Zeitschrift für
Ernährungswissenschaft Z Ernährungswiss 24:1–18 (1985)

ORIGINAL CONTRIBUTIONS

Effect of Acarbose on the production of hydrogen and methane and on hormonal parameters in young adults under standardized low-fibre mixed diets

M. Fritz*, H. Kasper, J. Schrezenmeir**, and G. Siebert***

* Division of Experimental Dentistry, and ** Department of Internal Medicine, University of Würzburg (F.R.G.)

Summary

Short and middle term effects of Acarbose were studied in volunteers on a standardized, low-fibre, mixed diet for the development of tolerance phenomena with gas exhalations and some peptide hormone levels as main parameters. Both hydrogen and methane were measured quantitatively as diurnal profiles. Acarbose caused an about 20-fold increase of H_2 exhalation and had only moderate effects on methane production, indicating the presence of fermentable carbohydrates in the large bowel. Methanogenic individuals exhaled significantly less H_2 than did non-methanogenic subjects. Changes in blood glucose, serum insulin, GIP, gastrin, and plasma glucagon, caused by Acarbose, reflected delayed glucose absorption and were plausible within the regulatory framework of carbohydrate assimilation. When the Acarbose regime was maintained for 5 weeks on a controlled diet, abdominal sensations like e.g. meteorism declined remarkably while carbohydrate fermentation remained high and lowered GIP was sustained. Thus functional responses of the gastro-intestinal tract to altered carbohydrate supplies, elicited by Acarbose, were found by 3 independent parameters: anaerobic gas production, peptide hormone levels, and subjective abdominal sensations. The objective parameters seem to remain constant in the longer run, while subjective parameters show long-term adaptation.

Zusammenfassung

An gesunden Probanden unter standardisierter, ballaststoffarmer Mischkost mit bzw. ohne Acarbose wurden kurz- und mittelfristige Einflüsse auf Toleranzerscheinungen mittels Bestimmung von Peptidhormonen und Atemgasmessungen untersucht. Wasserstoff und Methan wurden im Tagesprofil quantitativ bestimmt. Dabei bewirkte Acarbose infolge von Kohlenhydratvergärung im Dickdarm einen rund 20fachen Anstieg der Wasserstoffexhalation, die Methanexhalation änderte sich im Mittel nur wenig. Methanbildende Probanden exhalierten nach Stimulierung durch Acarbose signifikant weniger Wasserstoff als Personen ohne Methanbildung. Die unter Acarbose erniedrigten Glukose-, Insulin- und GIP- bzw. erhöhten Glukagonspiegel zeigen die verzögerte Glukoseresorption an und sind im regulatorischen Rahmen der Kohlenhydratassimilation verständlich. Im Laufe einer fünfwöchigen Acarboseeinnahme zusammen mit standardisierter Kost nahmen die aufgetretenen abdominellen Empfindungen wie z. B. Meteorismus deutlich ab, während die mikrobielle Kohlenhydratfermentation erhöht und die GIP-Sekretion erniedrigt

blieben. Funktionelle Reaktionen des Gastrointestinaltrakts auf die durch Acarbose bewirkte veränderte Kohlenhydratzufuhr in das Colon wurden somit anhand von drei unabhängigen Parametern untersucht: anaerobe Gasproduktion, Freisetzung von Peptidhormonen und subjektive abdominelle Empfindungen. Die objektiven Parameter scheinen längerfristig konstant zu bleiben, während subjektive Parameter in dieser Zeit Anpassung zeigen.

Key words: Acarbose, hydrogen exhalation, methane exhalation, insulin, gastric inhibitory polypeptide, intestinal bacteria

Introduction

In healthy adults, the dietary carbohydrates which appear in microbially colonized lower parts of the gastro-intestinal tract are comprised of fibre material (19), of oligosaccharides undigested in the small intestine (59), as well as of small amounts of digestible carbohydrates like sucrose (5), fructose (43), and starch (2, 23, 36, 56). In addition, a major, though variable, source of carbohydrates stems from glycoproteins of intestinal secretions (1). Carbohydrates which thus arrive in the human colon are degraded to a limited extent or completely, depending on their chemical structure and physical properties, by anaerobic intestinal bacteria (18, 31, 60). The great majority of short-chain fatty acids formed in the fermentation are absorbed by the colonic mucosa (20, 47) and utilized as caloric fuel by the colonocytes (45). Another group of fermentation products, intestinal gases like hydrogen and methane, also underlies partial absorption in the colon and is excreted via the lungs (10). Fermentation of a certain amount of carbohydrates in the large bowel is in principle regarded as a physiological process (55); its extent is not well quantified, however. Additions to the human diet of nutritive sweeteners (29, 51), dietary fibre (9, 24, 28), of β-lactulose (7), and also of Acarbose (12) may considerably enhance the extent of carbohydrate fermentation in the lower gut.

Acarbose, a competitive inhibitor of α-glucosidases isolated from Actinomyces cultures (50) delays and diminishes the digestion of dietary carbohydrates in the upper intestine (41); thus a sharp postprandial increase of plasma glucose levels may be avoided. In numerous studies (see [17] for review), Acarbose has been found to be effective and useful in treating diabetic patients. The longer persistence in the gut and the translocation into ileum and colon of dietary carbohydrates, with the consequence of bacterial degradation, may lead to some intestinal symptoms like flatulence and meteorism. Aiming at a closer study of such symptoms, exclusive products of microbial degradation of carbohydrates, hydrogen (H_2) and methane (CH_4), were studied in this paper in a quantitative manner. Since a decreased assimilation of carbohydrates may result in altered release patterns of gastro-intestinal and pancreatic hormones (4, 25, the peptide hormones gastrin, GIP[1]), insulin, and glucagon were determined in blood together with the metabolites glucose, triglycerides and cholesterol when a standardized, low-fibre mixed diet was given with or without Acarbose for one or five weeks to young healthy adults.

[1]) "gastric inhibitory polypeptide" or "glucose-dependent insulinotropic polypeptide"

Materials and methods

Substances

Acarbose was supplied by Dr. I. Hillebrand, Bayer AG, Wuppertal. β-Lactulose was purchased from Merck, Darmstadt. The investigations were part of a clinical study of Acarbose on healthy volunteers and were performed in accordance with the provisions of the German drug law, when Acarbose had undergone pharmacological and toxicological testing and it had been determined that no objections existed against its use in man. The dosage of 2× 100 mg or 3× 100 mg, respectively, per day was chosen from experience with diabetic patients. Acarbose tablets of 100 mg each were taken with the first bite or gulp of the respective meals.

