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THE HYDROGEN BREATH TEST AND GASTRO-INTESTINAL DISORDERS

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■ The hydrogen breath-analysis test as a means of diagnosis of gastrointestinal disorders was first introduced in 1969.[1,2] During the past 12 years, progress has been made in its technology, diversification of application, and in understanding its potential.

In recent years, emphasis on precision and accuracy of assessment and also comfort and safety of the patient has led to a search for and an application of noninvasive procedures in clinical diagnosis. The primary attraction of the hydrogen breath test is the noninvasive nature of the collection procedure. It involves only the sampling of air exhaled by the patient after ingestion of a nonradioactive, usually natural, substrate.

INTESTINAL HYDROGEN PRODUCTION

When a carbohydrate is exposed to bacterial flora of the human intestinal tract under the appropriate conditions of pH and stasis, anaerobic fermentation results in the production of hydrogen gas. The hydrogen formed in the intestine by bacterial action has several possible destinations. The majority is expelled in the postprandial flatus; 14% to 21%, is absorbed from the colon and quantitatively expelled in expired air as breath hydrogen.[3] The same amount of hydrogen is produced in a given person for a given amount of nonabsorbed carbohydrate substrate whether the source be a simple sugar, a disaccharide, or a starch polymer. Thus, a number of hydrogen breath tests of clinical interest have been designed using the oral administration of carbohydrates including lactose, sucrose, glucose, lactulose*, D (−) xylose, and dietary fiber.

BREATH COLLECTION AND STORAGE

In the early days of the hydrogen breath test a closed system of rebreathing to collect expired air for analysis was used. Subsequently, a system of collecting breath samples at timed intervals (e.g., every 30 or 60 minutes) after administering the carbohydrate dose has been adopted. Air present in the bronchial tree represents an "anatomical dead-space" that acts during the expiratory cycle to dilute the concentration of the gas sample compared to the breath at the alveolus. To reflect the hydrogen

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*Lactulose (4-O-β-Galactopyranosyl-D-fructofuranose) is a nondigestible, and therefore nonabsorbable disaccharide of galactose and fructose. It is metabolized by colonic bacteria and serves as a nonabsorbable reference marker for hydrogen breath analysis.

concentration at the alveolar level, therefore, most collection systems for the interval open-sampling of breath, involve either a Haldane-Priestly tube or the end-expiratory gas.

Because of their painless, noninvasive nature, breath tests are especially suitable in pediatric diagnosis. Collection systems appropriate for infants and young children have been devised.[4-7] If a mask, valve, and gas bag are used (Figure 1), one must accept a constant 30% dilution in the hydrogen concentration attributable to the anatomic dead-space in the tracheobronchial tract. The mask-valve-bag system is well tolerated by children when presented as a game of balloon inflation. Soft nasal prongs or nasal catheters in the posterior nasopharynx are often used in children to collect air that reflects alveolar concentration.[4,8] Collection may be complicated by crying or irregular ventilation, however, regardless of the system used. This complication is not usually severe, but it has been suggested that the hydrogen concentration can be normalized by referring it to another gas in expired air such as CO_2 or O_2.

Figure 1. Procedure for collecting expired air at intervals using mask, one-way valve, and gas-bag, and obtaining mixed pulmonary gas samples.

Hydrogen is the most diffusible of gases, raising important considerations regarding storage of breath samples before analysis. Expired air should be collected in or immediately transferred to an appropriate gas-tight vessel. Many laboratories have constructed special gas envelopes made of mylar-impregnated foil paper to conserve a constant hydrogen concentration for seven weeks.[8] Rubber-stoppered, glass-walled test tubes [Vacutainer] can maintain hydrogen for three weeks.[8] Oiled glass syringes or plastic syringes can be used for storage of breath samples during a 12 to 24-hour period before analysis without significant loss of hydrogen.[8] The syringe collection and storage technique allows a patient to administer the breath test at home or office, or a parent to test a child at home.

