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Nutrition and gut health: the impact of specific dietary components – it's not just five-a-day

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Abstract

The health benefits of fruit, vegetables and dietary fibre have been promoted for many years. Much of the supporting evidence is circumstantial or even contradictory and mechanisms underlying health benefits of specific foods are poorly understood. Colorectal cancer shows marked geographical differences in incidence, probably linked with diet, and explanations for this require knowledge of the complex interactions between diet, microbiota and the gut epithelium. Dietary fibres can act as prebiotics, encouraging growth of saccharolytic bacteria, but other mechanisms are also important. Some but not all soluble fibres have a "contrabiotic" effect inhibiting bacterial adherence to the epithelium. This is particularly a property of pectins (galacturonans) whereas dietary fructans, previously regarded as beneficial prebiotics, can have a proinflammatory effect mediated via toxic effects of high butyrate concentrations. This also suggests that ulcerative colitis

could in part result from potentially toxic faecal butyrate concentrations in the presence of a damaged mucus layer. Epithelial adherence of lectins, either dietary lectins as found in legumes, or bacterial lectins like the galactose-binding lectin expressed by colon cancer-associated *Fusobacterium nucleatum*, may also be important and could be inhibitable by specific dietary glycans. Conversely, emulsifiers in processed foods may increase bacterial translocation and alter the microbiota thus promoting inflammation or cancer. Focussing on one condition is of limited value though in developing public health messages and growing evidence for impacts of dietary components on all-cause mortality is gaining more attention. We are only just starting to understand the complex interactions between food, the microbiota, and health.

Which five-a-day?

The scientific basis of five-a-day is somewhat hazy. Low rates of cardiovascular mortality in Southern Mediterranean countries were attracting attention by the 1960's and prompted assessment of the possible health benefits of a "Mediterranean" diet. Although the pioneering epidemiological "Seven Countries Study" of Mediterranean diet and mortality by Ancel Keys and colleagues emphasised a possible beneficial effect of olive oil[1], the fruit and vegetable content of a typical Mediterranean diet, estimated at 400 grams/day ("excluding potatoes and other starchy tubers"), was promoted by the World Health Organisation (WHO) in 1990 as an appropriate target[2]. "Five-a-day" was a clever marketing slogan, first used in California in the 1980's, adopted by the USA National Cancer Institute in 1991 and by the UK Department of Health in 2003 and based on the 400 gram target with 80 grams as an average portion size. The question that follows is "what counts towards my five-a-day?" The UK NHS, like the WHO, recommends fruits and vegetables that are not typically eaten for their high starch content so potatoes, yams, cassava and plantains "don't count" but "root vegetables such as sweet potatoes, parsnips, swedes and turnips do count …because they are usually eaten in addition to the starchy food part of the meal"[3]. There is however very little evidence underlying this particular selection of foodstuffs and some evidence (see later) that plantains for example might be particularly beneficial.

Dietary fibre and colorectal cancer

Colon and rectal (colorectal) cancer has a much higher incidence in western and westernised countries[4] so is a good place to start when trying to assess the impact of diet on health. Dennis Burkitt famously noted the rarity of colorectal cancer in Africa and suggested a high fibre intake as the explanation[5]. Sheila Bingham confirmed a striking inverse correlation across different countries between average intake of non-starch polysaccharide and mortality from colon cancer[6]. It

