# Beneficial health effects of low-digestible carbohydrate consumption

Wolfgang Scheppach*, Hardi Luehrs and Thomas Menzel

*Department of Medicine, University of Wuerzburg, D-97080 Wuerzburg, Germany*

Low-digestible carbohydrates represent a class of enzyme-resistant saccharides that have specific effects on the human gastrointestinal tract. In the small bowel, they affect nutrient digestion and absorption, glucose and lipid metabolism and protect against known risk factors of cardiovascular disease. In the colon they are mainly degraded by anaerobic bacteria in a process called fermentation. As a consequence, faecal nitrogen excretion is enhanced, which is used clinically to prevent or treat hepatic encephalopathy. Low-digestible carbohydrates are trophic to the epithelia of the ileum and colon, which helps to avoid bacterial translocation. Short-chain fatty acids are important fermentation products and are evaluated as new therapeutics in acute colitis. They are considered in the primary prevention of colorectal cancer. The bifidogenic effect of fructo-oligosaccharides merits further attention. Unfermented carbohydrates increase faecal bulk and play a role in the treatment of chronic functional constipation, symptomatic diverticulosis and, possibly, the irritable bowel syndrome. In conclusion, low-digestible carbohydrates may play a role in the maintenance of human digestive health. However, the strength of evidence differs between disease entities.

**Low-digestible carbohydrates: Dietary fibre: Non-starch polysaccharides: Short-chain fatty acids: Total parenteral nutrition: Colorectal cancer**

## Introduction

Recently, Burkitt's hypothesis (Burkitt, 1971) of primary prevention of colorectal cancer by dietary fibre has been challenged by data from the Nurses' Health Study (Fuchs *et al.* 1999), which did not support the existence of an important protective effect of dietary fibre (DF) against colorectal cancer or adenoma. Consequently, the complex issue of potential health benefits provided by low-digestible carbohydrates (LDCs) has become more controversial. On the other hand, plausible mechanisms have been demonstrated by which LDCs interact with the gastrointestinal tract and which may explain their protective role in various Western diseases. In this concise review the evidence of possible links between LDC consumption and human health is presented.

## LDCs in the gastrointestinal tract

Low-digestible carbohydrates represent a heterogeneous group of substances. They have in common a resistance against enzymatic degradation in the small intestine. In a complex fashion they interact with the digestion and absorption of nutrients in the small gut. Once LDCs reach the colon, their fate is determined by their bacterial fermentability. Short-chain fatty acids which are produced as endproducts of anaerobic carbohydrate breakdown affect the colonic epithelium in various ways. Other less-degradable fibre constituents act especially on the distal colon by their water-holding capacity, which is associated with a faecal bulking effect. Fig. 1 presents a summary of regional LDC effects and possibly related health benefits.

## LDCs and vascular disease

The 'metabolic syndrome' comprises several risk factors that interact in a complicated and poorly understood fashion in the pathogenesis of cardiovascular disease: obesity, non-insulin dependent diabetes mellitus, combined hyperlipidaemia, and hypertension. There is evidence that LDCs may affect any of these risk factors.

The epidemiologic Health Professionals' Study (Rimm *et al.* 1996) suggested an inverse association between fibre consumption and myocardial infarction. The relative risk of infarction was most effectively reduced by high cereal fibre intake. The protective effect of fibre persisted after correction for fat intake, i.e. fibre did not simply act by substituting fat in the diet. In other cohorts similar data were obtained (Khaw & Barret-Connor, 1987; Humble *et al.* 1993). Thus, fibre *per se* reduced the risk of coronary heart disease and was not simply an indicator of a healthy lifestyle.

The lack of fibre in the diet may be a contributing factor in obesity. In overweight subjects, the intake of fibre has been found significantly reduced, compared with lean control persons (Alfieri *et al.* 1995). Consequently, a fibre-rich diet has been advocated in the treatment of obesity

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* **Corresponding author:** Wolfgang Scheppach, fax +49-931-201-3534, email w.scheppach@medizin.uni-wuerzburg.de
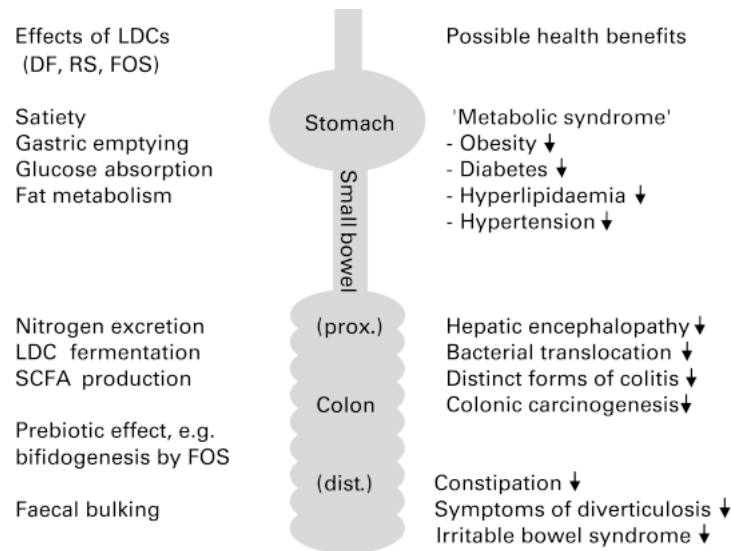
**Fig. 1.** Physiological effects of low-digestible carbohydrates (LDCs, left column) and possibly related health benefits (right column). DF, dietary fibre; RS, resistant starch; FOS, fructo-oligosaccharides; SCFA, short-chain fatty acids.

(Pasman *et al.* 1997). Fibre may facilitate compliance with low-energy diets by causing early satiety secondary to gastric distension.

