Progress report

Diarrhoea: Mechanisms and treatment

Diarrhoea can usefully be considered as a disturbance in the balance between the mechanisms controlling secretion and absorption of water resulting in an excess loss of water in the faeces. In this economy, the quantity of water in food and drink is of little importance, for compulsive water drinkers, who may drink 10 litres of water a day, do not develop diarrhoea.

Flow of water across the gut occurs mainly to maintain isotonicity with the plasma in a rapidly changing chemical environment. Thus intraluminal digestion increases the osmotic attraction of water into the bowel, while absorption or secretion of solute is accompanied by absorption or secretion of water. In the upper small bowel the absorptive forces are augmented by active transport of sugars and amino acids coupled with rather a weak sodium pump. In the ileum and colon a powerful sodium pump is capable of transporting sodium isotonically against large electrochemical gradients. These transport systems are closely integrated with the transfer of a number of other substances such as the interchange of chloride for bicarbonate. Although these transfers may not play a direct part in drawing water out of the intestinal lumen, the pathways are so interdependent that a severe disturbance of any of them may result in diarrhoea. The study of the humoral, electrochemical, and structural factors which control these processes has led to useful advances in the treatment of diarrhoea, although our understanding of the underlying mechanisms remains fragmentary. The well tried remedies such as chalk and kaolin and the opium alkaloids and their derivatives, which decrease intestinal ‘motility’, remain very valuable. We have selected the following topics for review since they have recently become growing points in our understanding of diarrhoea.

Acute Diarrhoea

Over 4 million working days were certified as lost through acute diarrhoea in England and Wales in the year 1966-1967, and the rate in the USA appears to be similar. Acute diarrhoea is usually mild and self-limiting, but may be dangerous in infants. Pathogenic organisms which can be demonstrated in only a minority of cases include enteropathogenic E. coli (as in recent serious infantile epidemics), non-invasive salmonellae, and Shigella sonnei. A preformed toxin is occasionally responsible. Enteroviruses, especially echoviruses, have been isolated in mild diarrhoea at a rate slightly higher than in control subjects, but there is as yet no conclusive proof that such viruses can cause acute diarrhoea.

Antibiotics are not generally indicated for acute diarrhoea in Great Britain, since they do not appear to shorten the illness and may prolong symptomless excretion of pathogens and encourage the emergence of resistant strains. This resistance can be transferred to previously susceptible enterobacteria.

In tropical countries, acute diarrhoea is more serious. Cholera, one of
the world's major fatal infections, may kill up to 60% of those infected, sometimes within four hours of the onset of symptoms. 

**MECHANISMS OF FLUID LOSS IN ACUTE DIARRHOEA**

Two main mechanisms have been held responsible for acute diarrhoea. 

1. Excessive secretion of water and electrolytes into the intestine stimulated by bacterial toxins: in these diseases, of which cholera serves as the model, the intestinal mucosa remains intact. 

2. Mucosal injury by bacteria resulting in inflammation, exudation of serum and blood, and impaired absorptive function as in bacillary dysentery.

**Cholera and related diarrhoeas**

Rapid advances in the understanding of intestinal fluid movements have come from the study of cholera in man and in animal models using the vibrio endotoxin, a protein with a molecular weight of about 90,000. Cholera is characterized by the rapid onset of diarrhoea with 'rice water' stools of low protein content. The patient may excrete more than a litre every hour and becomes dehydrated and acidotic. Despite its high mortality, the disease is self-limiting and effectively treated by the replacement of fluid and electrolytes.

Studies in patients with cholera show an imbalance between small intestinal mucosal secretion and absorption, leading to a great excess in the net secretion of water and electrolytes. The small intestinal mucosa appears structurally intact, even by electron microscopy. Colonic function remains normal, but its absorptive capacity is overwhelmed by the sheer volume of fluid presented to it.

