

answered. In this communication we have been able merely to outline the problems involved and the progress made towards solving some of them. It is evident that this is still a new field of study which can make a contribution to the understanding not only of gastroenterological but also of general medical and pharmacological problems.

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Absorption and secretion by the colon

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Various aspects of colonic absorptive function in man have been dealt with in a number of reviews (Phillips, 1969; Turnberg, 1970; Wrong, 1971; Shields, 1972; Sladen, 1972; Edmonds and Pilcher, 1972).

Electrolytes and Water

The role which the colon plays in conserving water and electrolytes has been known for some time,

deduced largely from a comparison of the volume and composition of ileostomy effluent with that of faeces and confirmed by perfusion of the colon *in vivo*. The quantity of these substances absorbed daily by the colon has, however, to be revised, since it has been shown that the flow of ileal contents into the colon each day is three times the normal volume of ileostomy effluent (Kanaghinis, Lubran, and Coghill, 1963; Phillips and Giller, 1973). Fasting ileal flow rates, measured by slow intestinal

perfusion techniques, have been reported by several groups and vary between 0.3 and 1.6 ml/min (Soergel, 1971; Phillips and Giller, 1973; Rask-Madsen, 1973; Cummings, Milton-Thompson, Billings, Newman, and Misiewicz, 1974). After meals the flow rate in the ileum peaks to 4-8 ml/min giving an overall flow into the colon of 1500 ml/day. The electrolyte composition of ileal contents varies little in health and is very similar in those diarrhoeal diseases where ileal flow has been shown to increase (Banwell, Pierce, Mitra, Brigham, Caranasos, Keimowitz, Fedson, Thomas, Gorbach, Sack, and Mondal, 1970; Banwell, Gorbach, Pierce, Mitra, and Mondal, 1971). The exceptions to this are congenital chloridorrhoea (Turnberg, 1971; Pearson, Sladen, Edmonds, Tavill, Wills, and McIntyre, 1973) and the Cronkhite-Canada syndrome (Johnson, Soergel, Hensley, Dodds, and Hogan, 1972) where bicarbonate concentrations are reduced.

When the daily load of water and electrolytes delivered to the colon is compared with their faecal excretion it is apparent that the normal colon absorbs 1350 ml water, 200 m-equiv sodium, 150 m-equiv chloride, and 60 m-equiv bicarbonate each day. The amount of potassium entering and leaving the colon each day is about equal.

Sodium, the main cation entering the colon, is absorbed by active transport and is responsible for the large electrical gradient across the mucosa (Edmonds and Pilcher, 1972). Using colonic perfusion (Levitan, Fordtran, Burrows, and Ingelfinger, 1962; Shields and Miles, 1965; Devroede and Phillips, 1969) and other techniques, the colonic mucosa has been shown to absorb sodium from luminal concentrations as low as 15 m-equiv/l and against a potential difference of 40 mV (luminal side negative). Unlike in the jejunum, sodium absorption in the colon is not stimulated by glucose (Powell and Malawer, 1968; Billich and Levitan, 1969), bicarbonate (Devroede and Phillips, 1969) or amino acids (Grady, Duhamel, and Moore, 1970). Whilst active transport is the major pathway for sodium absorption it is possible that sodium movements may be coupled to hydrogen ion secretion as in the ileum (Turnberg, Bieberdorf, Morawski, and Fordtran, 1970) or that coupled non-electrogenic transport may occur (Binder and Rawlins, 1972). However, the failure of the luminal pH to fall during colonic perfusion studies where chloride has been replaced by sulphate is against the existence of a Na^+/H^+ exchange although faecal pH falls when sodium sulphate is taken by mouth (Down, Agostini, Murison, and Wrong, 1972; Bown, Sladen, Rousseau, Gibson, Clark, and Dawson, 1972).

Movement of water in the colon is passive and occurs in response to solute transport. As sodium is

the main cation it closely parallels sodium movements. When net sodium transport is zero water absorption is minimal (Devroede and Phillips, 1969). This close relationship holds also during secretion into the colon induced by bile salts (Wingate, Krag, Mekhjian, and Phillips, 1973) and villous adenoma of the colon (Duthie and Atwell, 1963).

