

# Probioticbulletin

## Hello!

Welcome to our very first issue of the Probiotic Bulletin. Due to the many enquiries we receive about Yakult and probiotics in general, we thought you would welcome a regular newsletter to update you on all the latest research and developments.

In each issue, we intend to focus on one key topic of current interest. We are hoping in future issues to interview experts, and ask them about their views and experiences with probiotics. Finally, we will keep you updated on all things Yakult! We hope to keep this flow of information coming – but we need your help. Let us know any topics you would like us to cover, or anyone you would like us to talk to.

This issue concentrates on the potential of probiotics in relation to colon cancer – a hot topic because of a recent publication from the pan-European research group working in this area. We were delighted that Professor Ian Rowland (previously at the University of Ulster, now at University of Reading) was able to present some of these results at our Yakult Symposium in October last year, which was immediately reported in a national newspaper.



The chairmen and speakers at the Yakult Symposium, London 2006. Left to right, Dr. Tony Leeds, Prof. David Richardson, Prof. David Candy, Prof. Tom MacDonald, Catherine Collins, Prof. Ian Rowland, Prof. Glenn Gibson, Prof. Jeremy Hamilton-Miller and Prof. Alastair Forbes.

Our symposium brought together a panel of experts to review the current scientific evidence on probiotic health benefits. The event was attended by a range of healthcare professionals (with a substantial discount for NHS employees), from whom we received excellent feedback. We hope to repeat this again in the future. ●

## This edition's focus: Colon cancer and probiotics

There is much evidence to indicate that the intestinal microbiota are involved in the aetiology of colorectal cancer. For example, many of the more harmful bacteria in the gut, such as species of clostridia and bacteroides, can produce carcinogenic and toxic compounds (amines, phenols, indoles, etc). Bacterial species that are considered beneficial, such as lactobacilli and bifidobacteria, can help reduce levels of these harmful substances – by inhibiting the growth and activities of the bacteria concerned and also by producing anti-carcinogenic substances. Experts think that manipulation of the gut flora in favour of these beneficial bacteria, may be one strategy that could help reduce the risk of colon cancer. ●

### A FEW STATISTICS...

Colorectal cancer is the 3rd most common cancer in men and 2nd most common in women in the UK. Approximately 35,000 new cases are diagnosed each year in the UK.

The EPIC study has confirmed the link between diet and colon cancer, for example:

- A diet high in fibre **reduces** risk.
- A diet high in red or processed meat **increases** risk.
- A high fat diet is a general cancer risk.

## Rafter et al (2007) Dietary synbiotic reduce cancer risk factors in polypectomized and colon cancer patients. *Am J Clin Nutr* 85(2), 488-496.

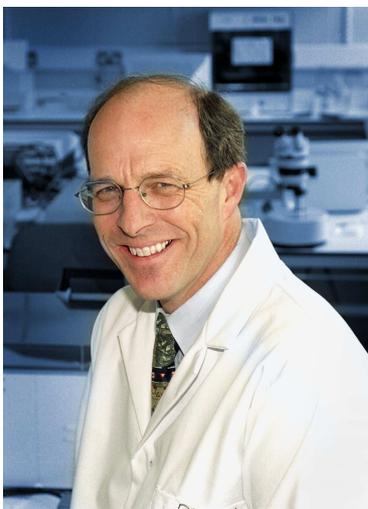
This large, multi-centred study involving Professor Ian Rowland's eminent group at the University of Ulster examined whether a synbiotic (a combination of a probiotic and prebiotic) could reduce the risk of colon cancer. The randomised double-blind placebo-controlled trial investigated 37 colon cancer patients and 43 polypectomized patients (a polyp is a growth that is usually benign, however certain types can become malignant over time). The patients were given a placebo or the synbiotic containing two probiotic bacteria reported as *Bifidobacterium lactis* Bb12 and *Lactobacillus rhamnosus* strain GG (LGG) and a prebiotic oligofructose-enriched inulin for 12 weeks.

The effects of the intervention were assessed by analysis of colorectal biopsies, faecal and blood samples for a range of intermediate biomarkers for colon cancer. Biomarkers were used because cancer is an impractical endpoint because of the large numbers of patients and the time taken for the disease to be evident.

