Dose dependence of breath hydrogen and methane in healthy volunteers after ingestion of a commercial disaccharide mixture, Palatinit®

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1. Breath hydrogen and methane were determined by gas chromatography in eleven normal individuals given a low-fibre, mixed diet (control) and after ingestion of 20–50 g Palatinit®/d, an equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®).

2. A linear relation was found (r 0·85; $P < 0·001$) between the amount of Palatinit ingested and breath H_2 per 10 h in subjects who did not exhale methane. If methane was formed in addition to H_2, the sum of both gases followed a linear dose–effect relation.

3. The mouth-to-caecum time, indicated by the first increase in breath H_2 after ingestion, was shortened by about half, yet no sign of diarrhoea was observed. Stool weight and stool frequency did not change significantly.

4. The linear relation between a dose of 20–50 g Palatinit and exhalation of H_2 (eventually plus methane) indicated that a relatively constant fraction of the dose given underwent cleavage and absorption in the small intestine, the remainder being transported into the large bowel. Microbial gas formation in the colon as well as the fractional transfer of these gases into the expiratory air occurred at fixed proportions, thus allowing an insight into colonic microbial contributions to carbohydrate utilization in the human large bowel.

Dietary oligosaccharides, not digested in the small gut (Wiggins, 1984), as well as small amounts of digestible carbohydrates like sucrose (Bond *et al.* 1980), fructose (Ravich *et al.* 1983) and starch (Anderson *et al.* 1981; Levine & Levitt, 1981; Feibusch & Holt, 1982) are transported into the lower, microbially colonized part of the digestive tract in healthy individuals. Together with dietary fibre (Cummings, 1984), variable amounts of glycoproteins from the intestinal secretions (Allen, 1981; Perman & Modler, 1982) mix in the colon with the above-mentioned dietary components to form the carbohydrate pool on which intestinal micro-organisms thrive by anaerobic fermentation (Cummings, 1983; Hungate, 1984). However, the amount of fermentable carbohydrates in the upper human colon is not precisely known. In an attempt to characterize and quantify microbial fermentations in the large bowel, we used the sugar substitute Palatinit® as a chemically well-defined material whose mammalian metabolism has been thoroughly investigated (Grupp & Siebert, 1978; Gau *et al.* 1979; Ziesenitz, 1983), including some aspects of its microbial utilization in the large intestine.

Palatinit, an equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®), is reported to undergo small-intestinal digestion in ambulatory ileostomy patients by about 40% (Kroneberg *et al.* 1979), the remainder, together with non-absorbed D-mannitol and D-glucitol (D-sorbitol), being fermented by the intestinal microflora (Grupp & Siebert, 1978; Schnell-Dompert & Siebert, 1980; Ziesenitz, 1983). End-products of fermentation include hydrogen and methane which, at a certain proportion,

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diffuse from the colon into the blood and are thus detectable in the expired air (Calloway & Murphy, 1968).

About 44% of the adult human population produce methane (Bjørneklett & Jenssen, 1982), which is formed by reduction of carbon dioxide with H_2 in methanogenic bacteria (Bryant, 1979; Doddema *et al.* 1979; Winter & Wolfe, 1980). Depending on the completeness of H_2 consumption, CH_4 or H_2, or both, are found in the expiratory air.

Frequently, the non-invasive breath test for H_2 in the end-expiratory air has been used in the diagnosis of various types of carbohydrate malabsorption (Bond & Levitt, 1977; Caspary, 1978; Hepner, 1978; Paige & Bayless, 1981). However, since the simultaneous determination of CH_4 requires more sophisticated experimental procedures, much less is known about its formation. In general, the usual breath test leads to qualitative information only (Bjørneklett & Jenssen, 1980). Since a substantial part of Palatinit is degraded microbially in the large bowel, we employed a quantitative assay system for H_2 and CH_4 in order to check whether a dose effect of Palatinit could be established on the exhalation of H_2 and CH_4, with the provision of a standardized, low-fibre diet and of an adaptation period of several days to the experimental conditions. In the present study a close correlation between the pulmonal gas excretion and the oral dose of the sugar-substitute Palatinit was established.

EXPERIMENTAL

Materials

Palatinit was a gift from Dr H. Schiweck, Obrigheim, and β-lactulose was purchased from E. Merck, Darmstadt.