looks "obvious" from these data that there must be a causative association but large prospective cohort studies, which should address this more robustly, have produced contradictory results. The Nurses' Health study in the USA reported on 88,757 women followed for 16 years and showed no protective effect for dietary fibre against combined risk of colorectal cancer or adenoma (RR for highest versus lowest quintile of fibre intake 0.95 (95%CI 0.73, 1.25))[7]. Even more surprisingly, it showed that people in the top quintile for vegetable fibre intake actually had an increased risk for subsequent development of colorectal cancer (RR 1.35 (95%CI 1.05, 1.72; P 0.004 for trend) whereas cereal and fruit fibre intakes were not significantly related to risk. The European Prospective Investigation into Cancer and Nutrition (EPIC) study followed 519,978 individuals for 1,939,011 person years and did show a protective effect of fibre – HR for those in the top quintile 0.75 (0.59, 0.95; P=0.005 for trend)[8]. The protective effect of fibre in the EPIC study was predominantly against proximal (right-sided) colon cancer[9]. However, a sub-study (EPIC-Oxford) of 63,550 people showed an increased incidence rate ratio for colorectal cancer in vegetarians compared with meat eaters (IRR 1.39 (95% CI 1.01,1.91))[10] even though meta-analysis of 21 prospective cohort studies has shown a strong association between colorectal cancer risk and increased intake of red and processed meat[11]. One possible conclusion from these contradictions is that it may not be helpful to generalise about health impacts of large food groups. It has been suggested for example that red meat might be "OK", for health if not for the environment, providing it is not burnt to create potentially carcinogenic heterocyclic aromatic amines[12]. Here though I want to concentrate on the possible differing impacts of specific fruit and vegetable components and the mechanisms that may underlie them.

Colorectal cancer (and inflammatory bowel disease) as a bacterial disease

Continuing with colorectal cancer as an exemplar, there has long been a suspicion that bacteria have an important role in its causation, not least because cancer is so relatively rare in the small intestine (0.4% life-time incidence) compared with the colon and rectum (6% life-time incidence in western countries) and bacteria are approximately 10^4 more numerous in the colon. If this is the case, food components might impact on colorectal cancer risk by altering microbiota-epithelial relationships.

In faecal studies an increase in *Fusobacterium nucleatum* in colon cancer has been particularly consistent[13]. Studies looking at mucosa-associated bacteria have also shown an increase in *E. coli,* as well as *Bacteroides fragilis* and *Fusobacterium nucleatum*[14]. *E. coli* had not been found so frequently in earlier faecal studies, possibly because it is micro-aerophilic and tends to thrive better in the relatively high oxygen tension environment close to the mucosal surface, however a recent meta-analysis of faecal studies using state-of-art "shot gun" metagenomics has shown that in colon

cancer there are highly significant increases in *E. coli* polyketide synthase *(pks)*, a gene complex that generates the production of colibactin, a metabolite that damages DNA and induces experimental colon cancer,[15] and also found increases in *Fusobacterium nucleatum* adhesin and Clostridial bile salt dehydroxylase[16].

Using conventional microbiological culture studies our group showed that colonic mucosal biopsy samples from which surface mucus had been removed contained more *E. coli* in colon cancer than controls,[17] confirming previous studies by Swidsinski and colleagues[18]. Subsequent analysis of the colon cancer *E. coli* isolates from our study, in collaboration with the Jobin group, showed that expression of the *pks* gene complex was commoner in *E. coli* isolates from human sporadic colon cancer and parallel studies showed that *E. coli* that expressed *pks*, but not those in which this was deleted, were able to induce colon cancer in an inflammation-associated cancer mouse model[15]. Phenotypically similar *E. coli*, albeit less commonly expressing *pks*[19], are also found adherent to the ileal and colonic mucosa in Crohn's disease[17, 20-22]. Indeed the spectrum of increased mucosa-associated *E. coli* and *Fusobacterium nucleatum* and also reduced *Faecalibacterium prausnitzii*[23] is common to both Crohn's disease and colon cancer.

Possible mechanisms for bacteria-induced carcinogenesis in the colon include DNA damage (eg *E. coli* pks/colibactin), activation of beta-catenin signalling (eg *Fusobacterium nucleatum*), or signalling from Toll-like receptors through MyD88 and other pro-inflammatory pathways, with consequential inhibition of protective apoptosis[24].