Jenkins *et al.* (1981) have introduced the glycaemic index to determine the effect of various food items on the postprandial blood glucose concentration. Although this approach simplifies the complex process of gastrointestinal digestion and absorption, the index has proved useful in the clinical setting. Fibre-rich foods are usually associated with a low postprandial blood glucose rise. Concerning fibre supplements, primarily gel-forming guar has been shown to delay small-intestinal glucose absorption, either by inhibiting the diffusion of glucose within the chyme (Blackburn *et al.* 1984) or by increasing the unstirred water layer (Blackburn & Johnson, 1983). The principle of slowing carbohydrate absorption ('lente carbohydrate') may have beneficial metabolic effects in diabetes and is considered in nutritional recommendations from diabetes societies (Toeller *et al.* 1999).

Certain soluble fibre constituents, e.g. oat bran, exhibit a modest cholesterol-lowering effect (reduction of total serum cholesterol by 5–15 % of the initial value). The mechanism of action is not entirely clear; fibre may act by interfering with cholesterol absorption or affecting bile acid metabolism. Another explanation could be the production of propionate during bacterial LDC fermentation in the colon which is absorbed into portal blood and reduces hepatic cholesterol production in experimental animals (Kasper, 1988). There is also evidence that some LDCs (e.g. fructo-oligosaccharides) lower plasma triglyceride concentrations (Agheli *et al.* 1998). For clinical purposes, it can be stated that soluble fibre makes a small but significant contribution to dietary therapy of hypercholesterolaemia (Brown *et al.* 1999).

In the Nurses' Health Study (Ascherio *et al.* 1992) as well as in the Health Professionals' Study (Ascherio *et al.* 1996) it has been found that an increased intake of fibre (and magnesium) was inversely associated with self-reported systolic and diastolic blood pressures. A high fibre consumption reduced the relative risk of stroke among hypertensive men significantly (Ascherio *et al.* 1998). In spontaneously hypertensive rats a high-fibre and low-fat diet reduced systolic and diastolic pressure values by 10–15 mmHg (Bagger *et al.* 1996). It is not known which fibre component is most effective in lowering elevated blood pressure.

In conclusion, a high-fibre diet can reduce several risk factors associated with cardiovascular disease although the underlying mechanisms of action are not well understood.

## LDCs and prebiotic effects

Prebiotics are defined as 'non-digestible food ingredients that beneficialy affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon' (Gibson & Roberfroid, 1995) as opposed to probiotics that can be defined as viable cultures of micro-organisms that benefit the host by improving the qualities of the indigenous microflora (Havenaar *et al.* 1992). Among the LDCs, fructo-oligosaccharides occupy a key position by their ability to change significantly the composition of the colonic microflora. They stimulate selectively the growth of bifidobacteria ('bifidogenesis') in experimental animals and also in human volunteers making these bacteria the predominant genus in faeces (Gibson *et al.* 1995). A well-tolerated daily dose (10 g) of short-chain fructo-oligosaccharides is sufficient to increase significantly faecal bifidobacteria in healthy subjects (Bouhnik *et al.* 1999). Owing to this property fructo-oligosaccharides are classified as prebiotics.

A number of health benefits may be associated with bifidogenesis. Possibly detrimental bacteria, e.g. clostridia, may be displaced by bifidobacteria. The gut barrier function may be strengthened and the invasion of

pathogens prevented (Catala *et al.* 1999). The stimulation of the gut-associated immune system by prebiotics has been discussed. By releasing n-butyrate into the colonic lumen or alternative mechanisms bifidobacteria may affect the carcinogenic process (see below). Other health claims are related to carbohydrate and lipid metabolism of the macro-organism. Although interactions between fructo-oligosaccharides and functions of the large intestine are of scientific interest it has still to be proven that they contribute to human health (Roberfroid, 1997).

### LDCs and hepatic encephalopathy (Fig. 1)

Lactulose, a synthetic disaccharide consisting of fructose and galactose subunits, has been widely used since 1966 in the treatment of hepatic encephalopathy (Bircher *et al.* 1966). This complication of advanced liver disease occurs as a consequence of reduced hepatic clearance of nitrogenous compounds (ammonia and others) which have entered the portal bloodstream mainly from the colon. When the colonic flora metabolizes lactulose, bacterial incorporation of nitrogen increases as does the bacterial mass. The administration of lactulose to humans causes an increase in faecal nitrogen and reduction of luminal ammonia concentrations (Fig. 2). The fermentation of carbohydrates results in the production of short-chain fatty acids (SCFAs) which reduce the diffusion of ionized ammonia into the portal blood in an acid environment (Weber *et al.* 1987).

Other LDCs, particular those contained in dietary fibre or resistant starch, seem to have similar effects to those of lactulose. In a faecal buffered homogenate *in vitro*, pectin, various starches and lactulose gave similar results in reducing ammonia concentrations (Aminosharie & Weber, 1993). In lactase-deficient subjects, especially in third world countries, the drinking of milk is another possible way to increase faecal nitrogen excretion (Uribe-Esquivel *et al.* 1997). Likewise, the administration of a glucosidase inhibitor (e.g. acarbose) stimulates fermentation and contributes to faecal nitrogen excretion (Scheppach *et al.* 1988). These interventions are powerful tools to suppress hepatic encephalophathy in cirrhotic patients.
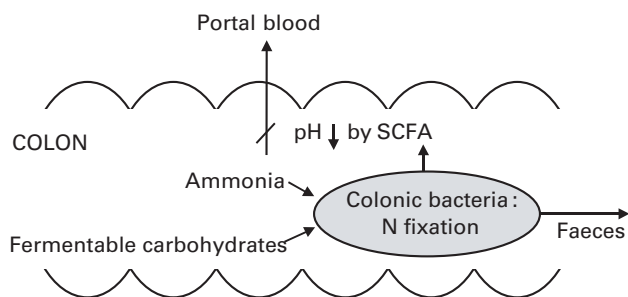


**Fig. 2.** Effect of fermentable carbohydrates on colonic nitrogen metabolism. Carbohydrate substrates stimulate bacterial proliferation which leads to incorporation of nitrogen (from ammonia and other sources) into bacterial cell walls and consequent excretion in faeces. Short-chain fatty acids (SCFAs) (endproducts of bacterial carbohydrate fermentation) lower colonic luminal pH which reduces diffusion of (ionized) ammonia into portal blood.

