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SPECIAL REPORTS AND REVIEWS

Intestinal Permeability: An Overview

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The noninvasive assessment of intestinal permeability in humans has a 20-year history. Because the tests are increasingly used in clinical practice and research and because there is much controversy, we reviewed the literature and outlined the potential and possible shortcomings of these procedures. Data was obtained from personal files and from a systemic search through MEDLINE and EMBASE. The principle of the differential urinary excretion of orally administered test markers is explained with reference to the desired physicochemical properties of the markers and how the principle can be exploited to allow assessment of various other gastrointestinal functions. The use of intestinal permeability tests for diagnostic screen for small bowel disease and assessment of responses to treatment, the pathogenesis of disease, normal intestinal physiology, and the effect of drugs and toxins on the intestine is described and reviewed. The controversy surrounding the anatomic location of the permeation pathways that the markers use is highlighted. Noninvasive tests of intestinal permeability have fulfilled early promises of usefulness in clinical practice and research. There is now a need for integrated research into the basic mechanisms of regulatory control of the intestinal barrier function.

Conventional noninvasive absorption tests provide information on the mechanisms of malnutrition, and some have found clinical application as screening procedures for gastrointestinal diseases. The development of methods for assessing the intestinal barrier function became practical after the introduction of nonmetabolized oligosaccharides as test substances in the 1970s. Although the concept of the intestinal barrier function is straightforward, accurate noninvasive assessment requires close attention to technical details of test dose composition and analytical procedures.[1] The intestinal barrier function has implications for the etiology and pathogenesis of various intestinal and systemic diseases,[2–4] and the techniques may be used in screening for small intestinal disease, assessing the response to treatment, and predicting the prognosis.

Our purpose is to review the field of intestinal permeability with special reference to human studies and to highlight areas of consensus, controversy, and apparent paradoxes.

Physiological Concepts and Terms

The concept of permeability relates to that property of a membrane that enables passage of a solute by unmediated diffusion. The diffusion of a solute across a simple membrane is determined both by the structure (composition, charge, thickness, and so on) of the membrane, the physicochemical properties of a solute (molecular size, shape, charge, and solubility), and its interaction with the media (solvent).

Permeation can be estimated accurately by several methods in vitro, but the noninvasive assessment of human intestinal permeability is crude by comparison because a number of concessions have to be made to simplify the situation. One is that the intestinal epithelium is nonhomogenous. Also, current techniques use water-soluble test substances that only allow assessment of selected permeability characteristics of the human intestinal tract.

We distinguish between absorption and permeation to describe carrier-mediated and -unmediated modes of transport across the intestine, which has implications for nutrition and the intestinal barrier function, respectively. Transport in the neonatal period is well covered in a previous review.[5]

Noninvasive Techniques

Fordtran et al. were instrumental in the development of ideas for assessing intestinal permeability,[6] but it was Menzies who introduced oligosaccharides as test substances for the noninvasive assessment of intestinal permeability in 1974[1] and subsequently formulated the

Abbreviations used in this paper: AIDS, acquired immunodeficiency syndrome; PVP, polyvinylpyrrolidione; ^{99m}Tc-DTPA: ^{99m}Tc-diethylenetriaminopentaacetate.

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Table 1. Factors Affecting the Urinary Excretion of Orally Administered Test Substances: The Principle of the Differential Urinary Excretion of Ingested Test Substances

Factors affecting the urinary excretion of orally administered test substances	Monosaccharide	Nonhydrolyzed disaccharide	Hydrolyzed disaccharide	^{51}Cr-EDTA or ^{99m}Tc-DTPA
Premucosal				
Completeness of ingestion	Identical/equal[c]	Identical/equal	Identical/equal	Identical/equal
Gastric dilution	Identical/equal	Identical/equal	Identical/equal	Identical/equal
Gastric emptying	Identical/equal	Identical/equal	Identical/equal	Identical/equal
Intestinal dilution	Identical/equal	Identical/equal	Identical/equal	Identical/equal
Intestinal transit	Identical/equal	Identical/equal	Identical/equal	Identical/equal
Bacterial degradation	Identical/equal	Identical/equal	Identical/equal	Identical/equal
Unstirred water layer	Identical/equal	Identical/equal	Identical/equal	Identical/equal
Digestion hydrolysis	Does not take place	Does not take place	Mainly by intestinal disaccharidase activities	Does not take place
Mucosal				
Route of permeation	Different routes of permeation[d]	Different routes of permeation	Different routes of permeation	Different routes of permeation
Intestinal blood flow	Identical/equal	Identical/equal	Identical/equal	Identical/equal
Postmucosal				
Metabolism	Does not take place	Does not take place	Does not take place	Does not take place
Endogenous production[a]	Does not take place	Does not take place	Does not take place	Does not take place
Tissue distribution	Different distribution[e]	Different distribution	Different distribution	Different distribution
Renal function	Identical/equal	Identical/equal	Identical/equal	Identical/equal
Timing and completeness of urinary collection[b]	Identical/equal	Identical/equal	Identical/equal	Identical/equal
Bacterial degradation	Mainly when test solution enters cecum	Mainly when test solution enters cecum	Mainly when test solution enters cecum	Does not take place
Analytical performance	Identical/equal	Identical/equal	Identical/equal	Identical/equal

NOTE. When a nonhydrolyzed disaccharide (i.e., lactulose) and a monosaccharide (L-rhamnose or mannitol) are ingested together, all of the above factors will contribute to their (percent of oral dose) excretion in urine. However, because all of the premucosal and postmucosal determinants of their excretion affect the two test substances equally, the differential 5-hour urinary excretion ratio (lactulose/L-rhamnose) is not affected by these variables. The urinary excretion ratio of lactulose/L-rhamnose thereby becomes a specific index of intestinal permeability. Lactulose differs only from lactose, sucrose, or palatinose in respect to their rate of hydrolysis in the intestine, which in turn governs the amount of intact disaccharide available for transport across the mucosa. The 10-hour differential urinary excretion of lactose, sucrose, or palatinose/lactulose is thereby proportional to reductions in intestinal lactase, sucrase, and palatinase (isomaltase) activities. In normal subjects, the urinary excretion (percent dose) ratios of hydrolyzable to nonhydrolyzable disaccharides is <0.3, but with increasing severity of disaccharidase deficiency (primary or secondary), this ratio approaches 1.0, at which time there is no disaccharide hydrolysis. Lactulose and ^{51}Cr-EDTA are nearly identical physicochemically. Their permeation rates across the small intestine are equal, but because lactulose is degraded by colonic bacteria, the difference in the 24-hour urine excretion of ^{51}Cr-EDTA less that of lactulose can be used as an index of colonic permeability.

