dom J

Schuermans V see Verhaegen H

Schultz SG see Frizzell RA

Schwartz CJ, Kimberg DV, Sheerin HE, Field M, Said SI. Vasoactive intestinal peptide stimulation of adenylate cyclase and active electrolyte secretion in intestial mucosa. J Clin Invest 1974 Sep;54(3):536-44

Vasoactive intestinal peptide (VIP), originally isolated from hog small intestinal mucosa, has been shown to cause small intestinal secretion. More recently, this peptide has been identified in the plasma and tumors of patients with the so-called "pancreatic cholera" syndrome. To explore the possible role of VIP in the pathogenesis of this syndrome, the following were examined: the effects of this peptide and other hormones on the cyclic adenosine 3',5'-monophosphate (cAMP) levels, adenylate cyclase activity, and ion transport in in vitro preparations of ileal mucosa. In rabbit ileal mucosa, VIP (20 µg/ml) caused a prompt five-fold increase in cAMP level, whereas nine other hormones, which have been postulated to cause intestinal secretion, failed to exert such an effect. Pentagastrin and glucagon also failed to increase cAMP levels in canine ileal mucosa. An increase in mucosal cAMP levels was observed at a VIP concentration of 0.1 µg/ml and appeared to be nearly maximal at 2.0 µg/ml. VIP (100 µg/ml) stimulated adenylate cyclase activity in a membrane preparation from rabbit ileal mucosa. Secretin (6.0×10^{-5} M) failed to do so. When added to the serosal side of isolated rabbit ileal mucosa clamped in an Ussing chamber, VIP (2 µg/ml) increased short-circuit current and caused net secretion of both Cl and Na. Net Cl secretion exceeded net Na secretion. These effects of VIP on mucosal cAMP metabolism and ion transport are similar to those observed with cholera enterotoxin and certain prostaglandins. VIP was also tested with normal human ileal mucosa. At a concentration of 2 µg/ml, it caused a five-fold increase in cAMP level and an increase in short-circuit current of the same magnitude as that caused by 5 mM theophylline. Addition of a second 2-µg/ml dose of VIP and addition of theophylline after VIP, produced no further change in short-circuit current. It is concluded that the VIP stimulates adenylate cyclase and active ion secretion in both rabbit and human ileal mucosa. This may be related to the pathogenesis of diarrhoea in patients with the pancreatic cholera syndrome. (Modified author's abstract)

Serebro HA, Iber FL, Yardley JH, Hendrix TR. Inhibition of cholera toxin action in the rabbit by cycloheximide. Gastroenterology 1969 Mar;56(3):506-11

Pretreatment of rabbits with cycloheximide (20 mg/kg, given intravenously), a potent inhibitor of protein synthesis, prevented cholera exotoxin-induced fluid production by in vivo jejunal loops. Glucose absorption was unaffected, and the chief histological alteration in the epithelium was decreased mitotic figures in the crypts. At higher intravenous doses (40 mg/kg), greater histological damage was seen in the crypts and fluid production was prevented, but glucose absorption was also impaired. One interpretation of these results is that cholera exotoxin induces synthesis of a protein mediator of fluid secretion, and that this secretion originates in the crypts of Lieberkuhn. (Modified author's abstract)

Shah DM see Desai AB

Shah KM see Desai AB

Sharda DC. Berberine in the treatment of diarrhoea of infancy and childhood. J Indian Med Assoc 1970 Jan;54(1):22-4

Berberine was tried in 50 children with gastroenteritis and was compared with an equal number of controls. The overall recovery in 5 days in both mild and severe cases was 92%. Berberine proved to be an effective drug in controlling gastroenteritis and worked well as an antidiarrhoeal agent. It is supplied as a palatable suspension which can easily be administered to children. Berberine is not an antimicrobial drug and is free from hazards of antibiotic treatment, and treatment with it is short.

Sharma R, Joshi CK, Goyal RK. Berberine tannate in acute diarrhoea. Indian Pediatr 1970 Sep;7(9):496-501

Berberine tannate was tried in 65 Indian children, aged under 5 with acute diarrhoea for its antidiarrhoeal action and compared with an equal number of controls. This study was conducted from October 1968 to March 1969. The recovery in berberine-treated children was faster. Berberine tannate is effective in diarrhoeas caused by Escherichia coli, Shigella, Salmonella B, Klebsiella and Faecalis aerogenes. Berberine tannate has been used as an antidiarrhoeal agent to achieve the control of diarrhoea and the correction of dehydration. Berberine tannate was found as effective as the combination "thalyl-sulphathoazole+streptomycin" and streptomycin+chloramphenicol, and better than sulfaguanidine. Berberine tannate, is an effective antidiarrhoeal drug for diarrhoea cases among children.

