Leading article

Dietary fibre and the risk of colorectal cancer

It has long been accepted that a high fibre diet is a "good thing" and protects against colon cancer: however, recently there has been a spate of extensive studies, published in prestigious journals, which have not supported this claim. This started with the report from Boston tracking the eating habits of 88 000 female nurses over 16 years which found no protective action of fibre on the development of colorectal cancer or polyps.[1] This year saw the publication of more epic studies which found that low fat/high fibre diets[2] and dietary supplement with wheat bran fibre did not protect against recurrent colorectal adenomas.[3] Fruit and vegetables also seem to have null associations.[4 5] The recent report by the European Cancer Prevention Organisation Study Group has even found that a soluble fibre supplement had a deleterious effect on recurrence of colorectal adenomas[6]; similar increases in tumour yield in APC mutant mice following supplementation with fibre-like substrates have also been reported.[7]

The implications of this are obviously a cause of some concern but most pundits would appear to be in a state of denial. This is exemplified by the papers themselves and by the published comments. The study of Fuchs and colleagues[1] actually found that those individuals who ate the most vegetables (significantly) increased their risk of colon cancer by 35%. When reviewed in *Gastroenterology*,[8] the conclusion was that it was too early to throw away the "baby with the bath water" and ended with the standard American advice to consume 25 g of fibre a day (the UK recommendations are less as it was not thought that such intakes could be sold to the public). These articles,[2 3] while appropriately stating that high fibre cereal supplements or a low fat/high fibre diet do not protect against adenoma recurrence, still concluded on a positive note for dietary fibre, despite the trend towards *more* cancer in both groups (and significantly so in women[3]).

This state of denial is exemplified by the six letters published in the *New England Journal of Medicine* following the above articles: five argue about the experimental detail and only one dares asks the question "could fibre be harmful?". Even this author feels the need to adopt a "tongue in cheek" approach. While all this may appear to be baffling and totally unexpected, previous reviews of the literature have concluded that the evidence of fibre being beneficial to the colon was not as well established as was previously implied. Moreover, if one concentrates on one of the many actions of fibre, namely fibre as a potential mitogen, the logical conclusion is that dietary fibre could be a *risk factor*, as has indeed been demonstrated in many animals studies (a similar number of studies have also shown reduced risk). When we pointed this out in a commentary in the *Lancet* a few years ago,[9] there was a lot of hostile comment for not being "on message"[10 11] and suggestions that human intervention trials would provide the definitive answer (which would be different to that obtained from animal studies).[12] These latest studies have substantiated our earlier contentions and led some researchers to say that it is now time to abandon the idea that fibre can help prevent colon cancer.[13] Other commentators hope the fibre hypothesis will still turn out to be true and remind us that fibre may none the less reduce the risk of cancer in other tissues and that it has a role in other diseases such as heart disease, diverticulitis, and diabetes.[13]

The choice of model and experimental detail of such intervention studies are of course of vital importance[14] as there are severe limitations in the range of intakes available in the prospective studies. Furthermore, intervention studies are limited by the need to use intermediate end points which, at best, are only part of the carcinogenetic process. This may be especially so for colon cancer which has a very long "gestation" period. These details have already been extensively discussed elsewhere and the aim of this article is to try to take a broader view.

The first consideration is to attempt to decide what one means by dietary fibre. This is by no means an easy task. "Fibre" is a broad term which encompasses a wide range of material. The most abundant organic material on this planet is cellulose but the sugar molecules in cellulose are linked in such a way that mammalian digestion cannot break them down. However, symbiotic bacteria in the hindgut of monogastric mammals, such as humans, ferment cellulose. Other mammals have developed complex foregut fermentation chambers and gain over 70% of their daily energy intake from the production of short chain fatty acids by microbial fermentation. Not all "fibre" is of plant origin as the second most abundant organic material on Earth is chitin, which makes up the exoskeleton of arthropods and also requires similar fermentation for its breakdown. Chitin can thus be regarded as a dietary fibre and some whales digest crustaceans by a fore-stomach fermentation similar to that seen in ruminants.[15] The shellfish industry generates large quantities of waste chitin and chemically modified chitin is widely used as a dietary fibre supplement.

Fibre is consequently best regarded as a concept or even as a spectrum of concepts[16] rather than a substance. Several attempts have been made to persuade us to use better appellations, such as non-starch polysaccharide or plant cell remnants. However, these attempts have not been very successful and further confusion exists in that there is still an acrimonious continuing argument about the means used to analyse "fibre" as different methods of analysis can give quite large differences in the "fibre" content of foodstuffs.[17]

The hypothesis linking fibre to a reduced risk of colon cancer dates back to the early 1970s following the paper by a British missionary surgeon Denis Burkitt[18] who observed that rural Africans had much less colon cancer than affluent Westerners. The original contention of TL Cleave was that it was an unrefined diet that was protective and he indicted manmade fibre depleted foods as the cause of our problems, summarised as "*What God hath put together let no man put asunder*".[16] Burkitt emphasised the protective value of fibre as "*Nature's laxative*" rather than the dangers of fibre depletion, and this positive approach had great appeal. Cleave's contention may however prove to be the more robust as it may be that the benefits of high fibre diets are not due to fibre itself but in what such diets also contain. Natural high fibre diets are rich in vitamins and

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various active plant materials, the so called phytoprotectants. Thus a third definition of fibre can be as "*prison walls*"[16] which protect and deliver these beneficial compounds. The converse of the prison wall hypothesis is that dietary fibre is also a good marker for what the diet does not contain, as high fibre diets have a low calorie density and are low in fat and other potentially harmful components.