Contrasting impact of fibre components on bacteria-epithelial interactions - "contrabiotic" pectins (galacturonans) "good" and fructo-oligosaccharides "bad"

Given the increase in mucosally-adherent *E. coli* in both colon cancer and Crohn's disease plus their ability to promote intestinal inflammation and colon cancer in experimental mice we investigated the possibility that soluble dietary fibres and other complex carbohydrates might be able to inhibit *E. coli* adherence to the epithelium. Initial experiments showed that soluble fibre from plantain bananas (*Musa* spp) and bovine submaxillary mucin but not simpler carbohydrates could block attachment to and invasion of epithelial cells by human colonic mucosal *E. coli* isolates[17]. Further studies showed that soluble fibre from plantain and broccoli but not from apple or leek can block bacterial translocation across microfold (M) cells and follicle-associate epithelium, the initial portal of entry for all gut-invasive organisms[25]. The effects are not specific for mucosa-associated adherent *E. coli,* for similar inhibitory activity was seen against *Salmonella*

typhimurium, *Shigella sonnei*, *Clostridium difficile* as well as for enterotoxigenic *E. coli*[26]. Soluble plantain non-starch polysaccharide added to the feed was then shown to prevent intestinal invasion by *Salmonella typhimurium* in chickens[27]. In view of this broad action of some but not all soluble fibres against bacterial adhesion to and invasion of the gut epithelium we think this may be a very important generic protective effect and have termed it "contrabiotic"[28]. The inhibitory effect against epithelial adhesion of bacteria is due primarily to the homogalacturonan-rich pectin component of the plantain non-starch polysaccharides and is mediated by an action on the epithelium itself rather than by interaction with the bacteria[27]. Pectins are rapidly fermented in the colon[29] so might be predicted to have more impact on bacterial adhesion and translocation in the terminal ileum and proximal colon. This is in keeping with the EPIC study finding that a high fibre intake was more protective against proximal colon cancer although this lost significance when fruit and vegetable fibre were separately analysed[9]. Given the marked similarities in the microbiota of colon cancer and Crohn's disease, it is also notable that people in the highest quintile for fruit fibre consumption in the Nurses' Health study had approximately 40% lower risk for future development of Crohn's disease whereas high consumption of either cereal or vegetable fibre had no significant effect[30]. These dietary-microbiota-epithelial interactions are summarised in Figure 1.

Further support for a specifically beneficial effect of dietary pectins comes from some detailed mechanistic studies that have shown contrary effects of citrus pectin (beneficial) and inulin (harmful)[31]. In these studies it was shown that blockade of the anti-inflammatory cytokine interleukin-10 (IL-10) in mice induced colitis that was ameliorated by a diet in which cellulose was largely replaced by citrus peel pectin (galacturonans) whereas a diet containing a similar amount of inulin (fructo-oligosaccharides) exacerbated the colitis. The harmful effects of the inulin were found to correlate with high faecal concentrations of butyrate generated by its metabolism whereas the pectin diet preferentially enhanced acetate. Suppressing butyrate production by use of metronidazole, which preferentially depletes butyrate producers, or administering hop beta-acids which suppress fermentation, were both effective at reducing inflammation whilst addition to the feed of tributyrin, which markedly increased caecal butyrate, greatly worsened the inflammation. A pro-inflammatory effect of fructo-oligosaccharides is also supported by a negative controlled trial of dietary supplementation in active Crohn's disease[32]. Reduction in intake of fructo-oligosaccharides is also one of the key components of the low FODMAP diet increasingly widely used for treatment of symptoms in irritable bowel syndrome but also shown to improve symptoms in some patients with Crohn's disease, albeit without impacting on inflammatory markers[33].

Could too much butyrate be part of the problem in ulcerative colitis?

Although butyrate is widely regarded as beneficial to the colonic epithelium it is perhaps insufficiently recognised that this benefit is very much dose-related. High concentrations of butyrate, eg above approximately 3mM in direct contact, have been known for a long time to be toxic to colon epithelial cells *in vitro*[34] and our group showed that butyrate stimulation of mucus synthesis by colonic explants was greatest at very low concentrations of butyrate c0.1mM and fell at concentrations above 1mM[35]. Much higher concentrations are commonly present in the colonic lumen (c20mM)[36,37] but the epithelium in health is shielded by its continuous adherent mucus layer [38], moreover butyrate metabolism by surface epithelial cells adds to protection of the more sensitive stem cells at the crypt base[39].