Perhaps the most significant and at first sight surprising finding is that absorption of electrolytes, sugars, and amino acids remains unimpaired or nearly so. This suggests oversecretion rather than underabsorption as the cause of the diarrhoea, and in turn indicates a therapeutic approach. Since actively transported sugars and amino acids increase both the rate of sodium absorption and the flow of water out of the intestine, it should be possible to increase absorption and correct dehydration by the oral or intragastric administration of glucose-electrolyte solutions. This is in fact so, and the addition of glycine further increases the efficiency of the mixture.

The study of cholera has highlighted the secretory function of the intestinal mucosa. It has shown that secretion can be dissociated from absorption, and recent work suggests that secretion occurs mainly from the crypts and absorption through the villous tips. It has led to a search for the intimate control of these functions by mineralocorticoids, prostaglandins, and the cyclic AMP system. Lastly, recent advances in treatment have demonstrated how such experimentally derived information can be applied in practice.

These discoveries have led clinicians to consider the role of various other enterotoxins, such as those produced by *E. coli*, *Staph. aureus*, *Shigella dysenteriae*, and *Clostridium perfringens* in the pathogenesis of acute diarrhoea. *E. coli* diarrhoea can resemble cholera in several respects. (1) It may present with profuse, watery diarrhoea. (2) When it does so, the organisms colonize both small and large intestine without producing any gross mucosal damage. (3) Studies have shown net fluid secretion into the small bowel, but
not the colon, during the acute stages. Cell-free enterotoxin can reproduce the secretory flux in loops of animal bowel.

*E. coli* enterotoxin may be responsible for severe infantile enteritis\(^{48,49}\) and some forms of traveller's and acute tropical diarrhoea.\(^{46,47,50,51}\) Enterotoxin production has recently been demonstrated in strains of *E. coli* not previously classified as pathogenic by traditional methods of serotyping and biochemical taxonomy.\(^{46,50}\) The enterotoxin of *Clostridium perfringens* can also be shown to stimulate small-intestinal fluid secretion under certain conditions and resemble cholera exotoxin in its effect on adenyl cyclase activity.\(^{51}\) Unfortunately present methods of demonstrating enterotoxin production are not routine procedures, nor does animal pathogenicity prove pathogenicity for man.\(^{52}\)

**Acute mucosal damage**

In shigella dysentery, the large intestinal wall is invaded, becoming hyperaemic and sometimes ulcerated.\(^{53}\) The stools may contain blood and mucus, and in severe cases have a characteristic pea-soup appearance. Sonnei dysentery, the commonest in Great Britain, is usually a mild, short-lived disease. An enterotoxin has been demonstrated only in the more virulent shigella dysenteriae (shiga).\(^{54}\) A shigella-like dysentery can also be produced by some strains of *E. coli* which do not elaborate an enterotoxin.\(^{51}\)

Small bowel morphology in acute diarrhoea has rarely been studied and little is known about the ways in which mucosal damage produces diarrhoea.\(^{55}\) However, two recent studies have shown that when the small bowel is damaged by staphylococcal endotoxin,\(^{56}\) or by *Salmonella typhimurium*,\(^{57}\) there is an outpouring of fluid and electrolytes by the small intestine. In the last study, rats were infected with a strain isolated from a human infection. In those rats developing diarrhoea, net ileal secretion occurred. This was corrected by administering glucose-electrolyte solution in only half the animals, suggesting that, in contrast to cholera, absorptive mechanisms may be severely disrupted.\(^{58}\)

**Stagnant Loop Syndrome**

Bacterial contamination of the normally almost sterile upper small bowel\(^{59}\) may interfere with digestion and absorption of nutrients, leading to diarrhoea, steatorrhoea, and vitamin B\(_{12}\) deficiency.\(^{60,61}\) (This subject has recently been reviewed in this journal.\(^{62}\)) The cause of the diarrhoea is not fully understood. It is tempting to ascribe it to bacterial endotoxins, but there is no evidence for a direct effect of the contaminating organisms on the control of salt and water exchange. The suggestion by Dawson and Isselbacher in 1960\(^{63}\) that the steatorrhoea is due largely to degradation of bile salts has been supported by more recent work.\(^{64-71}\)