DETECTION AND QUANTIFICATION

In the fasting state, the normal individual expires a low, but detectable, amount of hydrogen ranging in concentration from 2 to 20 ppm and remarkably constant. Three analytical techniques have been used to measure the concentration of hydrogen in the breath including—thermal-conductivity gas chromatography; helium-ionization gas chromatography; and mass spectrometry. Thermal-conductivity gas chromatography is most widely used and most practical clinically. The instrumentation for determining and recording breath hydrogen concentrations by thermal-conductivity chromatography can be obtained for as little as $2000.

Malabsorption of a carbohydrate is detected by an increase in the production of hydrogen above the usual baseline rate. Since the continuous, closed rebreathing systems of collection have given way to interval sampling procedures, quantitation of the concentration of hydrogen in the breath has replaced determination of the rate of hydrogen production. The response of breath hydrogen to an oral dose of carbohydrate depends on the amount of substrate given and the inherent absorbability of the carbohydrate. Accumulated experience from many laboratories suggests that when the hydrogen breath test is used as an absorption test, an increase in breath hydrogen concentra-

tion above baseline (fasting) levels in excess of 20 ppm represents biologically significant malabsorption of the carbohydrate. This criterion is widely accepted in clinical practice as an index of absorptive abnormality.

Some investigators sample only at two times, before the dose and two hours after the dose.[9] We advocate that samples be collected for six hours, at 30-minute intervals in children and at 60-minute intervals in adults to provide suitable sensitivity using the interval sampling procedures.[10,11] With this number of data points, a quantitative expression of the total excess hydrogen excretion (i.e.,. the rate of breath hydrogen excretion above baseline conditions) can be derived by integrating the area under the discontinuous curve of hydrogen concentration.[5,10] The increase in pulmonary hydrogen excretion per gram of carbohydrate not absorbed is about 2 cc/2 hours.[10,12] An actual chromatogram and its translation into a curve of the change in breath hydrogen concentration is shown in Figure 2.

Table 1 • Major Clinical Applications of the Hydrogen Breath Test in Gastrointestinal Diagnosis

Lactose malabsorption
Sucrose malabsorption
D(–)xylose malabsorption
Bacterial overgrowth
Intestinal transit time

DIAGNOSTIC APPLICATION

A number of hydrogen breath tests have been developed, and their major clinical applications are listed in Table 1.

Lactose Malabsorption

The use of the hydrogen breath-analysis technology to measure lactose absorption was the earliest clinical application and remains the most common.[1] Other diagnostic approaches for lactose malabsorption—intestinal

