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Efficacy studies of probiotics: a call for guidelines – reply by Sanders

Hamilton-Miller & Gibson (1999) make some excellent points in their letter regarding the importance (and difficulty) of clinical evaluation of probiotic bacteria and of delivering suitable levels of active bacteria. I would like to clarify my perspective on delivery of probiotic bacteria in dietary supplement (pill) format to foods.

Either format can be effective in delivering therapeutic levels of viable probiotic bacteria. It is a fact, however, that current probiotic levels in some dairy products require consumption of a large volume of product to achieve therapeutic daily doses of probiotic. This is not inherent to probiotic-containing food products, *per se*, but only to current formulation practices, which in the USA generally target about 10^6/ml or g at the end of shelf-life. Concentration technology makes formulation of dried dietary supplements at much higher dose levels achievable, but in practice not all supplements deliver the high levels they claim, as documented by Hamilton-Miller and his colleagues, among others. To add to the problem, the consumer has no resource to sort out products with high levels from those with low levels. What this suggests is that, considering current practices, there is room for improvement of probiotic delivery in both formats.

Is there an advantage to the consumer of one vehicle over the other? A case can be made that the delivery of probiotic bacteria as components of fermented dairy products (or other foods), as long as levels are sufficiently high, may be preferable. In addition to delivery of high probiotic cell numbers, fermented dairy products provide a nutrient-dense food source, including high quality protein, calcium, vitamins, and a plethora of recently identified ingredients that have been proposed to provide additional healthful attributes, such as antimicrobial fermentation endproducts, physiologically active peptides and proteins, anticarcinogenic conjugated linoleic acid and sphingolipids, and perhaps others not yet discovered. On the other hand, dietary supplement products may be more convenient at delivering biotherapeutic concentrations of probiotic bacteria to patients suffering from disease (especially in a clinical setting) and for those preferring this format. Dietary supplements may also be blended with other functional ingredients to enhance their value to the consumer.

This discussion, of course, is predicated on the assumption that viable count in the product is the relevant criterion in determining a functional dose of probiotic. In fact, this may be a gross oversimplification, as strain-specific and target-specific characteristics such as survival through the stomach and small intestine, the ability to replicate *in vivo*, the specific active component by which the probiotic delivers the effect on the target (viable cell, cellular enzymes, cell wall components, fermentation byproducts), all may or may not be accurately reflected by initial viable count. These facts further complicate the identification and description of an effective 'dose'.

The challenge in the probiotic-containing food market, including the USA market, is for food formulators to be convinced of the value of potent concentrations of probiotic bacteria, and develop processes and formulations which deliver high, stable concentrations of probiotic bacteria as part of healthy foods. More conclusive clinical evaluations, and understanding of mechanisms of probiotic effect and improvement of strain stability characterists will provide the evidence food manufacturers need to be persuaded. In general, meaningful measures of probiotic activity in humans (reduction of incidence, duration or severity of diarrhoea, improved digestion of lactose in intolerant populations, reduction in mutagenic/carcinogenic activities) have required high daily consumption (10^9–10^{11} probiotic bacteria). Changes in other bio-indicators (e.g. faecal flora populations) may occur at lower levels of feeding (10^8/d), but these changes have not been clearly correlated with a physiological effect. Until the dose studies have been conducted and the active component better defined, I believe it is prudent to assume that the higher levels are generally necessary for a meaningful, physiological effect.

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Functional food properties of non-digestable oligosaccharides

We were very interested to read the papers by Gibson *et al.* (1999) and the ENDO project group (Van Loo *et al.* 1999) in the February issue of the *British Journal of Nutrition*. They give a useful introduction to the field and list over a dozen different potential health advantages of altered gut bacteriology. When we last attempted to prepare a list of physiological actions of fermentable substrates on the hindgut we gave up after thirty. One of these actions, which was not mentioned in the two papers, was the stimulation of cell proliferation in the intestinal mucosa by the production of short-chain fatty acids (SCFA). There is substantial confusion on the actions of the SCFA, as *in vitro* studies have shown them to be powerful stimulators of differentiation and apoptosis; however, *in vivo* they are clearly powerful mitogens (Goodlad *et al.* 1989), moreover there is poor evidence for pro-apoptotic effects *in vivo*. The implications of this significant proliferative effect are as yet still unclear, but increased proliferation is traditionally regarded as a potential risk factor in the development of carcinogenesis (Wasan *et al.* 1996). Fermentation in the colon also has other biological–cellular actions on the process of crypt fission (McCullough *et al.* 1998), which we have implicated as a critical event in the initiation–development of colorectal carcinogenesis (Wasan *et al.* 1997).

It would appear that this consensus paper is somewhat biased towards the positive evidence, and one must be clearly aware that most clinical dietary interventions have not had the intended beneficial outcomes. This is especially worth stressing in light of the unanticipated results of most of the randomized human β-carotene studies, vitamins C and E and fibre-polyp prevention studies. In these human clinical trials, either no benefits were seen or, more worryingly, detrimental, (i.e. pro-carcinogenic) effects were observed, which led to the early closure of some of the studies (ATBC, 1994). Thus no prospective human clinical study has ever confirmed the purported theoretical benefits. Indeed, worryingly, a fair proportion of dietary fibre studies in animals have also shown pro-carcinogenic effects (Hill *et al.* 1996).

A further complication may be that the addition of fermentable substrate supplements to a 'Western' diet may result in a feast or famine pattern of fermentation (McBurney *et al.* 1987) in which there are sudden surges in bacteriological activity followed by a lack of substrate, in which case the colonic flora must either ferment each other (cannibalism) or the colonic epithelial mucosa and mucins.

We therefore agree with the ENDO group that there is a great need for more in-depth research, but would caution against over enthusiasm in instigating human trials based on the currently available scientific data.

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