Metabolism of bile salts in the small bowel occurs only where conditions favour the growth of anaerobes, particularly bacteroides.\(^{71-74}\)

Bacterial deconjugation of bile salts can have the following consequences. (1) It reduces the concentration of detergent conjugated bile salts at the very site at which fat absorption normally takes place.\(^{70}\) (2) It increases the concentration of unconjugated bile salts. Some of these, such as deoxycholate, have been shown to have a toxic effect *in vivo* on mucosal structure\(^{77,78}\) and function,\(^{66,67,79,80}\) especially when the concentration of conjugated bile salts
is low. However, unconjugated bile salts are absorbed much more rapidly than conjugates from the upper small bowel, so that their relative concentration may fall towards the ileum. (3) Unconjugated bile salts have been shown to inhibit salt and water absorption in both the small and large bowel. They, or the bacteria themselves, also appear to interfere with the normal digestion and absorption of carbohydrates and other components of the intestinal contents.

The irritant and osmotic effects of organic acids derived from bacterial breakdown of carbohydrate and fat in preventing water and salt absorption remain to be evaluated. The hydroxy fatty acid ricinoleic acid is thought to be responsible for the purgative effect of castor oil. The calcium soaps of hydroxy fatty acids and the calcium salts of certain bile salts are insoluble, and it has been claimed that feeding calcium bicarbonate relieves the diarrhoea of small bowel resection.

It is not yet clear to what extent diarrhoea and malabsorption are due to a reduced concentration of conjugated bile salts, toxicity of their bacterial metabolites, or a direct effect of bacteria on the mucosa.

Treatment with conjugated bile salts has been shown to reduce steatorrhoea, but not diarrhoea. Steatorrhoea, therefore, seems to depend primarily on an effect of the bacteria on the intraluminal contents. Effective treatment of the diarrhoea consists in removing the bacteria, either with the appropriate antibiotic or by resecting the stagnant segment.

Humoral Agents in Diarrhoea

Intestinal motility, absorption, and secretion are influenced by hormones and by mediators at the cellular level, such as cyclic AMP. For instance, thyroid hormones increase intestinal motility and transit rate, administration of cholecystokinin increases small bowel motility, diarrhoea occurs in adrenal failure, while mineralocorticoids increase salt and water absorption from the colon. Indeed aldosterone secretion may be increased by the loss of sodium in diarrhoea. The balance between the biochemical regulators is clearly complex, but study of certain endocrine abnormalities has demonstrated their importance in the control of intestinal function.

ZOLLINGER-ELLISON SYNDROME

Diarrhoea is sometimes a prominent feature of this syndrome. While the abnormally high gastrin levels increase the volume of gastric secretions, the most important cause of diarrhoea and steatorrhoea is the increased acidity of the intestinal contents. This leads to defective lipolysis because of irreversible inactivation of lipase and precipitation of bile salts. Small intestinal absorption of water and electrolytes is impaired, and the jejunal mucosa may show defective fatty acid esterification and amino-acid uptake. Mucosal structure may be altered to the extent of villous atrophy and gastric metaplasia, although this probably contributes little to the diarrhoea.

Non-beta pancreatic islet-cell tumours may also be associated with the syndrome of watery diarrhoea, hypokalaemia, and usually diminished gastric acid secretion. The role of hormones in this syndrome has been the subject of much speculation, but resection of the tumour, as in the Zollinger-Ellison
syndrome, cures the diarrhoea.\textsuperscript{106–115} Intestinal transit times appear to be normal.\textsuperscript{116} Pancreatic hypersecretion and loss of normal water and electrolyte conservation by the small bowel have been produced by the administration of large doses of either secretin, glucagon, or both,\textsuperscript{117} but neither hormone has been identified unequivocally from the tumour. Whatever the agent, high doses of corticosteroid appear to have a beneficial effect on the diarrhoea.\textsuperscript{110} This is also unexplained.