Potassium movements are mainly passive, occurring in response to electrochemical gradients. Potassium is secreted into isotonic saline solutions perfused through the colon (Levitan *et al*, 1962) and absorbed from perfusate containing more than 15 m-equiv/l of potassium (Devroede and Phillips, 1969). Edmonds and Godfrey (1970), on the basis of electrolyte movements and pd measurements in the rectum, suggest that there is also an active component to potassium movements, although Giller and Phillips (1972), after measuring right colonic pd during perfusion experiments, say that potassium movement is passive and entirely predictable from the pH using the Nernst equation. The various regions of the colon appear to handle potassium differently and this may be explained by the greater permeability of the proximal colon compared with that of the rectum (Billich and Levitan, 1969; Edmonds and Pilcher, 1972). Increased secretion of potassium into the colon was noted during perfusion of low pH solutions, which may alter permeability (Bown *et al*, 1972). The more restricted permeability of the distal colon and rectum may in part explain concentrations of potassium of up to 140 m-equiv/l that occur in normal stool water (Wrong, Metcalfe-Gibson, Morrison, Ng, and Howard, 1965).

Strong evidence exists for a chloride-bicarbonate exchange system in the colon as occurs in the ileum. Chloride is absorbed from luminal solutions containing as little as 25 m-equiv/l (Devroede and Phillips, 1969). More chloride than sodium is absorbed from equimolar solutions and the difference can invariably be accounted for by bicarbonate secretion. Replacement of chloride by sulphate in the perfusate inhibits bicarbonate secretion, and increased chloride absorption occurs at low luminal pH, where bicarbonate secretion should be stimulated (Bown *et al*, 1972). Bicarbonate is secreted into the colon against electrochemical gradients. The role of carbonic anhydrase in this anion exchange in man is not clear but in several animal species this enzyme is present in high concentration in the caecum and right colon (Kuriaki and Magee, 1964; Maren, 1967; Carter and Parsons, 1968).

As already noted, regional differences in colonic function exist. Sodium flux rates in both directions in the rectum are reduced compared with data derived from colonic perfusion work (Edmonds

and Pilcher, 1972), and, whilst the rectum is able to absorb salt and water, it is only at a reduced rate (Edmonds, 1971; Rask-Madsen, Hammersgaard, and Knudsen, 1973). Furthermore the response of the colon to aldosterone differs between the left and right sides (Edmonds and Marriott, 1967). Devroede, Phillips, Code, and Lind (1971), measuring sodium insorption (mucosa-to-serosa flux), have shown that this is most rapid in the caecum and decreases progressively towards the rectum. This concept of regional differences finds some backing in clinical experience. In a review of colonic surgery by Gazet (1968) patients with right hemicolectomies were six times more likely to have significant diarrhoea subsequently than those who had a left hemicolectomy even after taking into account those with previous ileal disease.

Various hormones influence colonic electrolyte handling. Aldosterone stimulates colonic sodium and water absorption in a manner analogous to its effect on the renal tubule, although the colon does not 'escape' from this effect as does the kidney (Levitan and Ingelfinger, 1965; Wrong, 1968; Charron, Leme, Wilson, Ing, and Wrong, 1969). Patients with primary hyperaldosteronism have decreased Na/K ratios in their stools (Richards, 1969), and the increase in rectal pd found in these patients, due to stimulation of sodium transport, has been used as a screening test in the diagnosis of this condition (Edmonds and Richards, 1970). Shields, Mulholland, and Elmslie (1966) and Shields, Miles, and Gilbertson (1968) have also demonstrated potassium secretion by the colon with aldosterone. Spirolactone blocks the effects of aldosterone (Elmslie, Mulholland, and Shields, 1966; Edmonds and Pilcher, 1972) whilst 9α -fluorohydrocortisone also stimulates salt and water absorption (Levitan, 1967). Some doubt exists as to whether the other adrenal cortical hormones effect the colon (Duthie, Watts, de Dombal, and Goligher, 1964) but patients with raised plasma cortisol levels have decreased faecal Na/K ratios (Charron *et al*, 1969; Richards, 1969). Angiotensin at low concentrations stimulates colonic sodium absorption (Davies, Munday, and Parsons, 1970; Hornych, Meyer, and Milliez, 1973) and Parsons and Munday (1972) have made a strong case for its role in normal colonic sodium metabolism. By contrast, antidiuretic hormone, when given to well hydrated subjects at 1 unit per hour, decreased salt and water absorption (Levitan and Mauer, 1966), and *in vitro* increases short-circuit current (Grady *et al*, 1970). Unlike their effect on the small intestine, both pentagastrin (Gingell, Davies, and Shields, 1968) and prostaglandin $F_{2\alpha}$ (Cummings *et al*, 1974) fail to alter colonic electrolyte handling whilst little is known about the effect of

other hormones on this part of the gut. What is known has been reviewed by Matthy and Noble (1972).