### LDCs, colonic mucosal proliferation and the gut barrier

Dietary fibre components (especially those which are highly fermentable) are trophic to the colonic epithelium of rats, as shown by an increase in mucosal DNA, RNA, and protein content (Jacobs & Lupton, 1984). The same effect occurs when starch is malabsorbed and serves as a fermentable substrate to the microflora. Inert bulk (kaolin), however, does not affect the crypt cell production rate of mouse colonic mucosa (Goodlad & Wright, 1983). The proliferative effect of fibre on rat colonocytes is seen in conventional but not in germ-free animals (Goodlad *et al.* 1989). It can be concluded from this finding that products of fibre breakdown and not fibre *per se* stimulate cell proliferation. Indeed, SCFAs enhance colonic mucosal proliferation *in vivo* (Kripke *et al.* 1989) and *in vitro* (Scheppach *et al.* 1992).

This trophic effect may be physiologically important if it improves large intestinal function under certain stress conditions. This issue was addressed in a series of rat studies. Colonic infusion of SCFA accelerated wound healing after colonic transection and re-anastomosis. Spontaneous anastomotic dehiscence was significantly less in the SCFA than in the control group; the anastomotic suture line burst in fewer colons from the SCFA group when tension was applied to the bowel wall (Rolandelli *et al.* 1986). After 80 % small-bowel resection (i.e. in a model of the short-bowel syndrome) pectin (a highly fermentable dietary fibre) enhanced intestinal adaptation by increasing colonic mucosal DNA, RNA, and protein contents (Koruda *et al.* 1986); this resulted in a less pronounced postoperative weight loss than under control conditions. Summarizing these data from animal studies, there is evidence that the trophic effect of SCFA may enhance intestinal adaptation to surgical stress. To date, it is unclear if these effects obtained in animal experiments can be translated into improved postoperative performance of patients receiving enteral formula diets fortified with fibre.

A complex system with interrelated factors prevents the penetration of the small and, more importantly, the large intestinal wall by bacteria: the gut barrier. Little is known about the effect of fibre or its degradation products on the gut-associated immune system. There is a preliminary report showing stimulated DNA synthesis by lymphocytes *in vitro* in the presence of sodium butyrate (Carpaneto *et al.* 1991). Unspecific epithelial defences may also add to the gut barrier function. In the rat model, the effect of fibre on bacterial translocation from the gut to mesenteric lymph nodes, liver, and spleen has been tested. The addition of cellulose to an orally administered total parenteral nutrition (TPN) solution reduced the incidence of bacterial translocation (compared with TPN alone) (DaZhong & Deitch, 1998); supplementation with citrus pectin had no effect in this experimental setting (Spaeth *et al.* 1990). The addition of corn cobs, but not soy fibre, to a defined fibre-free formula diet reduced the translocation rate significantly (Alverdy *et al.* 1990). Both glutamine and fibre (psyllium), when added to a fibre-free formula diet, prevented loss of bowel mass, but neither substance protected effectively against spontaneous or endotoxin-induced bacterial translocation (Barber *et al.* 1990), a phenomenon primarily

noted in experimental animals. It seems that less fermentable fibre components are most effective concerning the prevention of translocation. No information is available concering potentially protective effects from resistant starch or oligosaccharides. The applicability of these data to the clinical setting is uncertain, although translocation has been shown to occur in humans and to be associated with the likelihood of sepsis (Sedman *et al.* 1994).

### LDCs and colitis

The idea that SCFAs may play a role in distinct forms of colonic inflammation was derived from Roediger's fundamental experiments in isolated colonocytes. He showed that luminal n-butyrate produced during bacterial carbohydrate fermentation was the main luminal source of energy for these cells and was preferred over glutamine or glucose (Roediger, 1980*a*). He also demonstrated a limited ability of colonocytes in ulcerative colitis to oxidize SCFAs despite their abundance in the colonic lumen (Roediger, 1980*b*). From these and other observations Roediger set up the hypothesis of 'nutritional colitis': when luminal nutrition (by SCFAs) is inadequate during oral starvation colonic mucosal atrophy develops after a few days. Due to reduced absorptive capacity of the malnourished epithelium diarrhoea occurs which is even worsened by rapid refeeding. Prolonged mucosal starvation may not only lead to functional but also to structural changes such as ulceration. Inflammation of the mucosa may (at least partly) be due to a lack of luminal SCFAs (e.g. diversion colitis) or a diminished capacity of the mucosa to oxidize SCFAs (e.g. ulcerative colitis) (Roediger, 1990). Recently, anti-inflammatory effects of butyrate have been described; *in vitro*, butyrate inhibits the activation of nuclear factor kappa B which is a critical transcription factor of pro-inflammatory cytokines (Luehrs *et al.* 1999).

This intriguing hypothesis has prompted a number of empirical clinical trials testing SCFAs as a cure for distinct forms of colitis. SCFAs have been tested as a cure for diversion colitis, pouchitis and radiation proctitis; the majority of trials, however, have been performed in ulcerative colitis.