Sharma VD see Kumar A

Sheerin HE see Field M

Sheerin HE see Schwartz CJ

Sherwin RS see Dharmsathaphorn K

Shimizu M see Sohji Y

Siegel BW, Wiech NL. RM1 12330A: an inhibitor of cholera toxin induced intestinal hypersecretion which also inhibits adenylate cyclase activity. Gastroenterology 1976 May;70(5,pt 2):937

Sircar BK see De S

Smith PL, Field M. In vitro antisecretory effects of trifluoperazine and other neuroleptics in rabbit and human small intestine. Gastroenterology 1980 Jun;78(6):1545-53

The inhibitory effects of several neuroleptic agents on intestinal secretion were examined in vitro by measuring short-circuit current, net Cl flux, and cyclic nucleotide concentrations. In rabbit ileal mucosa, trifluoperazine (0.2-0.5 mM) did not significantly alter basal transport rates, but partially inhibited responses to the following secretagogues: theophylline, 8-Br-cyclic adenosine 3'5'-monophosphate (cAMP), vasoactive intestinal peptide (VIP), dimethyl-prostaglandin (PG) E_2 and Escherichia coli heat-stable enterotoxin [a cyclic guanosine 3',5'-monophosphate (cGMP) agonist]. Trifluoperazine completely inhibited the response to Ca ionophore A23187. In human small intestinal mucosa, trifluoperazine (0.1-0.5 mM) inhibited electrical responses to VIP and theophylline almost completely. The inhibitory action of trifluoperazine was manifest only on serosal addition. Trifluoperazine did not significantly alter cAMP or cGMP concentrtions either under basal conditions or in the presence of secretagogues. It also did not diminish the electrical response to luminally added D-glucose. Three other neuroleptics were tested and found to have antisecretory action; their order of potencies were trifluoperazine > chlorpromazine > haloperidol > chlorprothixene. Since all four agents are potent inhibitors of calcium-dependent regulator in the bovine brain, this ubiquitous protein may also be useful for their antisecretory action in intestine. (Modified author's abstract)

Smith PL see Field M

Sninsky CA see Leibach JR

Snyder SH see Reynolds IJ

Soeparto H see Soeparto P

Soeparto P, Noerasid H, Djupri L. Chlorpromazine-HCl in acute infantile diarrhoea (a brief clinical observation). Paediatr Indones 1982 Mar-Apr;22(3-4):43-8

To evaluate the effect of chlorpromazine hydrochloride, when given as a single drug versus when it is combined with antibiotics in infants suffering from acute watery diarrhoea, 78 patients, aged 2 months to 3 years, were studied in two groups. In the first group, 57 patients received chlorpromazine 1 mg/kg body weight.day, divided into 3 oral doses for 5 days. In the second group, 21 patients were given a combination of chlorpromazine 1 mg/kg body weight.day, and antibiotics. Both groups also received oral glucose-electrolyte solution. Diarrhoea stopped within 3 days in 70.4% of the patients in the first group and in 70% in the second group. Within 7 days, stools became normal in 85.2% of the patients in the first group, and in 85% in the second group. No significant difference was observed between the two groups. Three patients in the first group (5.3%) and one patient in the second group (4.8%) were given intravenous fluid, due to worsening diarrhoea. The side-effects observed during chlorpromazine treatment were irritability in one patient, heavy sedation in two, and uncoordinated movements in one patient.

Soeparto P, Subiyanto MS, Noerasid H. Cholestyramine in the management of recurrent diarrhoea in infancy. Paediatr Indones 1982 May-Jun;22(5-6):104-10

The possibility that bile acids are involved in the pathogenesis of recurrent diarrhoea prompted the authors to compare the response to cholestyramine treatment with that of the usual antibiotic modes of therapy in recurrent diarrhoea. Use of cholestyramine in children has been increasing, as its oral administration has been beneficial in cases where diarrhoea is considered to be caused by the cathartic effect of increasing amounts of bile acid reaching the colon. Since cholestyramine is a basic anion exchanger which binds both bile acids and endotoxin, the hypothesis was that the drug might effectively treat intractable diarrhoea. Ninety-nine patients, aged 3 months to 3 years suffering from recurrent diarrhoea, were divided into two groups. Forty-six patients received antibiotics, while 53 patients received oral cholestyramine, in a modest dosage of 4-6 g/day in each episode of diarrhoea for at least 6 days. The dosage was adjusted to each patient's needs and response. Patients who could be followed up for at least 6 months after initial treatment were considered eligible for evaluation. Accordingly, only 38 of the 53 patients with cholestyramine and 35 of the 46 others finally were evaluated. Favorable response to treatment did not differ significantly between the two groups. No cholestyramine side-effects were seen. And it is suggested that cholestyramine might be used for recurrent diarrhoea rather than long-term antibiotics, to avoid development of resistant microorganism strains in the gut.