Human subjects

The study was done in two parts with eleven subjects (1 week experiments), and with four subjects (35 days experiments), altogether with 15 healthy, female volunteers of 19–23 years of age, weighing 57–86 kg (Broca index 0.86–1.21). Prior to the experiment, a high-fibre diet and a single dose of 10 g β-lactulose were used to establish that all persons did expire H_2 in their breath. Only the qualitative capability to produce H_2, and an interval free of antibiotics of at least 3 months before the study was begun were the necessary criteria in selecting the volunteers, who were subjected to a complete medical check-up and did not show any deviations from normal standards in clinical chemistry and hematology. 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. The conditions of the German drug law for the protection of man in clinical studies (§ 40 AMG, 24. 08. 1976) were fully met, especially in regard to consent and insurance coverage.

Table 1. Design of an experimental week (experiment I).

← 1 experimental week →							
Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu
						experimental day	
2× daily test substance in orange juice and yoghurt, respectively							
				Standard diet			
				Collection of stools			
Record on abdominal sensations daily						hourly	

Experimental design

1 week studies (experiment I). 11 volunteers were supplied, in randomized order for 1 week each, with 200 ml orange juice for breakfast and 150 g yoghurt for lunch, containing 20 g sucrose without (control) or with 100 mg Acarbose. In a second control week, 2× 10 g β-lactulose was given on the experimental day (table 1) only. Each experimental week was followed by an interval of at least 7 days without any addition to the diet. On each 7th day of an experimental week (table 1), exhalation of H_2 and CH_4 was determined before and at hourly intervals after the breakfast for 10 hours. During the first five hours, venous blood samples were taken. On each 5th–7th day of an experimental week (table 1), standardized diets (see below) were given, and stools were collected for these 72 hours. A record with entries for eructation, abdominal noise, fullness, meteorism, flatulence, abdominal pain, eventual diarrhea, and general feeling was made at hourly intervals on the 7th day whereas on the 1st–6th days this record was made only once a day.

35 day studies (experiment II). In order to check for accustoming to both the standardized diet (see below) and Acarbose with respect to intestinal gas production and hormonal parameters, 4 healthy volunteers received in a cross-over design for 5 weeks each the standardized diet without (control) or with 3× 100 mg Acarbose. The wash-out interval was 2 weeks. Gas exhalation was determined on each 7th day of the 5 week periods, as outlined in experiment I above. Venous blood was collected on the 7th and 35th days only, but for 10 hours. In every other respect, experiments I and II were identical.

Dietary conditions

The diet was standardized on days 5–7 of each experimental week (table 1) in regard to major nutrients and menu. In experiment I, 8.2 MJ were given with (energy-percent) protein, fat and carbohydrates = 20/35/45 %. The meals were composed similar to the mixed diet of the German population. Dietary fibre (according to Paul and Southgate, [39]) was kept at no more than 14 g/day which guarantees reproducible low H_2 production in the control period, as shown repeatedly in a pilot study (27). The last meal on day 6 of an experimental week (table 1) was taken at 17.30 hrs, thus allowing a fasting period of 14 hours before the first sample of respiratory air was collected on day 7.

In experiment II, the dietary conditions were identical with those of experiment I, except that for better acceptance up to 10 % of the energy intake on days 1–4 (table 1) was allowed to be consumed in free choice, however, under no circumstances were additional dietary fibre, nutritive sweeteners, antibiotics or laxatives permitted during the whole course of both experiments. Meal compositions on day 7 (experimental day) are given in table 2. Only in experiment I was a formula breakfast used.

Sampling of respiratory air and analysis for H_2 and CH_4

For the quantitative determination of H_2 and CH_4, exhaled air was concentrated in a slightly modified VT-3 spirometer (Hellige, Freiburg) by rebreathing for 5 minutes. Aliquots of the spirometer air were analysed in the gas chromatograph GC 5720 A (Hewlett Packard) with a thermal conductivity detector. 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 per minute. A detailed description of the whole procedure was recently published (29).

Mouth-to-caecum transit

According to Bond and Levitt (8), the first significant increase of H_2 exhalation above the fasting value after breakfast was taken as the time between ingestion of a

Table 2. Composition of breakfast and lunch on the experimental days during experiments I and II.

	Energy (kJ)	Protein (g)	Fat (g)	Carbo-hydrates (g)	Dietary fibre (g)
Experiment I					
Breakfast:					
500 ml liquid formula	2100	19	17	69	–
Lunch:					
100 g turkey leg	502	21	3.5	–	–
60 g curry rice (unboiled weight)	924	4	1	48	1.5
200 g zucchini	79	1	–	3	1.2
10 g margarine	318	–	8	–	–
10 g oil	389	–	10	–	–
5 g cream	67	–	1.5	–	–
150 g yoghurt	429	6	6	7	–
200 ml orange juice	410	1	–	22	0.1
	3118	33	30	80	2.8
Experiment II					
Breakfast:					
coffee or tea					
20 g sucrose	330	–	–	20	–
80 g white bread	866	7	1	40	2.2
10 g margarine	318	–	8	–	–
50 g curds	243	6	3	2	–
25 g strawberry jam	272	–	–	16	0.3
100 ml currant juice	210	–	–	12	–
	2239	13	12	90	2.5
Lunch:					
100 g pork cutlet	703	21	8	–	–
100 g paprika	117	1	–	5	0.9
150 g potatoes	546	3	–	28	3.0
30 g lettuce	20	–	–	1	0.4
10 g oil	389	–	10	–	–
100 g orange filets	226	1	–	12	2.0
20 g sucrose	330	–	–	20	–
	2331	26	18	66	6.3

meal and the arrival of fermentable material in the upper colon (mouth-to-caecum transit).

Hormonal and other assays in blood samples

Blood samples were taken from the cubital vein with an Abbocath® and an obturator prior to breakfast and then at intervals for 5 or 10 hours on experimental days (Table 1). Immunoreactive gastrin (44) and insulin (61) were determined with RIA kits (^{125}I) from Becton Dickinson Co., Orangeburg, N.Y., and from Behring-

werke AG, Marburg, respectively. Glucagon was determined (52) with a RIA kit (^{125}I) specific for pancreatic glucagon from Serono GmbH, Freiburg. The gastric inhibitory polypeptide (GIP) was measured with a radioimmunoassay of our laboratory, modified from those of Kuzio et al. (34) and Thomas et al. (58), respectively; rabbit anti-GIP was obtained from Novo, Bagsvaerd, Denmark. ^{125}I labelling of GIP was performed with the chloramine-T-method (32), ^{125}I-GIP was separated on microfine silicate (Quso G 32). Glucose was assayed with glucose dehydrogenase, triglycerides with GPO-PAP, and total cholesterol with CHOD-PAP using standard methods.

Statistical evaluation

The data were evaluated on the TR 440 machine of the computer centre of the University of Würzburg; as software, MEDAS programs as well as self-developed ALGOL programs were used.