[a]There may be some but minimal endogenous production of mannitol.

[b]Roughly equal for the monosaccharides and disaccharides, but see different distribution[e].

[c]Identical or affects all of the test substances equally.

[d]Indicates different routes of permeation. See text for detailed discussion.

[e]Monosaccharides and disaccharides have a different volume of distribution following intravenous administration; hence, there is a slight difference in the speed and completeness of their urinary excretions. This is for practical purposes not of major importance.

concept of the principle of differential urinary excretion of orally administered test substances.

The Principles

Intestinal permeability is assessed noninvasively in vivo by measuring urinary excretion of orally administered test substances. Initially, single test substances (lactulose, various polymers of polyethylene glycol [PEG], ^{51}Cr-labeled ethylenediaminetetraacetic acid [^{51}Cr-EDTA], and ^{99m}Tc-diethylenetriaminopentaacetate [^{99m}Tc-DTPA]) were used, but test results (Table 1) were influenced by a change in any of the premucosal or postmucosal factors apart from intestinal permeability itself. This led to the formulation of the principle of differential urinary excretion of test substances, which provides a specific index of intestinal permeability.[2,7] It is conventional to use a disaccharide and monosaccharide together, but there is no reason why other suitable probes could not be used.

The differential urinary excretion principle has been useful empirically and in practice, but there are several aspects that need clarification. One claim is that the

precise timing of urine collection may not be important,[8] which is doubtful because the rates of urinary excretion of the individual probes after intravenous injection differ.[9,10] Also, the question of the route that the markers use during passage across the intestine requires further study.

Extending the Principle

By careful attention to the details underlying the formulation of the principle of differential urinary excretion of orally administered test substances, it is possible to devise ways of assessing several different specific intestinal functions without sacrificing the noninvasive nature of the test. One example is to administer lactulose and ^{51}Cr-EDTA together[11] with the total 24-hour urinary excretion of ^{51}Cr-EDTA less that of lactulose, providing an index of colonic permeability (Table 1).

Table 1 also explains how it is possible to specifically quantify intestinal disaccharidase activities in humans[12–14] noninvasively. This technique has been used to show transient lactase deficiency following *Rotavirus*-induced enteritis in children, combined sucrase and palatinase deficiency in asucrasia, and the effectiveness of α-glucosidase inhibitors on sucrose hydrolysis.[12,13,15]

Sutherland et al.[16] have suggested that it may be possible to predict gastroduodenal mucosal abnormalities by ingestion of sucrose (100 g) solution and its measurement in timed urine samples. The idea is that the sucrose reaching the small intestine is rapidly and completely digested so that urinary excretion predominantly reflects the state of gastroduodenal integrity. Although in some contradiction to the above statement, initial results have been encouraging and independently confirmed, but the test is not strictly in accordance with the differential urinary excretion principle.

Properties of Probe Molecules

The "ideal" permeability probe[17,18] has certain desirable physicochemical properties identical to those required of nonabsorbed reference compounds or dilution indicators, including water solubility, first-order kinetics of permeation, nontoxic, nondegradable, and not metabolized before, during, or after permeating the intestine. Preferably, the probes should not be naturally present in urine, urinary excretion should be complete following intravenous instillation, and measurement of the probe should be sensitive, accurate, and easy.

Ethylene Glycol Polymers

Ethylene glycol polymers have the general formula $H(OCH_2CH_2)_nOH$. PEGs have an n value from 4 to about 150 with those above this molecular weight forming a solid at room temperature. Commercially available PEGs used for permeability assessments (PEG 400, 600, 900, 1000, 3000, and 4000) come as a mixture of different molecular weight polymers but with a batch-to-batch variation in the relative proportion of each polymer from the same supplier. PEGs are widely used as solvents, as food additives, as water-soluble ointment base, in sugar paste, and in suppositories. PEG 4000 is also used as a purgative in preparation for colonoscopy, and the addition of PEG to wines is well known, albeit illegal, which may fool even the greatest wine connoisseurs. High concentrations of PEG 6000 facilitates cell fusion.[19] Although there is a wide safety margin between toxic doses and amounts used in permeability studies, there is a noticeable interspecies variation in the toxicity of PEG polymers.[20]

The most widely used PEG in human studies is PEG 400, which represents a range of polymers of a molecular mass of about 194–502. Five to 10 grams of PEG 400 is taken orally after an overnight fast in a fixed volume of water, and urine specimens are collected for 5–6 hours for analysis. Extraction of PEG polymers is time-consuming, but separation and quantitation is readily achieved by gas or high-pressure liquid chromatography.

Whereas PEG 400 fulfills many of the theoretical requirements of an "ideal" test substance,[17,18] it has a rather unpleasant taste and the variable urine excretion after intravenous administration, ranging from 26% for PEG 194 to 69% for PEG 502,[9] is somewhat unsatisfactory.

There is a lack of consensus of how to express PEG results. This can be done as (1) a percentage (or weight) of the orally administered dose in urine, (2) corrected for the variable urine polymer excretion following intravenous administration, (3) urine excretion ratios of the various polymers,[17,18] (4) as a single artificial numerical value (N1/2) that is calculated from the pattern of urine excretion of PEG polymers,[21] or as (5) a filter function following mathematical manipulation of the raw polymer data.[22] For routine use, (2) is impractical and (3) does not seem to increase the sensitivity of the procedure. Calculation of N1/2 (4) or expression of the data as a filter function (5) is reported to increase the sensitivity of the procedure. The use of PEGs, although criticized by a number of workers, provides intriguing findings, but their interpretation continues to be challenging.

Oligosaccharides

Lactulose is the most widely used disaccharide probe for intestinal permeability studies and is commercially available at a reasonable price as 67% wt/vol lactulose syrup. The syrup contains small amounts of other sugars, which may exert some osmotic effect, but the use of purified

crystalline lactulose is prohibitively expensive. Other suitable oligosaccharides include melibiose, raffinose, stachyose, and dextrans, but cellobiose should be avoided because there is some small intestinal cellobiase activity.[23] The above oligosaccharides meet most of the criteria for a "deal" test substance. There are two points of special importance. First, the dose of saccharides should be as low as possible and certainly no higher than 5 g, as explained later. Secondly, the analytical procedures need particular attention because each technique has its merits and problems, but important factors to consider are the performance (accuracy, sensitivity, and precision) and resolution. A common pitfall is to overcome an analytical sensitivity problem by increasing the amounts of sugar in the oral test solution, and care has to be taken because some of these sugars are found in food.