Soeparto P, Djupri L, Soeparto H, Noorasid F. Loperamide for acute diarrhoea in infancy (a clinical experience). Paediatr Indones 1981 May-Jun;21(5-6):115-8

To assess the efficacy of loperamide in controlling acute watery diarrhoea, a clinical trial was designed in Indonesia. Ninety-four infants, aged between 3 months and 3 years arriving with acute watery diarrhoea of less than 3 days, were included in the study. They were arbitrarily divided into two groups. Group 1 with 46 patients received solely loperamide (Normotil) in addition to oral glucose-electrolyte solution; Group 2 with 48 patients was treated with loperamide and oral fluid in combination with antibiotics. The dose of loperamide given was 0.04 mg/kg body weight divided into 3 doses. When examined after 3 days, the stool became formed in 69.6% of patients in the loperamide group and 86% in the loperamide-antibiotic group. Within 7 days of onset of treatment, formed stool was passed by 87% of loperamide group and 95.4% of the loperamide-antibiotic group. Failure, as indicated by the worsening of diarrhoea within 24 h necessitating intravenous fluid administration, occurred in 5 patients. No side-effect of loperamide was noted during the present study.

Sohji Y, Kawashima K, Nakamura H, Shimizu M. Pharmacological studies of loperamide, an antidiarrheal agent. I. Effects on diarrhea induced by castor oil and prostaglandin E_1. Folia Pharmacol Jpn 1978;74:145-54

Speight TM <u>see</u> Heel RC

Sperow JW <u>see</u> Mir GN

Spraggs CF, Bunce KT. Alpha$_2$-adrenoceptors and the delay of castor oil-induced diarrhoea by clonidine in rats. J Pharm Pharmacol 1983 May;35(5):321-2

Although clonidine has been reported to inhibit castor oil-induced diarrhoea in rats, the receptor type involved in this action of clonidine has not been characterized. Investigated here was the α-adrenoceptor subtype involved in the antidiarrhoeal action of clonidine using phenylephrine, prazosin and

yohimbine. Male wistar rats (200 g) were starved overnight, but allowed free access to water. The rats were injected intraperitoneally with 0.9% NaCl (saline) (1 ml kg^{-1}; control) or with the appropriate test drug(s). Thirty min later, each rat was dosed orally with 2 ml of castor oil and was then observed at 30 min intervals for up to 6 h for the onset of diarrhoea. The drugs used were: clonidine, phenylephrine, yohimbine, prazosin and castor oil. All control rats developed diarrhoea within 2 h of castor oil treatment. Clonidine from 0.1 to 1.0 µmol kg^{-1} caused a dose-related delay of the onset of diarrhoea, the highest dose- preventing diarrhoea for greater than 6 h. In contrast, high doses of phenylephrine (1 to 100 µmol kg^{-1}) failed to delay the onset of castor oil-induced diarrhoea. Yohimbine produced a dose-related reversal of the clonidine-induced delay of diarrhoea. In contrast, prazosin caused no significant reversal of clonidine's antidiarrhoeal effect. Yohimbine and prazosin alone had no significant effect on the time of onset of castor oil-induced diarrhoea. It was shown that clonidine produced a dose-related inhibition of castor oil-induced diarrhoea in the conscious rat in a range of 0.1 to 1.0 µmol kg^{-1} intraperitoneally. Comparison of these antidiarrhoeal doses of clonidine and those reported to exert cardiovascular effects in the rat is complicated by the different routes of administration used. Despite the relatively large doses of clonidine required for its antidiarrhoeal activity, such effects did not appear to be mediated by α_2-adrenoceptors, since large doses of the α_1-agonist phenylephrine did not significantly delay the onset of castor oil-induced diarrhoea. (Modified author's abstract)

Srinivasan G see Mandangopal N

Steel ED see Reiter B

Stein H see Kahn E

Steinhoff MC, Douglas RJ, Jr., Greenberg H, Callahan DR. Bismuth subsalicylate therapy of viral gastroenteritis. Gastroenterology 1980 Jun;78(6):1495-9

Steven K, Lange P, Bukhave K, Rask-Madsen J. Prostaglandin E_2-mediated secretory diarrhea in villous adenoma of rectum: effect of treatment with indomethacin. Gastroenterology 1981 Jun;80(6):1562-6

Biochemical and clinical evidence is presented to indicate that prostaglandin (PG) E_2 is the mediator of fluid and electrolyte secretion by villous adenomas of the rectum. A 64-year-old man with a 2-month history of mucous diarrhoea had, on admission, prerenal uremia, severe hyponatremia, and hypokalemia. At sigmoidoscopy, an 11x11-cm villous adenoma of the rectum was revealed. The rectal fluid discharge was 1800-1825 ml/day, with sodium and potassium concentrations of 150 and 12 mEq/l respectively. Immunoreactive PGE_2 levels in the rectal effuents were high (e.g. 1160-1250 pg/ml vs 200-395 pg/ml) compared to those in stool water from patients with infectious diarrhoea. Indomethacin treatment resulted in a gradual decrease in the volume of rectal discharge reaching a minimum value of 860 ml amounting to a 50% reduction. A larger reduction occurred in the rectal PGE_2 concentrations reaching a value of 75%. The rectal sodium loss paralleled that of fluid excretion while the potassium loss remained constant. The concentration of vasoactive intestinal polypeptide (VIP) in the tumor was lower (e.g. 10.5 pmol/g vs 100-700 pmol/g) than in normal colonic mucosa. The results suggest that the fluid and electrolyte secretion by villous adenomas is mediated by PGE_2 released from the tumor tissue. The lower VIP concentrations may be explained by the absence of vasoactive intestinal polypeptidergic neurons in the tumor tissue. By