Subjects

The investigations were carried out on eleven healthy female volunteers, aged 19–23 years. Their mean body-weight was 65·7 (SE 8·0) kg, the relative body-weight according to Broca's index was evaluated as 0·96 (SE 0·1). In preliminary trials, it was found that with a high-dietary fibre meal and a single oral dose of 10 g Palatinit, all subjects were H_2-responders. Apart from this ability, and the absence of any administration of antibiotics in the previous 90 d, the selection of the volunteers was randomized. Clinical check-up and laboratory values were taken before the start of the experiment; all values were found to be normal.

Experimental design

The volunteers received with their breakfast 200 ml orange juice and with their lunch 150 g yoghurt (control). Palatinit was added to the orange juice and the yoghurt for 1 week in a randomized order (for dosage of Palatinit, see Table 1). For purposes of calibration, two doses of 10 g β-lactulose (D-galactosyl-β(1 → 4)-D-fructose) as a non-digestible disaccharide were given at the end of a further control week. Each of the five experimental weeks (Table 1) was followed by an interval of at least 7 d.

Preliminary experiments had shown that a single dose as low as 5 g Palatinit led to a positive H_2 response (G. Siebert and P. Guinand, unpublished results), and that the adaptation and de-adaptation times of the H_2 excretion were less than 2 d (M. Fritz and G. Siebert, unpublished results). Therefore, we chose an adaptation period of 6 d in the present experiment with Palatinit, in accordance with Marthinsen & Fleming (1982), who found 5 d sufficient to establish a stable gas excretion after the addition of several dietary fibre components.

The regimen of each experimental week is detailed in Table 2. The first sample of respiratory air (see p. 392) was collected in the morning from fasted subjects and, after

Table 1. *Daily doses of Palatinit®* during five experimental weeks when half was administered at breakfast with 200 ml orange juice, and half at lunch with 150 g yoghurt*

Experimental week	No. of subjects	Palatinit dose (g) on days						
		1	2	3	4	5	6	7†
(1) Control	11†	—	—	—	—	—	—	—
(2) Palatinit	11	20	20	20	20	20	20	20
(3) Palatinit	7 or 4	20	20	30 or 35	30 or 35	30 or 35	30 or 35	30 or 35
(4) Palatinit	7 or 4	20	20	30 or 35	30 or 35	40 or 50	40 or 50	40 or 50
(5) β-Lactulose	11‡	—	—	—	—	—	—	20§

* An equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®).
† Sampling day (see Table 2).
‡ Five of the eleven subjects received additionally two 25 g doses of sucrose/d.
§ β-Lactulose, two 10 g doses.

Table 2. *Details of procedures during an experimental week*

Experimental day..	1 Thu	2 Fri	3 Sat	4 Sun	5 Mon	6 Tue	7 Wed
Administration of Palatinit®* twice daily (Table 1)	×	×	×	×	×	×	×
Entries on abdominal sensations	×	×	×	×	×	×	×
Standardized low-fibre diet	.	.	.	.	×	×	×
Stool collection	.	.	.	.	×	×	×
Analyses for hydrogen and methane in respiratory air during 10 h	.	.	.	.	.	.	×
Sampling of blood for serum analyses during 5 h	.	.	.	.	.	.	×

* An equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®).

breakfast, in hourly intervals for 10 h. Analyses of blood serum by standard procedures for glucose, triglycerides, cholesterol and insulin were performed on fasted subjects, and after breakfast, in intervals for 5 h. Serum analysis values from subjects receiving Palatinit were not significantly different from those of the controls (values not shown).

Dietary conditions

On days 5 and 6 of each experimental week (Table 2) a standardized mixed diet was given which contained, in energy-related percentages (total 8·2 MJ), protein 16%, fat 38%, carbohydrate 46%. Dietary fibre according to Paul & Southgate (1978) was 12 g/d and lactose (only from yoghurt) amounted to 6 g/d. The last meal before taking respiratory-air samples was given at 18.00 hours on day 6, thus allowing for a fasting period of 14 h before the measurements began. The diet on day 7 was balanced in nutrients as on days 5 and 6 except that a formula drink was given for breakfast. On days 1–4 of each experimental week, and in the intervals between experimental weeks, the diet could be chosen freely with the following restrictions: no dietary-fibre supplement, no extra sugar-substitute, no laxative.