As no slow release formulation for oral use is available, trials using rectal enemas have been confined to proctitis, proctosigmoiditis or left-sided ulcerative colitis (Scheppach *et al.* 1996; Breuer *et al.* 1997). Most of nine studies reported so far suggest a benefit from SCFAs, although lack of a control arm and small sample size has been criticized in some studies. Obviously, a large confirmatory trial is needed to finally assess this new mode of treatment which would be free of side-effects and cost saving. It has been learned from the pilot studies that patients with new onset of disease or after prolonged periods of remission may respond best. Trial periods should extend over six weeks and include enemas twice daily. The optimum composition of the enemas (mixture of SCFAs, butyrate monotherapy, combination with 5-aminosalicylic acid) has not yet been established (Cummings, 1997).

### LDCs and colorectal carcinogenesis

The fibre hypothesis has originally been proposed by Denis Burkitt who found low incidence rates of colorectal cancer (CRC) in rural Africans consuming a high-fibre diet (Burkitt, 1969). Two meta-analyses of case-control studies reported a significant reduction of CRC risk with increasing consumption of dietary fibre (Trock *et al.* 1990; Howe *et al.* 1992). Prospective cohort studies, however, found no association between fibre consumption and cancer risk (Willett *et al.* 1990; Fuchs *et al.* 1999). The evidence of dietary fibre and CRC risk has recently been evaluated at a consensus conference sponsored by the World Health Organization (Scheppach *et al.* 1999).

Experimental studies have revealed that, together with non-starch polysaccharides (NSP), a major component of dietary fibre, resistant starch reaches the colon. On a high-starch diet, the amount of starch in the colon may even exceed the amount of NSP (Macfarlane & Cummings, 1991). Due to the lack of food-composition data the epidemiological evidence relating resistant starch with cancer risk is currently insufficient (Cassidy *et al.* 1994).

In animal experiments, fructo-oligosaccharides reduce the occurrence of aberrant crypt foci and colonic tumours (Pierre *et al.* 1997; Reddy *et al.* 1997). It is unknown whether this effect is due to increased numbers of bifidobacteria, enhanced butyrate production or other mechanisms.

Complex carbohydrates (NSP, resistant starch, oligosaccharides) are broken down by the microflora to SCFAs. There is growing experimental evidence that SCFAs, particularly n-butyrate, could have a protective role in the carcinogenic process by their effects on proliferation, apoptosis and gene expression (Fig. 3).

Normal proliferation of colonocytes occurs in the basal 60 % of the crypts. In the upper 40 % of the crypts, however, proliferation stops and colonocytes become fully differentiated, to be extruded after approximately 7 days of upward migration. The expansion of the proliferative compartment to the crypt surface (hyperproliferation, involving the upper 40 % of the crypt length) is considered a preneoplastic biomarker. Butyrate diminishes hyperproliferation in colonic mucosa obtained from patients with ulcerative colitis, a disease with well-known neoplastic potential (Scheppach *et al.* 1997). In uninflamed mucosa, butyrate antagonizes hyperproliferation that has been induced by incubation with cocarcinogenic deoxycholic acid (Bartram *et al.* 1993).

A disruption of the balance between cell gain through mitosis and cell loss through programmed cell death (apoptosis) is thought to be an important event in carcinogenesis. Hague *et al.* (1993) have found apoptosis to be increased when colonic adenoma and carcinoma cells were incubated with butyrate. The effect was less pronounced with decreasing chain length (n-butyrate>‴ propionate>acetate) (Hague *et al.* 1995). The action of SCFAs may be due to increased expression of genes that favour apoptosis (Bax, Bak) and, concomitantly, a reduced expression of counterplayers that prevent apoptosis (Bcl-2, Bcl-$X_L$) (Hague *et al.* 1997; Schauber *et al.* 1999). Important links between butyrate, the inhibition of
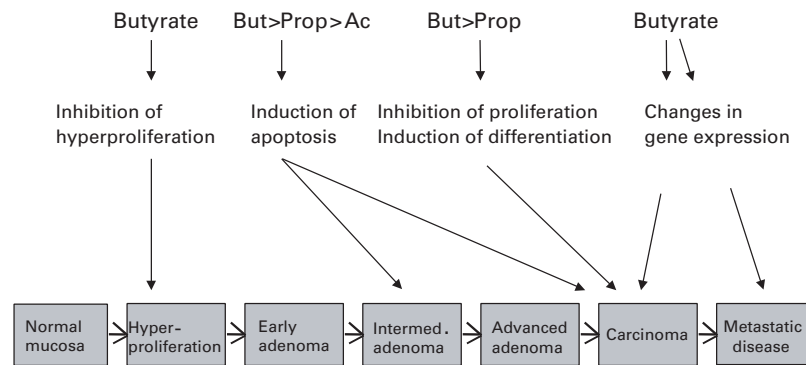
**Fig. 3.** Effects of short-chain fatty acids on cells in various stages of the adenoma–carcinoma sequence (based on *in vitro* experiments). But, n-butyrate; Prop, propionate; Ac, acetate; Intermed., intermediate.

cyclo-oxygenase-2 and apoptosis have been reported by Tsujii & DuBois (1995).

Abundant literature has accumulated on butyrate-induced inhibition of the growth of human colon cancer cell lines. In these isolated tumour cells, butyrate suppresses proliferation at concentrations between 1 and 5 mmol/l, without impairing cell viability. There is good evidence that butyrate does not inhibit growth of colon cancer cells simply by cytotoxic action. On the contrary, this fatty acid induces markers of differentiation at the same time as it inhibits proliferation. In the presence of butyrate, tumour cells assume a phenotype more like the original non-neoplastic tissue. Other markers of differentiation induced by butyrate include alkaline phosphatase and other hydrolases. It should be emphasized that the differentiating action of butyrate is observed in tumour cells, but not in non-neoplastic colonocytes cultured under identical conditions (Deng *et al.* 1992; Gibson *et al.* 1992).