discontinuing medication, a rise in the rectal excretion of PGE_2, fluid and sodium was observed. The results suggest that the use of PG synthetase inhibitors may facilitate the preoperative correction of severe fluid-electrolyte deficits in patients with large villous adenomas of the rectum.

Stokholm KH, Abildgaard U. Calcium in the treatment of diarrhoea and hyperoxaluria after jejunoileal bypass for obesity. Int J Obes 1980;4(2):105-10

This study examines how efficiently calcium supplementation reduces diarrhoea after jejunoileal bypass for obesity. Fourteen patients with jejunoileal bypass for obesity were treated for one week with a calcium supplement of 3 g daily. During this period, diarrhoea was significantly ($p<0.005$) reduced by 23% (97% confidence limits: 7-46%). Ten of the 14 patients had hyperoxaluria (median vlaue 961 µmol/24 h; range 633-2742 µmol/24 h). The treatment with calcium significantly ($p<0.005$) decreased the concentration of oxalate in urine by 23% (98% confidence limits: -5--+ 54%). The calcium supplement did not increase urinary calcium-excretion rate or albumin-corrected serum calcium. (Modified author's abstract)

Stoll BJ, Holmgren J, Bardhan PK, Huq I, Greenough WB, III, Fredman P, Svennerholm L. Binding of intraluminal toxin in cholera: trial of GM1 ganglioside charcoal. Lancet 1980 Oct 25;2(8200):888-91

A study was undertaken to investigate whether toxin produced in the gut lumen contributes significantly to clinical illness and whether binding such toxin by GM_1 ganglioside adsorbed onto charcoal could alter the clinical course of disease. Forty-six patients with severe cholera receiving standard intravenous therapy were randomly assigned to one of three groups: GM_1 ganglioside-charcoal (16), charcoal alone (16), or water (14). The results demonstrated that patients were given sufficient GM_1 ganglioside-charcoal to bind all luminal toxin produced by Vibrio cholerae in their intestines. Patients treated with GM_1 ganglioside tended to have a greater reduction in purging than patients treated with either charcoal alone or water. This difference was statistically significant soon after beginning medication (8-15 h), and the reduction in fluid loss was especially pronounced in patients with very severe purging who had been ill only for a short time before admission. These results suggest that toxin produced in the gut lumen increases fluid loss early in cholera, but that later in the course of disease, toxin which is inaccessible to luminal binding agents is the major stimulus of purging. (Author's abstract)

Studt WL see Douglas GH

Subiyanto MS see Soeparto P

Subramaniam R see Mandangopal N

Sullivan P see DuPont HL

Suyatna FD see Wilmana PF

Svennerholm L see Stoll BJ

Tai YH, Feser JF, Marnane WG, Desjeux JF. Antisecretory effects of berberine in rat ileum. Am J Physiol 1981 Sep;241(3):G253-8

The in vitro antisecretory effects of the alkaloid berberine (1.0 mM) on intestinal ion secretion and mucosal adenylate cyclase and Na-K-ATPase activities were studied in the rat ileum. Mucosal berberine did not alter the individual basal net ion fluxes and basal adenylate cyclase activity, but decreased short-circuit current and increased the net absorption of chloride plus bicarbonate. In the cholera toxin-treated tissue, mucosal berberine stimulated absorption of Na and Cl and inhibited the increased adenylate cyclase activity, but did not change the specific Na-K-ATPase activity, whereas serosal berberine stimulated Na secretion and decreased short-circuit current. Mucosal berberine also decreased short-circuit current, increased Cl permeability, and reversed the ion secretion induced by dibutyryl cyclic adenosine 3',5'-monophosphate (cAMP), Escherichia coli heat-stable enterotoxin and methylprednisolone administration. The antisecretory effects of mucosal berberine may be explained by stimulation of Na-Cl-coupled absorptive transport process. The mechanism of action of serosal berberine remains to be elucidated. It is clear that mucosal berberine affects intestinal ion transport by mechanisms different from stimulation of the Na-pump and probably a step distal to the production or degradation of cAMP or cyclic guanosine 3',5'-monophosphate.