Sampling of respiratory air and analyses for H_2 and CH_4

Since H_2 and CH_4 concentrations in single expirations were very low for the simultaneous estimation with one detector (Tadesse *et al.* 1979), exhaled air was concentrated, under absorption of CO_2 with soda lime, in a spirometer (VT-3; Hellige Co., Freiburg) with an initial oxygen pressure (P_{O_2}) of 43 kPa. Due to the large difference in partial pressures of H_2 and CH_4 between respiratory and spirometer air, concentrations of H_2 and CH_4 increase in a linear fashion during 5 min rebreathing into the spirometer. After exactly 5 min sampling, a 5 ml sample of air was drawn from the spirometer and 2 ml injected into the gas chromatograph. The analytical set-up was as follows: GC 5720A (Hewlett Packard) with thermal-conductivity detector; carrier gas N_2 at 30 ml/min; two stainless-steel columns in series, 3·0 m × 3 mm i.d. and 3·6 m × 3 mm i.d. packed with molecular sieves 5A and 13X, 60/80 mesh (Supelco Inc.); oven temperature 125°; detector temperature 150°; bridge current 150 mA. Peak areas were evaluated in comparison with standard gas mixtures (20 and 100 μl/l each of H_2 and CH_4 in N_2; Linde, Munich). With a correction for the respective bronchial and spirometer volumes, determined by the helium dilution method, the volumes of exhaled H_2 and CH_4 respectively were calculated as ml or μl gas/min.

Colonic functions

Stools were collected and stool frequency was noted on days 5–7 and the wet weight of the 72 h samples determined. An additional check for the eventual formation of CH_4 was made by gas chromatographic analysis of 2 ml gas sampled above the stool immediately after defaecation.

Mouth-to-caecum time was estimated as described by Bond & Levitt (1975). On day 7, in each experimental week, the volunteers recorded hourly the eventual occurrence of burping, abdominal noise, fullness, meteorism, flatulence, and abdominal pain; on days 1–6, these symptoms were noted once daily.

Statistical analysis

Differences between mean values were evaluated using Student's paired t test or, in the case of skewed distributions, with the Wilcoxon matched-pairs signed-rank test. Areas under the curve of the H_2 and CH_4 10 h profiles were calculated as the sum of the hourly determined values. These 10 h values were intra- and inter-individually correlated with the doses of Palatinit ingested. Correlations were tested for significance, and regressions were compared by means of one-way ANOVA.

Ethical considerations

The purpose, nature, risks and benefits of the experiment were described to the volunteers, and they were given the opportunity to ask and to have answered all pertinent questions. Informed written consent was obtained from all subjects.

RESULTS

Exhalation of H_2 and CH_4

Mean values of H_2 exhaled by seven subjects who had received 20, 30 and 40 g Palatinit respectively (Fig. 1) were significantly different ($P < 0{\cdot}0001$) from control values beginning with the second hour of the experiments until their completion in the evenings. The 10-h profiles after Palatinit ingestion were basically similar but higher with increasing doses of Palatinit. In the majority of experimental points (Fig. 1), H_2 exhalations after 20 and 40 g Palatinit differed significantly ($P < 0{\cdot}05$) from those after the 30 g dose. The integral of the

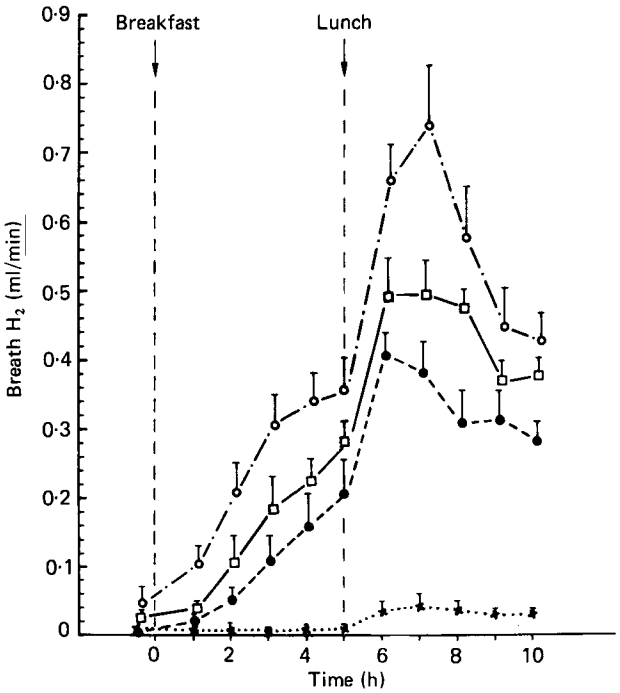

Fig. 1. Profile of breath hydrogen by non-methanogenic subjects on a low-fibre control diet (×) and with the addition of 20 g (●), 30 g (□) or 40 g (○) Palatinit®/d (an equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®)). Values are means with their standard errors, represented by vertical bars, for seven subjects.