H_2 and CH_4 excretions as well as blood parameters were calculated from their time integrals over 5 and 10 hrs, respectively. Differences between mean values were evaluated with Student's t-test, in the case of skewed distributions, however, with the Wilcoxon matched pairs signed rank test; significance is reached with $p < 0.05$.

Results

Hydrogen exhalation

After 6 days with 2× 100 mg/day Acarbose (experiment I), H_2 exhalation ($\bar{x} \pm$ s.d.) amounted to 235 ± 63 ml/10 hrs, compared with 9.9 ± 6.8 ml H_2/10 hrs in the control period, whereas 2× 10 g/day of β-lactulose led to 148 ± 51 ml H_2/10 hrs (fig. 1). The increase of H_2 exhalation during the day occurs in synchrony with the meal timing, with a maximum at late afternoon. The difference between the Acarbose and β-lactulose is significant at afternoon peak times ($p < 0.01$).

When Acarbose was also given with the supper (experiment II), fasting values of H_2 exhalation the next morning were about 5 times higher than in the breakfast/lunch dosing scheme of experiment I. The mean integrals ($n = 4$) of H_2 exhalation during continuous administration of 3× 100 mg/day Acarbose over 5 weeks were not significantly different amongst themselves (fig. 3a), as was the case in the 5 weeks of the control period.

Methane exhalation

Six volunteers (40 %) had distinct amounts of CH_4 in their respiratory air. In addition to these 6 subjects, two more had CH_4 (10 times and more the exspiratory value) in the gas phase above fresh stool. CH_4 exhalation was, in contrast to the behavior of H_2, relatively constant over 10 hours, without recognizable peaks dependent on meal intakes (fig. 2). The administration of Acarbose or β-lactulose did not result in changes of CH_4 exhalation (fig. 2). Compared with 1 week controls, Acarbose elicited considerable alterations of CH_4 exhalation, though not in a uniform manner.

In experiment II, 3 subjects were producing rather constant amounts of CH_4 in the control period of 35 days; when 3× 100 mg/d Acarbose was given over 35 days, CH_4 exhalation changed considerably with the indi-

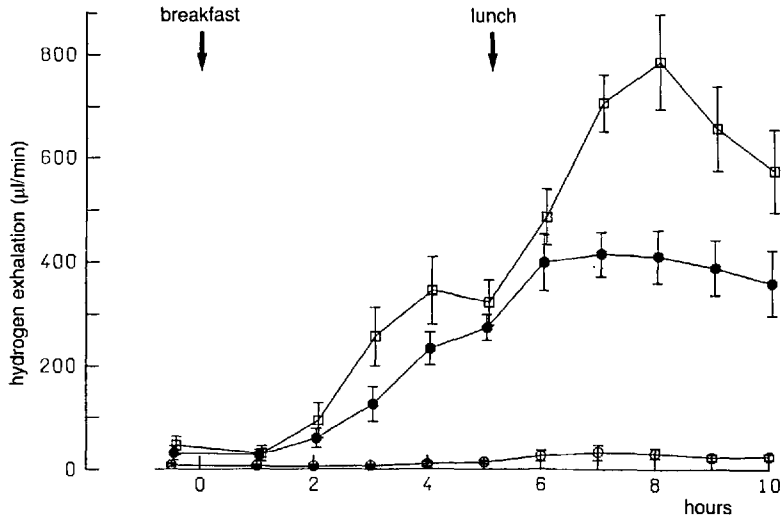

Fig. 1. Exhalation of H_2 ($\bar{x}$; s.e.m.; n = 11) by subjects on a low-fibre standardized, mixed diet (control) (○), after administration of 2× 100 mg/day of Acarbose for 6 days (□) or after 2× 10 g β-lactulose on the experimental day (see table 1) (●), at breakfast and lunch (experiment I). Significance of differences between areas under curve: control/Acarbose and control/β-lactulose $p < 0.001$; Acarbose/β-lactulose $p < 0.05$.

Significance at each hourly sampling time:

	Sampling times (hrs; breakfast = 0)										
	0	1	2	3	4	5	6	7	8	9	10
Control/Acarbose	n.s.	n.s.	*	**	**	***	***	***	***	***	***
Control/β-lactulose	n.s.	n.s.	*	*	***	***	***	***	***	***	**
Acarbose/β-lactulose	n.s.	n.s.	n.s.	*	n.s.	n.s.	n.s.	**	**	*	*

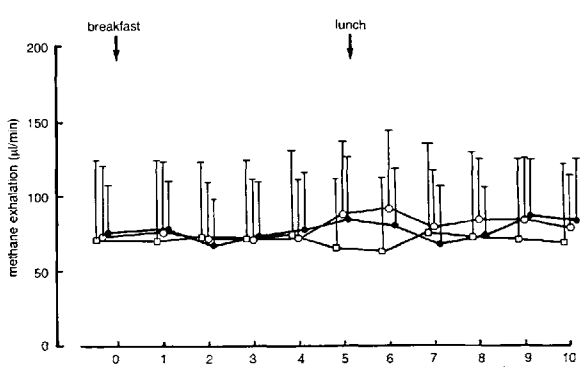

Fig. 2. Exhalation of CH_4 ($\bar{x}$; s.e.m.; n = 3) by methanogenic individuals on a low-fibre standardized, mixed diet (control) (○), after administration of 2× 100 mg/day of Acarbose for 6 days (□) or after 2× 10 g β-lactulose on the experimental day (see table 1) (●), at breakfast and lunch (experiment I). No significant differences were found.

