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Model of the epidemic of childhood atopy

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Summary

The reasons for the steep rise in the prevalence of atopic diseases such as asthma, atopic eczema and allergic rhinitis are unexplained. Studies have shown that immune regulation in the intestinal mucosa-associated lymphoid tissue (MALT) plays an important role in atopic sensitization and is influenced by the intestinal microflora. The hypothesis presented here is based on the following assumptions: 1. Mothers transfer some of their intestinal microflora to their children at birth and by close contact. 2. The intestinal microflora has the properties of an ecosystem that may react unexpectedly to changing conditions. 3. Modern lifestyle and diets negatively influence the intestinal ecosystem during the lifespan. Thus, from one generation to the next, there may be cumulative degradation of the intestinal microflora. Children inherit a non-physiological gut flora that is further degraded in later life and contributes to atopic sensitization in the following generation. Linear changes in environmental conditions and lifestyle may lead to non-linear changes in the gut flora and, possibly, to an increasing susceptibility to atopic diseases. Clinical studies using probiotics and dietary intervention should be the focus of future research.

key words: asthma • epidemic • atopy • intestinal flora • probiotics

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BACKGROUND

The reasons for the rapid increase in childhood atopic disease remain unclear [1]. Several factors are associated with atopy, such as family size [2], breastfeeding [3], frequency of infectious diseases [4], passive smoking [5], and diet [6]. The rise is especially pronounced in Western countries and in countries that are currently undergoing Westernization [7]. On the molecular biological level, an imbalance between TH1 and TH2 helper cell immune response has been widely proposed, leading to the formulation of the hygiene hypothesis [8].

Despite the scarcity of reliable prevalence data before 1980, it may be correct to state that the epidemic curve of atopic disease is atypical for a chronic disease. Diet and lifestyle in Western countries have certainly undergone significant changes during the last 20 or 30 years, but probably not on an order of magnitude that would readily explain recent trends [9], even allowing for some effect modification among the known risk factors.

It has been suggested to take a step back from the narrow view of molecular findings or environmental factors acting on individual persons, in favor of a more synthetic perspective, taking into consideration evolutionary aspects of health on the population level [10]. The line of argumentation presented here attempts to apply a population-based view to an issue that seems to be of particular importance in the pathogenesis of allergic disorders: the interaction of microbes with the intestinal mucosa-associated lymphoid tissue (MALT) [11].

INTESTINAL MICROBIAL EXPOSURE AND ATOPIC DISEASES

Maticardi et al. examined exposure to gastrointestinal and airborne pathogens in young men with and without atopy and observed that frequent intestinal microbial exposure, rather than respiratory, prevents atopy [4]. Björkstén et al. found significant differences in the indigenous intestinal flora between allergic and non allergic 2-year-old Swedish and Estonian children. Lactobacilli and bifidobacteria were more frequent in the non-allergic, whereas coliforms and *Staphylococcus aureus* were more common in allergic children [12]. Kalliomäki et al. found that a reduced ratio of bifidobacteria to clostridia in early gut microflora precedes the development of atopy [13]. Experimental studies have shown that certain strains of lactobacilli, bifidobacteria and other commensals indeed promote immune regulation, by decreasing allergic tendencies while enhancing defense mechanisms [11].

A large body of evidence underscores the importance of the maternal microbiological repertoire for initial immune regulation in the newborn. Gronlund et al. found delays in fecal symbiotic colonization in children born after cesarean section as compared to those delivered vaginally [14]. Separation of mother and child directly after birth is associated with increased risk of allergic rhinitis [15]. Later in life, this microbiological inheritance may be subject to degradation, for example by antibiotic treatment [16,17]. Further, typical Western food items rich in refined sugar but low in non-

digestible food ingredients and microbes might enable non-symbiotic bacteria to out-compete the symbionts [4,18,19]. It has been shown that a diet rich in such non-digestible food items as oligosaccharides, abundant in many vegetables, legumes and unprocessed grains, favors commensal bifidobacter strains and compromises the growth of clostridia by lowering the gut pH [20]. Lifestyle factors such as living in an environment with an unnatural or sparse microbiological spectrum may also be of importance. Riedler et al. have shown that early childhood exposure to cattle and non-pasteurized farm milk could prevent the development of atopy [21]. Similarly, pets have recently been demonstrated to protect from allergy, rather than inducing it [22].

It would seem that while hypersensitivity is largely determined in early childhood, the disturbance of the gastrointestinal bacterial flora by external factors continues throughout life. There is some rationale for applying ecological principles to the gastrointestinal tract [23]. If so, the intestinal micro-ecosystem may be susceptible even to small environmental changes and may subsequently undergo degradation. Physiologic processes in the host organism connected to the intestinal microflora, as seems to be the case for immune regulation, may consequently be subject to dramatic impairment and disease. The model presented in the following sections is based on the assumption of progressive degradation of a partially inherited intestinal ecosystem over the lifespan, following small changes in dietary and lifestyle patterns within Westernized populations. For purposes of simplification, dietary, lifestyle and environmental influences will be designated here as 'environmental factors.'

