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Editorial

When it comes to finding a suitable *in vivo* experimental model for the human gastrointestinal tract (GIT), it seems that the pig is more equal than other animals. While non-human primates might seem the obvious choice, they are too difficult to work with in practice, partly because their very human-ness generates public dismay at their experimental use. The case in favour of the pig is here put by Guilloteau *et al.* [1] who argue that it is particularly appropriate for studies investigating nutritional programming of the GIT, due to the similarities in structure, function and stage of maturation during fetal and postnatal periods between the two species. Furthermore, the nutritional needs of the omnivorous pig are well characterised, and its nutrient intake can be manipulated and controlled experimentally. Of particular interest at the moment is the influence of body weight at birth on the risk of chronic disease in adulthood; thus it is particularly useful that sows conveniently produce 'runts' that have been growth-retarded *in utero* (i.e. are small-for-gestational-age) as well as appropriate-for- and large-for-gestational-age (LGA) piglets, often in the same litter (thereby reducing genetic effects). In addition, evidence is presented supporting the 'sow–piglet' dyad as the most promising model for the 'human mother–infant' dyad in the study of the effects of intra-uterine growth retardation, while further work is needed in the area of LGA (hardly investigated), and on the long-term effects of nutritional programming on the GIT, for which there are surprisingly few data given its important role in nutrient uptake. The reproductive and physiological characteristics of pigs allow the study of short-, mid- and long-term effects of nutritional programming on the offspring; in addition, surgical procedures such as cannulation are relatively easy and the use of pigs presents fewer economic and ethical constraints than would be involved with non-human primates. Ultimately, work with this versatile animal could provide useful preventative and treatment strategies in the areas of hypertension, CVD, obesity and diabetes for we humans.

The relative lack of interest in the effects of infant feeding on the functional development of the GIT is a point made also by Le Huërou-Luron *et al.* [2] in a review highlighting the results, including from their own work using the pig model, showing that the infant diet modulates postnatal developmental changes in intestinal and pancreatic function. Formula-feeding produces various alterations in gut development (hypertrophy, increased intestinal permeability and bacterial translocation) which might affect absorptive capacity and gut-associated immune function; basal blood glucose concentration is increased and plasma ketones decreased by formula-feeding, while postprandial effects (including the insulin response) are, as yet, unclear. Infant formulae can be modified, for example, by reducing the protein content or adding prebiotics, in order to attempt to ameliorate the gut response such that infant development more closely resembles that of the breast-fed infant; it is in this context that these authors argue strongly that the long-term effects of different feeding strategies on the development of the GIT and the nutritional and immunological consequences should be further studied, using animal models to control some of the many confounding factors. This work is necessary in order to help us understand better the mechanisms involved in the health benefits of breast-feeding in both the short term (lower incidence of diarrhoea and necrotising enterocolitis) and in later life (lower incidences of obesity, type 2 diabetes and inflammatory bowel disease). The intestinal microbiota may play a significant role here, a role further explored in the review by Adams[3] examining the beneficial biological responses generated by both living and dead cells in probiotic products, a phenomenon he terms the probiotic paradox. Probiotics are generally understood to be dietary supplements containing viable micro-organisms which interact in a beneficial manner with the indigenous gut microflora and the immune system. Modification of the gastrointestinal microflora by probiotic therapy could be useful in the treatment of clinical conditions affecting the GIT, such as inflammatory bowel disease and Crohn's disease, and has been effective against (infectious and rotoviral) diarrhoea in children and antibiotic-associated diarrhoea; probiotics also inhibit pathogenic bacteria (*Salmonella*, *Helicobacter pylori*), secrete bacteriocins and enzymes, and remove cholesterol in the GIT (by assimilation and binding to the cell surface). Potential benefits extend beyond the gut, and could include the control of inflammatory disease, prevention of allergic diseases, and prevention of cancer, and respiratory disease via the stimulation of the immune system. The micro-organisms in probiotics could achieve their effects directly in the gut (for example by killing/inhibition of pathogens) or, indirectly, by competition for binding sites on the wall of the GIT (required by pathogenic bacteria in order to produce symptoms of disease). More subtly, probiotics can interact with the cells of the immune system, affecting, for example, the balance of pro- and anti-inflammatory cytokines. In practice, Adams argues, many probiotic preparations contain varying (and usually unknown) amounts of live and dead cells, and, furthermore, even the living cells may not survive their journey through the stomach and small intestine; thus some of the benefits attributed to these preparations could be actually be due to dead probiotic cells, or their metabolites. Dead (usually heat-killed) probiotics and their components have been investigated, and a variety of biological responses reported, including an enhanced immune reaction against resistance to vancomycin-resistant enterococci in chicks fed heat-killed *Enterococcus faecalis* (which would have commercial