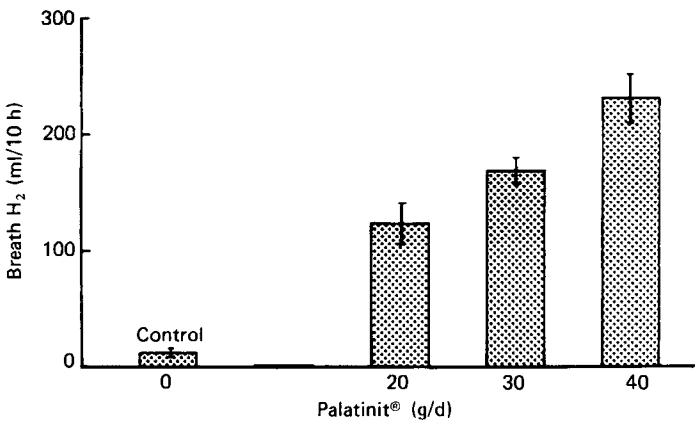

Fig. 2. Integral of 10 h total volumes of breath hydrogen in non-methanogenic subjects on a low-fibre control diet and with the addition of 20 g, 30 g or 40 g Palatinit®/d (an equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®)). Mean values with their standard errors, represented by vertical bars, for seven subjects.

10 h total H_2 volume (Fig. 2) increased in proportion to the amount of Palatinit ingested. The values in Figs. 1 and 2 include only those subjects whose CH_4 exhalation was below or at the level of detectability (5 μl/l = approximately 10 μl/min).

Three persons excreted in expired air or produced in the gas phase above their fresh stools, or both, CH_4 in excess of 5 μl/l (Table 3); in these persons proportionality between

Table 3. *Exhalation of hydrogen and methane (ml/10 h) after various doses of Palatinit®* by three methanogenic subjects after 6 d of adaptation*

Subject no.	Control		Palatinit dose (g/d) 20		35†		50‡	
	H_2	CH_4	H_2	CH_4	H_2	CH_4	H_2	CH_4
1007	26	10	175	9	157	10	221	—§
1010	2	34	59	61	161	54	190	114
1011	8	48	150	23	201	78	186	195

* An equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®).
† Subject no. 1007 received 30 g/d.
‡ Subject no. 1007 received 40 g/d.
§ CH_4 was not detectable.

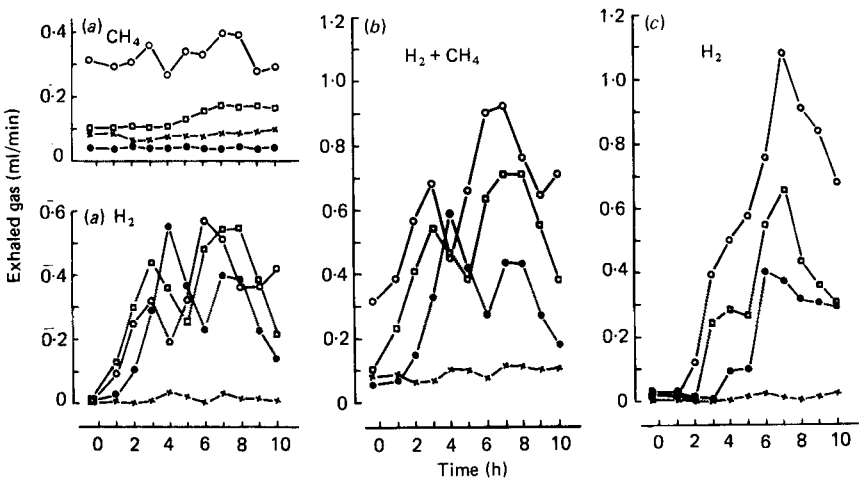

Fig. 3. Exhalation profile of (*a*) methane and hydrogen, and of (*b*) H_2+CH_4 by a methanogenic subject on a low-fibre control diet (×) and with the addition of 20 g (●), 35 g (□) or 50 g (○) Palatinit®/d (an equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®)), in comparison with the exhalation profile of (*c*) H_2 by a non-methanogenic subject; breakfast and lunch were served shortly after the first breath sampling and 5 h later as indicated in Fig. 1.

exhalation of H_2 and dose of Palatinit was diminished or eliminated. An example is given in Fig. 3 for one subject with elevated but almost peakless CH_4 values after Palatinit (Fig. 3(*a*)) and sharply raised but not dose-proportional H_2 values (Fig. 3(*a*)). When H_2 and CH_4 values were added, a methanogenic individual demonstrated a similar dose dependence (Fig. 3(*b*)) as did a non-methanogenic person (Fig. 3(*c*)).