SCENARIO 1: ALLERGY-PROTECTIVE ENVIRONMENT

In a population without increasing prevalence of atopic disease, newborns would be exposed to a maternal bacterial flora similar to that of the mother at her birth. The proallergic properties or potential of these flora would predispose to normal risk of atopy in that population, designated here as 1, corresponding to a relative risk of 1.0 between generations. Later, regular gastrointestinal infections and colonization by commensals, as would be expected in a natural environment, would further promote immune regulation. A natural diet rich in oligosaccharides and other non-digestible food ingredients continuously favors symbiotic gut flora. The circle is closed when adult women transmit their maternal flora to the next generation of infants. As shown in Figure 1, the proallergic potential of the intestinal microecosystem would remain stable throughout life.

SCENARIO 2: THE INTRODUCTION OF CHANGES IN ENVIRONMENTAL FACTORS

In this scenario, a female newborn is delivered by a mother whose microbial spectrum corresponds to scenario 1. The child would inherit a proallergic potential of 1. At this stage, the population undergoes a change in hygienic and dietary patterns assumed to be detrimental to intestinal flora and to immune regulation in the MALT. In Figure 2, this process is described as a linear

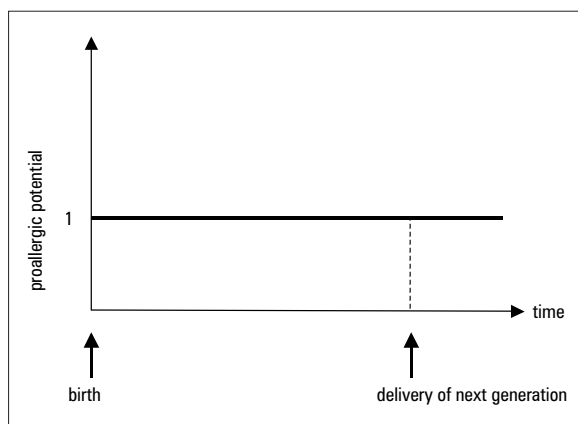


Figure 1. Allergy-protective environment.

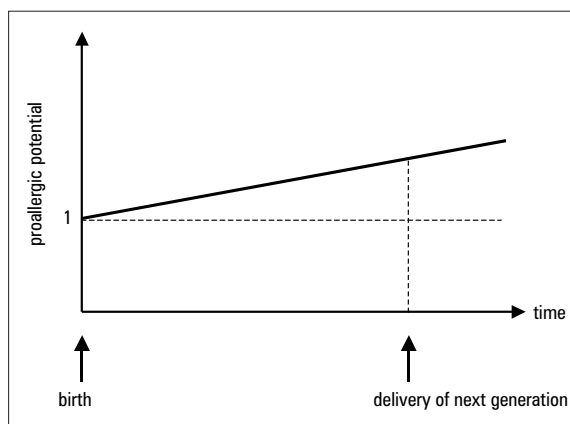


Figure 2. The introduction of environmental changes.

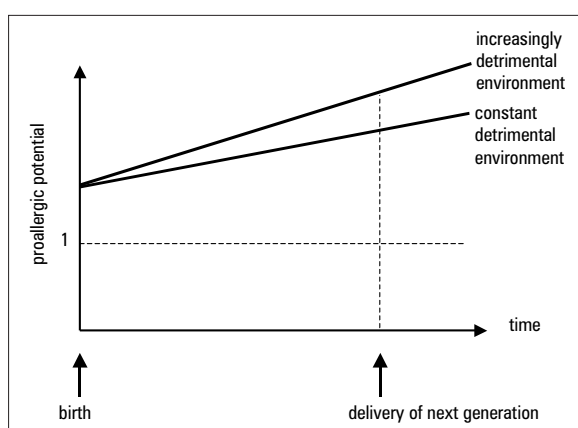


Figure 3. Inheriting abnormal microflora.

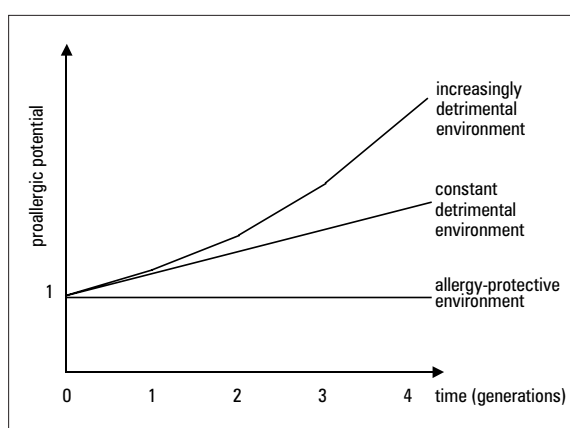


Figure 4. Effect over generations.

increase in the proallergic potential of the intestinal micro-ecosystem. It should be noted that the line does not necessarily reflect the relative risk, except at time 0 or shortly after. Since sensitization predominantly takes place during infancy, a later change in the gut micro-ecology could remain without any consequences in this generation. At delivery, however, the offspring of this maternal population is exposed to a changed microflora.