In a wide variety of diarrhoeal diseases faecal sodium concentration correlates very closely with faecal output (unpublished observations) reflecting the same close correlation found in colonic perfusion studies. Colonic absorptive function has been investigated in only a few such diseases, mainly ulcerative colitis and Crohn's disease. In these inflammatory diseases there is agreement that both the colon and rectum show a reduced capacity to absorb sodium and water (Duthie *et al*, 1964; Levitan and Brudno, 1967; Head, Heaton, and Kinel, 1969; Rask-Madsen, 1973; Edmonds and Pilcher, 1973). Increased potassium secretion also occurs (Archampong, Harris, and Clark, 1972; Harris and Shields, 1970). It is not yet clear whether this impaired ability to absorb sodium is due to a defect in the sodium 'pump', thus diminishing sodium insorption, or to increased mucosal permeability, or both. In studies of villous adenoma of the colon sodium secretion into the colonic lumen has been shown, suggesting that these tumour cells are different from the normal colonic mucosa (Duthie and Atwell, 1963; Shields, 1966). In chloridorrhoea chloride malabsorption both in the ileum and colon is the primary defect due to a failure of the Cl/HCO₃ exchange (Turnberg, 1971; Pearson *et al*, 1973; Bieberdorf, Gorden, and Fordtran, 1972). Increased sodium and water output are due to trapping of sodium in the colonic lumen by the chloride ion, with ammonium and hydrogen ion making up the cation deficit that occurs.

Urea, Ammonia, and Nitrogen Metabolism

Daily urea synthesis exceeds urea output in the urine by about 20%. The difference is due to breakdown of urea in the intestine (Walser and Bodenlos, 1959). After the administration of intestinal antibiotics urea synthesis approximates more closely to urinary urea loss (Jones, Smallwood, Craigie, and Rosenoer, 1969). Thus between 6 and 9 g of urea, that is about 20% of daily urea synthesis, is catabolized in the gut each day. This process is thought to occur mainly in the colon and is due to the colonic microflora. The maximum amount of urea entering the colon each day from the ileum is about 0.4 g (Gibson, Sladen, and Dawson, 1973) and as there is no urea in faeces and only 1-3 m.mol of ammonia, its main metabolite (Wrong *et al*, 1965), almost all the 6-9 g of urea must be secreted into the colon each day, metabolized, and the metabolites absorbed. The capacity of the colon to absorb urea is minimal (Billich and Levitan, 1969; Wolpert, Phillips, and

Summerskill, 1971). Urea is hydrolysed in the colonic lumen to ammonia and carbonic acid by bacterial urease, and this process may be inhibited by antibiotics (Evans, Aoyagi, and Summerskill, 1966; Wilson, Ing, Metcalfe-Gibson, and Wrong, 1968). Very little colonic mucosal urease activity is present in man (Aoyagi, Engstrom, Evans, and Summerskill, 1966) and its role in urea hydrolysis is probably small. Urea hydrolysis occurs in a juxtamucosal situation, as intravenously administered urea is metabolized more rapidly than urea perfused through the colonic lumen (Wolpert *et al.*, 1971). The relative impermeability of the colonic mucosa to urea raises the possibility that small intestinal ureolysis may be important. Gibson *et al.* (1973) have shown that urea breakdown in man continues in only slightly reduced amounts in ileostomists, and it is considerably increased in the stagnant loop syndrome (Jones *et al.*, 1969). The small gut is much more permeable to urea than the colon and has slightly higher mucosal urease activity (Aoyagi *et al.*, 1966).

If the colon is the main site for urea catabolism then 6-9 g of urea will give rise to 200-300 m.moles of ammonium and half as much bicarbonate each day. Ninety-nine per cent of the ammonia is absorbed across the mucosa by simple non-ionic diffusion (Castell and Moore, 1971; Bown, Sladen, Clark, and Dawson, 1971; Down *et al.*, 1972). At colonic pH (6.0-7.0) ammonia is present largely as the ammonium ion NH_4^+ which may itself be absorbed when present at very high concentrations (Bown *et al.*, 1971). Supportive evidence for the non-ionic diffusion of ammonia comes from the close relationship between pH and ammonia absorption during colonic perfusion experiments and in the faeces (Down *et al.*, 1972). As luminal pH falls so does ammonia absorption whilst faecal ammonia excretion rises as faecal pH falls. Wrong (1971) has suggested that ammonia absorption proceeds by coupled non-ionic diffusion in which bicarbonate and ammonium ions form ammonia and carbon dioxide which then diffuse freely across the mucosa, leaving no net change in either pH or ionic balance. The presence of bicarbonate in the colonic lumen facilitates ammonia absorption. Other parts of the gut handle ammonia in a similar way (Summerskill, 1970). In the hamster an active transport process may be present (Mossberg and Ross, 1967) although it is disputed (Price, Schwartz, Molavi, Britton, and Voorhees, 1967).