The thin-layer chromatography with scanning densitometry described by Menzies[24] is satisfactory and essential if absorptive capacity (3*O*-methyl-D-glucose, D-xylose) is assessed at the same time. The technique is labor-intensive and requires manual skill, but it is not possible to quantitate mannitol by this method. High-pressure liquid chromatography with reactive index or pulsed amperometric electrochemical detection is also suitable for quantitation of sugars. A problem with some early work was that the columns could not separate lactulose and lactose,[25–27] raising the possibility that lactosuria caused by intestinal lactase deficiency was mistakenly perceived as increased intestinal permeability. The application of enzyme methods needs careful thought on the specificity of the disaccharidase and assurance that the product of the reaction does not occur naturally in urine.

Monosaccharides

L-rhamnose and mannitol, a sugar alcohol, are both commonly used. The urinary excretion of L-rhamnose 24 hours after intravenous administration is incomplete (about 74%), whereas that of mannitol is reported to lie between 67% and 100%.[8,28] Small amounts of endogenously produced mannitol make a negligible contribution to the urinary excretion if 1 g is ingested.[28] Monosaccharide assay is performed by the same techniques described above.

Nondegraded Radiolabeled Chelates

^{51}Cr-EDTA and ^{99m}Tc-DTPA share many physical properties with oligosaccharides but have the advantage of ease of measurement and the disadvantage of being radioactive. They are widely used for assessment of glomerular filtration rates. The choice between using ^{51}Cr-EDTA and ^{99m}Tc-DTPA is one of convenience. ^{51}Cr has a half-life of 27 days so that it can be made up in batches, whereas ^{99m}Tc-DTPA requires doses to be made up individually and urine specimens to be analyzed soon after collection. The radiation received following a 100-μCi dose of ^{51}Cr-EDTA is <0.12 milliSieverts (effective dose equivalent) and even less following an equivalent amount of ^{99m}Tc.

The radiolabeled chelates are ingested after an overnight fast in 2–300 mL of water. Urine is collected for 24 hours because the discrimination between normals and patients with small intestinal disease is greatest at this time.[29] A 5-hour ^{51}Cr-EDTA/monosaccharide urinary excretion ratio simplifies the interpretation of results and increases the specificity of the test.[30–32] However, a possible disadvantage in comparison with disaccharides and monosaccharides is that ^{51}Cr-EDTA is not degraded, which raises the possibility that bacterial overgrowth or an extremely rapid intestinal transit could lead to an increased differential urinary excretion ratio without an attendant increase in intestinal permeability.

The use of [^{14}C]mannitol together with ^{51}Cr-EDTA requires a crossover correction because the latter is a β as well as a γ emitter.

Polyvinylpyrrolidine (PVP) has only rarely been used as an intestinal permeability probe. PVPs come in different molecular weight ranges from 11,000 to 100,000 daltons. Renal excretion following intravenous instillation of PVP is restricted above a molecular weight of 40,000 but approaching that of inulin below this weight.[33] The backbone of the polymer can be labeled with ^{14}C, but clinical experience is very limited and there is little information on its inertness or whether it binds to mucus or cellular constituents.

Physiological Factors Affecting Permeability and Anatomic Location of Pathways

It is important to distinguish between the intestinal response to hyperosmolarity of an ingested test solution and osmotic fluid retention caused by the presence of poorly absorbed solutes.

Hyperosmolar Stress

An early observation described increasing levels of sucrosuria in children by increasing the concentration of ingested sucrose (total amounts ingested were unchanged).[34] Later, Menzies et al. showed that the permeation of lactulose and oligosaccharides is markedly increased in normals when test dose osmolarity is increased beyond 1500 mOsm/L.[1,9,35,36] The effect is evident with most readily absorbed solutes (glycerol, mannitol, NaCl, KCl, and so on), but the magnitude of the changes vary with each osmotic filler and there is individual susceptibility to this effect[1,36] that is found at much lower test

dose osmolarities when ^{51}Cr-EDTA is used by itself.[37] Permeation of monosaccharides (L-rhamnose, mannitol) is not affected, even when the solution is made up to 3600 mOsm/L.

Moderate hyperosmolarity may cause structural damage.[38] Test solutions (500 mOsm/L) cause subepithelial blebs with loss of cellular regularity and loss of contour of epithelial cells with eventual loss of cells. At the ultrastructural level, the situation is more complex.[39] Hyperosmotic lysine increased paracellular permeability to lanthanum ions,[40] whereas Madara found hyperosmotic mannitol to decrease paracellular permeability.[41]

Osmotic Fluid Retention of Poorly Permeating Solutes

Poorly permeable solutes retain fluid within the intestinal lumen and thus accelerate intestinal transit, which reduces the contact time between the test probes and the area under interest. As little as 5 g of lactulose is sufficient to reduce the permeation of L-rhamnose by 30%, and while it does not affect intestinal permeability, it does reduce the sensitivity of the procedure.[10]

Practical Implications of Test Dose Osmolarity

The amounts of lactulose in the test solution should be kept to a minimum because the fluid retention effect of poorly permeating substances (i.e., 5 g lactulose) reduces the sensitivity of the test.[10]

When disaccharides were used by themselves, the diagnostic discrimination of the test for patients with celiac disease was enhanced by increasing the osmolarity (by addition of sucrose) of the ingested test solution from 230 to 1500 mOsm/L, whereas this produced no significant effect on healthy volunteers. This was then widely extrapolated to the differential urine excretion tests[1,7,35,36,42] but in practice does not increase the sensitivity of the procedure.[10] If the test solution is rendered hyperosmolar, then glycerol is satisfactory, whereas sucrose or lactose may be inappropriate (their intestinal hydrolytic rates vary unpredictably); glucose is not ideal because it is cotransported with sodium. Most workers now have abandoned osmotic fillers in favor of more physiological iso-osmolar tests. Standardization of test dose composition is simple and essential so that results between groups can be compared directly.

