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Intestinal Absorption and Secretion

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Transmucosal passage of inert molecules in health and disease

I.S. MENZIES

Absorption from the healthy intestine is highly selective. Intestinal transport systems have affinity for nutrients such as sodium, amino acids and D-glucose which are absorbed at rates far greater than would be expected for unmediated diffusion. 'Inert molecules', those without mediation or other biochemical involvement, pass across the absorptive surface at much slower rates, determined largely by concentration gradient, time, and area of exposure, but also by the permeability of the intestinal mucosa. The latter demonstrates marked discriminatory features with respect to molecular dimension and solubility which become impaired in diseases associated with mucosal damage.

'Inert molecules' suitable for use as probe-markers of transmucosal permeation have the following applications.

(1) Clinical investigation of intestinal permeability, for diagnostic purposes and to monitor therapy.

(2) As 'internal markers' to overcome the effect of irrelevant variables for oral and tube-perfusion test procedures involving the principle of differential absorption (see Figure 45.1).

(3) Research applications, in particular: to identify drugs and dietary constituents that might damage the intestine, and to investigate the absorption of substances, such as antigens, of medical significance.

Progress in the study of intestinal permeability has been limited by the considerable technical difficulty of its measurement. Some of the problems
Figure 45.1 The principle of 'differential absorption'. Simultaneous administration of two test markers, A and B, chosen to respond in an identical way to each variable except that selected for investigation, provides a non-invasive method for studying specific aspects of intestinal function. When correctly devised, the A/B excretion ratio (of the percentages recovered in the urine) provides a specific index of the state of the function selected for investigation, remaining unaffected by the other variables enumerated

which complicate 'in vivo' estimation of human intestinal permeability are discussed in relation to the various techniques available, especially the choice of probe-marker, influence of osmotic factors and interpretation of the changes associated with intestinal disease.

METHODS EMPLOYED FOR ASSESSING HUMAN INTESTINAL PERMEABILITY

Human intestinal permeability was first evaluated by Fordtran et al. using an indirect method based upon the measurement of reflection coefficient. Their investigations, reported in 1965, were confined to the behaviour of molecules smaller in size than mannitol (mol.wt. 182, r = 0.4 nm) which was selected as a non-absorbable reference solute for the tube-perfusion technique employed. They demonstrated the presence of mucosal 'water channels' with effective radii of about 0.78 and 0.34 nm in human jejunum and ileum, respectively, but considered the method unsuitable for investigating patients with malabsorption. Exploiting the principle of restrictive diffusion, the same authors simultaneously compared
absorption of lipid-insoluble solutes of different molecular size thought to be non-mediated (tritiated water, urea, erythritol, and L-xylose; r = 0.15, 0.23, 0.32 and 0.35 nm, respectively) by perfusion through a multi-lumen tube introduced into the jejunum \(^3\). They found evidence of reduction in the effective mucosal pore-size in patients with coeliac disease and tropical sprue.

These early studies establish that permeation of the human small intestinal mucosa by inert solutes below 0.4 nm molecular radius is substantial, with an uptake from the lumen that can be adequately measured by tube-perfusion techniques. By contrast, solutes of 0.5 nm molecular radius and above have a very restricted permeation which makes measurement by disappearance from the lumen impractical. Transmucosal permeation of the latter can, however, be estimated by monitoring the fraction that enters the lumen from the circulation, or the circulation from the lumen, after administration of selected probe-markers by an appropriate route. Permeation in these two different directions may show important differences.

Loehry et al. \(^4\) perfused the human jejunum to estimate blood-to-lumen clearance of urea, creatinine, uric acid and \[^{57}\text{Co}\]cyanocobalamin (mol wt. 60, 120, 168 and 1350 respectively), and indirectly assessed permeation of parenterally administered \[^{125}\text{I}\]polyvinylpyrrolidone (mol wt range 10 000 to 80 000) into the intestine by measuring excretion in the stool. The latter principle is widely employed for the clinical investigation of protein-losing enteropathy \(^5\).