Dose–effect relations

The integrals of the 10 h total volumes of H_2 (and of H_2+CH_4 volumes, see preceding paragraph) showed a positive significant correlation with the intake levels of Palatinit. For each of the eleven subjects, individual regressions were calculated for control and three Palatinit intake values (inset, Fig. 4) and their slopes were found not to differ significantly; accordingly, a regression line covering all experiments with Palatinit may be constructed

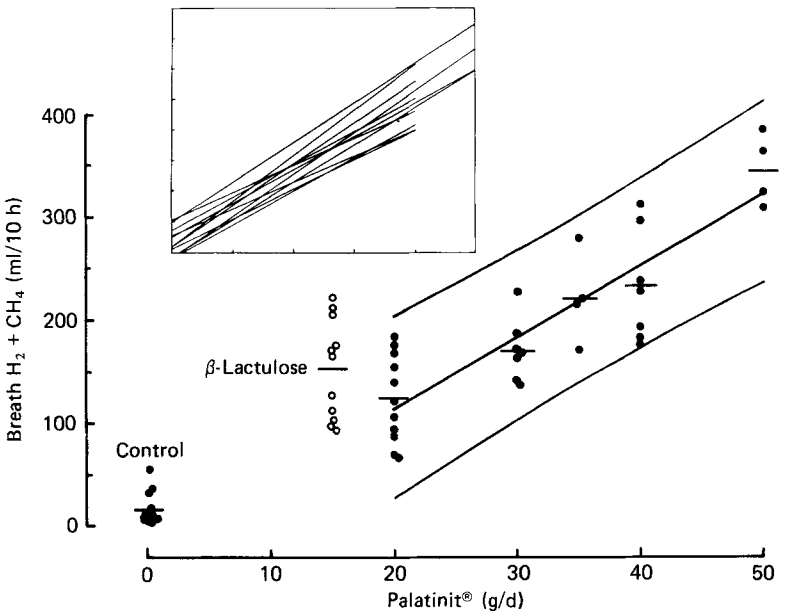

Fig. 4. Dose–effect relation of the integral of the 10 h total volume of hydrogen + methane in eleven healthy volunteers on a low-fibre control diet, with 20 g β-lactulose, and with various doses of Palatinit® (an equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®)). Regression line with 95% confidence interval; r 0·85; $P < 0·001$. Mean values are represented by horizontal bars. Inset: individual regressions.

(Fig. 4), characterized by r 0·85 ($P < 0·001$). It then follows that in 10 h, 6·4 (SE 1·6) ml H_2 or $H_2 + CH_4$/g Palatinit were excreted with the respiratory air.

β-Lactulose

Exhalation of H_2 after two doses of 10 g β-lactulose (Fig. 4) was higher than after the same amount of Palatinit, as expected from the inability of human small-intestinal enzymes to cleave β-lactulose; however, the difference between mean values was not significant. H_2 or $H_2 + CH_4$ exhalations after β-lactulose did not significantly correlate with exhalations after any dose of Palatinit.

Mouth-to-caecum transit time

The first significant increase of H_2 exhalation above the fasting value was caused by the breakfast containing Palatinit, since mouth-to-caecum times were shorter than the breakfast-to-lunch interval of 5 h. In Fig. 5, mouth-to-caecum times after different doses of Palatinit are depicted; they differed significantly from control values but their decrease was not linear with the respective doses of Palatinit. Diarrhoea, however, was never observed under the experimental conditions of the present study.

Weight and frequency of stools

Although higher bacterial activity in the large bowel was indicated by increased H_2 production, wet weights of 72 h stools did not change significantly (Fig. 6). Stools were frequently found to be softer and of less intense colour on days 5–7 but were never watery; in the adaptation period of days 1–4 (Table 2), eight subjects reported occasional thin stools.