Microbial metabolism of urea is of major importance in animal nutrition (Stangell, 1967; Salter, 1973) but much less so in human nutrition. The absorbed ammonia is transported to the liver where it enters the nitrogen pool and is available for urea or amino acid synthesis. Ammonia is a more efficient

source of nitrogen than urea for protein synthesis so that colonic metabolism of urea is an important step (Richards, 1972). When dietary protein is plentiful the contribution from non-protein nitrogen to protein synthesis is very small (Richards, Metcalfe-Gibson, Ward, Wrong, and Houghton, 1967) but this may increase to significant amounts and enable nitrogen balance to be maintained in malnutrition (Picou and Phillips, 1972) or during protein-restrictive regimes in uraemia (Richards *et al.*, 1967). The enterohepatic circulation of urea and ammonia is also of importance in the genesis of hepatic encephalopathy in liver disease.

Organic Anion and Volatile Fatty Acids

Organic anion is the major solute in faeces. Normal stools contain around 179 m-equiv/l (Rubinstein, Howard, and Wrong, 1969), an amount which far exceeds the concentration of any other compound. It is measured by titration in a similar way to that of organic anion in urine (Van Slyke and Palmer, 1920) and represents all the buffering between pH 2.7 and 8.0, except that due to bicarbonate and phosphate. The anions which make up this major fraction of faeces have never been completely identified. The short-chain, or volatile, fatty acids (VFA), acetate, propionate, butyrate, etc, make up about 47%, and a further 3% is made up of small quantities of a number of anions such as fumarate, lactate and succinate. The composition of the remaining 50% is unknown. The volatile fatty acids, of which acetate comprises about 60%, are thus the major known component of organic anion and are important in colonic metabolism.

Only 1-3 m-equiv/l of volatile fatty acids are found in ileal fluid (Newton, Bennett, Billings, and Milton-Thompson, 1972) whilst normal faeces contain 80-90 m-equiv/l. In patients with diarrhoea volatile fatty acid output may rise to 160 m-equiv per day (Grove, Olmsted, and Koenig, 1929; Cummings, James, and Wiggins, 1973). They arise in the colon mainly from bacterial metabolism of unabsorbed dietary residues. Reduced amounts are found in the faeces after antibiotics and in 'germ-free' studies (Gompertz, Brooks, Gaya, and Spiers, 1973; Rubinstein *et al.*, 1969). Diffusion through the colonic mucosa and other bacterial metabolism may contribute a small amount. How much volatile fatty acid is produced in the colon each day is unknown but it is almost certainly in excess of that found in the faeces. The metabolism of 10 g of dietary fibre, such as was observed by Southgate and Durnin (1971) in young men eating a diet containing wholemeal bread, could alone give rise to over 100 m-equiv of acetate per day.

Volatile fatty acids have three possible fates in the colon. About 12 m-equiv is excreted in the faeces each day, some may be metabolized by bacteria to H_2 , CH_4 , H_2O , and CO_2 and some, possibly the largest proportion, are absorbed. In herbivores such as the rabbit the absorption of volatile fatty acids from the colon and caecum represents for them a major source of energy. Up to 22% of the rabbit's basal energy requirements come from absorbed volatile fatty acids, whilst the porcupine is able to absorb 83% produced in the caecum and 64% entering the colon (McBee, 1970). However, caecal pH is lower in herbivores than in man and absorption of volatile fatty acids in man has received only scant attention. Volatile fatty acids are absorbed in man in both the colon and small intestine by non-ionic diffusion. The rate of absorption is slow and dependent on the carbon chain length of the compound and the ambient pH (Dawson, Holdsworth, and Webb, 1964; Sallee and Dietschy, 1973). Longer chain length and low pH favour absorption. Active transport of volatile fatty acids (Smyth *et al*, 1957) is not now thought to occur but the availability of H^+ may be important (Clarkson, Rothstein, and Cross, 1961). Volatile fatty acids in the rat colon stimulate salt and water absorption (Parsons, 1967). The contribution of absorbed volatile fatty acids to energy balance in man is small but may reach significant proportions where dietary fibre intake is high.

The increased excretion of organic anion and volatile fatty acids in diarrhoea has led to the suggestion that they play a major role in determining stool bulk (Fernandez, Gonzalez, Marzi, and Paolo, 1971; Torres-Pinedo, Lavastida, Rivera, Rodriguez, and Ortiz, 1966; Fordtran, 1971). The pK of the VFA is about 4.8 which means that at colonic pH they are virtually all present in the dissociated form. As absorption of such charged water-soluble molecules is very limited they will tend to accumulate in the lumen and cause an osmotic diarrhoea. However, the concentration of volatile fatty acids in the stools falls with increasingly severe diarrhoea, probably due to decreased colonic transit time in these patients allowing less time for their production (Cummings *et al*, 1973). It seems unlikely that the role of volatile fatty acids in diarrhoea in adults is anything other than passive.

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