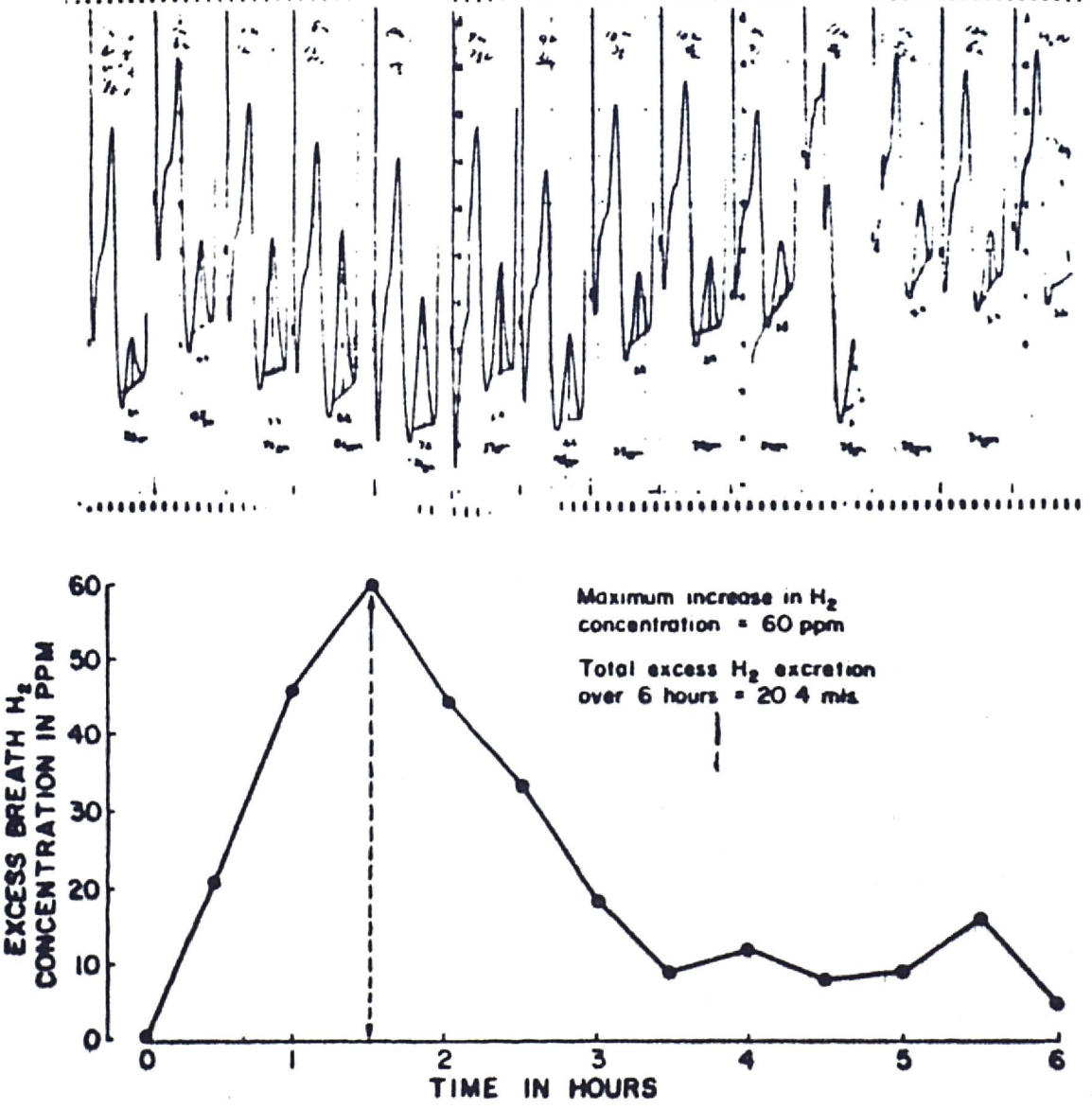

Figure 2. Above, chromatogram obtained 1.75 gm lactose was administered to a lactose-malabsorbing preschool child. Below, transcription of the hydrogen concentration data to calculate maximal rise and excess volume of breath hydrogen in response to the lactose load. (From Solomons NW, et al.[5] Used with permission.)

biopsy, plasma glucose or galactose monitoring ^{14}C-lactose breath tests, stool pH, fecal reducing-substances, intestinal perfusion and lactose-barium radiography—have some disadvantage of invasiveness, radiation exposure, or lack of accuracy. A number of studies have indicated correspondence of flat glucose curves and increments of 20 ppm in breath hydrogen after conventional oral lactose loads using the interval sampling.[10,13] Moreover when compared to intestinal biopsy mucosal lactase activity, or lactose perfusion techniques, the hydrogen breath test was the indirect method with the best sensitivity and specificity.[8,14] Unlike the plasma glucose approach, the hydrogen breath test is sensitive enough to detect lactose malabsorption from an oral dose of 12.5 gm lactose, equivalent to the content of 8 ounces of milk, or from lactose in the form of cow's milk or cheese.[1,11,14,15] Figure 3 illustrates the results of hydrogen breath tests using lactose, milk, or glucose and galactose in a lactose-malabsorbing child.