Tapper EJ see Powell DW

Taqi S see Haqqani AH

Taub M, Bonorris G, Chung A, Coyne MJ, Schoenfield LJ. Effect of propranolol on bile acid-and cholera enterotoxin-stimulated cAMP and secretion in rabbit intestine. Gastroenterology 1977 Jan;72(1):101-5

Stimulation of the net secretion by deoxycholic acid in the colon and by cholera enterotoxin in the jejunum is mediated by cyclic adenosine 3',5'-monophosphate (cAMP). Propranolol inhibits adenylate cyclase activity and net secretion induced by bile acid in the colon. This study assesses the organ specificity of deoxycholic acid and cholera enterotoxin as well as the selectivity of propranolol inhibition. Three colonic and three jejunal loops were prepared in each of 8 rabbits treated intravenously with propranolol, 4 mg/kg, ½ h before loop construction and in each of 10 untreated control rabbits. One milliliter of deoxycholic acid, 6mM, cholera enterotoxin, 10 μ/ml, or heat-inactivated cholera enterotoxin or 0.9% NaCl, as basal controls were injected in random order into each of the loops. The volume of luminal fluid and mucosal adenylate cyclase were measured in each intestinal loop 5 h later. Deoxycholic acid in the colon stimulated adenylate cyclase 2-fold ($p<0.01$) and luminal fluid 15-fold ($p<0.01$). Cholera enterotoxin in the jejunum stimulated adenylate cyclase 2-3 fold ($p<0.01$) and luminal fluid 9-fold ($p<0.01$). No significant effects on volume or adenylate cyclase occurred in response to cholera enterotoxin in the colon or to deoxycholic acid in the jejunum. Propranolol pretreatment completely prevented the stimulation of adenylate cyclase and luminal fluid by deoxycholic acid in the colon, but did not affect the action of cholera enterotoxin in the jejunum of the same animals. Thus, deoxycholic acid and cholera enterotoxin are organ-specific stimulants of cAMP systems, and propranolol is a selective inhibitor of certain inducers of cAMP and net secretion. (Modified author's abstract)

Thomas DD, Knoop FC. The effect of calcium and prostaglandin inhibitors on the intestinal fluid response to heat-stable enterotoxin of Escherichia coli. J Infect Dis 1982 Feb;145(2):141-7

The role of calcium and prostaglandins (PG) in the intestinal fluid response to Escherichia coli heat-stable (ST) enterotoxin was investigated in infant mice. Drugs that inhibit calcium uptake - cromolyn sodium, diltiazem, and nifedipine - caused a significant ($p<0.02$, $p<0.02$, and $p<0.01$ respectively) decrease in the fluid response when administered with ST enterotoxin. The effect of cromolyn sodium and nifedipine was dose-dependent; both agents were effective when administered 30 min before toxin challenge. Inhibitors of PG synthesis - quinacrine hydrochloride and zomepirac sodium - caused a significant ($p<0.05$ and $p<0.02$ respectively) reduction in the fluid response when administered with or 30 min before ST enterotoxin. The fluid response to cyclic 8-bromo-guanosine 3',5'-monophosphate or to nitropruside which directly activates guanylate cyclase, was not altered by inhibitors of calcium uptake of PG synthesis. These observations indicate that calcium and PGs are involved in the initial events that result in an intestinal fluid response to E. coli ST enterotoxin. (Modified author's abstract)

Tin-U see Khin-Maung-U

Tripp JH see Sandhu B

Tripp JH see Sandhu BK

Tsuei CT see Douglas GH

Turjman N, Cardamone A, Gotterer GS, Hendrix TR. Effect of nicotinic acid on cholera-induced fluid movement and unidirectional sodium fluxes in rabbit jejunum. Johns Hopkins Med J 1980 Dec;147(6):209-11

Cholera toxin produces intestinal secretion and elevation of intestinal cyclic adenosine 3',5'-monophosphate. Nicotinic acid has been shown to prevent these responses. The effect of nicotinic acid on cholera toxin-induced secretion could be caused by decreased plasma-to-lumen flux, increased lumen-to-plasma flux, or a combination of both. The purpose of this study is to define the effects of nicotinic acid on net fluid movement and unidirectional sodium fluxes in rabbit jejunal loops exposed to cholera toxin. In the untreated animals receiving no nicotinic acid, the cholera toxin-exposed loops secreted 0.91 ml/cm.4 h above the control loops receiving no cholera toxin ($p<0.01$). On the other hand, pretreatment with 100 mg/kg nicotinic acid caused a striking decrease in secretion in the cholera toxin loop, so that the cholera toxin loop was not significantly different from the control loop. Unidirectional sodium fluxes in untreated animals showed that cholera toxin caused an increase in the plasma-to-lumen flux and a decrease in the lumen-to-plasma flux. Both effects were abolished by pretreating the animals with nicotinic acid. These studies indicate that nicotinic acid prevents cholera toxin-induced secretion by restoring the unidirectional fluxes to control levels. (Author's abstract)