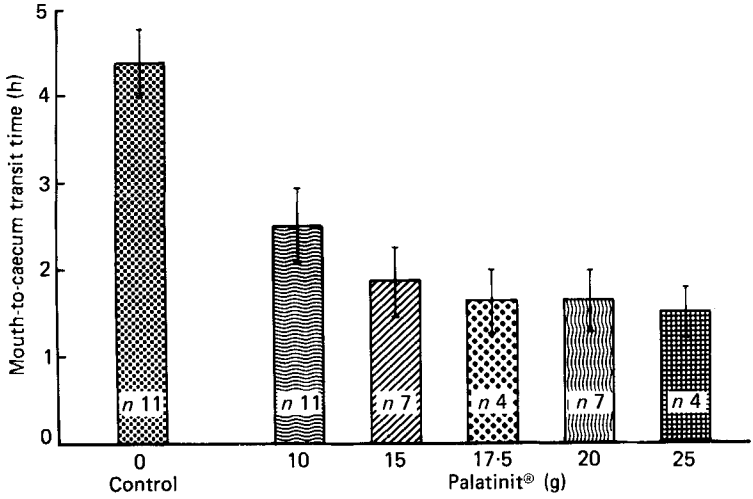

Fig. 5. Mouth-to-caecum transit time after formula breakfast (control) and after additional Palatinit® (an equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®)). Mean values with their standard errors, represented by vertical bars. Statistical significance of differences: control *v.* Palatinit® $P < 0{\cdot}001$; Palatinit® 10 g *v.* 20 g or 25 g $P < 0{\cdot}05$.

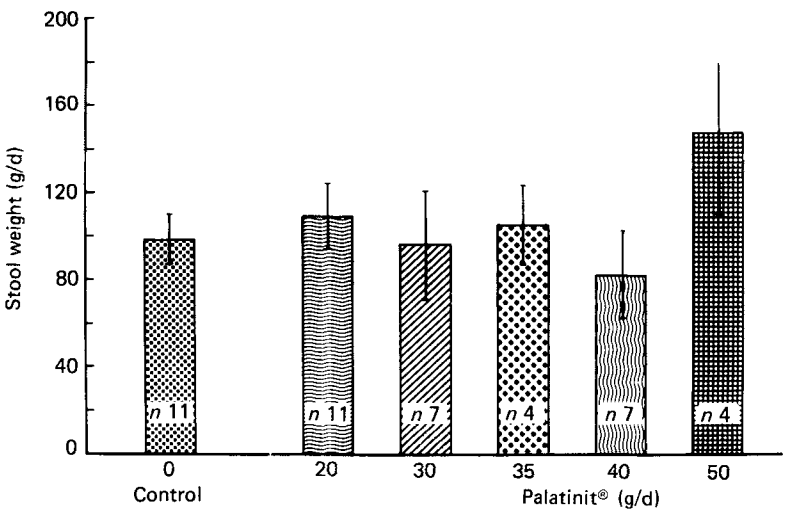

Fig. 6. Stool weights (g wet weight/d) on a low-fibre control diet and with the addition of 20, 30, 35, 40 or 50 g Palatinit®/d (an equimolar mixture of D-glucosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®)). Mean values with their standard errors, represented by vertical bars. Differences were not statistically significant.

Mean stool frequency was 1·1 (SE 0·2) in the controls and did not change significantly with the low, medium and high doses of Palatinit; corresponding values were 1·2 (SE 0·1), 1·0 (SE 0·2), and 1·3 (SE 0·2) respectively ($P < 0{\cdot}05$; *n* 11).

Abdominal sensations

Mean values of hourly recorded entries on day 7 of each experimental week (Table 2) are presented in Fig. 7. Abdominal noise, fullness and flatulence were more frequent with