Attempts have been made to investigate the effects of butyrate on proliferation and differentiation of neoplastic cells at the molecular level. Early trials have focused on acetylation, phosphorylation and methylation of DNA–histone complexes in various cell lines (Whitlock *et al.* 1983). Although the action of butyrate on histones is considered non-specific, there is evidence that this fatty acid may affect gene expression in a highly specific manner (Kruh *et al.* 1994). The butyrate effects may be summarized as follows. The synthesis of a limited number of proteins is induced, which includes alkaline phosphatase, glycoproteins, hormone receptors and ion-binding metallothioneins. Butyrate suppresses cancer-specific properties in tumour cells, which recover normal molecular characteristics; little is known about the genes that may be involved. Butyrate inhibits proliferation of colon cancer cells, probably by causing an arrest at the early G1 phase (Toscani *et al.* 1988). This could, at least partly, result from the effect of butyrate on the expression of genes involved in the control of the cell cycle, including oncogenes (Wang & Friedman, 1998).

It is likely that colonic carcinogenesis is an example of how endogenous (genetic) and exogenous (nutritional) factors interact. According to Vogelstein's model (Fearon & Vogelstein, 1990), genetic alterations in the colonic mucosa accumulate over one or two decades which lead up to the formation of a malignant tumour. There is, however, evidence that nutritional factors determine the speed of progression in the adenoma–carcinoma sequence. Protective factors (SCFAs and others) may outweigh the detrimental effects of accelerating factors (e.g. secondary bile acids). Future research should be focused on the molecular mechanisms whereby nutrition affects carcinogenesis in the human large bowel. This approach could form the basis for prevention stategies.

## LDCs, constipation, diverticulosis and the irritable bowel syndrome

The faecal bulking effect was studied most extensively at the beginning of dietary fibre research. Basically it was shown that the consumption of fibre was associated with a higher stool mass. Due to their water-holding capacity low-fermentable fibres were most effective in raising faecal output (Cummings *et al.* 1978). Later it was learnt that fermentable fibres, too, increase stool weight as a consequence of increased faecal bacterial matter (Stephen & Cummings, 1980). A faecal bulking effect has also been shown when starch malabsorption was induced by inhibition of small-intestinal glucosidases (Scheppach *et al.* 1988) or when resistant starch was consumed (Hylla *et al.* 1998). Thus, most LDCs increase faecal bulk, however, by different mechanisms.

The consumption of a high-fibre diet is accompanied by an increase in stool weight in healthy volunteers and also in patients with functional chronic constipation (Prynne & Southgate, 1979). Psyllium and isphaghula have been most studied in constipated individuals and proved to be effective stool bulking agents. The consumption of sufficient amounts of fluid together with a fibre supplement and a gradual increase in dose seem important for the clinical success. In the evaluation of chronic constipation a dietary fibre trial should be conducted before technical investigations (Voderholzer *et al.* 1997). The failure of such a trial usually identifies subgroups of constipated patients with either 'slow colonic transit' or 'rectal outlet obstruction'. In these cases surgical repair may be required.

Diverticular disease of the colon is very common in

Western countries whereas it is rarely found in the Third World. It was suggested almost 30 years ago that this condition is a dietary deficiency disorder caused by an inadequate intake of dietary fibre. This view has recently been supported by investigators of the Health Professionals' Study who found that a diet low in total dietary fibre increased the risk of symptomatic diverticular disease (Aldoori *et al.* 1994). Colonic diverticulosis is more prevalent in non-vegetarians than in vegetarians (Gear *et al.* 1979). Experimental animals on a low-fibre diet develop diverticula more frequently in their lifetime than those on a high-fibre diet (Fisher *et al.* 1985). Once established, diverticula do not disappear when a person receives a fibre supplement. However, symptoms associated with diverticulosis (abdominal pain, straining on defaecation) are improved after administration of bran fibre (Brodribb & Humphreys, 1976).

In Europe and the United States the irritable bowel syndrome (IBS) is a frequent condition affecting about 20 % of the adult population. Its diagnosis is based on identifying positive symptoms consistent with the condition ('Rome criteria') and excluding other conditions with similar clinical presentations. For a subgroup of patients with predominant constipation increased dietary fibre intake is recommended (Drossman *et al.* 1997). The scientific evidence for this recommendation, however, is weak. In two randomized crossover studies the control groups had symptomatic improvement similar to that of the treatment groups (bran, corn fibre) (Lucey *et al.* 1987; Cook *et al.* 1990).

Taking all this information together, low-digestible carbohydrates probably confer intestinal health benefits in various ways. However, the strength of evidence relating these saccharides with human pathology is different between diseases.

## References

Agheli N, Kabir M, Berni-Canani S, Petitjean E, Boussairi A, Luo J, Bornet F, Slama G & Rizkalla SW (1998) Plasma lipids and fatty acid synthase activity are regulated by short-chain fructo-oligosaccharides in sucrose-fed insulin-resistant rats. *Journal of Nutrition* **128**, 1283–1288.

Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV & Willett WC (1994) A prospective study of diet and the risk of symptomatic diverticular disease in men. *American Journal of Clinical Nutrition* **60**, 757–764.

Alfieri MA, Pomerleau J, Grace DM & Anderson L (1995) Fiber intake of normal weight, moderately obese and severely obese subjects. *Obesity Research* **3**, 541–547.

Alverdy JC, Aoys E & Moss GS (1990) Effect of commercially available chemically defined liquid diets on the intestinal microflora and bacterial translocation from the gut. *Journal of Parenteral and Enteral Nutrition* **14**, 1–5.

Aminosharie ME & Weber FL (1993) Comparison of starch and lactulose, alone and in combination with antibiotics, on ammonia production in a fecal incubation system. *Gastroenterology* **104**, A859.

Ascherio A, Hennekens C, Willett WC, Sacks F, Rosner B, Manson J, Witteman J & Stampfer MJ (1996) Prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertension* **27**, 1065–1072.

Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B,

Willett WC, Sacks F & Stampfer MJ (1992) A prospective study of nutritional factors and hypertension among US men. *Circulation* **86**, 1475–1484.

Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi I, Stampfer MJ & Willett WC (1998) Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation* **98**, 1198–1204.

Bagger M, Andersen O, Nielsen JB & Ryttig KR (1996) Dietary fibres reduce blood pressure, serum total cholesterol and platelet aggregation in rats. *British Journal of Nutrition* **75**, 483–493.

Barber AE, Jones WG, Minei JP, Fahey TJ, Moldawer LL, Rayburn JL, Fischer E, Keogh CV, Shires GT & Lowry SF (1990) Glutamine or fiber supplementation of a defined formula diet: Impact on bacterial translocation, tissue composition, and response to endotoxin. *Journal of Parenteral and Enteral Nutrition* **14**, 335–343.

Bartram HP, Scheppach W, Schmid H, Hofmann A, Dusel G, Richter F, Richter A & Kasper H (1993) Proliferation of human colonic mucosa as an intermediate biomarker of carcinogenesis: effects of butyrate, deoxycholate, calcium, ammonia, and pH. *Cancer Research* **53**, 3283–3288.

Bircher J, Müller J, Guggenheim P & Haemmerli UP (1966) Treatment of chronic portal-systemic encephalopathy with lactulose. *Lancet* **i**, 890–892.

Blackburn NA & Johnson IT (1983) The influence of guar gum on the movement of inulin, glucose and fluid in rat intestine during perfusion *in vivo*. *Pfluegers Archiv* **397**, 144–148.

Blackburn NA, Redfern JS, Jarjis H, Holgate AM, Hanning I, Scarpello JHB, Johnson IT & Read NW (1984) The mechanism of action of guar gum in improving glucose tolerance in man. *Clinical Science* **66**, 329–336.

Bouhnik Y, Vahedi K, Achour L, Attar A, Salfati J, Pochart P, Marteau P, Flourie B, Bornet F & Rambaud JC (1999) Short-chain fructo-oligosaccharide administration dose-dependently increases fecal bifidobacteria in healthy humans. *Journal of Nutrition* **129**, 113–116.

Breuer RI, Soergel KH, Lashner BA, Christ ML, Hanauer SB, Vanaguas A, Harig JM, Keshavarzian A, Robinson M, Sellin JH, Weinberg D, Vidican DE, Flemal KL & Rademaker AW (1997) Short chain fatty acid rectal irrigation for left-sided ulcerative colitis: a randomised, placebo controlled trial. *Gut* **40**, 485–491.

Brodribb AJM & Humphreys DM (1976) Diverticular disease: three studies. *British Medical Journal* **i**, 424–430.

Brown L, Rosner B, Willett WC & Sacks FM (1999) Cholesterol-lowering effects of dietary fiber: a meta-analysis. *American Journal of Clinical Nutrition* **69**, 30–42.

Burkitt DP (1969) Related disease, related cause? *Lancet* **ii**, 1229–1231.

Burkitt DP (1971) Epidemiology of cancer of the colon and rectum. *Cancer* **28**, 3–13.

Carpaneto EM, Mariani MR & Ferrini S (1991) Stimulation of DNA synthesis in primary culture of human lymphocytes by sodium butyrate. *Proceedings of the American Association of Cancer Research* **32**, 331–336.

Cassidy A, Bingham SA & Cummings JH (1994) Starch intake and colorectal cancer risk: an international comparison. *British Journal of Cancer* **69**, 937–942.

Catala I, Butel MJ, Bensaada M, Popot F, Tessedre AC, Rimbault A & Szylit O (1999) Oligofructose contributes to the protective role of bifidobacteria in experimental necrotising enterocolitis in quails. *Journal of Medical Microbiology* **48**, 89–94.

Cook IJ, Irvine EJ, Campbell D, Shannon S, Reddy SN & Collins SM (1990) Effect of dietary fiber on symptoms and

rectosigmoid motility in patients with irritable bowel syndrome. *Gastroenterology* **98**, 66–72.

Cummings JH, Branch W, Jenkins DJA, Southgate DAT, Houston H & James WPT (1978) Colonic response to dietary fibre from carrot, cabbage, apple, bran, and guar gum. *Lancet* **i**, 5–9.

Cummings JH (1997) Short-chain fatty acid enemas in the treatment of distal ulcerative colitis. *European Journal of Gastroenterology and Hepatology* **9**, 149–153.

DaZhong X & Deitch EA (1998) Elemental diet-induced bacterial translocation associated with systemic and intestinal immune suppression. *Journal of Parenteral and Enteral Nutrition* **22**, 37–41.

Deng G, Liu G, Hu L, Gum JR & Kim YS (1992) Transcriptional regulation of the human placental-like alkaline phosphatase gene and mechanisms involved in its induction by sodium butyrate. *Cancer Research* **52**, 3378–3383.

Drossman DA, Whitehead WE & Camillieri M (1997) American Gastroenterological Association medical position statement: irritable bowel syndrome. *Gastroenterology* **112**, 2118–2137.

Fearon ER & Vogelstein B (1990) A genetic model for colorectal tumorigenesis. *Cell* **61**, 759–767.

Fisher N, Berry CS, Fearn T, Gregory JA & Hardy J (1985) Cereal dietary fibre consumption and diverticular disease: a lifespan study in rats. *American Journal of Clinical Nutrition* **42**, 788–804.

Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Stampfer MJ, Rosner B, Speizer FE & Willett WC (1999) Dietary fiber and the risk of colorectal cancer and adenoma in women. *New England Journal of Medicine* **340**, 169–176.

Gear JS, Ware A, Fursdon P, Mann JI, Nolan DJ, Brodribb AJ & Vessey MP (1979) Symptomless diverticular disease and intake of dietary fibre. *Lancet* **i**, 511–514.