The lactose absorption hydrogen breath test is ideally suited to field surveys. A high prevalence of lactose malabsorption has been detected in American Indians living on reservations and in Bangladeshi villagers.[9,16,17] It can also distinguish between milk intolerance (i.e., adverse symptoms following mild ingestion) and lactose malabsorption (i.e., incomplete hydrolysis of the sugar).[18,19] It has been used to investigate the role of lactose malabsorption in pediatric abdominal pain, senile osteoporosis, and postgastrectomy diarrhea.[20-22] Figure 4 shows the handling of a 1 gm/kg lactose load in various groups of adults, normal, lactase-deficient, or with prior gastric surgery.[22]

Sucrose Malabsorption

A rare condition of acquired or congenital absence of the mucosal disaccharidase responsible for the hydrolysis of sucrose—sucrase-isomaltase—will produce a maldigestion and malabsorption of dietary sucrose. Since consumption of sucrose usually exceeds that of lactose, the manifestations of this disease can be severe. A tolerance test based on the rise in plasma glucose level has been the traditional indirect method for evaluating hyposucrasia. An increase in breath hydrogen after an oral dose of sucrase has recently been shown to be

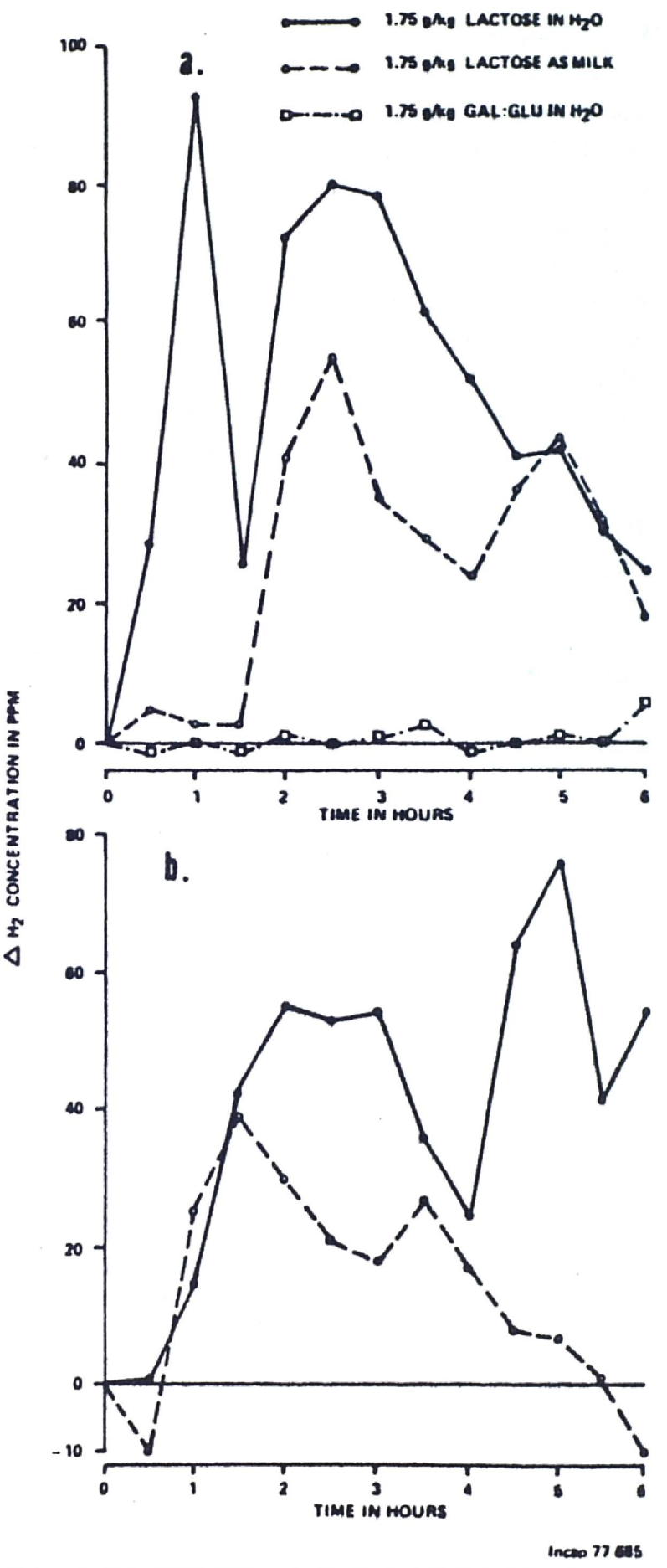

Figure 3. Serial determinations of breath hydrogen concentration after administering 1.75 gm carbohydrate to a lactose-malabsorbing preschool child on two occasions during his recovery from protein-energy malnutrition. Above, response to aqueous lactose, whole milk, and an equimolar glucose-galactose mixture. Below, responses to aqueous lactose and milk. Note persistence of lactose malabsorption despite nutritional recovery and a greater evolution of hydrogen in response to an aqueous solution compared to milk.

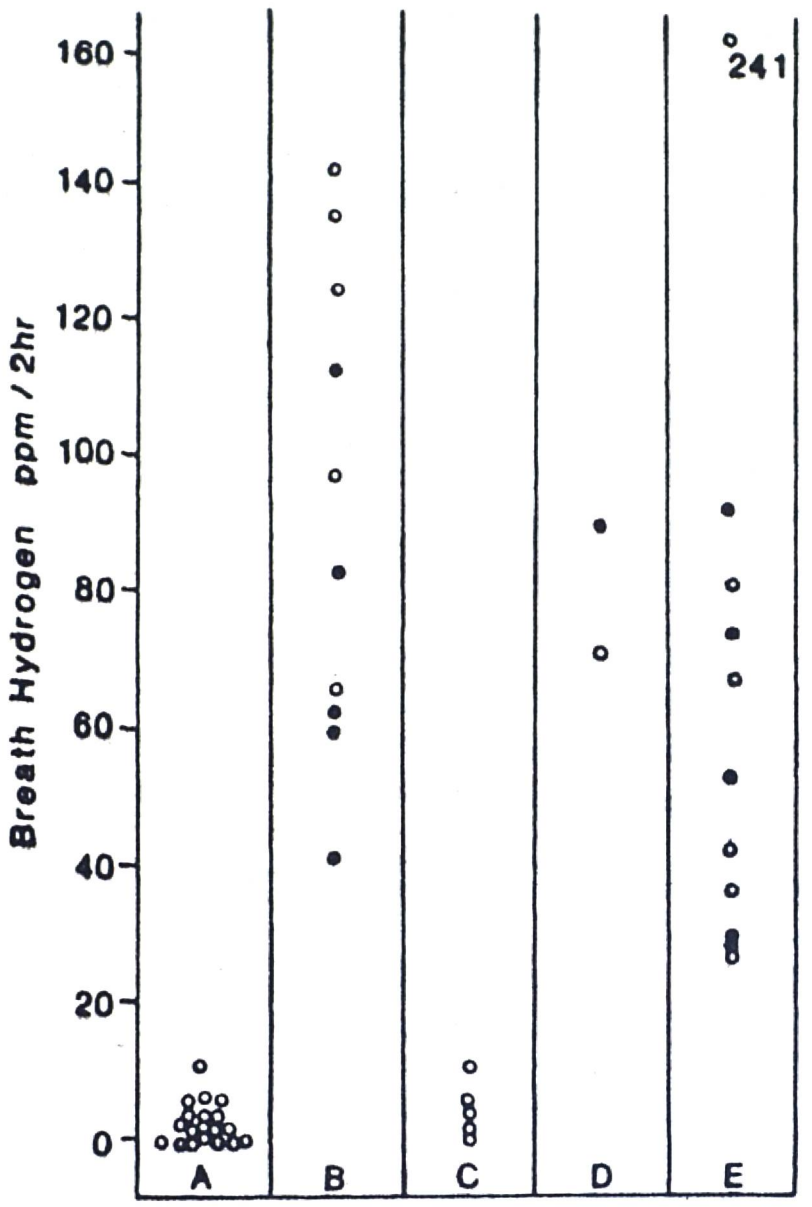

Figure 4. Circles represent the mean change in breath hydrogen concentration of 13 breath samples taken at 10-minute intervals over two hours following a dose of lactose 1 gm/kg weight in various groups of adults. Closed circles represent patients who had diarrhea with the test. A, subjects without prior gastric surgery and normal lactase activity; B, subjects without prior gastric surgery and low lactase activity; C, postgastric surgery subjects with normal lactase activity; D, postgastric surgery subjects with low lactase activity; E, postgastric surgery subjects with normal lactase activity. (From: Welsh JD, Griffiths WJ.[22] Used with permission.)