**Carcinoid Syndrome**

In this syndrome the diarrhoea, unlike the other features, seems to be directly due to serotonin. Serotonin stimulates small bowel motility but has a predominantly relaxant effect on colonic smooth muscle.\textsuperscript{118} Diarrhoea may therefore result from an increased intestinal flow rate due to a decrease in the intraluminal resistance of the colon. The serotonin antagonists, methysergide and parachlorophenylalanine, are often successful in relieving ‘carcinoid’ diarrhoea, but their effect is confined mainly to relief of gastrointestinal symptoms.\textsuperscript{119,120} Since patients with this syndrome may have had an ileal tumour resected, cholerrhoeic enteropathy sometimes contributes to the diarrhoea (see below).

In spite of the usefulness of methysergide and parachlorophenylalanine in resistant diarrhoea, the standard antidiarrhoeal drugs are often adequate and safer.

**Medullary Carcinoma of the Thyroid**

The diarrhoea which occurs in a third of patients with this carcinoma\textsuperscript{121} has aroused special interest since the discovery that these tumours sometimes secrete prostaglandins.\textsuperscript{122} Prostaglandins stimulate smooth muscle and normally occur within the gut wall. They are released from the gastrointestinal tract during peristaltic activity,\textsuperscript{123} and when type E\textsubscript{1} is fed in large doses it produces diarrhoea.\textsuperscript{124} The diarrhoea in these patients is associated with abnormally rapid intestinal transit but malabsorption of glucose, xylose, and fat does not usually occur.\textsuperscript{125} Prostaglandins might play a role in increasing gastrointestinal motility,\textsuperscript{126} or in influencing small bowel secretion,\textsuperscript{44} depending on the type of prostaglandin, but the links in the chain are still incomplete and their precise role in producing the symptoms remains uncertain.

**Cyclic AMP**

Many hormone actions on a variety of tissues are transmitted through an intermediate messenger, cyclic 3' 5'-AMP. The level of this substance can be augmented either through increase in activity of adenylyl cyclase, which catalyses its synthesis from ATP, or by depressing the activity of the phosphodiesterase which degrades cyclic AMP to 5'-AMP.

Cholera and certain prostaglandins increase adenylyl cyclase activity in the gut wall.\textsuperscript{44,45} Experimentally, cyclic AMP increases the net secretory flux of electrolytes and water in a way similar to that which occurs in cholera. Cholera toxin can produce its effect on the gut even when the vibrio is introduced into a remote segment connected to the rest of the bowel only by its blood supply.\textsuperscript{127} This all suggests that the toxin acts via some humoral agent,
most probably mediated by this messenger system. Possibly other bacterial enterotoxins will be shown to act through the same system.

**Osmotic Diarrhoea and Disaccharidase Deficiency**

Absorption of dietary carbohydrate depends on the presence of disaccharidases in the intestinal brush border of the absorptive cells at the villous tips.\textsuperscript{128,129} Deficiency of one or more of these enzymes leads to osmotic attraction of water by the unabsorbed disaccharides in the gut lumen.\textsuperscript{130} This isotonic sugar solution necessarily has a lower sodium concentration than the plasma,\textsuperscript{131} and the upper small bowel cannot absorb sodium from luminal concentration of less than 90 mM.\textsuperscript{6,34} Water absorption depends on the absorption of sodium and sugar which are themselves interdependent,\textsuperscript{5,122} Since these are both impaired, it is clear that water will accumulate in the intestine, distending it, causing abdominal bloating and cramps, probably accelerating transit rate, and thereby reducing the time for the more powerful ileal sodium pump to act. Perfusion studies on patients with lactase deficiency and diarrhoea have shown net secretion of fluid and increased transit rate in the small bowel.\textsuperscript{181,183} The effect on large bowel function is considered below.