Turjman N, Gotterer GS, Hendrix TR. Prevention and reversal of cholera enterotoxin effects in rabbit jejunum by nicotinic acid. J Clin Invest 1978 May;61(5):1155-60

The cholera enterotoxin produces intestinal secretion associated with an elevation of tissue levels of cyclic adenosine 3',5'-monophosphate (cAMP). This study determines whether intestinal secretion and cAMP elevation induced by cholera toxin could be prevented, or once initiated, reversed by nicotinic acid, an agent known to lower tissue levels of cAMP. In rabbits, four jejunal loops were constructed as alternating control (3-ml isotonic electrolyte

solution) and cholera toxin (same solution containing 50 µg purified cholera toxin) loops. Net intestinal secretion was determined by measuring fluid accumulation, after which intestinal biopsies were taken for cAMP assay. The animals were pretreated either subcutaneously with 50 mg/kg nicotinic acid in saline 3 h and 1 h before the introduction of cholera toxin, or intraluminally with 200 mg/kg nicotinic acid in Ringer's lactate solution 15 min before the instillation of cholera toxin. Under these conditions, nicotinic acid blocked the cholera toxin-induced secretion and the rise in cAMP measured 3 h after the loops were exposed to cholera toxin. The effect of the nicotinic acid administered within the lumen on net intestinal secretion was studied. Maximal inhibition of net intestinal secretion was achieved with an intraluminally administered dose of nicotinic acid of 100 mg/kg. This dose was chosen for testing the ability of nicotinic acid to reverse the effects of cholera toxin. When nicotinic acid was instilled into a fifth loop constructed distally to the four experimental loops 3 h after exposure of these loops to cholera toxin, both intestinal secretion and elevation of cAMP were reversed. These results suggest that nicotinic acid can prevent and reverse the secretory effects of cholera toxin and may have a role in the therapy of cholera and other cAMP-associated diarrhoeal diseases. (Author's abstract)

Turjman NA see Wald A

Turnberg LA see Hughes S

Turnberg LA see McKay JS

Tuttle R see Cassuto J

Vantrappen G see Pelemans W

Venkataraman A see Modak S

Verbeke S see Demeulenaere L

Verhaegen H, De Cree J, Schuermans V. Loperamide (R18553), a novel type of antidiarrheal agent. Pt. 7. Clinical investigation: efficacy and safety of loperamide in patients with severe chronic diarrhea. Arzneim Forsch/Drug Res 1974;24:1657-60

Vesikari T, Isolauri E, Maki M. Efficacy of cholestyramine in acute infantile diarrhoea: placebo-controlled double-blind trial in hospitalized children and in outpatients. J Diarrhoeal Dis Res 1984 Sep;2(3):151-8

The efficacy of cholestyramine in acute infantile diarrhoea was evaluated in two placebo-controlled, randomized, double-blind trials. In the first, cholestyramine, 2 g four times daily, or an equivalent amount of placebo were given, in addition to fluid replacement therapy, to 52 infants hospitalized for acute nonbacterial diarrhoea. The mean duration of watery diarrhoea was 2.6±1.4 days in the placebo group, which was considerably less than the mean of 0.8±0.7 days in the cholestyramine group ($p<0.001$). Cholestyramine-treated infants also showed a better tendency to gain weight. In the second trial, 40 infants with acute diarrhoea of less than 24 h' duration were treated as outpatients with cholestyramine (n=15) 2 g twice daily for 3 days, or with a placebo (n=25), in addition to oral fluids and rapid return to full feedings. The watery diarrhoea mean duration in infants receiving cholestyramine was 0.9±1.1 days, which was significantly less than the 2.9±1.5 days in the placebo

group ($p<0.001$). Weight gain was similar in both groups. Cholestyramine therapy was not associated with acidosis or hyperchloremia. It is concluded that 2 g of cholestyramine twice daily is effective in infants in shortening the course of watery diarrhoea of rotavirus or nonspecific origin. (Author's abstract)

von Muhlendahl KE, Bunjes R, Krienke EG. Loperamide-induced ileus [letter]. Lancet 1980 Jan 26;1(8161):209

The effectiveness of loperamide in the treatment of acute, sub-acute and chronic diarrhoeas of various etiologies has been studied by many workers, but it is questionable whether, in addition to rehydration, along with the maintenance of electrolyte balance and dietary treatment, a pharmacological adjunct is really necessary. An antiperistaltic agent or water-absorbent therapy may be dangerous by masking water losses into the bowel. A further argument against the use of loperamide is that it may induce ileus in children. In the Children's Hospital of the Free University in Berlin, a one-year-old patient who was given a single therapeutic dose (0.045 mg/kg) of loperamide, had a paralytic ileus with stool retention for 7 days. On the fifth day, surgery had to be considered. Less severe symptoms were seen after an overdose (1.4 mg/kg) in another patient aged 17 months. Loperamide previously was recommended by the manufacturers for use in children without any age limit; since 1977, it has been recommended for use in those aged over 2 in Germany.