a reliable index of sucrose malabsorption.[6,23,24] The test must be used selectively, however, as the condition is so rare that screening with sucrose absorption hydrogen breath tests in a population of children with gastrointestinal symptoms of unknown origin had a low diagnostic yield.[24]

D(–)xylose Absorption

The pentose sugar, D(–)xylose, is often used to evaluate suspected intestinal malabsorption. The conventional D(–)xylose absorption test involves the timed collection of urine or sampling of plasma for circulating xylose. The difficulty with both collection procedures, especially in children, has led investigators to explore the potential use of hydrogen breath analysis to detect and quantify the malabsorption of D(–)xylose. This has been only partially successful. Schneider found a reasonable correlation between D(–)xylose malabsorption as determined by urinary excretion compared with that assessed by breath hydrogen production. Our experience at the University of Chicago showed the breath-analysis approach with D(–)xylose to be unsatisfactory (Kirschner BS, Rosenberg IH, Solomons NW, et al., unpublished findings). The inherent problem with D(–)xylose is that, as an only partially absorbable substrate, some fermentation would be expected whenever 25 gm sugar is consumed, even by a normal individual. Thus, the discrimination of abnormal from normal amounts of post-xylose hydrogen production along a broad continuum is a virtually insoluble problem.

Bacterial Overgrowth

Colonization of the upper small bowel with fecal bacteria occurs in conditions such as fistulae, blind-loop, jejunal diverticulosis, diabetic gastroparesis, and others. Diagnosis by a hydrogen breath test has been reported by investigators using 50 gm glucose as the substrate; appearance of a peak >20 ppm within two hours of the glucose administration signified bacterial overgrowth in the upper intestine. The hydrogen breath test was specific but not highly sensitive. A number of false-negative (but no false-positive) results were seen. But, when combined with the ^{14}C-glycocholate breath test, diagnostic sensitivity was over 90%.[25]

Intestinal Transit Time

Diagnostic evaluation of a meal's transit time from the mouth to the colon has been the subject of numerous approaches in gastroenterology. Some involve intubation procedures; others involve radioisotopes or X-ray. The use of nonabsorbable carbohydrate markers and hydrogen breath-analysis was logical in searching for a less hazardous and less invasive measure of intestinal transit time.[26] The

procedure involves administering 10 gm lactulose and monitoring the time until a significant increase in breath hydrogen excretion is noted; this time marks the passage of the lactulose into the colon. It has been used in conjunction with a continuous collection, rebreathing system, but an interval sampling approach with frequent collections could be adapted.[26,27] In patients with a partial gastrectomy and chronic diarrhea the time interval was 35.2 minutes compared to 74.6 minutes in postgastrectomy patients with normal bowel function.[27] The increased transit also produced some glucose malabsorption in the postgastrectomy patients with diarrhea, also detectable by breath hydrogen analysis.

Miscellaneous Applications

The hydrogen breath-analysis has received a number of minor applications. The hydrogen response to xylose, lactulose, or lactose failed to distinguish British patients, recently returned from overseas with tropical malabsorption, from healthy individuals.[28,29] Some pediatric investigators reported that a substantial increment in breath hydrogen concentration heralds the onset of necrotizing enterocolitis in high-risk neonates, and its use in surveillance in neonatal intensive care has been proposed.[30] This finding has not been universally reproducible, however. The rare, idiopathic syndrome of pneumatosis cystoides intestinalis, characterized by gas-filled cysts in the intestinal walls and mesentery, is associated with a brisk excretion of excess breath hydrogen after administration of 50 gm oral glucose.[31]

INTERPRETATION OF TESTS

The pulmonary excretion of hydrogen in response to carbohydrate fermentation in the lumen of the intestinal tract depends on numerous factors including type and number of bacteria, colonic motility and milieu, and exogenous contaminants. Thus, a number of pitfalls in the application and interpretation of the hydrogen breath test have been identified (Table 2).