The intriguing studies by Singh et al showing the pro-inflammatory effects of inulin and their mediation via butyrate[31] should prompt us to look again at the possible role of butyrate in ulcerative colitis. Roediger and colleagues reported several decades ago that faecal butyrate concentrations were raised (to 35 mM) in active ulcerative colitis compared with an average 14mM in controls[40]. Roediger had proposed that the underlying problem was a defect in butyrate metabolism by the colonic epithelium in ulcerative colitis[41] however studies by our own group showed that butyrate metabolism by colonic explants from ulcerative colitis patients was similar to healthy controls when the biopsies were taken from patients in histological and clinical remission[42]. Roediger and colleagues also showed that 5-aminosalicylic acid (mesalazine), long used as an effective therapy for ulcerative colitis, inhibited nitrite-induced beta-oxidation of butyrate[43]. Although they interpreted this as evidence that mesalazine might be working by preventing excessive stimulation of fatty acid metabolism leading to an “exhaustion state” of fatty acid beta-oxidation in the colitic epithelium, perhaps a simpler explanation might be that prevention of butyrate oxidation is directly beneficial in this context. Kaiko and colleagues have further investigated the action of butyrate on colon stem cells and showed that butyrate inhibits histone deacetylase resulting in subsequent fox-O3 regulated inhibition of proliferation[39]. It is notable that the marked anti-proliferative effects of butyrate, seen at 1mM, were not seen with 1mM propionate or acetate. Similarly butyrate (8mM) but not acetate, succinate, lactate, formate, propionate, or malonate at the same concentration, was toxic to a murine colon epithelial cell line *in vitro* and this toxicity was largely abrogated by pre-treatment of the cells with either prednisolone or 5-aminosalicylic acid[44]. Similar dose responses to butyrate – beneficial at low concentration eg 2mM but toxic at 8mM, have also been demonstrated with Caco2 monolayers[45] and it has been shown that a combination of butyrate (8mM) and TNFalpha may be particularly damaging to the mucosal

barrier[46]. Given the marked weakening of the colonic adherent mucus layer in active ulcerative colitis[47-49], this supports the obvious implication that the relatively high luminal concentrations of butyrate present in active ulcerative colitis could, in the absence of this mucus layer, be contributing substantially to the damage. This would readily explain the anatomical distribution of colitis with consistent involvement of the distal colon. (Figure 2) Perhaps future treatment strategies for ulcerative colitis should look to block the effects of butyrate rather than to enhance them.

It is also worth noting that adenomatous and cancerous mucosa is devoid of goblet cells and consequently may have very little surface mucus, moreover the adenomatous polyp or cancer is likely to project out into the faecal stream. If the relatively high concentration of butyrate in the faecal stream is toxic to colon epithelial cells then the question follows as to how the dysplastic or cancerous mucosa resists this toxicity. It seems very plausible that the very marked down-regulation during carcinogenesis of the monocarboxylate transporter 1 (MCT1) that mediates butyrate uptake[50] could explain this.

Impact of dietary components on the microbiota

In the previous sections we have considered the impact of dietary fibres on interactions between the epithelium and the microbiota. Perhaps a more "obvious" consequence of dietary fibre might be its direct impact on the microbiota. This is quite difficult to unpick though. There is a substantial literature reporting associations between diet and microbiota across different populations but proof of causation is more difficult and relatively few dietary intervention studies, which give more direct evidence but are much more difficult, have been performed[51]. Studies have shown marked population differences in microbiota, for example between children in rural Africa and those in urban Italy[52]. The rural African children had a much higher fibre intake and higher faecal concentrations of short chain fatty acids, higher counts of *Prevotellaceae* and lower counts of Firmicutes and *Enterobacteriaceae*. Intriguing studies have been performed in the Hadza hunter-gatherer population in the African Central Rift Valley. Their diet is markedly seasonal with a higher meat intake in the dry season and more honey is eaten in the wet season. Some aspects of their microbiome including Firmicutes remain fairly constant whereas Bacteroidetes showed marked seasonal variation, increasing during the dry season[53].