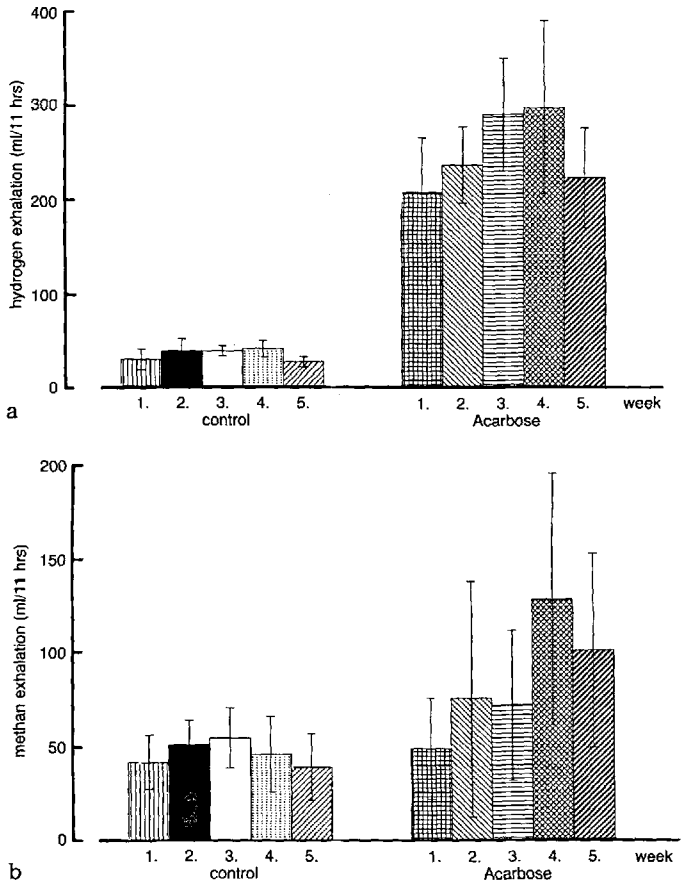

Fig. 3. Integrals of 11 hrs gas exhalation by 4 volunteers on a standardized, mixed diet without (control) and with 3× 100 mg/day of Acarbose ($\bar{x}$; s.e.m.). Panel a: data for H_2; panel b: data for CH_4. Amounts of gas = ml/11 hrs.

vidual subject, but not significantly (fig. 3b). Interestingly enough subjects producing H_2 exclusively exhaled significantly more H_2 in the afternoon than those subjects who also exhaled CH_4 (fig. 4). This applies to both experiments I and II, with 581 ± 245 ml H_2/10 hrs in pure H_2 producers (n = 7), and 424 ± 157 ml H_2/10 hrs in producers of both H_2 and CH_4 (n = 6).

Mouth-to-caecum transit

In the control week of experiment I, mouth-to-caecum transit was 4.4 ± 1.3 hrs ($\bar{x}$ ± s.d.; n = 11), and was shortened by 100 mg Acarbose to 2.6 ± 1.0 hrs ($p < 0.01$) but by 10 g β-lactulose to 2.3 ± 1.1 hrs ($p < 0.01$). Elevated pre-breakfast values of H_2 exhalation, due to the evening dosage of Acarbose (experiment II) rather prevented a clear-cut recognition of the H_2 peak and interfered with the gastro-colonic reflex of an immediate H_2 increase (57);

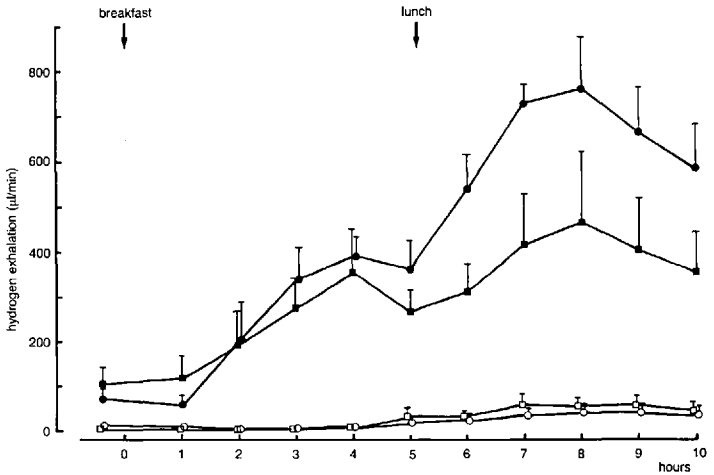

Fig. 4. Exhalation of H_2 ($\bar{x}$; s.e.m.) by 6 methanogenic and by 7 non-methanogenic subjects on a low-fibre standardized, mixed diet without (controls) (□, ○ respectively) and with Acarbose (■, ● respectively).
Significance at each hourly sampling time (breakfast = 0) after administration of Acarbose for 6 days:

	0–5	6	7	8	9	10
Methanogenic/non-methanogenic	n.s.	*	**	*	*	*

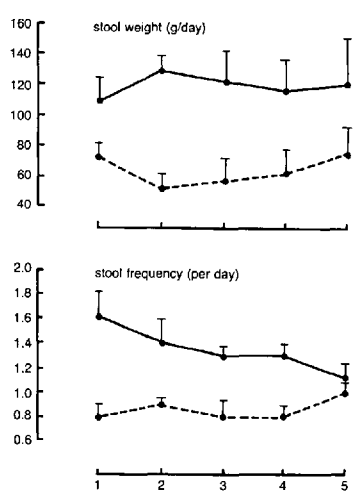

Fig. 5. Weights of stools and frequencies of defecations ($\bar{x}$; s.e.m.; n = 4) during 5 weeks of subjects on a relatively low-fibre mixed diet without (control) – – – and with Acarbose (3× 100 mg/day) ——.

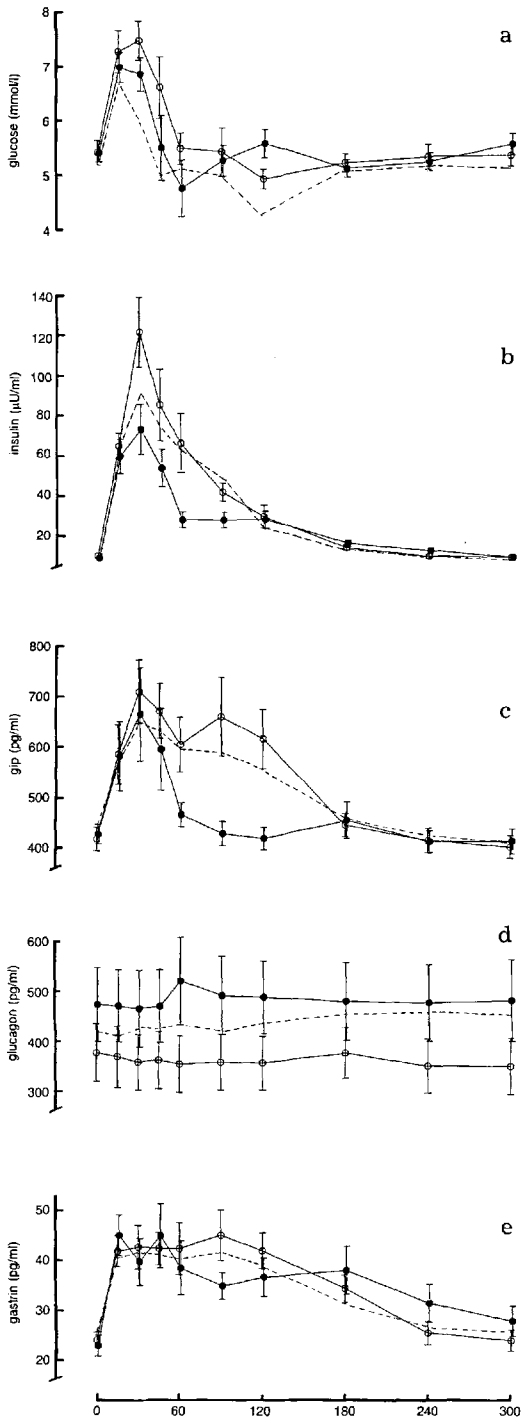

Fig. 6. 5 hour-profiles of glucose and some hormones in blood of 11 volunteers ($\bar{x}$; s.e.m.) when fasting for 14 hrs and after a mixed formula breakfast without additions (control) (○——○), with 100 mg Acarbose (●——●), or with 10 g β-lactulose (– – – –).
Fig. 6a: glucose (mmol/l);
Fig. 6b: immunoreactive insulin (mU/ml);
Fig. 6c: immunoreactive GIP (pg/ml);
Fig. 6d: immunoreactive pancreatic glucagon (pg/ml);
Fig. 6e: immunoreactive gastrin (pg/ml).