Gibson GR, Beatty ER, Wang X & Cummings JH (1995) Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. *Gastroenterology* **108**, 975–982.

Gibson GR, Moeller I, Kagelari O, Folino M & Young GP (1992) Contrasting effects of butyrate on the expression of phenotypic markers of differentiation in neoplastic and non-neoplastic colonic epithelial cells *in vitro*. *Journal of Gastroenterology and Hepatology* **7**, 165–172.

Gibson GR & Roberfroid MB (1995) Dietary modulation of the human colonic microbiota: introducing the concept of pre-biotics. *Journal of Nutrition* **125**, 1401–1412.

Goodlad RA, Ratcliffe B, Fordham JP & Wright NA (1989) Does dietary fibre stimulate intestinal epithelial cell proliferation in germ free rats? *Gut* **30**, 820–825.

Goodlad RA & Wright NA (1983) Effects of addition of kaolin or cellulose to an elemental diet in intestinal cell proliferation in the mouse. *British Journal of Nutrition* **50**, 91–98.

Hague A, Diaz GD, Hicks DJ, Krajewski S, Reed JC & Paraskeva C (1997) Bcl-2 and bak may play a pivotal role in sodium butyrate-induced apoptosis in colonic epithelial cells; however over expression of bcl-2 does not protect against bak-mediated apoptosis. *International Journal of Cancer* **72**, 898–905.

Hague A, Elder DJE, Hicks DJ & Paraskeva C (1995) Apoptosis in colorectal tumour cells: induction by the short chain fatty acids butyrate, propionate and acetate and by the bile salt deoxycholate. *International Journal of Cancer* **60**, 400–406.

Hague A, Manning AM, Hanlon KA, Huschtscha LI, Hart D & Paraskeva C (1993) Sodium butyrate induces apoptosis in human colonic tumour cell lines in a p53-independent pathway: implications for the possible role of dietary fibre in the prevention of large-bowel cancer. *International Journal of Cancer* **55**, 498–505.

Havenaar R, Brink BT & Huis in't Veld JHT (1992) Selection of strains for probiotic use. In *Probiotics: The Scientific Basis*, pp. 209–224 [R Fuller, editor]. London: Chapman and Hall.

Howe GR, Benito E, Castelleto R, Cornee J, Esteve J, Gallgher RP, Iscovich JM, Deng-ao J, Kaaks R, Kune GA, Kune S, L'Abbe KA, Lee HP, Lee M, Miller AB, Peters RK, Potter JD, Riboli E, Slattery ML, Trichopoulos D, Tuyns A, Tzonou A, Whittemore AS, Wu-Williams AH & Shu Z (1992) Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *Journal of the National Cancer Institute* **84**, 1887–1896.

Humble CG, Malarcher AM & Tyroler HA (1993) Dietary fiber and coronary heart disease in middle-aged hypercholesterol-emic men. *American Journal of Preventive Medicine* **9**, 197–202.

Hylla S, Gostner A, Dusel G, Anger H, Bartram H-P, Christl SU, Kasper H & Scheppach W (1998) Effects of resistant starch on the colon in healthy volunteers: possible implications for cancer prevention. *American Journal of Clinical Nutrition* **67**, 136–142.

Jacobs LR & Lupton JR (1984) Effect of dietary fibers on rat large bowel mucosal growth and cell proliferation. *American Journal of Physiology* **246**, G378–G385.

Jenkins DJA, Wolever TMS, Taylor RH, Barker H, Fielden H, Baldwin JM, Bowling AC, Newman HC, Jenkins AL & Goff DV (1981) Glycemic index of foods: a physiological basis for carbohydrate exchange. *American Journal of Clinical Nutrition* **34**, 362–366.

Kasper H (1988) Einfluss von Ballaststoffen auf die Serum-Lipidkonzentration. *Aktuelle Ernährungsmedizin* **13**, 75–76.

Khaw KT & Barret-Connor E (1987) Dietary fiber and reduced ischemic disease mortality rates in men and women: a 12-year prospective study. *American Journal of Epidemiology* **126**, 1093–1102.

Koruda MJ, Rolandelli RH, Settle RG, Saul SH & Rombeau JL (1986) The effect of a pectin supplemented elemental diet on intestinal adaptation to massive small bowel resection. *Journal of Parenteral and Enteral Nutrition* **10**, 343–350.

Kripke SA, Fox AD, Berman JM, Settle RG & Rombeau JL (1989) Stimulation of intestinal mucosal growth with intra-colonic infusion of short-chain fatty acids. *Journal of Parenteral and Enteral Nutrition* **12**, 109–116.

Kruh J, Tichonicky L & Defer N (1994) Effect of butyrate on gene expression. In *Short Chain Fatty Acids*, pp. 135–147 [HJ Binder, JH Cummings and K Soergel, editors]. Dordrecht: Kluwer.

Lucey MR, Clark ML, Lowndes J & Dawson AM (1987) Is bran efficacious in irritable bowel syndrome? A double-blind placebo-controlled crossover study. *Gut* **28**, 221–225.

Luehrs H, Schauber J, Boxberger F, Dusel G, Krott K, Kelber E, Menzel T & Scheppach W (1999) Butyrate-mediated inhibition of nuclear factor kappa B activation. *Gastroenterology* **116**, A563.

Macfarlane GT & Cummings JH (1991) The colonic flora, fermentation, and large bowel digestive function. In *The Large Intestine: Physiology, Pathophysiology, and Disease*, pp. 51–91 [SP Phillips, JH Pemberton and RG Shorter, editors]. New York: Raven Press.

Pasman WJ, Saris WH, Wauters MA & Westerterp-Plantenga MS (1997) Effect of one week of fibre supplementation on hunger and satiety ratings and energy intake. *Appetite* **29**, 77–87.