The impacts of fibre on microbiota are complex and also depend on the existing microbiota[54]. Mice colonised with human microbiota and maintained on a low-fibre diet through successive generations developed an increasingly low diversity microbiota that also became increasingly

resistant to reversal by increased fiber intake[55]. If the same applies in humans then populations in whom a Westernised diet has become habitual over several generations may have a microbiota that is relatively resistant to change. Short-term dietary intervention studies may miss this but have nevertheless produced some very interesting findings. O'Keefe and colleagues performed a two-week cross-over study in which African Americans and rural Africans switched between a typical high fibre, low fat African-style diet and a high-fat, low fibre western diet[56]. A switch to the African-style diet induced saccharolytic fermentation, butyrogenesis and suppressed secondary bile acid formation whereas switching to the low fibre, high fat diet induced contrary changes that included an increase in colonisation by *Fusobacterium nucleatum*. Similarly, David and colleagues showed that even a shorter five-day dietary switch between a predominantly animal-based diet and a plant-based diet induced marked changes with an increase in bile-tolerant bacteria and reduction in saccharolytic bacteria on the animal-based diet[57].

Inflammation, eg due to transient gastroenteritis, is itself also associated with marked changes in the microbiota including reduced diversity and increase in pro-inflammatory organisms such as gamma-proteobacteria including *E. coli*[58].

Altered epithelial glycosylation in cancer and pre-cancer, particularly TF expression and its potential to interact with mitogenic dietary and bacterial lectins – the lectin/galactose hypothesis

Mucin-type glycosylation, in which the initial sugar is *N*-Acetyl galactosamine *O*-linked to serine or threonine, is important at mucosal surfaces, not only because of its central role in the function of secreted mucins but also because of the potential role of *O*-glycans on transmembrane glycoconjugates to act as receptors for adhesins or lectins (carbohydrate-binding proteins of non-immune origin). Initial studies based on simple qualitative lectin histochemistry used fluorescein- or peroxidase-tagged lectins to identify altered glycosylation in tissue sections. They showed that in various tissues, including the colon, glycosylation changes occurred in cancer and also to a considerable extent in pre-cancerous adenomas and in inflammatory bowel disease[59-61]. One of the commonest changes seen was increased expression of the Thomsen-Friedenreich (TF) oncofoetal carbohydrate antigen (galactose beta 1,3 *N*-Acetylgalactosamine alpha – serine/threonine), the receptor for peanut lectin (peanut agglutinin, PNA). In colon cancer TF seems to be particularly expressed on high molecular weight splice variants of the adhesion molecule CD44[62] which is itself associated with the cancer stem cell phenotype and also with the transmembrane mucin MUC1 where it can act as a ligand for the human lectin galectin-3, an interaction that is important

in cancer metastasis[63,64]. The mechanism underlying the increased TF expression is complex but seems to involve Golgi disarrangement as a consequence of altered Golgi acidification[65].

Lectins are ubiquitous in living tissues and vary hugely in their structures and binding specificities. Some dietary lectins, notably legume lectins including peanut, are tightly globular structures that resist protease digestion and heat. Bioactive peanut lectin can therefore be extracted from human faeces after peanut consumption and is even extractable from dry roast peanuts[66]. Lectins typically have two or more carbohydrate binding sites and are able to cross-link cell surface receptors. Consequently, many lectins have mitogenic effects but these are not readily predictable. Study of dietary TF- binding lectins from peanuts, edible mushrooms (*Agaricus bisporus*), jackfruit (jacalin) and amaranth showed opposing effects with peanut and amaranth stimulating proliferation but mushroom lectin (which is inactivated by heat) and jacalin inhibiting it, but via different mechanisms[61]. Because of its widespread human consumption, we undertook a further study with peanuts. This showed that ingestion of 100g per day for 5 days in patients attending colonoscopy caused marked stimulation of rectal mucosal proliferation in those patients who, even though histologically normal, had increased (low level) TF expression[66].

We speculated that, if galactose-binding lectins could stimulate proliferation by interaction with TF expressed on the surface glycoconjugates of colon epithelial cells, then dietary galactose-containing oligosaccharides might be inhibitory. We conducted a case-control study of pre-illness diet in patients with colon cancer to investigate this hypothesis. This showed that risk of colon cancer was reduced in people who have a high intake of dietary galactose[67]. This was present mainly in vegetable fibres so was not separable from the protective effect of leafy green vegetables ie with legumes excluded. The protective effect was seen for right-sided colon cancer but not for more distal cancer, in keeping with likely loss of effect on fermentation. In the same study we also showed a small but significant association between regular peanut consumption and risk for colon cancer.