Renal excretion of orally administered non-metabolizable molecules has provided the basis for a convenient non-invasive method for assessing human intestinal permeation. Test solutions can be delivered by intubation when it is necessary to study specific portions of the intestine \(^6\). Probe-markers that are fully excreted by the kidney become concentrated in the urine to levels about 100-fold higher than those in the plasma, a phenomenon that can be exploited to estimate the very small quantities that permeate the intestine. Though sugars \(^7\)-\(^{11}\), polymers of ethylene glycol (PEG-4000, PEG-40000) \(^12\) and \[^{51}\text{Cr}\]EDTA \(^13\) have all been introduced as probe-markers, neither the pathways of mucosal permeation, nor the criteria for selection of suitable probe-markers, are yet fully established.

PERMEATION AND PERMEABILITY: THE INTRUSION OF IRRELEVANT VARIABLES

Estimations of intestinal permeability are obtained by measuring permeation (i.e. the quantity absorbed), but a correction is required for the state of experimental ‘exposure factors’ – time, area of mucosal surface involved, and concentration gradient. These variables are often
embarrassingly difficult to control, let alone measure, especially in the context of human investigation.

The need for a convenient method of dealing with such variables has been discussed in relation to intestinal perfusion by Fordtran, but deserves particular attention with respect to ingestion/renal-clearance techniques as they incorporate an even greater number of variables. The principle of 'differential absorption', illustrated in Figure 45.1, can be used to overcome the effect of variables, introducing into the test system an 'internal marker' subject to the same factors that affect the 'test marker' except the function to be investigated. A difference in the relative behaviour of the two markers can then be used as a specific index of the selected function, and quantified by the change in the test-marker/internal-marker ratio.

**SELECTION OF MUCOSAL PERMEABILITY MARKERS**

In the present context 'permeability' refers to the facility with which the intestinal mucosal surface can be penetrated by the unmediated diffusion of specified constituents. This is assessed by measuring permeation and it is necessary to formulate the requirements of a probe-marker for this purpose.

The behaviour of such a marker should reflect the state of intestinal permeability with minimal intrusion of other factors. Unmediated permeation of the absorptive surface, resistance to the action of intestinal enzymes and, when necessary, of bacteria, are essential requirements. When urinary excretion is used to evaluate intestinal permeation, renal clearance of the marker should be quantitative, and both this and the time-course for excretion following intravenous administration in the human should be verified. Molecular size, expressed as weight or radius (although volume may be more relevant) and lipid solubility are determinants of mucosal permeation that require specification, and it is necessary that the markers selected should be suitable for quantitative analysis in biological fluids and free from toxic effects.

The relative rates of absorption from the intestine and urinary recovery after intravenous administration of various test sugars have been assessed in healthy human volunteers10,16,17,26,29 (also Heyer, S. and Menzies, I.S.; unpublished observations), and average values are given in Table 45.1. Of the listed sugars L-rhamnose, D-mannitol, lactulose, melibiose and raffinose combine unmediated mucosal permeation with resistance to intestinal enzyme activity and a high recovery in the urine after intravenous administration which favour their use as markers for assessing intestinal permeability. Sensitive chromatographic techniques of satisfactory precision and accuracy, capable of estimating several different
types of sugar simultaneously in plasma or urine are available\textsuperscript{11,18-20}. Most sugars are degraded by bacterial activity and are therefore unsuitable for use in regions of the intestine, such as the colon, that support an active bacterial flora.

PEG-400\textsuperscript{9}, PEG-4000\textsuperscript{12} and \textsuperscript{[52Cr]}EDTA\textsuperscript{13} all resist degradation but, as discussed later, the polyethylene glycols should not be regarded as suitable substitutes for saccharides of the same molecular size as they evidently permeate the intestine by a different mucosal pathway.