The final definition of fibre is a result of its metabolism by the colonic bacteria, so that fibre becomes "*the colon's portion*". Fermentable fibre is a substrate for the multitude of bacteria which live in the colon. It is an interesting thought, especially from a democratic point of view, that there are more (bacterial) cells in our colon than human cells in the body. Colonic fermentation leads to the production of short chain fatty acids which are then used as an energy source for the host. A variety of other materials also reach the colon and can therefore also be classified as fibre by this definition. It is now known that a considerable proportion of starch may be resistant to conventional digestion and will be fermented in the colon. In addition, sloughed intestinal cells and intestinal mucus will also be broken down by the colonic flora and have "fibre-like" actions.

My own work has focused more on fibre as a substrate for the colonic microflora. While this has been useful, it is also dangerous, as this definition allows a host of other substrates to be thought of as fibre. Such an all encompassing definition may not always be a good thing, as it is now possible to use fermentable fibre-like substrates to supplement a "Western diet" to the recommended "fibre" levels.

This is particularly worrying as the recent extensive review of the (human) data by the American Gastroenterological Association[19 20] confused the differences between high fibre diets and "fibre" supplementation. There is now a potential for adverse effects if fibre intake is boosted by consuming various purified supplements, which are now available as "functional foods". This can be regarded as a corruption of Cleave's original contention that we should revert to a primitive unprocessed diet, not that we should add supplements to our "Western" diet which gives us the potential to have the worst of both worlds.

A further possible problem with several fibre supplements, which are now used extensively in an attempt to boost fibre intake to recommended levels, is that they tend to be fermented rapidly. This could lead to a massive surge in microbial activity but the microbes would soon deplete the substrate and starve, or resort to cannibalism or to attacking the colonic epithelial mucosa and mucins. As the carbohydrate to nitrogen ratio of the colonic contents decreases, fermentation becomes more proteolytic and subacute levels of fermentation products such as ammonia may be generated. This "feast or famine" scenario is unlikely to be beneficial, especially as the body is better at reacting to change than to absolute levels.[21]

It must be emphasised that fibre has a large number of actions on digestive physiology; at the last count, I could list over 40! Some actions are mechanical: thus fibre will bulk up the stool and dilute carcinogens as well as speeding up transit time. The benefits of fibre have been attributed to its binding to bile acids but fibre can also bind various other harmful materials. Vegetable fibre has several times more galactose than cereal fibre and this high galactose content will inhibit binding of mitogenic galactose binding lectins, such as peanut agglutinin,[22] which has been shown to stimulate cell proliferation in the human colon.[23]

Fibre can also have profound actions on the viscosity of the gut contents which can alter adaptive growth responses in the intestinal tract.[24 25] Fermentation of fibre leads to the production of short chain fatty acids which in vitro can promote apoptosis and differentiation.[26] However, in vivo, they stimulate mucosal cell proliferation.[27 28 29] The role of proliferation in the progression of carcinogenesis is still a matter of debate; nevertheless, increased cell proliferation is a risk factor in many models.[30] It can even be argued that proliferation is a non-genotoxic cause of human cancer.[31] Altered mucosal proliferation may be particularly important in the colon as some of the earliest changes in colonic carcinogenesis are not those expected from environmental mutagens, indicating that the effects of diet on the progression of colorectal cancer may be promotional rather than mutagenic in nature.[32]

Fermentation profoundly alters the milieu of the colon and has many other biological and cellular effects. In addition to increased cell proliferation, fermentation may also alter crypt fission[33] by which crypts can bifurcate and divide into two.[34] Crypt fission is altered by carcinogens[35] and increased in precancerous states (in patients with familial adenomatous polyposis and in the *Min* mouse) suggesting that fission is a critical event in the initiation and development of colorectal polyps[36] and is also the main mechanism by which neoplastic clones spread through the colorectal epithelium.[37]

In summary, the actions (and interactions) of diet and the gut are complex and one should be wary of over simplistic theories. Recent studies have demonstrated that it is now time to adopt a more open mind set when considering the benefits or otherwise of dietary fibre. There is still a great need for basic research to dissect out the effects on the colon of the several actions of fibre. The development of new animal models, such as the *Min* mouse, should help answer these questions. More human trials are required but these must have more power and also distinguish between the several types of fibre rather than using "catch all" definitions. Finally, what should we eat? and what should we advise? The usual advice to have a balanced diet and everything in moderation is still appropriate. Exercise and avoiding obesity are also very important. I still advocate eating plenty of fibre but only if it comes from fibre rich foods and would favour fruit and vegetables over cereal fibre. Such naturally high fibre diets are still likely to be beneficial, both for what they contain (micronutrients entrapped in the "prison walls" of the plant cell walls) and also for what they do not (fat and excess calories).

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