Probiotics in Childhood Diseases: From Basic Science to Guidelines in 20 Years of Research and Development

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INTRODUCTION

This JPGN supplement contains the papers presented at the 8th meeting on ''Probiotics, Prebiotics and New Foods'' which is held every two years in Rome since 1999. The Rome meeting was probably the first meeting that fully focused on functional nutrition and encompassed gastroenterologists, nutritionists, microbiologists, immunologists and pediatricians together with representatives from companies as well as consumers and members of regulatory bodies. Since its first edition, the meeting structure includes the ''Pediatric Day'' which is endorsed by ESPGHAN. The Pediatric Day is a highly qualified forum in which the various aspects of childhood functional nutrition are discussed by experts from all over the world and consistently shows how advanced is the pediatric world in the field of functional nutrition using probiotics, probiotics and new foods.

In the former editions, the meeting focused on the definitions of functional foods and the options to best investigate their effects in children. It became clear that the approach to functional nutrients was similar to that used for drugs. However, an interesting difference between drugs and nutrients was that the sequence of experimental phases with the classical sequence from *in vitro* to animal and finally to human clinical studies was not as strict with foods as it was with drugs. The opposite approach starting from clinical effects and then trying to understand their mechanisms through basic science was discussed in the earlier editions of the Rome meetings, raising the concept of ''reverse translational research'' applied to functional foods. Basic science however is broad and includes various approaches. Molecular microbiological methods led to the vision of intestinal microbiota as a major target of nutritional interventions. The idea of looking at single bacterial species to explain clinical observations was completely changed with the concept of dysbiosis which alludes to a global de-structure of intestinal microbiota involved in the pathogenesis of many chronic conditions in childhood. It also became evident that several chronic diseases have a ''microbial signature'', consisting in a specific change of intestinal microbiota. A similar pattern of de-structure could therefore be counteracted with a nutritional intervention with probiotics to restructure the intestinal microbiota.

It also became clear that in most diseases the structural-functional relationships between intestinal microbiota and clinical conditions is different from children and adults. For example selected probiotics are effective in adult but not in children with inflammatory bowel diseases. Also the pattern of effects in intestinal functional disorders is different in adults and children.

Therefore it is clear that age is a major determinant of intestinal microbiota and hence the success and failure of using pre- or probiotics shows an age-related pattern.

During the subsequent editions of the Rome meeting scientists met consumers and members of regulatory bodies from Europe as well as from North America to discuss definitions and rules in what was progressively becoming a major area of research with important consequences in human health. An entire edition of the meeting focused on definitions and the importance of health claims obtained with nutritional interventions. The issue was delicate as it had major implications in terms of consumers health as well as marketing. The importance to properly define an ''effect on health'' by a functional nutrient was discussed jointly by scientists and members of regulatory bodies. The European Food Safety Authority (EFSA) is in charge of reviewing claims proposed by companies and this had a major effect in driving the development of functional nutrition in recent years. The concept of obtaining solid scientific evidence to support a specific claim to be then presented to consumers was a major feature in driving research in nutrition. The importance of this approach was to shift more financial resources of companies from advertisement to science. Before advertising a (putative) claim, this had to be supported by scientific proofs. This translated in an advantage for consumers because what they were paying for had indeed an added value in terms of health.

However, there was often a gap between industry and regulatory bodies and the ''dossiers'' that were presented for scrutiny to health authorities sometimes did not comply with what was asked. This gap was a barrier against the implementation of a fruitfull collaboration between science and industry. As a matter of fact, investment into scientific research by companies did not fully translated into an advantage in terms of market. A guidance recently released by EFSA may be effective in fill the gap (1). This guidance is intended to assist applicants in preparing applications for the authorisation of health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms.

In the most recent edition of the Rome meeting, the discussion focused on the combined evaluation of clinical and basic science data and how the scientific evidence translated into guidelines. Metanalysis of RCTs on probiotics provide the material for guidelines. It became clear that well conducted RCTs were the basis for authoritative guidelines. This evolution in the world of probiotics was again functional to their successful development for prevention and therapy, and led to an even closer similarity between nutrients and drugs. In order to provide reliable indications on the use of nutrients there was a need for critical evaluation of data and metanalysis of RCTs. This pattern translated in an active role by scientific societies that started to release evidence-based recommendations on the use of probiotics for clinical purpose. The first guideline containing reference to the use of probiotics was the ESPGHAN/ESPID guideline for acute gastroenteritis (2). Today both in Europe and in the USA, probiotic use for clinical purpose is (critically) endorsed by guidelines (3–5), and this now applies to several guidelines on gastroenteritis at world level (6). The code of conduct adopted by scientific societies such as ESPGHAN provided further credibility to the authoritative role of societal papers, including position papers and guidelines. Papers presented at the last edition of Rome meeting provide a broad view of the most recent results obtained with probiotics in NASH and obesity, food allergy and functional intestinal disorders.

It is interesting to observe that probiotics are now included or proposed in virtually all areas of human and particularly childhood-

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health. In selected cases- as in acute gastroenteritis- the supporting evidence is very strong and the clinical effects are compelling. In other areas, the effects are less evident and difficult to investigate. This is the case of obesity in which the effects may occur several years after the administration of probiotics and often are the result of many variables. In other conditions such as in functional intestinal disorders, the results are loaded with substantial placebo effect. Definitions and outcome parameters are also a limit in this study and the Comment initiative has been active to solve those issues (7).

Finally there are conditions in which the use -or non use of probiotics may have very serious consequences as in the case of necrotising enterocolitis in preterm babies. In the latter, administration of probiotics has shown an effect on the most clearcut clinical outcome: survival rate! So we go from a simple and consistent evidence of clinical efficacy such as in gastroenteritis to life saving indication in selected condition. The mechanisms of the observed effects are also a target for research, as summarized in this issue of JPGN.

The reader may find an interesting balanced and well based overview on probiotics in this collection of papers from the 8th Rome meeting on ''Probiotics, Prebiotics and New Foods''.

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