When we confirmed a significant association between mucosal *E. coli* and both colon cancer and Crohn's disease we investigated the adhesion characteristics of the *E. coli*, hoping to find a link with altered glycosylation. To our disappointment we only found one colon cancer isolate that bound the TF glycan[17]. The story has moved on since then with the identification of the oral anaerobe *Fusobacterium nucleatum* as a putative causative organism in colon cancer and also associated with Crohn's disease. *Fusobacterium nucleatum* seems to be particularly associated with high-risk villous adenoma and carcinoma where it attaches to E cadherin and activates Wnt/beta

catenin signalling[68,69]. Its colonisation of the mucosa is dependent on binding to the TF disaccharide via its Fap2 lectin[70]. The association of *Fusobacterium nucleatum* with colon cancer is also related to diet – a "prudent" low meat, high fibre, diet is associated with a lower risk of *Fusobacterium nucleatum* - associated colon cancer[71].

The hypothesis can therefore be expanded into a logical sequence:

1. Pre-cancerous (adenoma) or inflammatory changes in glycosylation include increased TF (galactose beta 1,3 *N*Acetylgalactosamine -) expression by colonic epithelial surface glycoconjugates
2. This increased TF expression allows colonisation by *Fusobacterium nucleatum* which promotes adenoma to cancer progression
3. This colonisation is likely to be inhibited by specific dietary oligosaccharides eg galactose-containing

It should be noted that inhibition of binding of any specific lectin is not always easily predictable from its carbohydrate specificity since it is the secondary or tertiary structure of complex glycans that is probably more important than their carbohydrate content in determining their potential as inhibitors. Non-anticoagulant modified heparins, which are glycosaminoglycans, are for example also highly effective at blocking ligand interactions with the TF glycan[72]. More work is needed to clarify which dietary components might also have this function.

Direct uptake of intact lectin molecules and a possible link with Parkinson's disease

Ingested plant lectins, particularly those with a tightly globular tertiary structure that resist digestion, may not behave like other dietary proteins. Not only do lectins such as peanut lectin resist protease digestion[66] but, presumably as a consequence of interaction with cell surface glycoproteins and their subsequent internalisation, may be absorbed into the circulation as intact proteins. We have shown for example that intact peanut lectin can be detected in venous blood within an hour of ingestion[73]. We have speculated that this could, by mimicking the actions of the human lectin galectin-3, have the potential to promote cancer metastasis[74]. It is also feasible that intact lectins may be taken into nerve endings in the gut. In *C. elegans* it has been shown that a range of dietary lectins, including peanut lectin, can be transported intact along axons from the gut and gain access to dopaminergic neurons where some of the lectins induced toxic effects[75]. In a rat model of Parkinsonism it has been shown that oral gavage with *P. sativum* (garden pea) lectin plus low-dose paraquat induced Parkinsonism that was prevented by vagotomy[76]. These studies fit with

evidence that in humans prior truncal vagotomy performed more than 5 years earlier is associated with a substantial (c40%) reduction in risk for Parkinson's disease[77].

The importance of all-cause mortality as an endpoint

It is easy to focus on factors that impact on causation of a single condition. However, few of us (fortunately) know what conditions we are going to succumb to in our future. Interventions that focus on a single condition rarely impact significantly on all-cause mortality. Thus colon cancer screening, which impacts beneficially and cost-effectively on colon cancer mortality, has not yet been shown to have significant impact on all-cause mortality[78,79]. Breast cancer screening has been criticised on the same grounds. Similarly, recent studies of highly effective cholesterol-lowering agents have also failed to show a benefit in all-cause mortality, even in large numbers (27,564 followed for median 2.2 years) of people selected for high risk from cardiovascular disease[80]. Dietary advice to the general public should therefore address factors that reduce the risk of a range of conditions, not just one, and should ideally impact beneficially on all-cause mortality. Studies are at last starting to do this. There is for example, evidence that adherence to a Mediterranean diet, and its components – low meat, high fruit and vegetable, nuts, and olive oil impacts beneficially on all cause mortality[81,82]. Tree nuts impact more beneficially than peanuts – but even the latter seem beneficial overall although not impacting significantly on cancer mortality[83].