Wald A, Gotterer GS, Rajendra GR, Turjman NA, Hendrix TR. Effect of indomethacin on cholera-induced fluid movement, unidirectional sodium fluxes, and intestinal cAMP. Gastroenterology 1977 Jan;72(1):106-10

Cholera enterotoxin produces intestinal secretion associated with an elevation of intestinal cyclic adenosine 3',5'-monophosphate (cAMP). Indomethacin, a potent inhibitor of prostaglandin (PG) synthesis, decreases cholera enterotoxin-induced secretion, although a role for PG in in this process has not been demonstrated. The purpose of this study is to measure the effects of indomethacin on net fluid movement and unidirectional Na fluxes in rabbit jejunal loops exposed to cholera enterotoxin and to correlate these findings with intestinal cAMP levels. In untreated animals (no indomethacin), cholera enterotoxin loops secreted 0.37 ml/cm.4 h compared to absorption in control loops of 0.23 ml/cm.4 h ($p<0.001$). In indomethacin-treated animals, there was a striking reduction of secretion in cholera enterotoxin loops (0.07 ml/cm.4 h, ($p<0.001$). Absorption in control loops in indomethacin animals was greater than in untreated animals (0.42 ml/cm.4 h, $p<0.02$). Unidirectional Na fluxes were greatly depressed in indomethacin animals at 1 h in both cholera enterotoxin and control loops. This effect disappeared by 4 h. Intestinal cAMP levels in cholera enterotoxin loops, although not elevated at 1 h despite the onset of secretion, were significantly elevated at 4 h. Indomethacin did not alter cAMP levels at 1 and 4 h in either cholera or control loops. These studies support the view that PG synthesis is not involved in cholera enterotoxin-induced elevation of intestinal cAMP. Indomethacin may depress intestinal secretion by inhibiting a PG-mediated step beyond the generation of cAMP or by acting on some other, as yet unidentified, biological mechanism involved in intestinal secretion. (Modified author's abstract)

Walsh JH see Mogard MH

Watkinson G see Allen G

Watkinson M. A lack of therapeutic response to kaolin in acute childhood diarrhoea treated with glucose electrolyte solution. J Trop Pediatr 1982 Dec;28(6):306-7

This study assesses the therapeutic value of kaolin in children with diarrhoea who were also being treated with a glucose-electrolyte solution. The addition of kaolin to the therapeutic regime of West African village children, whose diarrhoea was being treated with glucose-electrolyte solution, did not shorten their diarrhoeal attacks, nor reduce their severity, nor did it alter their weight changes over an attack of diarrhoea. In both control and kaolin-treated groups, many of the study children had lost weight prior to initiation of treatment. Compliance with the prescribed therapeutic dose among patients was poor. Analysis of the results with special reference to the kaolin intake compliance did not reveal any therapeutic benefit for those who had taken appropriate or excessive amounts.

Wayburne S see Kahn E

Wenger J see Galambos JT

Wiech NL see Siegel BW

Wilmana PF, Suyatna FD, Darmansyah I. A double blind, placebo controlled trial on acute non-specific diarrhea. Asean J Clin Sci 1982 Dec;3(4):317-22

The clinical efficacy of a combination of Curcuma domestica, Acacia catechu and kaolin was assessed in a comparative double-blind, placebo-controlled trial among 299 outpatients (age: 12-50 years; 178 males) from 8 primary health clinics in Jakarta. The study was limited only to acute nonspecific diarrhoea cases. Patients were divided into 3 treatment groups to receive: (1) a combination of Curcuma domestica, 15 mg, Acacia catechu, 15 mg and kaolin, 500 mg per capsule (100 patients); (2) clioquinol, 250 mg per capsule (103 patients); and (3) placebo containing saccharum lactis (97 patients). Treatment course was 48 h, but extended to 96 h when necessary. Dosage schemes in all groups were similar - 2 capsules 3 times a day. Patients were divided further into 3 subgroups according to their stool fequency. Total cure rates for both 48 h and 96 h treatments were 94, 93 and 82.5% for the herbal combination, clioquinol and placebo respectively. Only in the moderate diarrhoea subgroup, the combination drug showed significantly better results than placebo (cure rate 97.6% vs 80.6%; $p<0.05$). The combination's efficacy, however, was equal to clioquinol (94.6%). Two patients on the combination drug showed generalized skin rashes during the trial. For moderate acute nonspecific diarrhoea, such a herbal combination is worth considering.