thus, mouth-to-caecum transit times were not evaluated in the 35 day studies.

Weight and frequency of stool

After 1 week with 2× 100 mg Acarbose/day, stool weights were significantly higher by 58 % than under the control diet (98 ± 37 g/day; $\bar{x}$ ± s.d.; n = 11). Mean stool frequencies were not significantly different with 1.5 defecations/day under Acarbose and 1.2 in control conditions.

With 3× 100 mg/day Acarbose in experiment II, weights of stools and frequencies of defecations are depicted in figure 5. Whereas the stool weight remained elevated over 5 weeks, stool frequencies approached control values after 5 weeks. Diarrhea was never observed under Acarbose; stools were less dark and of less consistency than in the control period.

Blood parameters

Information on the glucose assimilation under the influence of Acarbose was obtained by measuring glucose, insulin, glucagon, and GIP levels. Since the mixed formula breakfast, composed in accordance with the recommendations of the German Nutrition Society, produced only a moderate increase of blood glucose (fig. 6a), effects of Acarbose on blood glucose were small. As shown in figure 6b and 6c, however, Acarbose 2× 100 mg/day caused significant changes in insulin and GIP levels, thus indicating an effect of Acarbose on the regulation of the glucose metabolism. Glucagon levels (fig. 6d) were not influenced by the intake of test meals, probably due to the simultaneous supply of amino acids (enhancing) and glucose (lowering), however, Acarbose administration led to significantly higher glucagon levels in blood plasma.

β-Lactulose (figs. 6a–d) caused less pronounced, insignificant alterations of glucose, insulin, GIP, and glucagon levels in blood whose tendencies were similar to those after Acarbose treatment; glucose concentrations were diminished more by β-lactulose than by Acarbose.

Gastrin levels (fig. 6e) were not changed significantly over 5 hours by Acarbose and by β-lactulose but Acarbose caused some fluctuations at the 2nd and 5th hour of the experiment.

Table 3. Maximal post-prandial glucose concentrations after 1 and 5 weeks' treatment with 3× 100 mg/day of Acarbose in subjects on a standardized, mixed diet. (Blood glucose as mmol/l; $\bar{x}$ ± s.d.; n = 4).

Maximal post-prandial glucose concentration	1 week Acarbose		5 weeks Acarbose	
	−	+	−	+
After breakfast	8.94 ± 1.9	7.78 ± 0.3	8.72 ± 1.4	8.61 ± 2.2
After lunch	8.78 ± 1.5	9.50 ± 1.8	9.44 ± 1.6	9.22 ± 1.6

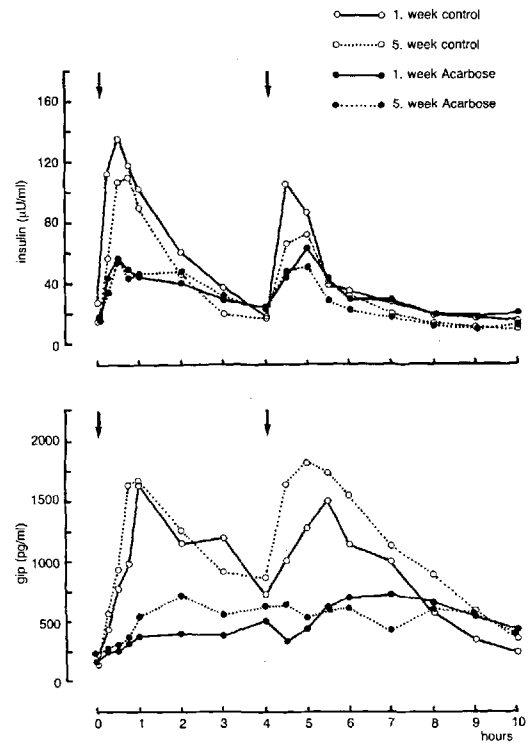

Fig. 7. Serum levels of immunoreactive insulin (7a) and GIP (7b), when fasting for 14 hrs and after taking meals (indicated by arrows) during 10 hrs ($\bar{x}$; n = 4), compared for a 1-week and a 5-week administration of Acarbose (3× 100 mg/day).

Some bloood parameters were compared, in experiment II, for the effects of Acarbose after 1 and after 5 weeks of administration. Data for post-prandial maxima of blood glucose are given in table 3 and demonstrate that only at breakfast after 1 week could a significant lowering of blood glucose be observed after 3× 100 mg/day of Acarbose; however,

Table 4. Mean values of blood triglycerides and total cholesterol after 1 and 5 weeks' treatment with 3× 100 mg/day of Acarbose in subjects on a standardized, mixed diet. The mean refers to 10 samples, drawn in hourly intervals, after the start of the experiment (mg/dl; $\bar{x} \pm$ s.d.; n = 4).

Mean concentration	1 week Acarbose		5 weeks Acarbose	
	−	+	−	+
Triglycerides	121 ± 29	108 ± 22	105 ± 23	111 ± 20
Total cholesterol	202 ± 30	197 ± 22	175 ± 22	179 ± 16

blood glucose maxima were delayed after lunch for about 30 min by Acarbose.

As seen from figures 7a and b, effects of 3× 100 mg/day of Acarbose were not significantly different after 1 and after 5 weeks on insulin and GIP levels, nor did control values differ to any greater extent. Thus, differences between control and Acarbose groups in regard to insulin and GIP levels in blood were maintained over a period of 5 weeks.

According to table 4, no effects were exerted by Acarbose on serum triglycerides and on total serum cholesterol after 1 week as well as after 5 weeks of treatment with 3× 100 mg/day. The tendency to lowered cholesterol levels after 5 weeks with Acarbose did not reach significance ($p < 0.1$).