**MODIFICATION OF INTESTINAL PERMEABILITY BY OSMOTIC FACTORS**

Effect of hyperosmolar solutions on intestinal permeability

It is well known that patients with various small-intestinal diseases show increased urinary excretion of unaltered dietary lactose and sucrose: this is due to a combination of decreased hydrolysis within the lumen and increased permeability to intact disaccharide, both features of mucosal damage\textsuperscript{8,11,21,22}. But there are also recorded instances where excessive urinary excretion of intact disaccharide has been due to a physiological mechanism unrelated to intestinal pathology. Utter (1927)\textsuperscript{23} induced a progressive increase in sucrosuria by raising the concentration of sucrose administered orally to children without altering the total amount ingested; and others have noticed an unexpected rise in urinary disaccharide when disaccharides were ingested together as a mixture\textsuperscript{24}, or in combination.

<table>
<thead>
<tr>
<th>Table 4.5</th>
<th>Disposition of various test sugars in the human. Average values are given for the relative rates of absorption from the jejunum (glucose = 100), and 12.5 h recovery in urine following intravenous administration in healthy human volunteers. Monosaccharide absorption was estimated by jejunal perfusion at concentrations of about 5 mmol/l (see text for sources)</th>
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<tbody>
<tr>
<td>Test sugar</td>
<td>Jejunal absorption</td>
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<tr>
<td>Mechanism</td>
<td>Relative rates</td>
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<tr>
<td>0-glucose</td>
<td>active mediated</td>
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<tr>
<td>0-galactose</td>
<td>passive mediated (?)</td>
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<tr>
<td>0-xylose</td>
<td>non-mediated</td>
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<td>0-mannitol</td>
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<td>lactulose</td>
<td>non-mediated and unaffected by human</td>
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<td>methylaspartose</td>
<td>disaccharides</td>
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<td>sucrase</td>
<td>sacrose</td>
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<td>lactose and cellobiose</td>
<td>isomaltose</td>
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with other sugars. In retrospect these findings can be attributed to the effect of hyperosmolar solutions on intestinal permeability. Though this phenomenon is incompletely understood, it is similar in many respects to the response of isolated frog skin and toad bladder to hyperosmolar solutions, first described by Hans Ussing in 1966.

Intestinal permeation indicated by the fraction of ingested lactulose excreted in the urine undergoes a marked increase when the administered solution is made sufficiently hyperosmolar by addition of a second solute. Though there is some individual variation, most healthy individuals show little change until the osmolality is raised to 1500 mOsmol/kg, above which a progressive increase takes place. Thus, raising the osmolality of an ingested solution containing lactulose (10 g in 160 ml water) from 1200 to 2500 mOsmol/kg by adding urea produced a 6-fold increase in lactulose permeation, the 5 h recovery in urine rising from 0.5 to 3.0% of the oral dose.

Intubation studies show that increased permeation of lactulose following ingestion of a hyperosmolar solution is related to increased duodenal rather than gastric osmolality, and not significantly altered by delivering the test solution beyond the pylorus. Both these findings suggest that the effect occurs mainly in the upper small intestine. Employing lactulose, melibiase and raffinose sequentially as probe-markers, the duration of the effect was found to be short, returning to normal within 2.5 h, and could be repeated in the same subject within a period of 5 h (Menzies, I.S. and Wheeler, P.G., unpublished results).

Solutions made hyperosmolar by addition of a wide variety of solutes, including monosaccharides, disaccharides, mannitol, glycerol, and salts (NaCl, KCl) produce the same effect as urea, though to a varying degree: but ethanol, even when ingested in very hyperosmolar solution, failed to increase intestinal permeation of lactulose. With regard to permeation, lactose, sucrose, melibiase, raffinose (mol. wt. 342, r = 0.5 nm), stachyose (mol. wt. 666, r = 0.62 nm), and fluorescein-labelled (FITC) dextran (mean mol. wt. 3000, r = 1.25 nm) all increase in the same way as lactulose, but ingestion of hyperosmolar solutions fail to increase permeation of the normal human intestinal mucosa by L-rhamnose or D-mannitol (mol. wt. 164 and 182, respectively; r = 0.4 nm). Lipophilic solutes of 0.4 nm molecular radius or below appear to permeate the human intestinal mucosa mainly by a transcellular route that is not available to oligosaccharides (r = 0.5 nm and above) and resistant to the effect of hyperosmolar stress.