importance), and enhanced *in vitro* pro-inflammatory cytokine production by macrophages cultured with heat-killed bifidobacteria. In contrast, anti-inflammatory effects have been reported in mice suffering from experimental arthritis treated with both a live and a heat-killed strain of *Lactobacillus*. Clearly, although some actions of probiotics depend on the cells being alive (effects on the intestinal microflora, immunomodulation), others do not (anti-inflammatory effects); and Adams suggests that the use of preparations of dead probiotic cells can offer several advantages – for example, they would present no risk to patients suffering from immunodeficiency. Furthermore, preparations of dead probiotic cells or specific extracts of their effective molecular components (for example, DNA, polysaccharides) would be easier to store, more standardised in their formulation than live preparations, better survive passage through the stomach, and could even include pathogenic organisms, thus providing potentially promising applications for both human and animal health.

Transport across the gut and placenta cell epithelial cell membrane is the subject of the review by Martel *et al.* [4], specifically the effect of polyphenols on this function. These compounds are antioxidants, and have attracted much interest due to their probable role in the prevention of various diseases associated with oxidative stress (cancer, cardiovascular, neurodegenerative and inflammatory diseases), an interest perhaps not unrelated to their presence in red wine, beer and tea. Polyphenols are also modulators of certain enzymes and cell membrane transporters (of, for example, certain nutrients, including glucose, bioactive amines and drugs) and these authors suggest that interference by polyphenols with the transport of some compounds could affect their bioavailability, at either the gut, or the placenta following absorption of dietary polyphenols into the mother's blood. In the case of thiamin, a connection is suggested between fetal alcohol syndrome and deficiency of this vitamin, while, for folate, *in vitro* studies indicate that different phenolic compounds have different effects on placental transfer of folic acid in both the short and long term. Similar work has suggested that the polyphenols in wine and beer (as well as ethanol) decrease the uptake of folic acid in the gut (unfortunately, tea and orange juice are also culpable here), contributing to the folate deficiency characteristic of this group. In contrast, a potentially useful clinical application for polyphenols could be in the regulation of glucose absorption in the gut in the management of diabetes, and could perhaps even protect against the development of the metabolic syndrome and/or type 2 diabetes. Given the variety of types and effects (including interferences and synergies between them) of polyphenols present in foods, especially what are considered to be healthy foods, and in beverages, it is difficult to draw firm conclusions from this review that could be translated into health promotion messages, other than the familiar mantra that one should consume a varied diet of healthy foods, with nothing in excess.

Whole-grain cereals are another group of healthy foods that have attracted interest, here investigated by Fardet[5] who looks beyond fibre in his heroic review of the mechanisms responsible for the health-promoting effects, particularly of whole wheat. In addition to their well-characterised antioxidant roles, the huge range of bioactive compounds in cereals (mainly in the bran) have recently been implicated in cell signalling and gene regulation (polyphenols), cardiovascular and hepatic protection, lipid metabolism and DNA methylation (methionine, betaine, choline, inositol and folates). Other roles and associations, such as that of B vitamins with the nervous system, oligosaccharides as prebiotics and the action of phenolic acids in the colon, require further elucidation. In addition, phytic acid and lignin, usually considered only in the context of fibre, turn out to have significant antioxidant properties. The complex and interconnected effects of whole grains clearly need to be investigated *in vivo*, and Fardet suggests that metabolomics would be a useful adjunct to the existing measurements of biomarkers used to date, for example, in the clarification of the effects on the immune system and hence protection against cancer. Further, he recommends that *in vivo* studies on gene-regulatory actions of the bioactive compounds present in whole grains should be performed, building on the mostly *in vitro* work carried out to date. He also outlines means by which the nutritional quality of cereal products could be improved, for example, by simply using more intact versions of cereal grain kernels in recipes, including flour that is less refined (high extraction rate) or by modifying the growing conditions, using fertiliser, or environmental stressors such as cold, to increase the content of minerals or antioxidants. More advanced strategies could include the breeding of new varieties with improved nutrient composition, and the use of processes such as fermentation, encapsulation, or extraction of the desired components (for example, the aleurone layer) for reincorporation into foods. This last would reduce potential risk from consuming pesticides or mycotoxins present in the outer layers, though it would obviously be better to produce cereals that are less contaminated in the first place. At the same time the point is made that we should continue to investigate the mechanisms involved in order to work out how the best physiological results can be achieved – a considerable challenge considering the complexity of cause and effect he describes.