Abdominal sensations

The entries recorded on the experimental days (table 1) of experiment I with 2× 100 mg/day of Acarbose are compiled in figure 8. No differences between Acarbose and β-lactulose (2× 10 g/day) were significant. However, significant differences were found between controls and experimental groups in regard to abdominal noise, fullness, meteorism, and flatulence. In the preceding 6 days before the experimental days, no signs of adaptation were observed. In general, the 11 subjects listed their state of health between good and very good.

In the 35-day experiment with 3× 100 mg/day of Acarbose, similar records were obtained as described above for experiment I. However, in the course of the 5 experimental weeks, the entries became less pronounced from the 2nd week or later, thus indicating a considerable adaptation of colonic processes to a longer-lasting exposure to Acarbose. In the control weeks abdominal sensations were noted only occasionally.

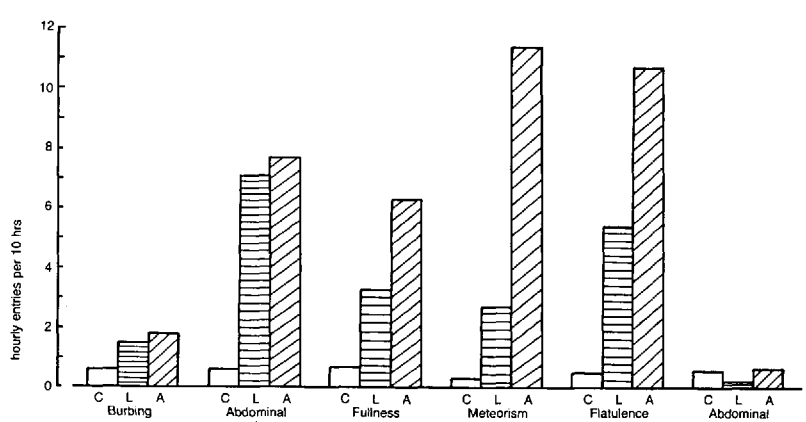

Fig. 8. Entries for abdominal sensations by 11 volunteers on a low-fibre, standardized, mixed diet (control = C) and with the addition of 2× 100 mg/day of Acarbose (A), or of 2× 10 g of β-lactulose (L). The subjects were asked to note on each hour for 10 hrs their sensations; the entries (low = 1, medium = 2, strong = 3) were averaged over the experimental day and are given as mean values.

Discussion

Acarbose causes an increase of hydrogen exhalation by a factor of about 20, thus indicating effective inhibition of intestinal carbohydrases with the consequence of large-bowel fermentation of those carbohydrates which were not split and absorbed during the passage of the small intestine. Diurnal profiles of H_2 excretion depend on the type of carbohydrate consumed, as previously shown for dissolved and solid sucrose by Lembcke et al. (35). In this investigation a mixed diet was used. Thus carbohydrates transferred into the large intestine as a result of carbohydrase inhibition cannot be uniform but represent a wide mixture of oligosaccharides. This condition might rather resemble the normal western situation. It depends on the time of intake of Acarbose whether early fasting H_2 values are low (fig. 1, last medication at the previous lunch) or high (last administration of Acarbose with the supper on the foregoing day, data not shown). One should expect, with the latter regime, that continuous intestinal secretions (see Introduction) are not as readily digested overnight as seems to be the case with a 20 hr interval of Acarbose intake (fig. 1).

A bimodal shape (fig. 1) of the diurnal 10 hr H_2 profile, though less pronounced, has also been observed with guar granules (28), when the H_2 peaks were delayed by several hours, and with Palatinit® (29) which demonstrated a strict dose-effect relationship between the amounts of Palatinit® given and $H_2 + CH_4$ exhaled.

Methanogenic subjects produce less H_2 after Acarbose intake than non-methanogenic individuals (fig. 5), a situation which was also found with a high-fibre diet (38) and after administration of β-lactulose (3). In our experience (see also 29) methanogenic persons demonstrate variable H_2/CH_4 ratios, thus suggesting the use of added values of $H_2 + CH_4$ in the evaluation of quantitative breath tests.

No easy explanation is at hand why methane production varies inter-individually, however, epidemiological surveys seem to indicate that the human race and sex as well as a close domestic contact (parents/children and amongst brothers and sisters) during the first years of life are of importance (40). Neither is it known why the H_2 exhalation reacts so fast on oral intake of suitable diets whereas the CH_4 exhalation behaves distinctly sluggishly. The methanogenic or non-methanogenic property of an individual does not seem to depend on the type of the diet (6) and cannot be altered by high doses of Acarbose (750 mg/day) or by trace amounts of $Ni^{2\oplus}$ (M. Fritz and G. Siebert, unpublished observations) which are required by methanogenic microorganisms. Once the capability of CH_4 production is established, dietary factors like a long-term consumption of pentose-rich polysaccharides (33) may enhance the CH_4 exhalation relative to H_2. When certain carbohydrates were overdosed and diarrhea observed, CH_4 exhalation stopped rather drastically (M. Fritz and G. Siebert, unpublished observations), a symptom which may also in the case of Acarbose be of some value in indicating a pre-diarrheic situation.

The decrease of the intensity of abdominal sensations with prolonged intake of Acarbose is taken as evidence of adaptation, leading to some kind of tolerance. In any case, it cannot depend on changes in the diet, as

suggested by Fölsch et al. (25), since the volunteers of this study strictly adhered to the diet provided; neither can it depend on a decrease of fermentative activities in the large bowel since essentially unchanged H_2 exhalations were observed over 5 weeks (fig. 3a); similar results were found by Ehle et al. (22) with a continued excretion of short-chain fatty acids by subjects on high-fibre diets while abdominal symptoms became less marked. In addition, stool frequencies decreased in the course of 5 weeks (fig. 5) while stool weights and gas exhalations did not decrease. The fact that abdominal sensation and stool frequency decreased, although stool weight and pH_2 production remained unchanged during the 5 week observation period, might be explained by an adaptation of atonic mobility to increased stool weight and volume in the gut lumen. A possible explanation might be that p_{H_2} may influence the strength of abdominal sensations as well as the activity of H_2 consuming bacterial systems (37). Tolerance phenomena are not unique to Acarbose but are also observed with long-term feeding of polyols (30, 51) and other systems and may be an expression of the flexibility of microbial life and function of the colon.

With the unproven, though not unrealistic assumption that the carbohydrate mixture, fermented in the colon after Acarbose administration, yields comparable amounts of H_2 as are obtained from β-lactulose, the H_2 exhalation data of figure 1 would indicate that about 32 g of carbohydrate has not been assimilated in the small intestine, an amount which represents about 20 % of the carbohydrates ingested with breakfast and lunch in this investigation (table 2). In the case of 100 g sucrose as carbohydrate and 200 mg Acarbose, Caspary (12) has calculated that about 40 % was fermented in the colon; yet, different experimental conditions prohibit a closer examination of this discrepancy.