After a challenge with a nonabsorbable carbohydrate 5% to 20% of individuals in a given population do not show any increase in breath hydrogen excretion. This finding has been attributed to the absence of an appropriate bacterial flora in the colon for fermentation of carbohydrate substrates. The administration of oral antibiotics, or mechanical procedures such as enemas, will similarly reduce the colonic flora, and attenuate or abolish the hydrogen response.[10,32,33] Either of these conditions will invalidate the application of a hydrogen breath test. When a patient is suspected of not having the appropriate flora for either idiopathic or iatrogenic reasons, his or her capacity to respond can be tested with the administration of lactulose.

Table 2 • Influences on Interpretation of Hydrogen Breath Tests

Idiopathic absence of the appropriate flora
Iatrogenically induced absence of the appropriate flora
Active diarrhea
Acidic colonic milieu
Delayed gastric emptying
Uninterrupted sleeping during test
Tobacco smoking
Inclusion of fiber or oligosaccharides in test meals

Numerous reports have shown that acute diarrhea reduces the rate of pulmonary excretion of hydrogen for a given amount of malabsorbed carbohydrate, possibly because of (1) reduction or alteration of the colonic flora, (2) change in the route of hydrogen excretion, or (3) decreased time for contact with the bacteria. Whatever the mechanism, the hydrogen breath test is rendered invalid in the presence of active gastroenteritis or persistent diarrhea.

Another factor in the hydrogen production appears to be the pH of the colon. Perman et al. showed that acidic conditions reduce bacterial fermentation of carbohydrates and impair the efficiency of the hydrogen response.[34] Ingestion of lactose over a period before a lactose absorption test might blunt the hydrogen response. Similarly, hydrogen breath tests in breast-fed infants known to have a normally acidic stool might suffer a similar distortion of the hydrogen response.

Infants and sick or malnourished children may have irregular gastric emptying and show

prolonged gastric retention of a carbohydrate. Since substrate must reach the colon for hydrogen to be produced, delayed passage of it from the stomach to the duodenum would delay or attenuate the appearance of hydrogen. The provision of the substrate as a food, such as milk, lowers the rate of gastric emptying compared to a comparable aqueous solution in children, but not necessarily in adults.[11,35] This points out the need for a six-hour period of observation.[10]

The concentration of hydrogen for a given amount of nonabsorbable carbohydrate is increased during sleep. Figure 5 shows the hydrogen response to 6 gm lactulose in the same three children studied twice, once while awake and again during uninterrupted sleep.[10] The mechanism for this increase in breath hydrogen concentration during sleep is not known, but it can complicate the interpretation of breath tests from infants who fall asleep and stay asleep immediately after ingesting carbohydrate.