Individual responses to hyperosmolar stress are quite consistent, though some healthy subjects are more susceptible than others: patients with coeliac disease show a greatly exaggerated response that often persists in spite of a good clinical response to treatment (see Figure 45.8). Cetrimide (cetyltrimethylammonium bromide), a detergent that has been employed
to produce experimental malabsorption in man and animals, produces a marked temporary increase in mucosal permeability to oligosaccharide when ingested in osmotically insignificant amounts (see Figure 45.3). Certain bile salts predispose to the effect of hyperosmotic stress on intestinal lactulose permeability without producing any change that can be detected with an iso-osmolar test solution.

Indirect effects due to osmotic retention of fluid within the intestine

Launila (1969) demonstrated that perfusion of poorly absorbed solutes (mannitol; and sucrose in a saccharic subject) increased the speed of bowel transit and reduced absorption of palmitic acid, D-xylene and arginine in the human intestine. Inclusion of mannitol in increasing doses

![Diagram](image)

**Figure 45.2** Indirect effect of osmogenic fluid retention on intestinal permeation. The effect of progressively inhibiting the absorption of 20 g co-ingested sucrose by adding increasing doses of the α-glucosidase inhibitor 'acarbose' on the permeation of three non-metabolized sugar markers. Renal excretion of l-rhamnose and lactulose indicates that a marked and approximately similar reduction in their intestinal permeation has been produced, whereas 3-O-methyl-D-glucose, absorbed by an active mediated process, is less affected. Seven healthy adult volunteers participated.
leads to a progressive reduction in the fraction of ingested D-xylose, lactulose and L-rhamnose excreted in the urine. Figure 45.2 demonstrates a similar reduction in lactulose and L-rhamnose permeation caused when the hydrolysis of 20 g of co-ingested sucrose was progressively inhibited by addition of the α-glucosidase inhibitor ‘acarbose’ (Bay g 5421®). It is of interest that though there was a marked decrease in total permeation, no significant change in the ratio of lactulose/L-rhamnose excretion took place.

Osmotic retention of fluid within the intestinal lumen reduces solute concentration gradients and speeds bowel transit by stimulating peristalsis. Both effects combine to reduce intestinal permeation. In contrast to permeation, intestinal permeability does not alter under these circumstances, the relative transmucosal passage of lactulose and L-rhamnose (radii 0.5 and 0.4 nm, respectively), expressed as a lactulose/L-rhamnose excretion ratio, remaining unchanged.

**INTESTINAL PERMEATION BY ETHYLENE GLYCOL POLYMERS**

PEG-400 consists of a mixture of low molecular weight ethylene glycol polymers (mol.wt. 194–502; n = 4–11) and was introduced in 1977 for the estimation of intestinal permeability by Chadwick, Phillips and Hofmann. As a multi-probe for this purpose it has many attractive features. The preparation contains a graded series of bacterial-resistant inert molecules which relate in dimension to a critical range of intestinal pore-sizes (r = 0.4–0.6 nm). Furthermore, each component can be specifically measured by gas–liquid chromatography, enabling results to be expressed as ratios of ‘differential permeation’ with the advantages already discussed.

However, a very marked discrepancy between the permeation of PEG-400 and inert oligosaccharides of the same molecular size soon became apparent. While less than 1% of ingested lactulose (mol.wt. 342) permeated the human intestine and appeared in the urine, more than 50% of PEG (fraction 4, mol.wt. 326) was excreted, representing 30 to 100-fold greater absorption. Regional perfusion studies indicate that absorption of PEG-400 from the human colon accounts for less than 20% of the total gastrointestinal permeation, therefore degradation of lactulose by colonic bacteria can explain no more than a very small part of this difference. Response by the two markers to villous atrophy in coeliac disease was also found to differ, permeation of PEG-400 decreasing while that of lactulose increased.