Treatment consists in avoiding the appropriate carbohydrate and this depends on the type of disaccharidase deficiency. The commonest type is alactasia,\textsuperscript{134} which when severe enough to produce diarrhoea, may require reduction of milk and dairy products. For this reason the distribution of dried milk to combat malnutrition in the poorer parts of Africa and Asia, where inherited lactase deficiency is common, may result in diarrhoea and abdominal cramps in those past infancy.\textsuperscript{135} Malnutrition itself may increase intolerance to milk.\textsuperscript{136}

Disease of the intestinal cell such as occurs in coeliac disease,\textsuperscript{137,138} tropical sprue,\textsuperscript{189,190} and temporarily after most acute infective diarrhoeal illnesses\textsuperscript{141,142} can result in deficiency of brush border disaccharidases which may contribute to the diarrhoea. Of the seven known disaccharidases, lactase 1 activity is the first to disappear,\textsuperscript{137} and restriction of dairy produce occasionally lessens the symptoms.

**Influence of Small Bowel Disease on Colonic Absorption**

Clearly the severity of diarrhoea in disorders of the upper gastrointestinal tract depends on the ability of the colon to absorb the water which flows into it. Colonic absorption has recently been reviewed in this journal\textsuperscript{143} and elsewhere.\textsuperscript{144} The colon normally absorbs about 0.5 to 1.5 litres of water in 24 hours, leaving only 20-150 ml in the faeces\textsuperscript{145} of people taking a 'western' type diet.\textsuperscript{146} The capacity of the colon to compensate for failure of small intestinal absorption depends on the composition and quantity of the ileal effluent and on how long the faecal stream remains in the colon.\textsuperscript{148} With faecal losses of over 3 litres a day, the colon is scarcely able to alter the composition of what flows through it.\textsuperscript{147,148}

The osmotic effect of unabsorbed solute on the small bowel is often augmented in the large bowel by bacterial breakdown of the molecule into several smaller fragments which are themselves poorly absorbed. This occurs in alactasia which, particularly in children, may lead to an acid diarrhoea due to bacterial breakdown of lactose to lactic and other organic acids.\textsuperscript{149}
Since the colonic sodium pump is very powerful, net water secretion does not occur. However, the osmotic attraction of lactose and its metabolites greatly impairs absorption and water loss closely parallels the excretion of organic anion. This mechanism is used therapeutically in hepatic encephalopathy, where acidification of the colonic contents prevents the absorption of ammonia. Since these patients generally have normal jejunal lactase levels, a synthetic keto-analogue of lactose, lactulose, is used, for which no mucosal disaccharidase exists. Magnesium sulphate, which is poorly absorbed, is another example of an osmotic purgative in general use.

It has recently been shown that diarrhoea can result from the entry of increased amounts of bile salts into the colon. Bile salts have long been recognized as purgatives and still appear in many proprietary laxative mixtures. Endogenous bile salts may have this effect in ileal disease or after ileal resection, when the enterohepatic circulation of bile salts is interrupted. It is estimated that normally 15-30 g of bile salts passes through the small bowel daily as a result of the repeated cycling of a bile salt pool of approximately 2-4 g. Daily faecal loss amounts to only 0-4 to 0-8 g. In the absence of the specific bile salt reabsorptive mechanism which is confined to the terminal ileum, at least 90% of the bile salt pool is lost into the faeces during the digestion of a single meal. Ileal disease or resection has two consequences: there is a dearth of detergent bile salt passing down the small bowel resulting in steatorrhoea, and an excess of unabsorbed bile salt in the colon causing diarrhoea. The first is due to the depletion of the bile salt pool, so that the bile salt perfusing the small bowel is only that quantity which the liver can synthesize anew from cholesterol, 2-4 g daily, instead of the normal 15-30 g. This is insufficient to produce the mixed micelles necessary for normal fat absorption. However, this 2-4 g now also passes through the large bowel instead of the normal 0-4-0-8 g. Bile salts inhibit salt and water absorption by the colon, especially when they have been deconjugated by colonic bacteria. Following ileal resection, patients may therefore develop a severe bile salt-induced watery diarrhoea called ‘cholerrhoeic enteropathy’, which is more troublesome than the steatorrhoea. Feeding bile salts makes the diarrhoea worse, but cholestyramine, an anion-exchange resin which binds bile salts and protects the colon from their action, relieves the diarrhoea at the expense of some increase in steatorrhoea. It is most effective when less than 100 cm of terminal ileum has been resected and when steatorrhoea does not exceed 20 g daily. The place of lignin, a fibre derived from pinewood, is more uncertain. Its interest lies in its presence in vegetable fibre and in its ability to adsorb certain bile salts, and it has been claimed to be of value in treatment. However, lignin has recently been shown to be less effective than cholestyramine in cholerrhoeic enteropathy and it has little effect on the enterohepatic circulation of taurocholate.

