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Commentary on: prebiotic effects: metabolic and health benefits

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In 2010, *British Journal of Nutrition* published a consensus review article entitled Prebiotic effects: metabolic and health benefits[1]. This was commissioned by International Life Sciences Institute, Europe and had twenty-one co-authors. The current article summarises how this review was planned and written. It deals with three questions regarding the context/background of the paper; what it told us and what happened next.

What was the background to/context for the paper?

I suppose that one possible backstory to this paper goes back to the mid-1990s when prebiotics were first introduced as dietary modulation tools for the human colonic microbiome (although it was just called microbiota in those days). The first author of the 2010 BJN review was Marcel Roberfroid, a Belgian pharmacy professor. We became colleagues in the 1990s when he used to be a consultant for the company who sponsored my first PhD student. The company was Raffinerie Tirlemontoise (later Orafti then Beneo) and the student was the phenomenally hard-working Xin Wang.

Marcel would make frequent trips to London and we would meet, usually in the Scandic Crown Hotel, near Victoria Station. Xin had been working on how inulin (taken from chicory root) could be metabolised by gut bacteria. *In vitro* (gut models) and one *in vivo* study were carried out and the inulin seemed to have a selective effect towards bifidobacteria, popularly used as probiotics then and now. As an aside, the human study had the grand total of eight volunteers! In those days, the molecular revolution in gut microbiology had not yet occurred and microbial assessments of faeces during intervention studies were carried out using growth media purportedly selective for major gut microbial genera. We enumerated nine groups of bacteria in this way. However, the word 'purportedly', as used previously, is relevant and we needed to confirm the identity of every single microbial colony by microscopy and biochemical profiles. The agar plates soon mounted up and eight volunteers was our limit. The paper reporting this was published in a very good journal (Gastroenterology)[2] but I suspect this would not be the case now.

Back to the Scandic Crown Hotel

Marcel and I began discussing whether using diet to fortify beneficial communities that were indigenous to the gut and decided to write a review on this. We also chose to give the concept a name and chose prebiotics*. The review was written pretty quickly and then published by the Journal of Nutrition[3]. To my amazement, it went on to be very well cited going so far as, in 2018, being the most highly quoted functional foods paper published up until then[4].

Fifteen years later, prebiotics had some momentum and this was attracting interest from high quality scientists in a range of other disciplines such as nutrition, biochemistry, immunology and biotechnology. As such, the International Life Sciences Institute (IFLSI) in Europe decided to bring together relevant specialities and update current prebiotic knowledge. Various scientists were asked to participate in the project through a workshop then taking responsibility to leading various sections of the written output. This is what was published in BJN in 2010.

What did the paper tell us and why did it become so highly cited?

One interesting idea for the BJN paper was to mention which authors led which sections. This is something I had not seen before or since, and at the time I remember some scepticism. However, in my view, it does make the publication more distinct and gives ownership to the sections. Also, readers are able to ascertain the principle expertise of all authors, which is usually not the case. The approach was therefore to have researchers draft sections within their expertise, circulate these, everyone to edit and then three main authors consolidated it all.

The paper therefore gave a far more expansive view of prebiotic science and hugely benefitted from the various experts. We were careful not to propose a new prebiotic definition as enough of that had happened already and still is. One thing I have learned about definitions is that if you propose one, then be ready for it to be changed, dismissed or ignored!

As the BJN paper title suggests, the focus here was on the health aspects of prebiotics, which had not really been extensively summarised in one article before. Sections were written on:

- Background to prebiotics.
- Prebiotic effects in the gut (Microbiota of the gastrointestinal tract; Prebiotic effects, fermentation and physiology; *In vitro*