SCENARIO 3: INHERITING ABNORMAL MICROFLORA

In scenario 3, the newborns do not start at a relative risk of 1 compared to the preceding generation, but at a relative risk somewhat higher, because they received altered microflora from their mothers in scenario 2 (Figure 3). Under the same living conditions, we may assume a parallel shift of the line along the y-axis. The accumulation of maternal and later acquired abnormal microflora leads to a steady increase in the proallergic potential from one generation to the next. If we now take into consideration further changes in living conditions, such as further increases in antibiotic use, sugar intake or avoidance of fiber, the slope will increase. As a result, the rise in the proallergic properties within a population exposed to a detrimental environment, diet and lifestyle would follow an over-additive, non-linear trend, as summarized in Figure 4.

DISCUSSION

The simplified model described above suggests that linear and slow changes in environmental factors may result in a non-linear degradation of intestinal microflora from one generation to the next. The model is based on a number of simplifications and linear trends, which may not reflect the reaction of a micro-ecological system to environmental changes. The resulting possibility of a negative inter-generation feedback phenomenon, however, resembles that of natural ecosystems [24]. Examples of seemingly stable macro-ecosystems that collapse after small changes in environmental or climatic factors, or in species diversity, are abundant [24].

The intestinal micro-ecosystem comprises over 500 different bacterial strains, connected by countless interdependencies [17]. The disruption of the bacterial flora, for example by antibiotic treatment, is generally believed to be transient at most, because long term consequences have rarely been observed. However, McKeever et al. recently found a significant dose-related association between antibiotic treatment and the development of asthma in a birth cohort study from the UK, which persisted after adjustment for consulting behavior [25]. Macro-ecosystems – and perhaps also intestinal micro-ecosystems – do not automatically re-establish

after disturbance, even when the detrimental factors have been removed. New interdependencies and steady states arise, hindering the restoration of the original ecosystem. A specific feature of the intestinal microecosystem is its *de novo* development in every newborn. The sterile neonate gut mucosa represents the ground for subsequent colonization with pioneer microorganisms. The model suggests that these pioneer microbes may undergo changes in diversity and abundance from one generation to the next.

The model can also be viewed from a infectious disease perspective. Non-symbiotic bacteria are vertically transmitted from mother to child. From one generation to the next the intestinal pathogen load would increase.

The protection of breastfeeding and maternal proximity against atopy seems to contradict the hypothesis presented here. According to the model, transmission of the maternal microflora would not be beneficial to the offspring. However, the role of breastfeeding itself is controversial [26]. Secondly, exposure to maternal bacteria might still be better than exposure to hospital or household germs. Thirdly, human milk may protect from atopy also by non-microbial factors [27]. The model does not exclude a significant contribution of other factors to atopic disease. For instance, imbalances in the dietary n-6/n-3 fatty acid ratio typically found in Western populations also affect immune regulation [28]. Further, many studies show that the risk factors for the different atopic diseases overlap, but are not identical, although clearly related. However, they all represent inflammatory diseases related to fundamental proinflammatory conditions [29]. The MALT system, which in turn is influenced by the gut flora, plays an important role in maintaining the balance between pro- and anti-inflammatory responses [11].

Both microbiological and epidemiological research may conceivably contribute to testing the hypothesis presented here. Birth cohort studies, including microbiological examinations in mother and child, could be a useful tool. It is not clear, however, whether microbiological stool analysis sufficiently reflects the composition of the gut flora [23]. Animal models have been helpful in examining intestinal host-microbial interactions [30]. In contrast, a comprehensive *in vivo* assessment of the ecological interactions in the human gut flora seems difficult.

Intervention studies have shown that there seems to be a sufficient rationale, with respect to safety and possible benefits, for attempting to re-establish the intestinal flora with probiotics and dietary changes. In a randomized study by Kalliomäki et al., a lactobacillus strain was given both prenatally to mothers and postnatally to their infants. The frequency of atopic eczema in the probiotic group was half that of the placebo group [31]. The promising result of the trial suggests that Kalliomäki et al. intervened at a very crucial point in atopic sensitization. Since the trial was relatively small, it should be regarded as a pilot study. An approach aiming at increased species diversity by applying a greater variety of probiotic bacteria combined with dietary intervention to provide favorable substrates for commensal bacteria seems even more

promising. Pregnant women or newborns present good study populations to further evaluate the role of microflora in atopic disease. Another important question with tremendous public health relevance is whether probiotics could be used to permanently re-establish a healthy gut flora after early childhood, with the aim of primary prevention or even medical treatment of atopy. A small Danish study on atopic eczema in children above the age of one year using a lactobacillus strain showed promising results [32]. It is possible that medium-sized randomized trials will provide more useful information than further large population-based studies.

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