Cholestyramine does not improve tropical diarrhoea, nor the diarrhoea of ulcerative colitis, so that bile salt catharsis does not appear to be a factor in these diseases.

**Disorders of Gut Motility**

A large number of different techniques have thrown light on the electrical
activity of intestinal smooth muscle, on its pharmacology, and on pressure changes and movement of markers within the lumen.174–179 Nevertheless few studies have combined these techniques to give a useful overall picture of how different types of diarrhoea are related to abnormalities of muscular activity and its control.174,180 Evidence that altered small intestinal transit by itself causes diarrhoea is mostly indirect.180,181 Steatorrhoea may accompany the increased transit rate in thyrotoxicosis,94 small bowel resection, and osmotic diarrhoea,182,183 and this may be evidence that the small intestine’s large reserve capacity has been exceeded. After massive small bowel resection, interposition of a reversed segment of bowel can sometimes slow transit sufficiently to diminish the diarrhoea.184 A similar technique has been used successfully for the puzzling diarrhoea that may follow vagotomy.185 Faecal loss of water and electrolytes after massive resections can also be diminished by substituting medium-chain triglycerides for most of the dietary fat.186 These are well absorbed, even in the absence of bile salts, by a different route than long-chain fats.187 This does not, however, fully explain their efficiency in reducing diarrhoea.

Decreased motility may cause the stagnant loop syndrome, as in systemic sclerosis,188 and in a small proportion of patients with diabetic diarrhoea.189–192 Faeces normally remain in the colon for from one to several days,179 but this is reduced by a high-residue diet.146,193 Most of the saccular colon’s muscular activity is segmental, churning the contents but moving them for only short distances.194 Propulsive movements occur infrequently, stimulated especially by physical activity.195 They consist of a series of mass movements, which shift a column of faeces three or four times a day over the length of about a third of the colon in the space of a few seconds, preceded by the sudden disappearance of haustral segmentation.196 The commonest cause of chronic diarrhoea is the irritable bowel syndrome, generally considered a psychosomatic disorder in which the various symptoms result from disordered motility.197 Consequently this aspect has been much studied.198–203 Diarrhoea is usually associated with reduced segmental contraction, thus offering less resistance to forward flow. There is also an abnormality in the emptying of ileal contents into the colon.201 In ulcerative colitis intraluminal pressures are also low,198,202,204 but the relationship between impetus to the faecal stream and generation of pressure in the lumen is altered by the fluidity of the faeces, and the change in tone which results in the characteristic ‘hose-pipe’ colon.199

Increased fluidity of the faeces itself seems to accelerate gastrointestinal transit.182 In one study it was reduced from 26 hours in controls to 4-6 hours in patients with osmotic diarrhoea induced by mannitol and 5-6 hours in cholerrhoeic enteropathy.188 The rationale of standard antidiarrhoeal therapy is post hoc. Morphine and its derivatives increase rhythmic segmentation of the small intestine and haustral contraction of the colon. In electrophysiological terms, they cap almost every pacemaker potential by spike discharges and a muscular contraction. In effect they stir the contents and foster absorption but do not empty the gut.205 Kaolin and the hydrophilic colloids may also act to increase resistance to flow by solidifying the colonic contents. Bed rest decreases the effect of gravity and also reduces the propulsive movements stimulated by physical activity.
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Much has been done to try to correlate psychological stress with neuromuscular activity. While there can be no doubt of the great clinical importance of central nervous activity, present research techniques have not yet given consistent and predictable results.