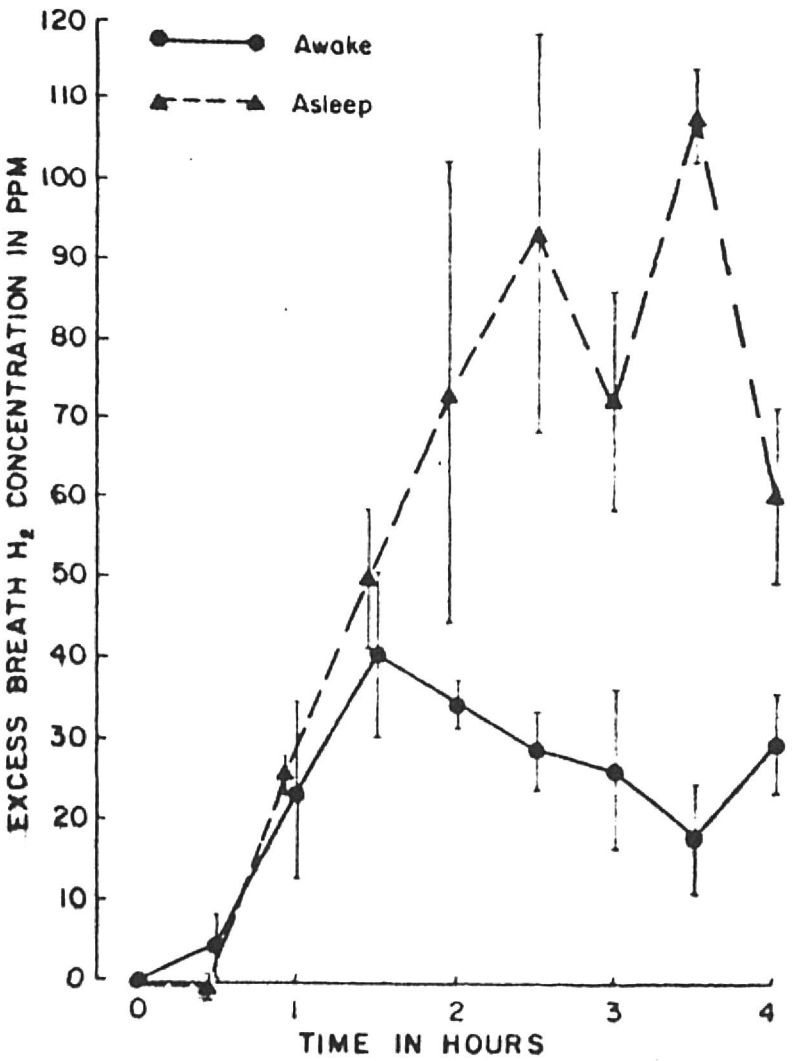

Figure 5. Serial determinations of breath hydrogen concentration after administering 6 gm lactulose to preschool children. The points represent the mean change in three children studied once while fully alert and awake, and one while asleep. Sleep increases the hydrogen concentration for a given dose of carbohydrate substrate. (From: Solomons NW, et al.[10] Used with permission.)

Finally, tobacco smoke contains exogenous hydrogen. Smoking during a hydrogen breath test produces artifactual rises in hydrogen concentration. Also, dietary fiber and oligosaccharides (such as found in beans) represent undigestible carbohydrates. If they are included in a test meal along with another reference carbohydrate, such as lactose, the interpretation of any rise in breath hydrogen production is difficult.

MALABSORBED CARBOHYDRATE

It was assumed that incomplete digestion or absorption of such nutritionally relevant carbohydrates as lactose or sucrose in the small intestine meant their loss from the energy economy of the organism. Recently, however, it has been demonstrated in experimental animals and in humans that much of the carbohydrate reaching the colon is converted by bacterial action into short-chain, volatile fatty acids.[36,37] These two-carbon fragments can be absorbed by the colonic mucosa, and presumably the carbon supply can be utilized for energy metabolism. If carbohydrate malabsorption accompanies or produces diarrhea, however, the efficiency of this colonic recovery of carbon is likely to be reduced. The important consideration is that hydrogen breath tests of absorption measure small bowel function and do not necessarily predict nutritional consequences.

CONCLUSIONS

The hydrogen test is simple, inexpensive, convenient, and versatile. The collection procedures are painless and noninvasive. Physiologic doses and food sources of carbohydrate can be substituted for the pharmacologic doses used in the past. The test is useful for assessing lactase and sucrase functions, transit time in the intestinal tract, and bacterial colonization. The sensitivity and specificity of the tests are not 100%, but they are generally better than, or comparable to, those of the more costly and invasive diagnostic procedures. In clinical ap-

plication, the practitioner must remain cognizant of the pitfalls that have been identified to avoid errors in the administration of hydrogen breath tests and in the interpretation of their results. ▲

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