Anatomic Location of Pathways

Because PEG 400, disaccharides, monosaccharides, and ^{51}Cr-EDTA all share similar physicochemical properties, it would be expected that the results obtained with their use in health and disease would be similar. There are, however, consistent differences in results that

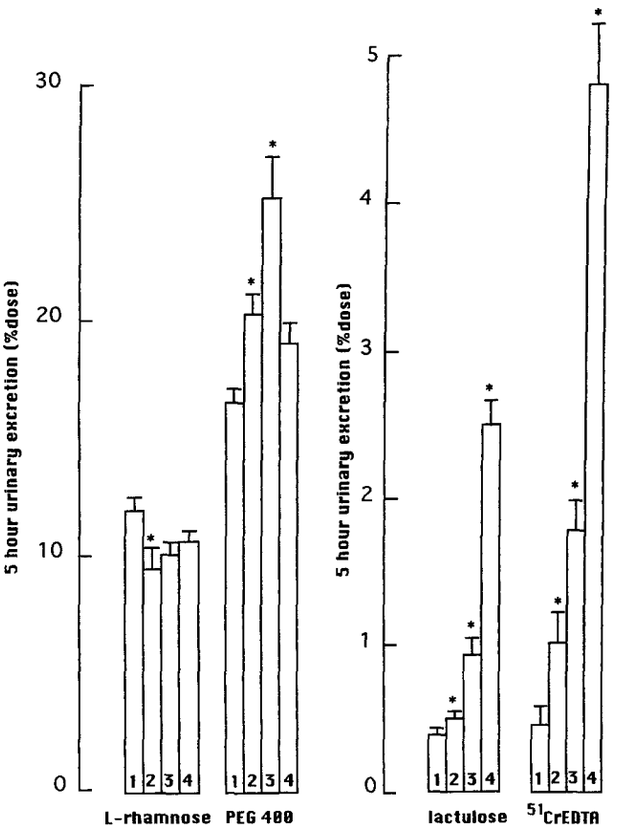

Figure 1. The 5-hour urine excretion of L-rhamnose, PEG 400, lactulose, and ^{51}Cr-EDTA after their simultaneous ingestion (150 mL) as (1) iso-osmolar solution, (2) hyperosmolar (1500 mOsm/L with glycerol), (3) hyperosmolar (2300 mOsm/L with glycerol), and (4) 150 mg cetrimide, a strong detergent. The urine excretion of L-rhamnose was unaffected by this, PEG 400 permeation increased in response to hyperosmolarity but not cetrimide, whereas lactulose and ^{51}Cr-EDTA permeation was significantly increased by all maneuvers. These results, along with the 50-fold greater permeation rates of PEG 400 as opposed to lactulose and ^{51}Cr-EDTA in normals,[9] form the basis of the three permeation pathway hypothesis.

cannot be explained on the basis of different techniques of marker analysis, test procedures, test dose composition, or variations in timing of urine collections. These differences are the basis of an ongoing lively debate, discussed below, but it should be stressed that the main issues are still unresolved.

Maxton et al.[9] gave healthy volunteers a combined test using PEG 400, lactulose, L-rhamnose, and ^{51}Cr-EDTA made iso-osmolar (300 mOsm/L) or hyperosmolar (1500 and 2300 mOsm/L) with glycerol and assessed the response to the detergent cetrimide. Figure 1 shows the overall results. Hyperosmolar stress increased the permeation of PEG 400, lactulose, and ^{51}Cr-EDTA, whereas cetrimide increased the permeation of lactulose and ^{51}Cr-EDTA but not that of L-rhamnose or PEG 400. There was a significant correlation between the permeation of

lactulose and ^{51}Cr-EDTA ($r = 0.98$; $P < 0.001$) but not between PEG 400 and either L-rhamnose, lactulose, or ^{51}Cr-EDTA. When the urine excretion of the markers is correlated with molecular mass (Figure 2), the permeation of PEG 400 is equaled only by that of D-xylose, a pentose with carrier-mediated intestinal transport.

On the basis of the above, it was proposed that there were three separate intestinal permeability pathways that the probes used. The proposed anatomic correlates are shown in Figure 3, namely, paracellular (lactulose and ^{51}Cr-EDTA), transcellular "aqueous" (L-rhamnose), and transcellular "lipid" (PEG 400).

The main attraction of this model is that it conveniently explains the behavior of the markers in health and disease and their response to physiological stresses. The shortcomings of the model center around three points. Firstly, it has not been possible to provide direct evidence for the anatomic presence of these pathways because most localizing techniques require binding of the markers to cellular components, and permeability probes are inert in this respect.

Secondly, the evidence for transcellular permeation of monosaccharides is controversial. Mannitol is used for osmotic shrinkage of membrane vesicles, which would not be possible if its permeation across cell membranes was unrestricted,[43] and many experimental physiologists use it as an extracellular fluid volume marker. In contrast, L-rhamnose passes into erythrocytes,[2] but extrapolation of erythrocyte data to transport across other cells is doubtful.

Thirdly and most importantly, the possible paracellular vs. transcellular permeation route of PEG 400 permeation is dependent on its possible lipid solubility and its geometric shape.[2–4,44] Significant lipid solubility of PEG 400 has been claimed by Menzies,[2,45] and others report a correlation between the partition coefficient (range, $2–4 \times 10^{-2}$) of each polymer in petroleum spirit and their urine excretion.[46,47] Hollander et al. calculated a petroleum-ether-water partition of PEG 400 around 8×10^{-6} (negligible) and could not show passage of PEG 400 into brush border membrane vesicles.[48–51] They concluded that permeation of PEG 400 occurred via paracellular junctions. In contrast, Iqbal et al.[52] have shown that PEG 400, but not lactulose, diffused from one chamber to another separated by a lipophilic media and aided by moderate amounts of phospholipid, again raising the possibility of transcellular lipid–dependent transport for PEG 400. It seems possible that while PEG 400 is highly water-soluble, it may also have a degree of affinity for lipid, which could in part account for its high permeation rates. On the other hand, permeation rates across pores

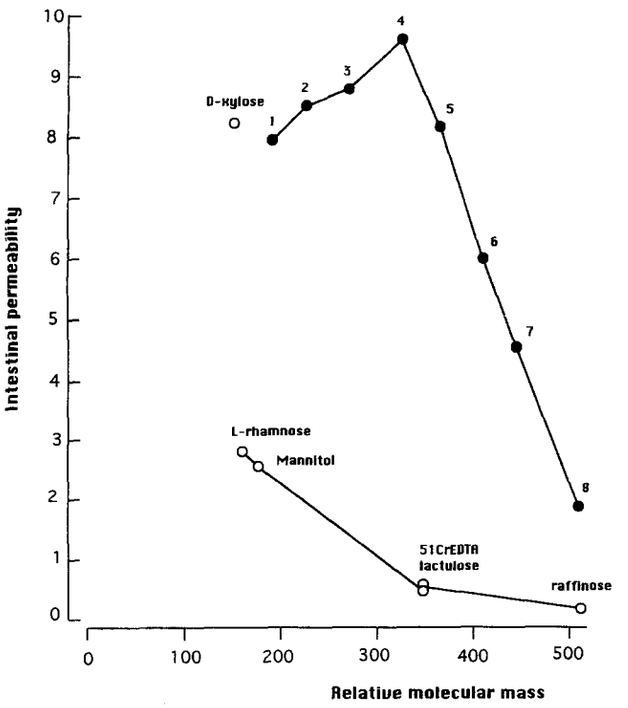

Figure 2. Relative intestinal permeability to the test probes as assessed by 5-hour urinary recoveries of the test markers (correcting for systemic loss and the effect of molecular mass on diffusion through aqueous media). Intestinal permeability to PEG polymers is far greater than for monosaccharides, disaccharides, and trisaccharides of comparable molecular weight other than D-xylose, which is transported across the intestine by a facilitated carrier.