Pierre F, Perrin P, Champ M, Bornet F, Meflah K & Menanteau J (1997) Short-chain fructo-oligosaccharides reduce the occur-rence of colonic tumors and develop gut-associated lymphoid tissue in Min mice. *Cancer Research* **57**, 225–228.

Prynne CJ & Southgate DAT (1979) The effects of a supplement

of dietary fibre on faecal excretion by human subjects. *British Journal of Nutrition* 41, 495–503.

Reddy BS, Hamid R & Rao CV (1997) Effect of dietary oligofructose and inulin on colonic preneoplastic aberrant crypt foci inhibition. *Carcinogenesis* 18, 1371–1374.

Rimm EB, Ascherio A, Giovannucci E, Spiegelman D, Stampfer MJ & Willett WC (1996) Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *Journal of the American Medical Association* 275, 447–451.

Roberfroid MB (1997) Health benefits of non-digestible oligo-saccharides. *Advances in Experimental Medicine and Biology* 427, 211–219.

Roediger WEW (1980a) Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. *Gut* 21, 793–798.

Roediger WEW (1980b) The colonic epithelium in ulcerative colitis: an energy-deficiency disease? *Lancet* ii, 712–715.

Roediger WEW (1990) The starved colon – diminished mucosal nutrition, diminished absorption, and colitis. *Diseases of the Colon and Rectum* 33, 858–862.

Rolandelli RH, Koruda MJ, Settle RG & Rombeau JL (1986) Effects of intraluminal infusion of short-chain acids on the healing of colonic anastomosis in the rat. *Surgery* 100, 198–203.

Schauber J, Luehrs H, Boxberger F, Dusel G, Krott K, Kelber E, Scheppach W & Menzel T (1999) Additive effects of combined treatment with butyrate and aspirin on human colon cancer cells. *Gastroenterology* 116, A498.

Scheppach W, Bartram P, Richter A, Richter F, Liepold H, Dusel G, Hofstetter G, Rüthlein J & Kasper H (1992) The effect of short-chain fatty acids on the human colonic mucosa *in vitro*. *Journal of Parenteral and Enteral Nutrition* 16, 43–48.

Scheppach W, Bingham S, Boutron-Ruault MC, de Verdier MG, Moreno V, Nagengast FM, Reifen R, Riboli E, Seitz HK & Wahrendorf J (1999) WHO consensus statement on the role of nutrition in colorectal cancer. *European Journal of Cancer Prevention* 8, 57–62.

Scheppach W, Fabian C, Ahrens F, Spengler M & Kasper H (1988) Effect of starch malabsorption on colonic function and metabolism in humans. *Gastroenterology* 95, 1549–1555.

Scheppach W & German-Austrian SCFA Study Group (1996) Treatment of distal ulcerative colitis with short-chain fatty acid enemas. A placebo-controlled trial. *Digestive Diseases and Sciences* 41, 2254–2259.

Scheppach W, Müller JG, Boxberger F, Dusel G, Richter F, Bartram HP, Dempfle CE & Kasper H (1997) Histological changes of the colonic mucosa following irrigation with short-chain fatty acids. *European Journal of Gastroenterology and Hepatology* 9, 163–168.

Sedman PC, Macfie J, Sagar P, Mitchell CJ, May J, Mancey-Jones B & Johnstone D (1994) The prevalence of gut translocation in humans. *Gastroenterology* 107, 643–649.

Spaeth G, Specian RD, Berg RD & Deitch EA (1990) Bulk prevents bacterial translocation induced by the oral adminis-tration of total parenteral nutrition solution. *Journal of Parenteral and Enteral Nutrition* 14, 442–447.

Stephen AM & Cummings JH (1980) The microbial contribution to human faecal mass. *Journal of Medical Microbiology* 13, 45–56.

Toeller M, Buyken AE, Heitkamp G, de Pergola G, Giorgino F & Fuller JH (1999) Fiber intake, serum cholesterol levels, and cardiovascular disease in European individuals with type 1 diabetes. EURODIAB IDDM complications study group. *Diabetes Care* 22, Suppl. 2, B21–B28.

Toscani A, Soprano DR & Soprano KJ (1988) Molecular analysis of sodium butyrate-induced growth arrest. *Onocogene Research* 3, 223–238.

Trock B, Lanza E & Greenwald P (1990) Dietary fiber, vegetables, and colon cancer; critical review and meta-analyses of the epidemiologic evidence. *Journal of the National Cancer Institute* 82, 650–661.

Tsujii M & DuBois RN (1995) Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxidase synthase 2. *Cell* 83, 493–501.

Uribe-Esquivel M, Moran S, Poo JL & Munoz RM (1997) *In vitro* and *in vivo* lactose and lactulose effects on colonic fermentation and portal-systemic encephalopathy parameters. *Scandinavian Journal of Gastroenterology* 32, Suppl. 222, 49–52.

Voderholzer WA, Schatke W, Mühldorfer BE, Klauser AG, Birkner B & Müller-Lissner SA (1997) Clinical response to dietary fiber treatment of chronic constipation. *American Journal of Gastroenterology* 92, 95–98.

Wang J & Friedman EA (1998) Short-chain fatty acids induce cell cycle inhibitors in colonocytes. *Gastroenterology* 114, 940–946.

Weber FL, Banwell JG, Fresard KM & Cummings JH (1987) Nitrogen in fecal bacterial, fiber, and soluble fractions of patients with cirrhosis: effects of lactulose and lactulose plus neomycin. *Journal of Laboratory and Clinical Medicine* 110, 256–263.

Whitlock JP, Galeazzi D & Schulman H (1983) Acetylation and calcium-dependent phosphorylation of histone H3 in nuclei from butyrate-treated HeLa cells. *Journal of Biological Chemistry* 258, 1299–1304.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA & Speizer FE (1990) Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *New England Journal of Medicine* 323, 1664–1672.