Chronic Colonic Disease

The profuse watery diarrhoea of ulcerative colitis is due in part to exudation through the damaged colonic mucosa, since the faeces contain pus and blood, and in part probably to impairment of colonic water and salt absorption. However, the role of exudation has been thought to be limited, since bypass of the diseased colon reduces colonic fluid loss considerably. There have long been suggestions that small intestinal dysfunction may constitute part of the extracolonic manifestations of the disease, and contribute to the diarrhoea. Indeed Truelove’s group, who have shown non-specific histological and histochemical abnormalities in the small intestinal mucosa of some patients with acute total colitis, have also shown that colonic sodium absorption may be very efficient in this disease. It is of particular interest, therefore, that a recent perfusion study has shown diminished jejunal absorption and even net secretion of water, sodium, and chloride in ulcerative colitis. Patients treated with corticosteroids did not show this defect. Jejunal absorption was much increased by adding glucose to the perfusate, raising the possibility that in untreated colitis, as in cholera, jejunal secretion is increased but absorptive capacity is retained. Thus a cholera-like syndrome has been added to abnormalities of colonic absorption, intestinal motility, lactase deficiency, and milk allergy as explanations of the diarrhoea in ulcerative colitis.

Coeliac Disease

Several of the mechanisms which have been described above probably operate to produce diarrhoea in coeliac disease. With destruction of the villi in the upper small bowel, carbohydrate absorption is impaired. This in turn should lead to inefficiency of the sodium pump. Since carbohydrate and sodium absorption are together the main stimuli to water absorption, this is likely to be impaired. This will be further compounded by the osmotic attraction of water by unabsorbed solute. Moreover coeliac disease is associated with hypertrophy of the crypts of Lieberkühn, which recent work suggests are the major source of intestinal fluid. Perfusion studies clearly show net jejunal secretion of water and sodium and, as expected, this is not reversed by adding glucose to the perfusate. In addition to these mechanisms, the permeability of the jejunum to solute has been shown to be reduced so that the resistance to sodium passing through the mucosal ‘pores’ is increased. All these abnormalities in intestinal function diminish lower in the bowel. The colon reabsorbs more water than normal, but its capacity is exceeded and diarrhoea results.

Conclusion

Until comparatively recently diarrhoea was considered merely as a symptom of a variety of diseases, and thought of in terms of malabsorption of food-
stuffs, overactivity of intestinal musculature, and colonic infection. In 1941 Florey predicted that an understanding of the important factors in the control of intestinal secretion might clear the fog surrounding many aspects of the pathology of the intestine, and in 1944 Visscher and his colleagues showed that intestinal absorption is the resultant of a massive two-way traffic of water and electrolytes across the mucosa. Much more attention has recently been paid to alterations in the balance of this traffic, especially in the small bowel. In cholera, acute enteritis, the stagnant loop syndrome, chlorellhioeic enteropathy, and brush border enzyme deficiency this has resulted in improvements in treatment. Nevertheless many important problems remain.

The relationship of small intestinal bacteria and mucosal damage to altered fluid exchange seems to have eluded analysis in tropical sprue: patients with similar degrees of mucosal damage or bacterial colonization may or may not have symptoms; treatment with antibiotics may remove symptoms without improving histological appearances. Lastly, until a satisfactory method is found for investigating the many patients with the irritable bowel syndrome, treatment will have to remain largely symptomatic.

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