It is not just the food but what we add to it – emulsifiers, detergents, and asbestos!

When studying the impact of food component on bacterial adherence to and translocation through the gut epithelium we speculated that emulsifiers present in food, which are essentially detergents, might damage the mucosal barrier. We found that polysorbate 80, a widely used food emulsifier, caused a marked increase in bacterial translocation across epithelial cell monolayers and across human ileal explants in short-term culture[25]. In health, bacterial translocation across the gut only occurs via the highly specialised microfold (M) cells in the dome epithelium overlying Peyer's patches in the distal ileum and lymphoid follicles in the colon. In the presence of Polysorbate 80, however, bacteria were found to translocate through (rather than between) non-M cell epithelial cells that would not otherwise allow translocation. We also noted that there has been a marked increase worldwide in consumption of emulsifiers in processed foods and that this might be a plausible explanation for increases in incidence of Crohn's disease seen in countries such as Japan with an increasingly westernised diet[84]. Chassaing and colleagues took this further by showing that feeds containing either polysorbate 80 or carboxymethylcellulose not only induced inflammation in mice but also induced metabolic syndrome[85]. In their studies the impact of the emulsifiers was

mediated via changes in the microbiota. They also showed a similar impact of emulsifiers on experimental colon cancer[86]. It remains to be seen whether or not these harmful effects are common to all emulsifiers.

It is also feasible that low level exposure to washing detergent might be harmful. It is common practice in the UK to use dishwashing detergents without rinsing. I have speculated that the remarkable epidemiology of coronary artery disease, rising to a peak by 1970 in the UK and USA, but with a much lower mortality in France despite a high smoking rate and saturated fat intake (the "French paradox"), and falling by more than 75% since 1970 might be accounted for in part by ingestion of detergent - with increasing use of dishwashing machines that automatically rinse associated with the subsequent fall in mortality[87]. Reduction in smoking is of course a strong factor too but does not explain the French data and cardiological advances such as statins and stenting post-date the start of the rapid decline in mortality.

Various other poisons or carcinogens have at times contaminated foodstuffs, sometimes with disastrous consequences. We have recently speculated that the marked rise in incidence of oesophageal adenocarcinoma, particularly in British males, might be due to the historical use of asbestos fibre to filter beer. Not only was this widely used in the brewing industry up till about 1980, it was also used in an uncontrolled fashion by unscrupulous public house landlords to allow reselling of beer "slops" to unsuspecting customers[88]. Occupational asbestos exposure is known to be associated with increased risk for this cancer and its time course (increasing from around 1970 and now plateauing) closely resembles that of mesothelioma, a known asbestos-associated cancer.

Coffee

Lastly, to finish on another eccentric note but with a strong and growing evidence base – coffee. If you are searching for a single dietary component that might prolong life there is arguably nothing that has a stronger case. Regular coffee drinking has been associated with reduced risk of type 2 diabetes, cardiovascular mortality, cancer, cirrhosis, and most importantly with a reduction in all-cause mortality[89-91]. Drinking 5 cups per day is associated with a reduction in risk ratio of around 20% and it does not seem to matter much whether the coffee is standard or de-caffeinated. Probably best taken in conjunction with a Mediterranean diet though!

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Conflict statement

The author together with the University of Liverpool and Provexis plc, holds a patent for use of a soluble fibre preparation as maintenance therapy for Crohn's disease plus a patent for its use in antibiotic-associated diarrhoea. He also holds a patent with the University of Liverpool and others in relation to use of modified heparins in cancer therapy.