This problem has been assessed by Reynolds and Menzies who have compared the behaviour of PEG-400, L-rhamnose and lactulose when administered simultaneously to healthy adult volunteers and patients with
coeliac disease. The average recovery in urine of PEG-400, l-rhamnose and lactulose after intravenous administration (0.5 g quantities, n = 3) was 78.2, 61.8 and 84.4%; and calculated intestinal permeation after ingestion (5, 1 and 5 g quantities, respectively, in 150 ml water) was 28.5, 20.0 and 0.6% of the dose in 5 h. Hyperosmolar and cetrimide stresses were found to produce 3.2 and 4.3-fold increases, respectively, in the excretion of lactulose but, as shown in Figure 45.3, PEG-400 and l-rhamnose were not significantly altered. Two patients with untreated coeliac disease were shown to have increased intestinal permeation of lactulose and a decreased permeation of PEG-400 and l-rhamnose when all three markers were ingested in iso-osmolar solution.

In all respects investigated, therefore, absorption of PEG-400 behaves like that of l-rhamnose (mol.wt. 164) and not like lactulose (mol.wt. 342). The ability of l-rhamnose and PEG-400 to enter human erythrocytes, illustrated in Figure 45.4, is not shared by lactulose and demonstrates that PEG-400 can, like l-rhamnose, cross cell membranes by a route denied to lactulose. Though very water-soluble, PEG-400 has a hexane/water partition of about 18% and therefore considerable solubility in lipid. Furthermore Laker has shown that, unlike the sugars, PEG-400 can enter liposomes, reaching equilibrium within 5 min. Though it has been suggested that PEG-400 might permeate through ‘water channels’ in cell walls by virtue of an elongated molecular shape, it can evidently penetrate such membranes with considerable ease in the absence of pores by means of lipid solubility.

Figure 45.3 Effect of hyperosmolar and cetrimide ‘stresses’ on human intestinal permeation of PEG-400, l-rhamnose and lactulose. Average renal excretion of ingested lactulose showed 2.4 and 3.5-fold increases following hyperosmolar and cetrimide-containing test solutions, respectively, but there was no significant alteration in PEG-400 or l-rhamnose. Nine healthy adult volunteers participated
Figure 45.4 Entry of sugar markers and PEG-400 into human erythrocytes. Test substances were added to a suspension of fresh human erythrocytes in a physiological saline solution: 59% transfer from the extracellular compartment corresponds to complete equilibration. 3-O-methyl-D-glucose entered very rapidly, PEG-400 and L-rhamnose took 60 and 120 min to reach equilibrium, but entry of lactulose into the erythrocyte compartment could not be detected.

Transmucosal passage of the markers discussed appears to be mainly by three different routes: PEG-400 through the lipid bilayer of the enterocyte, determined by lipid solubility; L-rhamnose by way of small ‘water channels’ present in the enterocyte wall; and lactulose by way of larger paracellular ‘water channels’ probably associated with the junctional complexes. There is a close correspondence here with the three main routes available to non-electrolytes for transepithelial passage mentioned by Erlij and Martinez-Palomó. Though the permeation of lactulose and other oligosaccharides is very slow and confined to the paracellular route, that of PEG-400 and L-rhamnose is substantial and mainly transcellular, but a small fraction must surely be accomodated by the paracellular route as well. Susceptibility of paracellular permeation to hyperosmolar and ‘ce·trime·de’ stress is evidently an important distinction between the two routes.

INTESTINAL PERMEABILITY IN DISEASE

The immense range of macromolecular dietary constituents that could produce medical complications invites attention to the aetiological significance of increased intestinal permeability. At the present time, however, there are no examples reported where disease is clearly the result of an absorption of allergens, carcinogens, gluten fractions, etc.
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accentuated by abnormal intestinal permeability, though the idea attracts great interest.

The temporary increase in intestinal permeability that accompanies ingestion of hyperosmolar solutions has already been discussed: modern diet often contains sufficient sugar to produce this effect, especially in predisposed individuals.