Due to the close correlation between the release of GIP (58) and the absorption of glucose and fat constituents, GIP is found diminished under conditions of impaired absorption (16). The insulinotropic effect of GIP (14) is not always evident (49) and depends on a significant hyperglycemia which does not pertain in these experiments (fig. 6a) although insulin increases strongly (4). The data on insulin and glucose responses (figs. 6 and 7) are nonetheless compatible with a potentiating (21) or contributing (4) effect of GIP and are in agreement with data on insulin and GIP by Collier and O'Dea (13) and by Fölsch et al. (26). In studies with Palatinit®, GIP has been found as a sensitive early parameter of carbohydrate assimilation (Fritz et al., unpublished observations); similar results are reported by Salminen et al. (48) in experiments with xylitol-adapted rats.

Pancreatic glucagon values (fig. 6d) correspond in an inverse manner with blood glucose data (fig. 6a) and the insulin drop (fig. 6b) and are taken as an expression of the regulatory function when glucose absorption from the small intestine is diminished under the influence of Acarbose. Whether glucagon exerts an inhibitory action on gastric and small-intestinal motilities (52) in the present experiments, remains uncertain.

Gastrin effects on gastric motility and eventually also on colonic motility (54) have been the reasons why gastrin levels were determined in these studies (fig. 6e). Changes in gastrin levels were very small indeed, although the mouth-to-caecum transit as evidenced from the H_2 peak after

breakfast was considerably shortened. Previous reports on changed gastrin response after Acarbose (42, 53) could not be confirmed in these experiments.

The combination of dietary measures and metabolic data on anaerobic gas production with hormonal parameters, as presented above, permits under controlled conditions a deeper insight into the physiology of the gut. Once Acarbose is given, altered intestinal functions remain, although in numerous aspects of a significant character, within the frame of functional responses of the gastro-intestinal tract to modified carbohydrate supplies.

The authors would like to thank Mrs. Beate Lampert and Mrs. Gerda Dusel for technical assistance with the radioimmunoassays, as well as Mrs. Monika Wild and Mrs. Elisabeth Zang for much help in designing and preparing the diets given.

References

1. Allen A, Cunliffe WJ, Pearson JP, Sellers LA, Ward R (1984) Studies on gastrointestinal mucus. Scand J Gastroenterol 19 Suppl 93:101–114
2. Anderson IH, Levine AS, Levitt MD (1981) Incomplete absorption of the carbohydrate in all-purpose wheat flour. New Engl J Med 304:891–892
3. Bjørneklett A, Jenssen E (1982) Relationships between hydrogen (H_2) and methane (CH_4) production in man. Scand J Gastroenterol 17:985–992
4. Bloom SR (1983) Endocrinology of nutrient entry. In: Ref 17, pp 19–28
5. Bond JH, Currier BE, Buchwald H, Levitt MD (1980) Colonic conservation of malabsorbed carbohydrate. Gastroenterol 78:444–447
6. Bond JH, Engel RR, Levitt MD (1971) Factors influencing pulmonary methane excretion in man. J Experim Med 133:572–588
7. Bond JH, Levitt MD (1972) Use of pulmonary hydrogen (H_2) measurements to quantitate carbohydrate absorption. J Clin Invest 51:1219–1225
8. Bond JH, Levitt MD (1975) Investigation of small bowel transit time in man utilizing pulmonary hydrogen (H_2) measurement. J Lab Clin Med 85:546–555
9. Bond JH, Levitt MD (1978) Effect of dietary fiber on intestinal gas production and small bowel transit time in man. Am J Clin Nutr 31:S169–S174
10. Calloway DH, Murphy EL (1968) The use of expired air to measure intestinal gas formation. Ann NY Acad Sci 150:82–95
11. Caspary WF (1978) Sucrose malabsorption in man after ingestion of α-glucosidehydrolase inhibitor. Lancet I:1231–1233
12. Caspary WF, Lembcke B, Creutzfeld W (1982) Inhibition of human intestinal α-glucosidehydrolase activity by Acarbose and clinical consequences. In: Ref 15 pp 27–37
13. Collier G, O'Dea K (1983) Effect of coingestion of fat on the glucose, insulin, and GIP responses to carbohydrate and protein. Am J Clin Nutr 37:941–944
14. Creutzfeld W (1979) The incretin concept today. Diabetologia 16:75–77
15. Creutzfeld W (ed) (1982) First international symposium on Acarbose – effects on carbohydrate and fat metabolism, Montreux, October 1981. Excerpta Medica (Amsterdam) 573 p
16. Creutzfeld W, Ebert R, Arnold R, Frerichs H, Brown JR (1976) Gastric Inhibitory Polypeptide (GIP), gastrin, and insulin: Response to test meal in coeliac disease and after duodenopancreatectomy. Diabetologia 12:279–283
17. Creutzfeld W, Fölsch UR (eds) (1983) Delaying absorption as a therapeutic principle in metabolic diseases (L Heilmeyer-Symposium 1982) Georg Thieme Stuttgart, 147 p