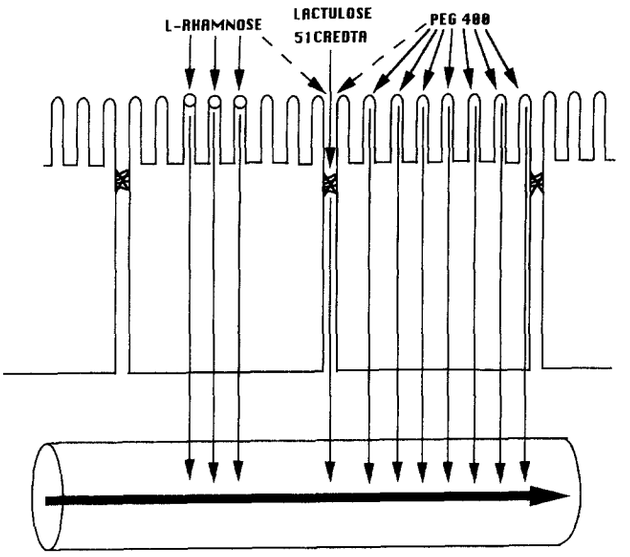

Figure 3. The three permeation pathway model predicts that transport of lactulose and ^{51}Cr-EDTA across the intestine occurs exclusively through the intercellular junctions. Whereas a small proportion (*broken line*) of L-rhamnose and PEG 400 also share this pathway, the main determinants of their overall permeation reside with the number of aqueous pores (L-rhamnose) or the lipid character of the brush border membrane (PEG 400).

are determined by the size and shape of probe molecules. Permeation rates of saccharides correlate with relative molecular mass in humans[9] with the permeation of PEG polymers clearly out of place (Figure 2). This is used in evidence for a lipophilic permeation pathway for PEG rather than aqueous pores. However, the molecular geometry of PEG (linear) differs from the other probes (coiled) so that its cross-sectional diameter is smaller.[53] Ma et al. found a correlation between the cross-sectional diameter of the probes and their permeation rates[54] (Figure 4). This suggested that the linear shape of PEG polymers might allow it access to aqueous pores and hence explain its high permeation rates. Under these circumstances, the length of the PEG molecule in relation to the channel pore length would obviously have some effect on permeation rates. The possible impact of lipid solubility and molecular geometry of PEG 400 and, hence, the validity of the three permeation pathway model remain important unresolved issues. The alternative hypothesis to the above[55] is highlighted by Hollander.[56] In vitro work with intestinal loops and intestinal cell monolayers indicate a structure-function relationship in the intercellular occluding junctions.[57,58] In general, it is found that the tightness of epithelial cell–occluding junctions correlate with electron microscopic freeze fracture strand counts and junctional depths. Strand numbers vary from 1 to 8 and correlate with measurements of transepithelial electrical resistance (proportional to the tightness of the junctions), which vary from 25 to 1500 ohm/cm^2. Transepithelial electric resistance relates inversely to mannitol fluxes, suggesting a paracellular route of permeation for this marker. Additionally, there is morphological heterogeneity among intercellular junctions in the small bowel,[59,60] which suggests increasing paracellular tightness as the cells migrate from the crypt to villus. Based on this and the need to explain the high permeation rates of PEG 400, it is suggested that all of the markers permeate via the paracellular junctions. Lactulose and ^{51}Cr-EDTA permeation, as suggested and schematically shown in Figure 5, would be confined to crypt tight junctions in this model and monosaccharides, and PEG 400, because of their smaller cross-sectional diameter, are free to permeate throughout the crypt-villus axis. The high permeation rates of monosaccharides and PEG 400 would additionally be due to their relatively unrestricted access to the villus epithelium. In disease, it is suggested that the different permeation rates of the markers are the outcome of an interplay between the tightness of the junctions and the accessibility of luminal contents to the crypts.[56] The validity of the common pathway theory is, as is the case with the three permeation pathway model, critically dependent on assumptions about the lipid (non) solubility of PEG and its geometry.

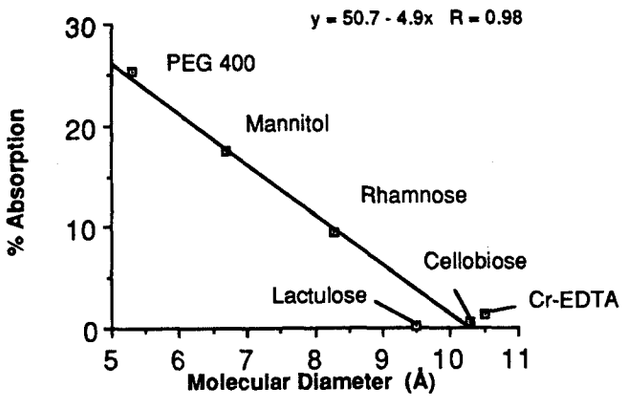

Figure 4. Percent urinary excretion of intestinal permeability test markers following oral administration (obtained from various published sources) plotted against the smallest effective molecular diameter of the probe. This suggests that geometry is an important determinant of their permeation rates.