The results of the synbiotic intervention for patients with intestinal polyps were remarkable: colorectal proliferation and DNA damage in these patients were significantly reduced. In addition, the faeces of these patients contained lower levels of chemicals associated with cancer, although no difference was found among patients already suffering cancer. ●

"Whilst this evidence is not definitive, the study does suggest that the extensive data showing anticancer activity from experiments in animals and isolated cells may be applicable to humans, and that more studies in human volunteers are warranted."

Professor Ian Rowland.



### SUGGESTED ANTI-CARCINOGENIC MECHANISMS OF PROBIOTICS:

- Anti-genotoxicity.
- Inhibition of carcinogenic colonic enzyme activity.
- Suppression of growth of pathogenic bacteria.
- Interaction with colonocytes.
- Stimulation of immune system.
- Suppression of food-derived urinary mutagens.
- Production of physiologically active metabolites.

### One mechanism of activity: Reduction of harmful substances in the gut.

Many hypotheses have been put forward to explain the mechanisms behind the possible anti-carcinogenic properties of probiotics (see above table). For example improvement of the ecological balance of the intestinal bacteria would alter the microbial metabolic activities in the gut, promoting microbial saccharolytic activity and suppressing proteolytic activity. This is considered beneficial because the products of the latter pathway are often toxic. Some of the metabolites produced may even cause cancer of the colon.

A research group in a Belgian university have developed two biomarkers (lactose[<sup>15</sup>N,<sup>15</sup>N] ureide and *p*-cresol) in order to quantify toxic metabolites in the gut and assess the level of proteolytic fermentation. In their recently published paper (De Preter *et al* 2007) the biomarkers were used to assess the benefit of *Lactobacillus casei* Shirota (LcS), taken as the probiotic drink Yakult, *Bifidobacterium breve* Yakult (BbY), a lyophilised powder of another probiotic strain and a prebiotic, Synergy 1. The subjects were given one of these products or placebos for 16 weeks, in a crossover trial.

Consumption of the prebiotic significantly reduced levels of the biomarkers and also increased numbers of bifidobacteria in the gut. Further beneficial effects associated with consumption of both probiotics, was a decrease in urinary <sup>15</sup>N excretion and also a significant decrease in *p*-cresol excretion.

The paper concluded that LcS, BbY and the prebiotic could favourably alter colonic ammonia and *p*-cresol levels, indicating a reduced risk of colon cancer. Such dietary supplements may also help in other disease states where proteolytic fermentation

predominates over saccharolytic fermentation, e.g. in cases of IBS and IBD where up to 50% of patients have an abnormal gut flora.

**Dietary factors and colorectal risk – evidence from epidemiological studies (World cancer Research Fund, 1997).**

Evidence	Decreases Risk	Increases Risk
<b>Convincing</b>	Physical Activity Vegetables	
<b>Probable</b>		Red Meat Alcohol
<b>Possible</b>	NSP/Fibre Starch Carotenoids	Sugar Total fat Saturated/animal fat Processed meat Heavily cooked meat Eggs
<b>Insufficient</b>	Resistant starch Vitamins C, D, E Folate Methionine Cereals Coffee	Iron

This is not the first time that probiotics have been linked to evidence of a possible decreased risk of cancer. An earlier trial (Ishikawa *et al* 2005) studied the benefit of LcS and fibre for 398 subjects with a history of colorectal tumours. Although the occurrence of new tumours was no different, the incidence of tumours with a grade of moderate atypia or higher was significantly lower in the LcS-supplemented group.

Diet is often linked to all types of cancer and there is growing evidence that it plays a role in the aetiology of colon cancer. Indeed, there is substantial evidence from epidemiological studies that a diet high in red meat and fat, and low in fruit and vegetables is associated with an increased risk of colon cancer (see table). Any food that reaches the colon undigested is a potential substrate for bacterial fermentation. Glycosides in the gut can be hydrolysed by the intestinal microbiota to aglycones - potentially toxic and carcinogenic compounds. Types of enzymes produced by the intestinal microbiota associated with carcinogen activity include  $\beta$ -glucuronidase,  $\beta$ -glucosidase and

nitroreductase. Many studies show a reduction in these enzymes following supplementation of probiotics. This has been shown with LGG, *L. acidophilus*, *L. casei* and *B. longum* (Goldin *et al*, 1980; Ling *et al*, 1994; Benno & Mitsuoka, 1992 and Spanhaak *et al*, 1998).