18. Cummings JH (1983) Fermentation in the human large intestine: Evidence and implications for health. Lancet I:1206–1209
19. Cummings JH (1984) Microbial digestion of complex carbohydrates in man. Proc Nutr Soc 43:35–44
20. Cummings JH (1984) Colonic absorption: The importance of short chain fatty acids in man. Scand J Gastroenterol 19 Suppl 93:89–100
21. Ebert R, Creutzfeldt W (1983) Inhibition of absorption and impaired secretion of Gastric Inhibitory Polypeptide (GIP). In: Ref 17, pp 126–135
22. Ehle FR, Robertson JB, van Soest PJ (1982) Influence of dietary fibres on fermentation in the human large intestine. J Nutr 112:158–166
23. Feibusch JA, Holt PR (1982) Impaired absorptive capacity for carbohydrate in the aging human. Dig Dis Sci 27:1095–1100
24. Fleming SE, Marthinsen D, Kuhnlein H (1983) Colonic function and fermentation in man consuming high fiber diets. J Nutr 113:2535–2544
25. Fölsch UR, Ebert R, Creutzfeld W (1981) Response of serum levels of gastric inhibitory polypeptide and insulin to sucrose ingestion during long-term application of Acarbose. Scand J Gastroenterol 16:629–632
26. Fölsch UR, Lembcke B, Ebert R, Caspary WF, Creutzfeld W (1982) Effect of Acarbose and fibre on glucose and hormone response to sucrose load or mixed meal. In: Ref 15, pp 97–106
27. Fritz M, Kasper H, Siebert G (1983) Abatmung von Wasserstoff und Methan unter verschiedenen Ernährungsbedingungen. Ern-Umsch 30:232–233
28. Fritz M, Kasper H, Schrezenmeir J, Siebert G (1984) Einfluß von Ballaststoffen auf die H_2- und CH_4-Exhalation bei Gesunden. Verhandl Dt Ges Inn Med 90: in press
29. Fritz M, Siebert G, Kasper H (1984) Dose dependence of breath hydrogen and methane in healthy volunteers after ingestion of Palatinit®. Brit J Nutr (submitted)
30. Grupp U, Siebert G (1978) Metabolism of hydrogenated palatinose, an equimolar mixture of α-D-glucopyranosido-1,6-sorbitol and α-D-glucopyranosido-1,6-mannitol. Res Experim Med (Berl) 173:261–278
31. Hungate RE (1984) Microbes of nutritional importance in the alimentary tract. Proc Nutr Soc 43:1–11
32. Hunter WM (1971) The preparation and assessment of iodinated antigens. Radioimmunoassay methods, edited by Kirkham KE and Hunter WM, pp 3–23, Churchill Livingstone (Edinburgh)
33. Kay L, Brydon WG, Eastwood MA, Smith JH (1981) Influence of pentose on breath methane. Am J Clin Nutr 34:2728–2733
34. Kuzio M, Dryburgh JR, Malloy KM, Brown J (1974) Radioimmunoassay for gastric inhibitory polypeptide. Gastroenterol 66:357–364
35. Lembcke B, Caspary WF, Fölsch UR, Creutzfeldt W (1981) Influence of neomycin on postprandial metabolic changes and side-effects due to α-glucosidehydrolase inhibition with Acarbose. Regulators of intestinal absorption in obesity, diabetes and nutrition (Vol 2), edited by Berchthold P, Coriella M, Jacobelli A and Silano V, pp 235–247, Società Editrice Universo (Rome)
36. Levine AS, Levitt MD (1981) Malabsorption of starch moiety of oats, corn and potatoes. Gastroenterol 80:1209
37. Levitt MD, Bond JH, Levitt DG (1981) Gastrointestinal gas. Physiology of the gastrointestinal tract, edited by Johnson LR, pp 121–133, Raven Press (New York)
38. Marthinsen D, Fleming SE (1982) Excretion of breath and flatus gases by humans consuming high-fiber diets. J Nutr 112:1133–1143
39. Paul AA, Southgate DAT (1978) McCance and Widdowson's the composition of foods. 4th ed, Elsevier (Amsterdam)
40. Pitt P, De Bruijn KM, Beeching MF, Goldberg E, Blendis LM (1980) Studies on breath methane: the effect of ethnic origins and lactulose. Gut 21:951–954

41. Puls W, Keup U, Krause HP, Thomas G, Hoffmeister F (1982) The concept of glucosidase inhibition and its pharmacological realization. In: Ref 15, pp 16–26
42. Raptis S, Creutzfeld W (ed) (1982) First international symposium on Acarbose – effects on carbohydrate and fat metabolism, Montreux, October 1981. pp 218–215. Excerpta Medica (Amsterdam)
43. Ravich WJ, Bayless TM, Thomas M (1983) Fructose: Incomplete intestinal absorption in humans. Gastroenterol 84:1189
44. Rehfeld JF, Stadil F, Vikelsoe J (1974) Immunoreactive gastrin components in human serum. Gut 15:102–111
45. Roediger WEW (1982) Utilization of nutrients by isolated epithelial cells of the rat colon. Gastroenterol 83:424–429
46. Röschlau P, Bernt E, Gruber W (1974) Enzymatische Bestimmung des Gesamt-Cholesterins im Serum. Z Klin Chem Klin Biochem 12:403–407
47. Ruppin H, Bar-Meir S, Soergel KH, Wood CM, Schmitt MG Jr.: Absorption of short-chain fatty acids by the colon. Gastroenterol 78:1500–1507
48. Salminen S, Salminen E, Marks V (1982) The effects of xylitol on the secretion of insulin and gastric inhibitory polypeptide in man and rats. Diabetologia 22:480–482
49. Sarson DL, Wood SM, Kausal P, Bloom SR (1982) Insulinotropic properties of GIP: A non-physiological phenomenon. Diabetologia 23:106
50. Schmidt DD, Frommer W, Jünge B, Müller L, Wingender W, Truscheit E (1982) α-Glucosidase inhibitors of microbial origin. In: Ref 15, pp 5–15
51. Schnell-Dompert E, Siebert G (1980) Metabolism of sorbitol in the intact organism. Hoppe Seyler's Z Physiol Chem 361:1069–1075
52. Schrezenmeir J (1979) Radioimmunoassay von pankreatischem Glukagon – Verbesserung der Methodik und Anwendung zur Ermittlung der Rolle von Glukagon im Polytrauma. Dissertation, Universität Würzburg
53. Schrezenmeir J, Fritz M, Kasper H (1982) Effekt von Acarbose auf gastroenteropankreatische Hormone – Beziehungen zu Wirkungen und Nebenwirkungen. Akt Endokr Stoffw 2:84
54. Snape WJ, Matarazzo SA, Cohen S (1978) Effect of eating and gastrointestinal hormones on human colonic myoelectrical and motor activity. Gastroenterol 75:373–378
55. Soergel KH (1983) The role of the colon in case of inhibition of carbohydrate absorption. In: Ref 17, pp 99–105
56. Stephen AM, Haddad AC, Phillips SF (1983) Passage of carbohydrate into the colon – direct measurements in humans. Gastroenterol 85:589–595
57. Tadesse K, Smith D, Eastwood MA (1980) Breath hydrogen (H_2) and methane (CH_4) excretion patterns in normal man and in clinical practice. Quart J Experim Physiol 65:88–97
58. Thomas FB, Shook DF, O'Dorisio TM, Cataland S, Mekhijan HS, Caldwell JH, Mazzaferri EL (1977) Localization of gastric inhibitory polypeptide release by intestinal glucose perfusion in man. Gastroenterol 72:49–57
59. Wiggins HS (1984) Nutritional value of sugars and related compounds undigested in the small gut. Proc Nutr Soc 43:69–75
60. Wolin MJ, Miller TL (1983) Carbohydrate fermentation. Human intestinal microflora in health and disease, edited by Hentges DJ, pp 147–165, Academic Press (New York)
61. Yalow RS, Berson SA (1960) Immunoassay of endogenous plasma insulin in man. J Clin Invest 39:1157–1175

Received November 16, 1984

Authors address:

Prof. Dr. G. Siebert, Abt. f. Experimentelle Zahnheilkunde, Universität Würzburg, Pleicherwall 2, 8700 Würzburg