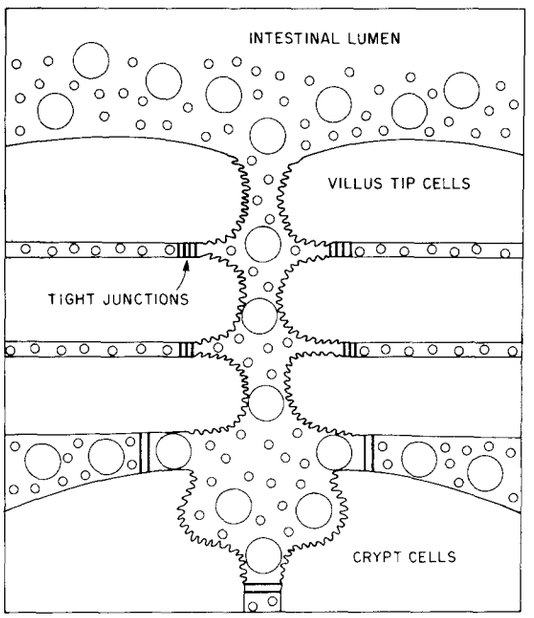

Figure 5. The single paracellular permeation model. It is suggested that L-rhamnose, PEG 400, lactulose, and ^{51}Cr-EDTA all permeate the intestinal epithelial barrier through paracellular junctions, and their different behavior in health and disease can be accounted for by regional permeability characteristics along the crypt-villus axis. It is suggested that the tightness and, hence, permeability of the tight junctions of adjacent enterocytes increase progressively from the crypt to villus tip. At the villus tip, there are numerous "tight" tight junctions that allow the relatively unrestricted permeation of L-rhamnose and PEG 400 (small bubbles) and hence account for their greater permeation rates in vivo but exclude lactulose and ^{51}Cr-EDTA (large bubbles) on account of their size. The crypt tight junctions do, however, allow some transfer of lactulose and ^{51}Cr-EDTA, but their access from the lumen to the crypt tight junctions is limited, hence their low permeation rates in vivo.

From these considerations, it is clear that we cannot be dogmatic at this time about the precise permeation pathways that the probes use. Equally clear is the fact that there is the scope for much work in this field to clarify the basic mechanisms that control the sites and rates of permeation of the different markers.

Potential Usage of Permeability Measurements

Intestinal Permeability as an Index of Intestinal Pathology for Diagnostic Screening and Monitoring of Therapeutic Responses

Tests of intestinal permeability are used as noninvasive screening procedures to anticipate or even replace the need for more invasive investigations of the small intestine. The tests, apart from PEG 400, compare favorably with respect to sensitivity with the D-xylose absorption test, fecal fat, and serum folates in the detection of patients with untreated celiac disease,[7,42,61,62] but a comparison with circulating antibodies (to gluten, gliadin, reticulin, or endomysium) has not been performed.

The differential urinary excretion of disaccharides and monosaccharides can be used to confirm the diagnosis of celiac disease[63] following gluten challenge, and sequential permeability measurements may obviate the need for follow-up jejunal biopsy.[63,64] Increased permeation to ^{51}Cr-EDTA seems to persist despite treatment, which may represent inadvertent gluten ingestion. The permeability changes are also found in patients with dermatitis herpetiformis who have a gluten-sensitive enteropathy.[65,66]

The differential urinary excretion of disaccharides and monosaccharides and the ^{51}Cr-EDTA test detect more than 90% of patients with small intestinal involvement of Crohn's disease. The test results are affected by disease activity and extent. However, sensitivity is markedly reduced in patients who have undergone intestinal resection.

Successful treatment of Crohn's disease with elemental diets is matched by significant reductions in intestinal permeability.[67,68] Normal intestinal permeability in patients with Crohn's disease has prognostic implications and may predict well-being.[69,70] Along with other observations, this has led to the hypothesis that disruption of the intestinal barrier is the central mechanism leading to relapse in inflammatory bowel disease.[51,56,71,72]

Other common intestinal disorders such as giardiasis, *Rotavirus* infection, and so on are also consistently associated with increased intestinal permeability.[15,73,74] The tests therefore clearly lack diagnostic specificity. In geographical areas with a high prevalence of tropical sprue, which is associated with increased intestinal permeability, it may be difficult to define an effective normal range of intestinal permeability.[75,76]

Intestinal Permeability and Pathogenesis of Disease

There are a number of diseases that have been thought to arise or be perpetuated by an increase in mucosal permeation of macromolecules. The possibility that extraintestinal disease may occur as a result of increased intestinal permeability, by the mechanism of simple or induced molecular mimicry, is inconclusive and controversial but somewhat strengthened by findings that increased intestinal permeability to ^{51}Cr-EDTA correlates with macromolecular permeation.[77–79]

Locally increased intestinal permeability leads to an imbalance in the normal interaction between luminal aggressive factors and mucosal defense, resulting in low-grade inflammation as best shown by nonsteroidal anti-inflammatory drug (NSAID)–induced enteropathy.[80]

Investigation of the Effects of Drugs and Toxins on Intestinal Integrity

Tests of intestinal permeability have been useful for documenting the intestinal toxicity of drugs and environmental toxins, sometimes disclosing problems where none were thought to exist. Perhaps the best example is the effect of NSAIDs on the small intestine.[80] NSAIDs increase intestinal permeability in humans within 12 hours of administration. This occurs predominantly during drug absorption, relates quantitatively to NSAID potency to inhibit cyclooxygenase, is partially reversed by concomitant prostaglandin administration, and is almost completely reversed with glucose-citrate formulations of indomethacin. Increased permeation of PEG is evident in experimental animals following NSAID administration,[81] but PEG 400, 1000, and 3000 permeation is normal or reduced in patients with rheumatoid arthritis receiving NSAIDs.[82,83] The permeability changes lead to small intestinal inflammation (NSAID-induced enteropathy) with bleeding, protein loss, ileal dysfunction, and strictures.[80]

A range of intestinal abnormalities is evident following chemotherapy for malignancies, and it is suggested that permeability measurements may provide an early warning of imminent drug toxicity as well as a means for assessing the possible protective effects of other drugs.[84–87]

Alcoholics have increased intestinal permeation of ^{51}Cr-EDTA, which returns to normal within 2 weeks of abstention.[88] The permeation of PEG 400, on the other

hand, is increased only during intoxication.[89] Intestinal permeability is not affected by inclusion of alcohol in the test solution,[1,90] but a modest dose of alcohol (0.5 g/kg) 15 hours before the test causes a significant increase in the permeation of ^{51}Cr-EDTA.[91] Studies in animals show that long-term alcoholic consumption increases paracellular permeability to horseradish peroxidase.[92] The clinical implications of increased intestinal permeability in alcoholics are speculative, but many alcoholics develop a low-grade enteropathy similar to NSAID enteropathy (unpublished results, January 1994). Other examples of drug-induced permeability changes in the small intestine include the effect of cetrimide[9] and neomycin (unpublished results, July 1994), but others are likely to emerge.

