

## Nutrition Discussion Forum

### *Efficacy studies of probiotics: a call for guidelines*

The series of papers published in the recent *BJN* Supplement on probiotics (Hasler, 1998) lead readily to the conclusion that probiotics have great potential in several fields. Possible uses that are cited include prevention and therapy of infections, reduction of malignancies, immunomodulation, blood-lipid lowering and, more non-specifically, promotion and maintenance of human health.

Issues surrounding foods that have 'functional' or even health-promoting properties are complex. However, certain experts believe that the potential is so large that probiotics may rapidly become part of mainstream medicine: time alone will tell whether this is the case or not. A few years ago such a sentiment would have seemed a very vain hope, but currently the tide of opinion appears to be changing, such that so-called 'unconventional medicine' is now more widely accepted by the medical profession (Alpert, 1995; Fontarosa & Lundberg, 1997; Kmietowicz, 1997; Ramos-Remus & Russell, 1997; Dalen, 1998). To quote the Editor of the prestigious *Archives of Internal Medicine*: "Promising unconventional therapies must be subjected to the same level of scientific scrutiny that we now require for drug therapies introduced by 'mainstream' medicine" (Dalen, 1998). It is therefore of crucial importance that considerable thought be put into the planning of large-scale, well-controlled trials in man on the efficacy of probiotics.

Endpoints may be straightforward to define in certain cases, e.g. by measuring serum cholesterol concentrations, determining the presence or absence of immunological markers, recording adverse events etc. The clinical indication should be chosen carefully, bearing in mind that showing a positive therapeutic effect may result in the particular product tested being thereafter regarded as 'medicinal' and thus subject to relevant (and highly stringent) regulations. However, assessing the contribution of prebiotics or probiotics to general 'health', 'bacterial balance' (Sanders, 1998) and suchlike claims, that are the driving force for sales of bioyoghurts and probiotic supplements, may present particular difficulties. The very detailed 'Quantity of Life' questionnaires that would be necessary may well defeat the will of even the most dedicated experimenter, leading to a high level of drop-out, and such studies would also have to be long-running and thus expensive. Prebiotics, non-viable food components directed towards the activities of certain indigenous gut bacteria for the same purposes as probiotics, should also be subject to a similar approach (Gibson & Roberfroid, 1995).

The test product(s) used must not only be standardized and defined, but should also be available for others to use to give reproducible results. For example, studies with yoghurts should state not only the amount consumed daily (g or ml), but also the viable count of all organisms present, and preferably details of such strains (e.g. strain

identification). It cannot be assumed for example that all strains of *Lactobacillus acidophilus* will have the same (or even any) desirable probiotic properties (Salminen *et al.* 1996). In a recent survey of fourteen bioyoghurts (Hamilton-Miller *et al.* 1999), many did not disclose what types of bacteria they contained and none gave any indications of numbers. Trials using supplements as a source of probiotics may be complicated by quality assurance problems, as on-label descriptions may be very misleading, especially in terms of quantification (Hughes & Hillier, 1990; Hamilton-Miller, 1996). Again, details of strains are necessary if results are to be repeatable. The use of advanced molecular procedures will, it is hoped, soon make strain identification a much more reliable and routine process.

Dosage represents another possible problem: no dosing studies have been done to determine the 'minimal effective dose' of a probiotic. A daily intake of  $10^6$  to  $10^9$  viable organisms has been suggested (Lee & Salminen, 1995) but in several therapeutic trials daily doses have exceeded this (Hamilton-Miller, 1996). In some studies the bacterial dose used is unknown. As Sanders (1998) points out, it can be very difficult taking large numbers of organisms other than in the form of supplements; here the caveat mentioned above concerning quality assurance is obviously crucial.

In conclusion, it would seem appropriate, in order that progress should occur at an optimal rate, for guidelines to be set up on the basis of mutual agreement between interested parties. This should lead to more productive human trials by which it can be established what indications exist for probiotic use and the mechanisms whereby probiotics and prebiotics are beneficial.

J. M. T. Hamilton-Miller

*Department of Medical Microbiology  
Royal Free and University College Medical School  
London NW3 2PF  
United Kingdom*

G. R. Gibson

*Department of Food Science and Technology  
University of Reading  
Whitenights  
Reading RG6 6AP  
United Kingdom*

### References

- Alpert JS (1995) The relativity of alternative medicine. *Archives of Internal Medicine* **155**, 2385.

- Dalen JE (1998) "Conventional" and "unconventional" medicine. Can they be integrated? *Archives of Internal Medicine* **158**, 2179–2181.
- Fontanarosa PB & Lundberg GD (1997) Complementary, alternative, unconventional, and integrative medicine. *Journal of the American Medical Association* **278**, 2111–2112.
- Gibson GR & Roberfroid MB (1995) Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *Journal of Nutrition* **125**, 1401–1412.
- Hamilton-Miller JMT (1996) Probiotics – panacea or nostrum? *British Nutrition Foundation Nutrition Bulletin* **21**, 199–208.
- Hamilton-Miller JMT, Shah S & Smith C (1996) "Probiotic" remedies are not what they seem. *British Medical Journal* **312**, 55–56.
- Hamilton-Miller JMT, Shah S & Winkler JT (1999) Public health issues arising from microbiological and labelling quality of foods and supplements containing probiotic organisms. *Public Health Nutrition* (In the Press).
- Hasler CM (1998) Prebiotics and probiotics, where are we today? *British Journal of Nutrition* **80** (Suppl. 2), S195–S233.
- Hughes VL & Hillier SL (1990) Microbiologic characteristics of Lactobacillus products used for colonization of the vagina. *Obstetrics and Gynecology* **75**, 244–248.
- Kmietowicz Z (1997) Complementary medicine should be integrated into the NHS. *British Medical Journal* **315**, 1113.
- Lee YK & Salminen S (1995) The coming of age of probiotics. *Trends in Food Science and Technology* **6**, 241–245.
- Ramos-Remus C & Russell AS (1997) Alternative therapies – medicine, magic, or quackery. Who is winning the battle? *Journal of Rheumatology* **24**, 2276–2278.
- Salminen S, Laine M, von Wright A, Vuopio-Varkila J, Korhonen T & Mattila-Sandholm T (1996) Development of selection criteria for probiotic strains to assess their potential in functional foods: a Nordic and European approach. *Bioscience Microflora* **15**, 61–67.
- Sanders ME, (1998) Development of consumer probiotics for the US market. *British Journal of Nutrition* **80** (Suppl. 2), S213–S218.

### *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 characteristics 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.