Womelsdorf AH see Moritz M

Wuster M, Herz A. Opiate agonist action of antidiarrheal agents in vitro and in vivo - findings in support for selective action. Naunyn Schmiedebergs Arch Pharmacol 1978 Jan-Feb;301(3):187-94

This study examines the opiate-like activity of a series of antidiarrhoeals in vitro and in vivo to grasp the mechanism underlying their specific constipating activity. The results of radioreceptor assay showed that the antidiarrhoeal agents competitively inhibited sterospecific ^{3}H-naloxone binding. Binding was increased in the absence of sodium. No differences in the affinities of these compounds to central and peripheral opiate receptors respectively, were found.

Antidiarrhoeal agents inhibited the electrically-induced contractions of the isolated longitudinal muscle-mysenteric plexus preparation of the guinea pig ileum. To obtain pharmacological effects on the isolates' organ, up to 70-fold lower concentrations were necessary in case of the antidiarrhoeals than was calculated from their affinities in the radioreceptor assay. The pharmacokinetic behavior of ^{3}H-loperamide was tested in mice after intravenous (i.v.) injection. Compared to morphine, loperamide was rapidly eliminated from the general circulation, and only small concentrations reached the central nervous system. Up to 2 h after i.v. administration of ^{3}H-loperamide, an increase in radioactivity in the wall of the small intestine was found. The surface tension-lowering effect is a common characteristic by which all antidiarrhoeals differed from narcotic analgesics and could be related to the peculiar behavior of these substances in vitro and in vivo.

Yamada T see Mogard MH

Yamada T see Mulvihill S

Yamamoto S see Nakaki T

Yardley JH see Sack RB

Yardley JH see Serebro HA

Ye X. [A further investigation on pathogeny, pathology and therapy in infantile diarrhoea by means of TCM-WM]. Chung Hsi I Chieh Ho Tsa Chih 1982 Oct;2(4):222-3

Experiments have shown that disturbance of enteric function (excessive secretion or malabsorption) which led to water retention in the intestine is the cause of infectious diarrhoea. This led to a further investigation of pathogenicity and pathology by means of TCM-WM, and offered scientific evidence for the theory of TCM. Following the combined method of TCM-WM, diarrhoea in a Chinese study was divided into 3 types: Waigan (infectious diarrhoea), Sangshi (food factor simply) and Pixu (prolonged enteritis). The three traditional Chinese drugs, "Ge Gen Qin Lian Tang", "Bao He Wan" and "Shen Ling Bai Zhu San", were given to 961 patients with diarrhoea in 1958-1978. The curative rate was 92.3%. Time of stoppage of diarrhoea and subsidence of fever were shortened for 1-2 days as compared with the WM group. The main pathogens were Escherichia coli and rotavirus. All pathogens in cases of bacterial diarrhoea were resistant to antibiotics in common use, but in viral diarrhoea, the use of antibiotic drugs was of no use. It was proved in the experiments with the ligation of rabbit intestine that the toxin of E. coli manifested a phenomenon of increasing intestinal secretion. The therapeutic mechanism of stopping diarrhoea with the given decoction (Ge Gen Qin Lian Tang) is related to the function of inhibiting secretion. Since the decoction contains berberine, the treatment of diarrhoea with Chinese medicine (if necessary combined with fluid therapy) is recommended for its high therapeutic effect, minimal side-effects and easy availability.

Yelnosky J see Mir GN

Zalipsky JJ see Douglas GH

Zfass AM see Carter RF

Zhu B, Ahrens FA. Effect of berberine on intestinal secretion mediated by Escherichia coli heat-stable enterotoxin in jejunum of pigs. Am J Vet Res 1982 Sep;43(9):1594-8

Intraluminal perfusion with Escherichia coli heat-stable (ST) enterotoxin reversed water and electrolyte movements from net absorption to net secretion in porcine jejunal segments. Addition of berberine hydrochloride (3.2×10^{-5} M) to the perfusate reduced the jejunal secretory response of water, sodium, potassium, and chloride to ST enterotoxin and enhanced water and electrolyte absorption in control segments. At lower concentrations (1.1×10^{-5}M), berberine reduced the secretory response in ST enterotoxin-exposed segments, but only the decrease of sodium flux was significant. In the presence of berberine, the mucosal enzyme activities of adenosine triphosphatase and disaccharidases were not significantly different between control and ST enterotoxin-exposed segments. Doses of 1,2,3,4,5, and 10 mg of berberine were injected into ligated loops of proximal part of the jejunum with 1 ml of ST enterotoxin filtrate. At doses of 2 or more mg/loop, berberine was effective in reducing water and electrolyte secretions induced by ST enterotoxin; the effect was dose-dependent. These findings indicate that berberine may be an effective antidiarrhoeal agent in E. coli ST enterotoxin-mediated secretory diarrhoea and may provide a basis for the frequent empirical use of berberine alkaloid and berberine-containing plants in gastroenteritis and infectious diarrhoea. (Modified author's abstract)

Zhu B see Ahrens FA

Zhu BL see Ahrens FA

Zigler M see Gyles CL

Zimmerman HK see Douglas GH

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