Application of Tests to Disease States

Celiac Disease

There is uniform agreement that the flat intestinal mucosa in patients with untreated celiac disease is associated with reduced in vivo permeation of PEG 400 and monosaccharides and increased permeation of oligosaccharides, ^{51}Cr-EDTA, and other poorly permeating test probes.[1-4,18,42,44,61,93] The permeability changes have been confirmed in vitro,[94] but when analyzed histomorphometrically, it is clear that while the total permeation of mannitol is reduced by as much as 35%, it is increased by at least twofold when related to mucosal surface area.[95] Similar calculations for raffinose showed a 65% increase in the tissue uptake of the marker, whereas per unit surface area, the permeability is increased fivefold.

Increased intestinal permeability is not a primary defect in patients with celiac disease because patients taking a particularly strict diet have normal intestinal permeability,[10] but it could predispose to the entry of gluten or of bioactive fragments thereof and, in consequence, perpetuate an existing lesion.[96] Alternatively[97] increased intestinal permeability (due to infection) may drive the enteropathy from minimal (latent) to overt. This is supported by the finding that first-degree relatives of patients with celiac disease have normal intestinal permeability despite subtle small intestinal morphological abnormalities.[98] In a naturally occurring animal model of celiac disease, increased intestinal permeability to ^{51}Cr-EDTA predates the characteristic mucosal lesion.[99,100]

Tests of intestinal permeability are inexpensive and sensitive in the detection of patients with untreated celiac disease, and useful in assessing strictness of gluten avoidance, the response to treatment, and confirming diagnoses. Their thoughtful use may often reduce the need for invasive investigations.

Inflammatory Bowel Disease

Tests of intestinal permeability are sensitive for the detection of patients with active small intestinal Crohn's disease, are useful for assessing treatment, and may have prognostic implications.[69,70] The behavior of PEGs, however, seems inconsistent and confusing in patients with Crohn's disease. The permeation of PEG 400 has been reported as both decreased and increased,[101-108] the permeation of PEG 1000 is reduced,[104,105] and that of PEG 600 is increased when instilled directly into diseased segments during surgery.[106] One suggestion is that abnormal intestinal permeability to PEG polymers occurs at a site away from the inflammation. This is in part supported by findings that the differential disaccharide permeation of raffinose and mannitol in vitro is increased in apparently unaffected parts of intestine from patients with Crohn's disease.[95]

An intriguing question is whether altered intestinal permeability plays a pathogenic role in Crohn's disease as opposed to the relapse.[51,56,102] Increased intestinal permeation of PEG 400 in first-degree relatives of patients with Crohn's disease suggested that a genetically determined abnormality of the intestine underlies the disease[102] or that the families were exposed to a common environmental toxin. These findings have, however, not been universally substantiated.[109-111] Moreover, intestinal permeability is usually normal in relatives when tested with the differential urinary excretion of sugars or ^{51}Cr-EDTA.[109,112] However, a proportion (around 10% in most studies) of relatives has increased intestinal permeability.[109,112-115] This is, in our view, within the variability of the method or due to transient disorders (not always apparent clinically) associated with increased intestinal permeability (alcohol, intestinal infections, and so on), but it is hoped that repeated permeability measurements and long-term follow-up of the above relatives will clarify the etiologic importance of a genetic basis for the permeability changes.

Intestinal Infections

Patients with *Giardia lamblia, Salmonella,* malaria, *Ascaris lumbricoides,* nonspecific gastroenteritis, hepatitis A, and *Rotavirus* infections have increased intestinal permeability as assessed by the differential urine excretion of sugars or ^{51}Cr-EDTA.[15,116-121] In *Rotavirus*-induced gastroenteritis, there is early normalization of the permeability changes when food is taken and persistence when patients fast.[117]

Strobel et al.[122] and Juby et al.[123] have shown that some apparently healthy subjects undergoing jejunal biopsy have increased intestinal permeability. On careful analyses of jejunal samples, these were found to be abnor-

mal, mainly with raised intraepithelial lymphocyte counts. It seems possible that these may represent an infective gastroenteritis that is insufficiently severe to cause diarrhea.

The permeation of PEG 400 and 1000 is undoubtedly reduced in *Giardia* and *Rotavirus* infection.[124,125] Permeation of PEG 400 may[126] or may not[127] be increased in *Yersinia* infection. PEG 400 permeation is reduced in patients who have undergone intestinal bypass surgery for morbid obesity, but the bypassed segment was not studied directly.[128]

Tropical malabsorption (tropical sprue) is probably a sequel to intestinal infection. Healthy residents of tropical areas have increased intestinal permeability in comparison with North Europeans,[75] which coincides with subtle jejunal morphological changes.[129] "Tourists" returning from the tropics have transient increases in intestinal permeability.[130]

Immunodeficient children with nonspecific intestinal bacterial overgrowth have increased intestinal permeability,[131] which may be important in the development of the enteropathy found in hypogammaglobulinemia.[132]

There are only a few studies on intestinal permeability in human immunodeficiency virus infection. Kapembwa et al. reported increased intestinal permeability in patients with acquired immunodeficiency syndrome (AIDS) with diarrhea.[27] Ott et al., however, found increased permeability in patients with AIDS regardless of intestinal symptoms most marked in patients with intestinal cryptosporidial infection.[133] These findings have been confirmed by two groups[134,135] who also showed that 20% of patients with human immunodeficiency virus infection without an AIDS-defining illness have increased intestinal permeability. Moreover, many patients with AIDS have severe malabsorption comparable or worse than found in untreated celiac disease, which may preclude attempts at enteral nutrition.[135]

Food Intolerance, Allergy, and Eczema

The subject of food allergy and intolerance is confounded by lack of agreed diagnostic criteria or when these are available (double-blind challenges); patients have not been subjected to them because of the work involved. Eczema is included in this section because of the suggestion that a genetically determined impairment of immunologic responsiveness to dietary antigens underlies this disease.[136] The distinction between adults and children is important when interpreting the findings from various sources, but there are still major discrepancies that cannot be explained rationally at this stage.

Adult patients with severe atopic eczema, half of whom had food intolerance, had normal in vivo and in vitro intestinal permeability,[137] which is similar to that reported by Barba et al.[138] Scadding et al. found that offending food in food-intolerant subjects caused increased permeation of ^{51}Cr-EDTA, but the changes were too small to be of diagnostic value.[139] Ukabam et al.[140] found increased lactulose permeation in adults with eczema. Newton et al. reported normal lactulose and reduced L-rhamnose permeation,[141] whereas Hamilton et al. found no consistent abnormalities.[142]

Using β-lactoglobulin as a permeability marker, Paganelli et al.[143] found food-intolerant patients to be normal, but the permeation of this marker decreased significantly following treatment with a hypoallergenic diet or sodium chromoglycate.

