

Clinical and Experimental Allergy

The gut microbiota: a complex ecosystem

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It has been suggested that modern living is associated with too little microbial stimulation early in life and that allergic disease and autoimmune disease could be regarded as a consequence of a 'microbial deprivation syndrome' [1]. According to this hypothesis, microbes are essential for the development of a normal immune regulation. The perspective that the microbiota of the large gut may have important roles in both human health and disease is by no means a new concept, as the Russian scientist Elia Metchnikoff already a century ago indicated the clinical importance of the host colonic microbiota. He also suggested that certain live micro-organisms might promote health. Despite this, there was for many years modest interest in this concept among researchers and it is only over the last 10 years that microbial ecology has again become a major research area. It is now generally accepted that the bacterial microbiota of the human gut is an integral component of the host defence system. This has generated considerable interest in the functional food/nutraceutical industry.

The total mucosal surface area of the adult human gastrointestinal tract is up to 300 m², making it the largest body area interacting with the environment. It is colonized with over 10¹⁴ micro-organisms, weighing over 1 kg and corresponding to more than 10 times the total number of cells in the body. The gut microbiota are thus the quantitatively most important source of microbial stimulation and may provide a primary signal for driving the postnatal maturation of the immune system and the development of a balanced immunity [2].

There is mounting evidence that commensal microbes acquired during the early post-natal period are required for the development of tolerance, not only to themselves, but also to other antigens. For example, T-helper type 2-mediated immune responses are not susceptible to oral

tolerance induction in germ free mice [3]. Oral tolerance was only induced after the introduction of components of the normal microbiota. It is also recognized that interaction with microbes, especially the normal microbial flora of the gastrointestinal tract, is the principal environmental signal for post-natal maturation of T cell function (in particular the Th1 component) [4].

The gastrointestinal tract of the newborn baby is sterile. Soon after birth, however, it is colonized by numerous types of micro-organisms. Colonization is complete after approximately 1 week but the numbers and species of bacteria fluctuate markedly during the first 3 months of life [2]. There are several studies showing that the composition of the gut microbiota differs between healthy and allergic infants [5–9] and in countries with a high and low prevalence of allergies [10]. Differences are apparent within the first week of life, preceding clinical symptoms [11, 12], and have even been recorded during pregnancy in the vaginal flora of mothers of children who develop allergy during early childhood [13]. These observations prompted an interest to explore the potential of allergy prevention through manipulation of the gut microbiota by the administration of probiotic bacteria in infancy.

Probiotics are live non-pathogenic micro-organisms which exert a positive influence on the health or physiology of the host beyond their nutritional value. Lactobacilli and bifidobacteria and other lactic acid producers are commensal bacteria common to the gut of all mammals, as well as various non-mammalian vertebrates. So far, probiotics with documented clinical beneficial effects are limited to a few strains of those species. There are numerous other bacteria on the market which still need to be properly clinically documented.

The use of live micro-organisms that might be beneficial to health has a long tradition and the safety of up to 10¹¹ live bacteria is well documented, even in newborn babies and in immunocompromised people [14]. Although used for many years, it is only recently that the mechanisms of action and effects of probiotics have begun to be studied using the same pharmacological approach as for drugs.

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They have been tried in a wide range of clinical situations, and shown efficacy in infectious gastroenteritis and diarrhoea, lactose intolerance and prevention of antibiotic-associated disorders [14]. Clinical studies suggest a modest or no beneficial effect in the treatment of infantile eczema [15–18] and possibly also in the prevention of infantile eczema [19, 20]. The latter findings have not been confirmed and the study is open to several critical remarks, as discussed by Weston et al. [17]. So far, no effects have been shown in the treatment or prevention of IgE-mediated allergic disease, nor have any beneficial effects eczema been demonstrated in adults.

If the efficacy of probiotics in the treatment of allergic symptoms is confirmed in subsequent studies, it is reasonable to suspect that this may be more obvious in, or even limited to infancy and early childhood, i.e. before the immune responses to allergens and immune regulatory networks have been established and at a time when the gut microbiota are not yet established.

The study results reported by Taylor et al. in this issue of the journal [21, 22] may appear disappointing for those who are believers in probiotics. It is important, however, that also largely negative results of well-designed studies are reported in a major journal. The study hypothesis that a *Lactobacillus* strain would modify innate immunity or non-specifically enhance immune responses is reasonable from our current understanding of the role of gut microbiota early in life. The study results should not be taken as an indication that the role of gut microbiota necessarily is smaller than that suggested by the enthusiasts. Studies testing the effects of only one or a few bacteria may represent a too reductionistic approach. The gut microbiota is very complex. Of the over 500 species, each comprising numerous different strains, less than 50% have been isolated and the bacterial genome is at least 30 times as big as the human genome. The internal environment may thus be as complex as the external environment. The gut microbiota represents an ecosystem which may be as complex as that of a rain forest. Under those circumstances, it may be futile to believe that administration of one strain out of hundreds of strains within one of hundreds of species would have a major clinical impact. In order to better understand the complex *milieu intérieur* we need a more holistic, truly interdisciplinary approach.

There are several problems when trying to interpret the outcome of clinical studies on probiotics, in addition to those inherent in all clinical trials. Probiotics are defined as live microbial organisms with beneficial effects beyond their nutritional values. Unfortunately, the term is sometimes loosely used for any microbes given to people, independent of previous clinical documentation. In most clinical trials, viability of the given microbes has not even been confirmed. The situation is similar to that giving a patient a pharmacological treatment with a compound of which it is only known that it is not toxic and without knowing if the putative drug is given in an active form.

Much remains to be studied before the precise role of the gut microbiota in health and disease can be defined. It is reasonable however to devote more interest to our 'internal environment' in order to obtain a better understanding of how the immune system is regulated and in the search for environmental risk and protective factors related to 'immunologically mediated diseases of affluence', such as allergy, autoimmune disease and inflammatory bowel disease. Such studies of the complex microbial ecology in the gut are likely to yield novel strategies for disease treatment and prevention in the future.

The hitherto published studies on lactic acid bacteria in the treatment and prevention of allergy have yielded inconclusive results. Therefore, the conclusion of a Position Paper issued by the European Academy of Allergy and Clinical Immunology is still valid, i.e. that evidence supporting the use of probiotics in the prevention or treatment of allergy is still preliminary [23].

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