Another recent paper by the Belgian group published (online only at present) in the European Journal of Clinical Nutrition describes a crossover study in which 53 healthy people were randomly assigned to receive a prebiotic (OF-IN or lactulose) or a probiotic (LcS, BbY, or the yeast *Saccharomyces boulardii*). The results showed that consumption of lactulose, OF-IN, LcS and BbY all resulted in a decrease in  $\beta$ -glucuronidase activity, however *S. boulardii* had no influence on the enzymes (results that confirm previous studies). Interestingly the administration of the synbiotic did not appear more beneficial than either the probiotic or the prebiotic alone.

LcS has also been associated with possible benefits for superficial bladder cancer. The mechanism for this is thought to be due to a combination of reduction of harmful substances reaching the bladder and stimulation of NK cell activity. ●

"Our studies have indicated that the consumption of Yakult by healthy volunteers has a favourable effect on the colonic protein and ammonia metabolism, and is also associated with a reduction of toxic metabolites by suppressing enzymes that have carcinogenic activities in the colon, which may



be considered beneficial for the host. In these studies, supplementation with a synbiotic did not appear to be more beneficial than the probiotic alone."

Dr Vicky De Preter

References

- Aso, Y *et al* (1995) Preventive effect of a *Lactobacillus casei* preparation on the recurrence of superficial bladder cancer in a double-blind trial. *Eur Urol* **27**:104-109
- Benno, Y & Mitsuoka, T (1992) Impact of *Bifidobacterium longum* on human faecal microflora. *Microbiology Immunology* **36**: 683-694
- Commane, D *et al* (2005) The potential mechanisms involved in the anti-carcinogenic action of probiotics. *Mutat Res* **591**: 276-289
- De Preter, V *et al* (2007) Effects of *Lactobacillus casei* Shirota, *Bifidobacterium breve*, and oligofructose-enriched inulin on colonic nitrogen-protein metabolism in healthy humans. *Am J Physiol Gastrointest Liver Physiol* **292**: G358-G368
- De Preter, V *et al* (2007) Effect of dietary intervention with different pre- and probiotics on intestinal bacterial enzyme activities. *Eur J Clin Nutr* **1-7**
- Goldin, BR *et al* (1980) Effect of diet and *Lactobacillus acidophilus* supplements on human faecal bacterial enzymes. *J Natl Cancer Inst* **64**: 255-261
- Ishikawa, H *et al* (2005) Randomized trial of dietary fiber and *Lactobacillus casei* administration for prevention of colorectal tumors. *Int J Cancer* **116**: 762-767
- Ling, WH *et al* (1994) *Lactobacillus* strain GG supplementation decreases colonic hydrolytic and reductive enzyme activities in healthy female adults. *J Nutr* **124**: 18-23
- Ohashi, Y *et al* (2002) Habitual intake of lactic acid bacteria and risk reduction of bladder cancer. *Urol Int* **68**: 273-280
- Spanhaak, S *et al* (1998) The effect of consumption of milk fermented by *Lactobacillus casei* strain Shirota on the intestinal microflora and immune parameters in humans. *European Journal of Clinical Nutrition* **52**: 899-907.
- Thomas, LV (2006) Probiotics and colorectal cancer. *ICON magazine* **4**:10-13.

## Recent publications of interest

Benton, D *et al* (2007) Impact of consuming a milk drink containing a probiotic on mood and cognition. *Eur J Clin Nutr.* **61**:355-361. Previous studies have shown a correlation between poor mood and degree of constipation. This study carried out at the University of Swansea reported a possible correlation between drinking Yakult and improvement in mood of people with relatively poor mood at the start of the study. Those who reported less constipation were more clear headed, confident and elated.

Kukkonen, K *et al* (2007) Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: A randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* **1**: p. 192-198. Mothers with a family history of atopic disease were given a mixture of four probiotic strains up to a month prior to delivery. Their infants were then given the probiotic and also a prebiotic for 6 months. Probiotic treatment significantly prevented eczema, especially atopic eczema. The gut flora has an important role in the aetiology of atopic eczema. Look out for a future issue of the Yakult Bulletin where this will be explored further.