Intestinal permeation by molecules below 0.5 nm radius such as mannitol\(^9,41,42\) and L-rhamnose\(^13\) is decreased in untreated coeliac disease, reflecting the characteristically reduced absorptive capacity associated with villous atrophy and usually demonstrated by the D-xylene absorption test. At the same time, however, intestinal permeation by lipophobic molecules of 0.5 nm radius and above, such as lactulose\(^8,10,11\), cellobiose\(^9,41,42\), raffinose, stachyose and dextran\(^10\), and \(^{51}\)CrEDTA\(^13\) becomes paradoxically increased.

An explanation of the opposing effects produced by villous atrophy is illustrated diagrammatically in Figure 45.5. This interpretation postulates that permeation of water-soluble, lipid-insoluble molecules of 0.4 nm radius or below can take place freely through numerous small 'water pores' situated in the cell membranes of the mucosal enterocytes, whereas those of greater size can only pass very slowly through large paracellular 'water channels' of low incidence (Figure 45.5a). Villous atrophy reduces the

\[ \text{particles} \quad \text{rate} \]
\[ \text{small} \quad c \quad X_{\text{sm}} \quad c \quad X/4 \quad \text{REDUCED} \]
\[ \text{large} \quad \text{Y}_{\text{lm}} \quad \text{Y}_{\text{lm}} \quad 2Y \quad \text{INCREASED} \]

Figure 45.5 Selective permeation through a restrictive membrane by inert molecules of differing size. (A) is a diagrammatic representation of the intestinal absorptive surface with 'high incidence' water pores which permit substantial permeation of molecules 0.4 nm radius and below; and a low incidence of larger water channels accommodating molecules of 0.5 nm radius and above. (B) shows the effect of villous atrophy: the absorptive area is reduced with a corresponding impairment of small molecular permeation, while a disproportionate increase in large water channels associated with 'mucosal damage' augments the permeation of larger molecules

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mucosal surface available with a corresponding reduction in 'small pore' permeation (Figure 45.5b); but, as a feature of mucosal damage, the incidence of large paracellular channels becomes augmented to such an extent that permeation of larger molecules may undergo a net increase. Large molecules sufficiently lipid-soluble to pass through cell membranes, like PEG-400, would behave like the smaller molecules, i.e. in the 'transcellular' mode.

In coeliac disease and other conditions associated with villous atrophy the relationship between 'mucosal cell damage' and loss of absorptive area varies considerably, but in a manner that is not always clinically predictable. The permeation of probe-markers of 0.5 nm molecular radius and above is affected by these two factors in opposing ways, so that interpretation is made easier when a second marker of smaller size, susceptible to changes in the transcellular 'small-pore' pathway, is included. This adaptation of the 'differential absorption' principle (see Figure 45.1) makes allowance for any changes in absorptive area and eliminates the effect of unwanted variables, as already explained, providing a ratio that specifically relates to the state of the intestinal large-pore/small-pore permeability profile.

The practical advantage of using such a permeation ration is demonstrated in Figure 45.6. This records the renal excretion of lactulose and L-rhamnose following ingestion of an iso-osmolar solution of these sugars in 19 patients with untreated coeliac disease and 29 healthy adult volunteers. The patients excrete more lactulose and less L-rhamnose that the healthy subjects, but a complete discrimination between the two groups is only obtained when the results are expressed as lactulose/L-rhamnose excretion ratios. The close similarity in the behaviour of L-rhamnose, and D-xylose is also demonstrated: though the latter is absorbed by a mediated process which produces a larger excretion than that of L-rhamnose, for the purpose of clinical discrimination the lactulose-xylose ratio serves as well as that of lactulose/rhamnose.