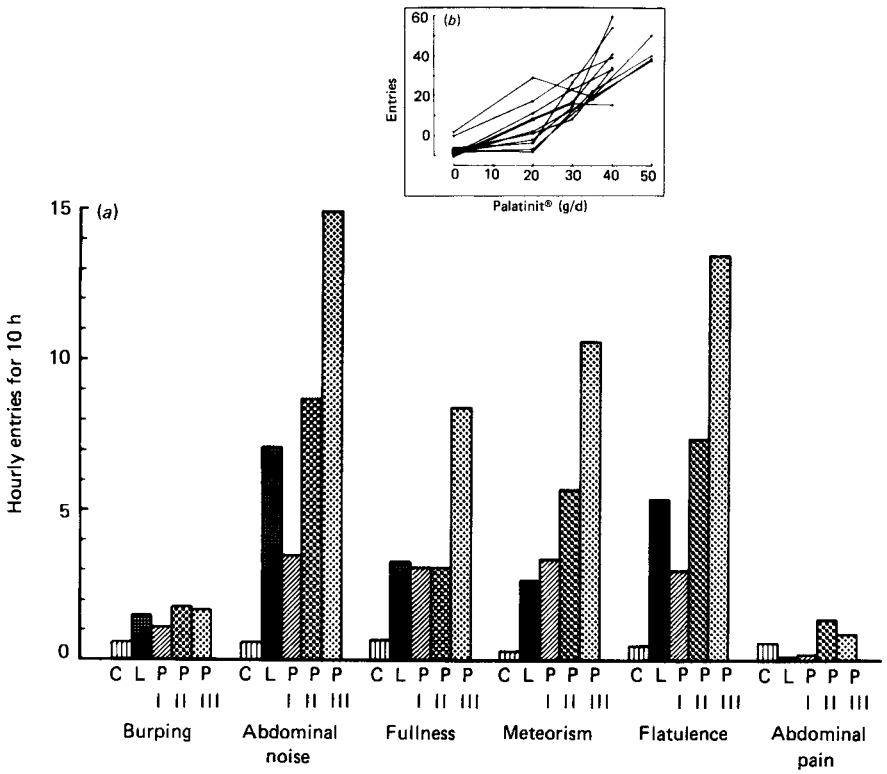

Fig. 7. (*a*) Hourly entries for 10 h (1 = mild, 2 = medium, 3 = strong) for abdominal sensations (means of eleven individuals) by volunteers on a low-fibre control diet (C), with the addition of two 10 g doses of β-lactulose (L), with the addition of two 10 g doses of Palatinit® (an equimolar mixture of D-glycosyl-α(1 → 1)-D-mannitol and D-glucosyl-α(1 → 6)-D-glucitol (Isomalt®)) (PI), two 15 g doses (*n* 7) or two 17·5 g doses (*n* 4) of Palatinit (PII), and with the addition of two 20 g doses (*n* 7) or two 25 g doses (*n* 4) of Palatinit (PIII). (*b*) Sum of abdominal sensations after various doses of Palatinit.

increasing doses of Palatinit but individual plots (Fig. 7(*b*)) indicated considerable variability of the symptoms. When compared with Fig. 4, abdominal sensations did not coincide regularly with H_2 or H_2+CH_4 exhalations. Even when several entries were made by the volunteers (Fig. 7), they noted their general state of health as good to very good.

DISCUSSION

Gas production in the large bowel is a ubiquitous physiological event, as generally exemplified by flatulence after certain meals and by the colonic utilization of dietary fibre; in western diets, 20–40 g fermentable carbohydrate are estimated to form the colonic pool of dietary and endogenous fermentable substrates (Cummings, 1981, 1983). With Palatinit as a representative of a whole group of nutritive sugar substitutes, colonic gas formation is enhanced (G. Siebert and P. Guinand, unpublished results). In contrast to dietary fibre material, Palatinit is a chemically well-defined substance. Thus Palatinit served in the present study both as a model compound for intestinal gas production and as the object of its more detailed investigation.

The exhalation of 6·4 (SE 1·6) ml H_2/g Palatinit in 10 h constitutes only an indirect measure of total colonic gas production. In the absence of an understanding of colonic H_2