In addition to the physical effects of fibre in modulating food intake, a new role for fibre in appetite regulation is proposed by Sleeth *et al.* [6] in their review focusing on free fatty acid receptor 2 (FFA2, formerly GPR43). This receptor, present in the gut wall (and also other tissues including the islet cells of the pancreas, bone-marrow, spleen, and white and brown adipose tissue), binds SCFA generated during fermentation in the colon, producing a satiety effect, possibly via secretion of peptide YY which then acts centrally to induce hypophagia; FFA2 may also stimulate secretion of products of the pre-proglucagon gene, including glucagon-like-peptide 1 (anorexigenic). In other tissues, stimulation by SCFA of FFA2 has been shown to reduce lipolysis and increase adipogenesis (adipose tissue), and improve glucose control and dyslipidaemia; thus some of the beneficial effects of fibre supplementation observed, for example, in the control of the metabolic syndrome, could be attributed to these mechanisms. These authors therefore associate our reduction in fibre intakes, and hence loss of the appetite-suppressive effect conferred via FFA2 by SCFA from fermentable fibre, with the rising tide of obesity

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experienced worldwide. When more fully investigated, a happy consequence of this link could be the development of dietary or pharmacological strategies targeting FFA2 that could help against the development of obesity and type 2 diabetes.

Current available pharmacological therapies for weight reduction include the inhibition of pancreatic lipase, thereby reducing the digestion and absorption of ingested lipid (these preparations must therefore be used with caution, due to the unpleasant and potentially embarrassing side-, or should I say end-?, effects…). There is apparently little (and inconsistent) literature concerning the physiological conditions affecting the action of this enzyme, prompting the review by Brownlee *et al.* [7], who are hopeful that investigation of this area could lead to the development of improved products that produce the wanted but not the unwanted effects. One group which might avail of such products is shift-workers, who, according to Antunes *et al.* [8], are particularly prone to overweight and obesity (also dyslipidaemia, the metabolic syndrome and CVD), perhaps due to metabolic disturbances, for example, in lipid or glucose metabolism (and the hormones governing them) caused by their abnormal circadian regimen. The circadian stage during which the meal is consumed affects eating patterns and food selection (high-fat foods tend to be chosen more at night) and also, intriguingly, diet-induced thermogenesis (lower in the evening); both effects could conceivably predispose to weight gain. Stress is also implicated, perhaps via hypersecretion of cortisol. The expression of the genes regulating food intake and body weight may also be affected by desynchronisation of circadian rhythms, and, excitingly, the discovery of circadian oscillator genes in adipose tissue could have potential therapeutic relevance.

Dietary fat, both total intake and composition, has for a long time been associated with breast cancer, a relationship subjected to scrutiny by Alexander *et al.* [9]. Their quantitative meta-analysis and review of epidemiological cohort studies published to date, focusing on fat intake from animal sources, actually does not support a positive independent association in humans. However, they point out that it must be borne in mind that the way in which food intake data were collected (for example, FFQ *v.* 7 d food diaries) could influence the accuracy of the results, and future studies using improved methodologies could provide a clearer picture. Also required is a plausible mechanism by which dietary fat could lead to breast cancer – some areas of investigation that could bear fruit include clarification of the exact composition of the dietary fat, the timing of the dietary exposure, and associations based on hormone receptor status. Clearly, though, if any solid relationship is ever to emerge, the quality of the dietary data upon which it is based will be of paramount importance.

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