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tests for prebiotic effect; Human studies showing prebiotics effect in healthy persons).
- Prebiotic effects and immune system (Outline of benefit area; Summary of key studies).
- Prebiotic effects in paediatrics (Oligosaccharides and prebiotic effects in infant formulae; Use of prebiotic effects in complementary foods for children; Use of prebiotic effects for paediatric disorders; Prebiotic effects and atopy).
- Prebiotic effects and gastrointestinal disorders (Prebiotic effects and gastrointestinal infections; Prebiotic effects and irritable bowel syndrome; Prebiotic effects and inflammatory bowel disease; Prebiotic effects and colon cancer; Prebiotic protective effects and bacterial activities; Mechanisms of anti-carcinogenicity and antigenotoxicity).
- Prebiotic effects and mineral absorption (Rationale behind prebiotic effects on mineral absorption; Clinical trials; From mineral absorption to health benefits).
- Prebiotic effects in weight management and obesity-related disorders (Description of prebiotic effects on obesity and related metabolic disorders; Prebiotic effects and glucose homoeostasis; Prebiotic effects and lipid homoeostasis, including steatosis and hepatic alterations; Relation between prebiotic effects and improvement of obesity and associated disorders; Methodological aspects)
- Conclusion and perspectives (Which data support the hypothesis of a causal relationship between a prebiotic effect and health effects/benefits?)

I have no evidence on why it was so well cited but my best guesses are:

1. The experts that brought a new perspective to the area.
2. Large tables were included that summarised existing studies. These took up several pages of the paper.
3. It was a long review and contained a lot of references.
4. Each section finished with a summary of key points and recommendations as appropriate.
5. BJN editorial and refereeing staff turned it around very quickly (online journals had only a low profile in those days). As such, the information was still new when it was published.
6. It was timely as molecular biologists had human gut microbiology on their radar and new diversity was being discovered all the time as well as the provision of culture independent tools for accurately measuring the microbiome.

What happened next?

In my opinion, the BJN article was right to focus on health aspects of prebiotics. This is what they are meant to achieve and it was good to see many areas being represented (today the article would no doubt have a section on gut–brain interactions and maybe viral infections). Hopefully, it spurred attention towards the beneficial properties of prebiotic use, not just as gut microbial fermentation substrates.

Inevitably, the focus for prebiotics was widened from beyond just the gut (although most studies still focus on this ecosystem). The prebiotic concept is now the subject of many international conferences, research articles, dietary products, new companies and media attention. There are now over 9000 research papers on this subject. Reports have estimated the global market for prebiotics at anywhere between $3–16 billion with double digit growth predicted until 2025 (http://www.gminsights.com).

One development that was very important for me was the instigation of a new society dedicated to probiotic and prebiotic science. This was International Scientific Association for Probiotics and Prebiotics (ISAPP) (see isappscience.org). ISAPP is a non-profit organisation which provides a forum for researchers, food and pharma industries to collectively discuss pro and prebiotics. ISAPP produces fundamental research papers, consensus documents, workshop reviews, media outputs, webinars, infographics, video, professional/consumer guidelines, blogs, newsletters and commentaries on the research area. It hosts an annual meeting and will be 20 years old this year. It also has several opportunities to bring on the next generation of pro/prebiotics scientists through several initiatives including a student and fellows association. I have been delighted to be involved in ISAPP and it has given me the best experiences of my professional career. This would not have happened without prebiotic research, the stellar people involved and expansion of the field that I hope our BJN paper helped along. My only negative is that everyone involved in the organisation aside from 2 or 3 of us pronounce its acronym wrongly. The abbreviation is not eye-SAPP, it is ISAPP (with the 'I' – remarkably enough – being spoken as it is in the word 'International').

** I slightly favoured 'parabiotics' over prebiotics for the concept name. In the 1990s, MASH (Mobile Army Surgical Hospital) was a popular comedy programme in the UK. It was an American series set in the 1950s Korean War. In it, paramedics would feature and these were people who helped medics. So, a parabiotic would help biotics. That made sense to me but we went with prebiotics in the end. Of course, a prebiotic in the traditional sense refers to the theory of life around 4 billion years ago – as exemplified by a 20th Century soup product containing inulin and called 'primordial soup!!' One common comment I get is 'you should have called it something else', my usual reply is 'such as?' and that usually elicits silence – but I still think I was right with parabiotics . . . . . .*

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