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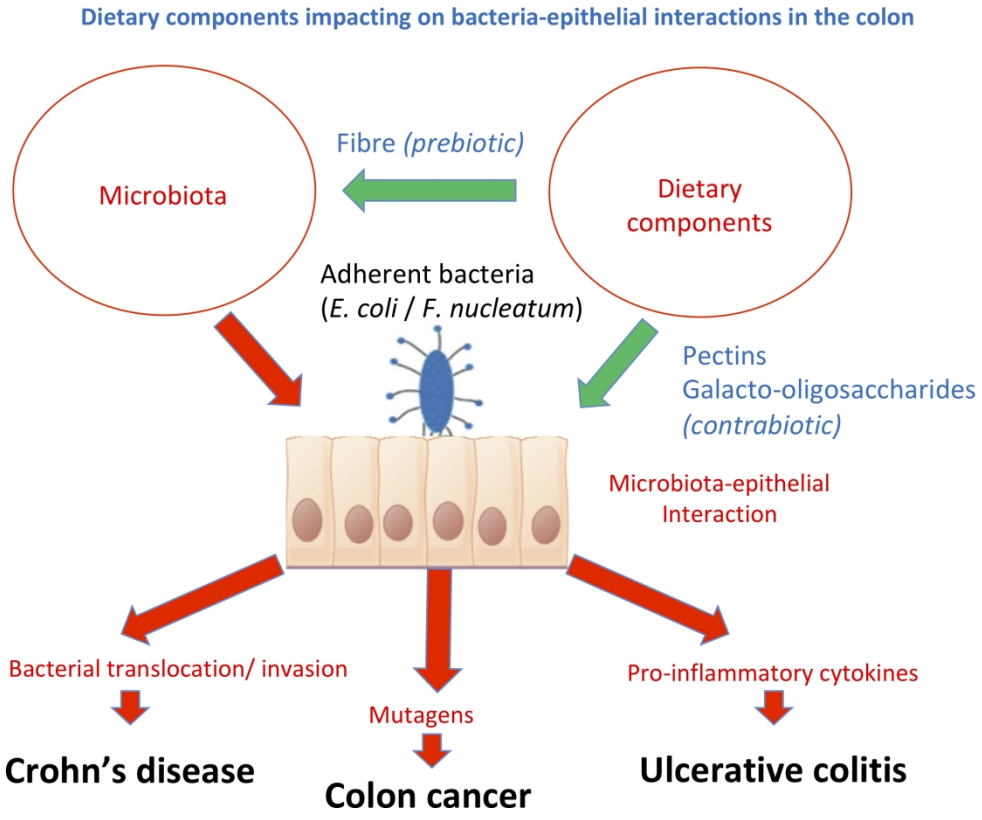
Legends to Figures:

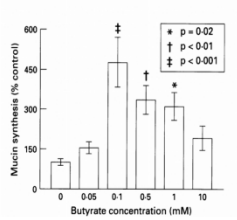
Figure 1: Potential interactions between dietary components – microbiota – epithelium in the pathogenesis of colon cancer and inflammatory bowel disease

Figure 2: Toxicity of high concentration butyrate when the colonic mucus barrier is disrupted – a possible factor in the pathogenesis of ulcerative colitis

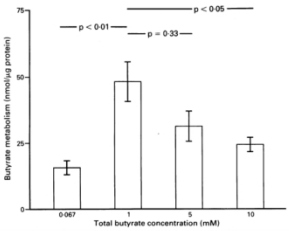


218x180mm (300 x 300 DPI)

Butyrate toxicity as a contributor to mucosal damage in ulcerative colitis



Butyrate enhances colonic explant mucus synthesis optimally at low concentration (0.1 – 1 mM)



Optimal butyrate metabolism also seen at 1mM

(Figures from Finnie et al [35, 42] with permission)

1. Luminal (faecal) butyrate c 15-20 mM (in humans) [36,37]
2. Faecal butyrate may be increased (35mM) in active ulcerative colitis [40]
3. >c3mM butyrate inhibits proliferation and induces apoptosis in stem cells [39] (acetate, lactate, propionate and other SCFA do not- & mesalazine protects against effects of butyrate [43,44])
4. Combination of butyrate (8mM) and TNFα particularly toxic[46]
5. Normal colonic continuous adherent mucus layer presumably protects the surface epithelium from toxic levels of butyrate but is damaged in active UC [47,48]
6. So is butyrate toxicity to the colonic mucosa inevitably present in UC?
7. - and this would explain distal distribution of colitis since it will be produced by fermentation during transit of fibre through the colon

255x187mm (300 x 300 DPI)