Rousseaux, C *et al* (2007) *Lactobacillus acidophilus* modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat Med* **13**: 35 – 37. An interesting new area of research investigating treatment of abdominal pain associated with IBS. The probiotic strain, *L. acidophilus* NCFM has been shown to induce cannabinoid and opioid receptors and mediated analgesic functions found in intestinal epithelial cells. The effect of the probiotic was of the same magnitude as subcutaneous administration of 1mg morphine per kg of body weight.

Tong, J L *et al* (2007) Meta-analysis: The effect of supplementation with probiotics on eradication rates and adverse events during *Helicobacter pylori* eradication therapy *Aliment Pharmacol Ther* **25**: (2): p. 155-168. Studies with certain probiotic strains (including LcS) have shown inhibitory activity against the stomach pathogen *H. pylori*. This meta-analysis concluded that probiotics can have a positive effect on side effects associated with *H. pylori* therapy, and were of benefit to eradication rates.

Tuohy, KM *et al* (Epub 2006) Survivability of a probiotic *Lactobacillus casei* in the gastrointestinal tract of healthy human volunteers and its impact on the faecal microflora. *J App Microbiol.* ISSN 1364-5072. Another double-blind, placebo-controlled study, this time conducted at University of Reading, reporting that the Yakult strain remains viable through the gut and increases numbers of faecal lactobacilli. As shown in previous studies, the level of bifidobacteria also increased during the intervention period, indicating that Yakult consumption may result in a gut environment more conducive to the growth of other beneficial bacteria.

Savino, F *et al* (2007) *Lactobacillus reuteri* (American type culture collection strain 55730) versus simethicone in the treatment of infantile colic: A prospective randomized study. *Pediatrics* **1**: p. E124-E130. *Lactobacillus reuteri* was compared with simethicone (an over-the-counter drug often given to children with colic). The probiotic improved colic symptoms within 1 week of treatment compared to simethicone. Daily median crying times were lower in the probiotic group compared to those on simethicone.

### JOURNAL ALERT...

Included in this month's Journal of Nutrition is a supplement on the effects of probiotics and prebiotics. Articles include probiotics and the immune system, anti-allergic effects, autoimmunity, diarrhoea, *H. pylori*, IBD and prebiotics. These articles were derived from the World Dairy Summit in 2003 at a symposium titled "Effects of Probiotics and Prebiotics on Health Maintenance – Critical Evaluation of the Evidence" from presentations and discussions.

J Nutr (2007) **137**: 739s-853s

## Travel Award

Every year we sponsor an award for researchers investigating probiotics or intestinal microbiota. All that is required is submission of an abstract for an original study that will be presented at a conference or symposium (as poster or presentation). These are judged by a panel of judges from different institutes and universities and the winner receives an award of £750, intended to help fund their travel costs. This year is the 10<sup>th</sup> anniversary of the Yakult Travel Award so to celebrate, the winner will be our guest in November at the International Yakult Symposium to be held in Verona! Sadly – the closing date for the competition has just passed. All the entries are currently being judged. Watch this space for the announcement of the winners - and keep this in mind for next year. ●

## Probiotic Literature

If you would like any of our free probiotic literature please visit the order page of our website. We have recently produced an easy to read review of Yakult science (A Guide for Healthcare Professionals.

*Lactobacillus casei* Shirota and Yakult). ●



## Next Issue's 'Best Question'

We would like to feature a "best question" from one of our readers, so if there is anything you want to know about probiotics, please contact us. The person posing the question featured in our newsletter will win a £20 book token. ●

## Contact Us

Please write, email or phone if you have any probiotic or Yakult enquiries. If you have any ideas or suggestions on how we can improve our newsletter please let us know. ●

Phone: 020 8842 7600

Email: [science@yakult.co.uk](mailto:science@yakult.co.uk)

Write: Yakult UK Ltd.  
Artemis,  
Odyssey Business Park  
West End Road  
South Ruislip  
Middlesex  
HA4 6QE

## Probiotic Seminars

The science team at Yakult provide free probiotic seminars to health care professionals, to help increase the awareness and understanding of probiotics. These can be customised to your requirements. If you are interested - contact us. ●

[www.yakult.co.uk](http://www.yakult.co.uk)

## Conferences

We regularly attend healthcare conferences. Come and meet us at the next one at the Community Nutrition Group annual conference in Derbyshire on the 3<sup>rd</sup> and 4<sup>th</sup> April in the exhibition area. Please visit our stand if you have any questions or would like copies of our literature, and of course to try some Yakult! ●