Intestinal permeation undergoes similar changes both in acute rotaviral gastroenteritis and tropical malabsorption. Figure 45.7 shows the renal excretion of ingested lactulose and L-rhamnose in infants during the acute phase of rotaviral gastroenteritis compared with that obtained after recovery 4 weeks later. As in coeliac disease there is better discrimination when results are expressed as lactulose/L-rhamnose excretion ratios. The presence of mucosal cell abnormalities, villous shortening and crypt hyper trophy has been reported in acute viral gastroenteritis, these changes may be temporarily severe and simulate the histological findings in coeliac disease. Intestinal permeability may also undergo the changes just described in bacterial gastroenteritis, Crohn's disease and following the administration of cytotoxic drugs. The effect of hyperosmolar solutions on intestinal permeation of oligo-
Figure 45.6 Intestinal absorption of lactulose, L-rhamnose and D-xylene in untreated coeliac disease following ingestion of iso-osmolar test solutions. Patients with coeliac disease (n = 19) excreted more lactulose and less L-rhamnose and D-xylene than healthy subjects (n = 29). Discrimination of the two groups is improved when results are expressed as lactulose/L-rhamnose and lactulose/D-xylene excretion ratios.

Figure 45.7 Intestinal permeation of lactulose and L-rhamnose following ingestion of iso-osmolar test solutions in infants during the acute phase of rotaviral gastroenteritis and after recovery. During the acute phase more lactulose and less L-rhamnose are excreted than after recovery 4 weeks later. Expression of results as lactulose/L-rhamnose excretion ratios improved discrimination between the ‘acute’ and ‘recovery’ responses.
Figure 45.8 Comparison of intestinal permeation of lactulose following ingestion of iso-osmotic and hyperosmotic test solutions in health and in patients with untreated coeliac disease and tropical malabsorption. Renal lactulose excretion became much accentuated following ingestion of a moderately hyperosmotic test solution (1500 mOsmol/kg) in patients with untreated coeliac disease and tropical malabsorption, but no significant change was produced in the healthy subjects.

Saccharide is increased in the presence of villous atrophy. Figure 45.8 shows the extent to which the renal excretion of ingested lactulose becomes accentuated in patients with coeliac disease and tropical malabsorption when the osmolality of the test solution is raised from 300 to 1500 mOsmol/kg, compared with the insignificant increase shown by a group of healthy adult subjects. By impairing transfer of solute and fluid, and possibly osmoreceptor function, villous atrophy is likely to increase intestinal exposure, and therefore the response, following ingestion of a hyperosmolar solution.

In coeliac disease, response to hyperosmolar stress often remains abnormal after a satisfactory clinical response to treatment has taken place, sometimes even though the jejunal villous architecture has returned to normal. These observations not only suggest that an alteration in mucosal response (or 'osmotic fragility') is involved, but that it could sometimes be a primary factor. The proximal end of the small intestine has the greatest exposure to hyperosmolar dietary contents, but is also the site of the initial lesion in coeliac disease. It is not yet known whether penetration of the intestinal mucosa by gluten fractions can be accentuated by this mechanism in the same way as oligosaccharide.

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CONCLUSIONS

Permeability of the intestinal mucosa is a complex phenomenon involving at least one paracellular and two transcellular routes, inadequately expressed unless several probe-markers with a range of specified physical characteristics are employed for assessment. Permeation of the healthy intestine is selective, the mucosa permitting small (or lipid-soluble) molecules to diffuse mainly by a transcellular route with 30 to 100-fold greater ease than lipid-insoluble molecules of slightly larger size (r = 0.5 nm, and above) which are confined to a paracellular pathway.

Measurement of differential permeation, combining a small probe-marker (mannitol, L-rhamnose) with a larger one (lactulose, melibiose, etc.) provides a convenient assessment of the relative states of both transmucosal routes. Mucosal damage, whether due to coeliac disease, tropical malabsorption, acute gastroenteritis or cytotoxic drug therapy, produces both an increase in paracellular and decrease in transcellular intestinal permeation at the same time. Though this seems a confusing paradox, it represents merely a reduction of normal selectivity – a familiar enough outcome of impaired function – which becomes completely lost in severe mucosal diseases when the lactulose/L-rhamnose permeation ratio may approach unity.

Besides diagnostic value as an index of mucosal damage, abnormal intestinal permeability caused by disease, drugs or constituents of the diet, is of medical interest as a potential factor of aetiological importance.

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