Andre et al. reported increased permeation of lactulose and normal permeation of mannitol in food-allergic patients.[144,145] Dumont et al. found normal intestinal permeability in food-allergic eczematous children[146] yet reported significant increases in intestinal permeability in children with irritable bowel syndrome following challenges to foods to which they were sensitive.[147] In contrast, Pike et al. found significantly increased permeability (lactulose/mannitol) in 26 atopic children, many of whom were on a restricted diet as part of their treatment,[148] but, curiously, a subsequent publication showed only 4 of 26 to have abnormal excretion ratios of lactulose/L-rhamnose.[149]

However, children with cow's milk intolerance have markedly increased permeation of ^{51}Cr-EDTA and lactulose/mannitol.[150–152] One study found a difference in intestinal permeability between breast-fed infants and those receiving cow's milk formula, all of whom were clinically well.[153]

The results reported with PEG have been more consistent, possibly because a single group has performed most of the work. Jackson et al.[154] found that patients with eczema had increased permeation of PEG 4000 regardless of concomitant food allergy but, paradoxically, the results of simultaneously administered PEG 600 were normal. Falth-Magnusson et al.[155] found no significant difference in the permeation of PEG 400 and 1000 between normal children and those with a diagnosis of food allergy. The same group also found normal intestinal permeability in a large number of women with atopic eczema.[156] Furthermore, children with cow's milk allergy were normal even with a challenge.[157] Patients with rhinoconjunctivitis due to birch pollenosis have normal permeation of PEG 400 and 1000,[158] and patients with nasal polyps have normal differential urine excretion of sugars.[159]

Thus, although no firm conclusion can be made with regard to the importance of altered intestinal permeability in patients with atopic eczema, food intolerance, or

allergy, there is some evidence of altered intestinal permeability in these subjects, in particular in children. It is hoped that with stricter diagnostic criteria a more complete picture may emerge.

Malignancy and Chemotherapy

The severity of gastrointestinal damage may be the limiting factor that determines the dose of cytotoxic drugs,[87] and their administration may lead to malabsorption, which compromises nutrition.

Siber et al. studied patients undergoing treatment with 5-fluorouracil for metastatic cancer following resection of colonic carcinoma[84] and found a 2–20-fold increase in the permeation of [^{14}C]PVP. Pearson et al. reported normal intestinal permeability (lactulose/mannitol) in children with acute lymphoblastic leukemia, but there was a marked increase following combined induction chemotherapy.[85] Increased intestinal permeability persisted during maintenance treatment with complete recovery following cessation of treatment. Using a less intensive treatment schedule with a variety of drugs, Pledger et al. found mostly reduced mannitol permeation in children undergoing treatment for solid tumors.[86] Selby et al. showed the intestinal toxicity of melphalan with ^{51}Cr-EDTA but more importantly showed how the test can be used to assess the effectiveness of various treatments aimed to reduce the gastrointestinal toxicity of cytotoxic drugs.[87,160,161] Permeability measurements are also useful in identification of graft-vs.-host disease[160,162] before it becomes clinically evident and graft rejection following intestinal transplants.[163,164]

PEG permeation has been less well defined. Lifschitz and Mahoney reported altered permeation of PEG polymers during methotrexate treatment in children during the maintenance treatment phase of acute lymphoblastic leukemia.[165]

Miscellaneous

There are reports showing altered intestinal permeability in a variety of different situations, including diabetes mellitus,[166] pulmonary sarcoidosis,[167] in smokers,[168] and cystic fibrosis,[169,170] in which it is suggested that the viscous mucus secretions predispose to infection and following prolonged fasting[171–173] but many require further study.

An intriguing study by Budillon et al. showed that intravenously administered cholecystokinin increased the 5-hour urine excretion of lactulose.[174] Pretreatment with chenodeoxycholic acid but not ursodeoxycholic acid augmented this response. Erickson and Epsten showed that single doses of chenodeoxycholic acid (750 mg) increased intestinal permeability in humans.[175]

In burn patients, increased intestinal permeability occurs within 30 hours,[176] is a significant risk factor for sepsis,[177] and subsequently correlates with the severity of sepsis.[178] The suggestion is that loss of intestinal barrier functions contributed to the infection, but the converse might hold true because intestinal permeability is increased following intravenous injection of endotoxins in humans.[179] An additional factor to consider in severely ill patients is the effect of uremia on intestinal permeability.[180,181]

Wood et al. examined the possibility that intestinal permeability might play a pathogenic role in schizophrenia[182] and found significantly increased cellobiose/mannitol urine excretion ratios. Others describe normal permeation of ^{51}Cr-EDTA in psychiatric patients.[183]

Children with recurrent abdominal pain ("recurrent syndrome"), which is regarded as a migraine equivalent, have increased permeation of ^{51}Cr-EDTA, which is interesting because alcohol and specific foods may cause migranous attacks.[184]

The aging human intestine maintains its integrity, whereas the permeation of PEG 400 and 900 increases with age in the rat.[185,186]

Cirrhotic patients with portal hypertension have normal intestinal permeability,[187] which is interesting because portal hypertension is one of the causes of a protein-loosing enteropathy. In addition, Wicks et al. showed that the damage to the small intestine during hepatic transplant surgery[188] is minimal and certainly less than found immediately following cardiopulmonary bypass,[189] following major vascular surgery,[190] or in the critically ill.[191] Milder degrees of intestinal hypoperfusion may account for the increased intestinal permeability in long-distance runners.[192]

Iron deficiency in children is associated with increased intestinal permeability (lactulose/L-rhamnose).[193] If substantiated, it will have important implications for interpretation of test results.

Indian curry "makes you hurry," but it does not alter intestinal permeability.[30]

Conclusions

The technical and clinical aspects of assessing intestinal permeability noninvasively in humans have come a long way in the last 20 years. The main milestone was the formulation and application of the principle of differential urinary excretion of orally administered test substances. Tests of intestinal permeability have been widely applied to various clinical conditions and found to be clinically useful as screening procedures for small intestinal disease, assessing response to treatment, confirming diagnoses, and, in some cases, predicting the

clinical course of disease. At present, experimental work designed to clarify the precise anatomic correlates of the permeation pathways and the various subcellular mechanisms of their regulatory control is clearly lagging behind the clinical studies but promises to be an exciting and rewarding area of future research.

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