and CH_4 formation (Wolin & Miller, 1983), the absolute amount of Palatinit degraded in the human colon cannot be assessed with certainty. It is thus surprising that such a close correlation between the oral dose of Palatinit contained in a whole meal and the pulmonal exhalation of H_2 or H_2+CH_4 (Fig. 4) could be established. It follows from this correlation that all processes between oral intake and breath exhalation should also occur with high regularity; e.g. enzymic cleavage, small-intestinal absorption, microbial fermentation, diffusion of H_2 and CH_4 into the bloodstream and then into expiratory air are not all dose-dependent after ingestion of Palatinit but occur at constant ratios independent of the dose. There is little doubt that a regular dose dependence will also be obtained with other carbohydrates and polyols, although perhaps at different absolute values. Such a regular dose dependence has not been, to the best possible knowledge of the authors, reported in the literature, except for β-lactulose in aqueous solution without pre-adaptation (Bond & Levitt, 1972). In the present study, the main factors contributing to the observed regularity are the 10 h quantification of gas exhalation and the introduction of suitable dietary conditions. The established dose–effect relation (Fig. 4) also demonstrates that the fermentative capacity of the colon is not exhausted by 50 g Palatinit: with 6·4 ml H_2/g Palatinit and about 14% of the produced H_2 showing up in exhaled air (Levitt, 1968), 45 ml H_2/g Palatinit or 2250 ml H_2/50 g Palatinit per 10 h are formed in the colon. If the fermentative capacity had been exceeded, diarrhoeal symptoms via the osmotic activity of intact carbohydrates (Saunders & Wiggins, 1981) should have occurred. It should be mentioned here also that undegraded Palatinit in stools in men (Musch *et al.* 1973) and animals (Grupp & Siebert, 1978; Kirchgessner *et al.* 1983; S. C. Ziesenitz, R. Vallon, E. J. Karle, C. Benning and G. Siebert, unpublished results) has never resulted in excretion levels exceeding 1% of the oral dose.

CH_4 exhalation occurs at relatively constant rates (Bond *et al.* 1971; Tadesse & Eastwood, 1978; Pitt *et al.* 1980; Tadesse *et al.* 1980; Bjørneklett & Jenssen, 1982), as was also observed in the present investigation (Fig. 3(*a*)) during 10 h when no sharp meal-related peak was found. The assumption of Wolin & Miller (1983) that CH_4 stems only from the fermentation of endogenous substrates cannot be entirely correct because two of our methanogenic subjects demonstrated, after 6 d of adaptation, a definite increase of CH_4 exhalation (Table 3), while H_2 exhalation alone showed little dose dependence (subjects 1010 and 1011). No qualitative alteration was observed in the present study in that methanogenic and non-methanogenic subjects stayed this way during the 15 weeks of experimentation.

Since dose-independent utilization of Palatinit in the small intestine must be inferred from these studies, and because limited small-intestinal utilization of Palatinit is one of the factors for its energy-reduced character, energy yield from Palatinit cannot depend on the dose administered within the range of the present study (20–50 g/d). H_2 and CH_4 formation from Palatinit is regarded as one of several reasons for the lowered energy yield; it may be calculated that 1 g Palatinit ($\simeq$ 16·3 kJ) giving rise to about 45 ml H_2 in the colon would lead to an energy loss of 3·5% due to colonic gas (1 g H_2 $\simeq$ 143 kJ; 45 ml H_2 $\simeq$ 0·57 kJ), which is much less than determined by more direct methods. The discrepancy will most likely be due to Palatinit utilization by micro-organisms not producing H_2 and to the lack of a quantitative understanding (Wolin & Miller, 1983) already mentioned.

β-Lactulose was tested in the present study because Bond & Levitt (1972) proposed its use as a reference substrate in measurements of H_2 in exhaled air. β-Lactulose acts quite differently when given in aqueous solution (La Brooy *et al.* 1983) compared with a whole meal (Read *et al.* 1980), and does not give a significant correlation with the gas formed after giving glucitol (Hyams, 1983) or Palatinit (present study). The discrepancy may be due to the method of administration, the competence of different bacterial strains (α- or β-glycosidic bonds respectively) and the absence of adaptation. However, whereas Bond & Levitt (1972)

found 1·9 ml H_2/g β-lactulose within 2 h, it may be roughly estimated that on a per h and per g basis, 1 ml H_2 after β-lactulose would correspond to 0·6 ml H_2 after Palatinit in the present study. Since β-lactulose is exclusively used in the large bowel, our findings could be tentatively interpreted as indicating that about 60% of the Palatinit given to our volunteers was metabolized in the large bowel.

Tolerance to Palatinit in doses of up to at least 50 g/d is demonstrated in the present study (Fig. 7). It is the experience of the present authors that with any kind of overdose, e.g. by an α-glucosidase inhibitor or by excessive doses of polyols, the breath H_2 behaves quite irregularly and breath CH_4 almost disappears (M. Fritz and G. Siebert, unpublished results). In consequence, the existence of tolerance is one of the conditions which must be met for quantitative breath analysis in dose dependence. Abdominal sensations were weak enough to suggest the existence of tolerance. Other conditions are a standardized, low-fibre diet 2 d before and during breath analyses, and the adaptation of the experimental subjects by pretreatment with increasing amounts of Palatinit.

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