

Editorial

Allergy and neonatal care

In this issue of *Allergy*, Montgomery et al. present results suggesting that neonatal care may have an impact on later development of hay fever (1). Thus, they have found that the odds for developing hay fever among infants spending their first night in a communal nursery, separated from their mothers, are 1.45. Although this association is weak, the increased risk is highly statistically significant. The authors consider that their results support the hypothesis tested, i.e., that the handling of the infant during its first day of life has an influence on the pattern of exposure to various microorganisms that may be important for later development of allergy.

Although this may be a plausible explanation of the findings, there are certainly a number of factors that might have influenced a decision to put the infant in a communal nursery away from the mother during the first night. Some of these potentially confounding factors have been adjusted for by the authors of the paper, but it is difficult to exclude the possibility that certain factors, such as low birth weight and reduced lung function in the baby, smoking during pregnancy, or poor antenatal care, which have all been found to be associated with development of asthma (2), might have had an impact on the decision to remove the child from the mother during the first night.

If the results of Montgomery et al. are indeed due to a change in the occurrence of environmental microorganisms, how could this have an influence on the development of allergy? It does not seem likely that the few hours of separation of mother and child would provide much opportunity for pathogenic viruses or bacteria to infect the baby. Besides, with few exceptions, infectious agents are thought to have a protective effect against, rather than a facilitating effect on, allergic sensitization and later development of atopy (3, 4). Acquisition of regular infections during the one-night stay in the communal nursery would therefore not be supposed to play any role in the later development of allergy.

Regarding nonpathogenic bacteria which constitute the normal microflora of the gut and the pharynx, the situation is different. The establishment of a normal microflora is known to start immediately after birth, and the handling of the baby at this time may be very important for the colonization by commensal bacteria. The early extrauterine development of the immune system is dependent on the gut microflora. Lipopolysaccharides (LPS) which are contained in the cell wall of Gram-negative bacteria play an important role in the development of immunologic oral tolerance. Thus,

germ-free mice fail to develop adequate oral tolerance (5). Immunostimulatory nucleotides containing the CpG motif are common in bacterial DNA and have the ability to stimulate Th1-type immunity preferentially (6). Different bacteria induce different cytokines. For instance, recent results have shown that Gram-positive bacteria have a special propensity to induce the formation of IL-12, whereas Gram-negative bacteria preferentially induce IL-10 (7). Together, these findings suggest that the pattern of the bacteria that colonize the neonate may have a decisive influence on the type of immunity that develops in the child. Further, indirect, support for a role of commensal bacteria in the development of immunity can be derived from studies such as that by Farooqi & Hopkin (8), who found that treatment with certain antibiotics in small children may greatly enhance the development of atopic disease.

Recent results indicate that the microflora may differ between allergic and nonallergic children (9). A certain emphasis has been placed on lactobacilli, but clear evidence of an allergy-preventing role of these bacteria is not available. Cross-sectional studies are of somewhat limited value in this regard. Instead, prospective studies, starting at the birth of the baby, may be supposed to yield more information. Such studies have indeed been initiated, as, for instance, by Dr Wold's group in Göteborg, Sweden. Preliminary, not yet published results of this study show that infants who later develop allergic disease in early life have a different pattern of early bacterial colonization in the gut from children who do not develop allergy.

It seems clear that the pattern of bacteria that colonize the gut in the neonate has changed over the last decades, in parallel with the rising prevalence of atopic disease (9), and that intestinal bacterial colonization in neonates is remarkably different between developing and industrialized countries (10). Moreover, infections by intestinal viral pathogens such as rotaviruses may frequently occur very soon after birth in developing countries, as has been shown in studies such as that from Nicaragua (11). Differences in allergy prevalence between developing and industrialized countries might therefore be related to differences in bacterial colonization of the gut or, possibly, to early intestinal viral infections.

The early encounter of different bacteria and, possibly, viruses by the neonate may have long-lasting consequences for development of the immune response. It is generally believed that the immune response of the neonate is skewed toward Th2-type immunity (12), but available evidence suggests that neonates are perfectly

able also to mount strong Th1-type responses (13). Regardless of the possible existence of a so-called Th1/Th2 balance, it is clear that the maturation of all parts of the specific immune system is highly dependent on stimulation by microbes and the cytokines they induce. It is tempting to speculate that microbes such as Gram-positive bacteria that preferentially induce the formation of Th1-type cytokines, such as IL-12, do have a preventive effect against the development of atopic disease. However, similar effects, i.e., suppression of development of Th2 responses and atopy, could also be evoked by bacteria that preferentially stimulate formation of IL-10, and perhaps other, generally immunosuppressive, cytokines. In addition, the tolerance-inducing effect of LPS, which is a part of these bacteria, may dampen all types of immune responses in the gut, and thereby possibly suppress the development of atopic diseases.

In conclusion, the multitude of effects of microbes on the immune system and the possibly decisive importance of the early colonization of the gut by

bacteria for the development of immune responses makes it theoretically possible that early separation of mother and child during the first night after delivery may indeed have long-lasting effects on immune responses, predisposing to hay fever or other atopic diseases. Although Montgomery et al. (1) favor this explanation, it should be borne in mind that there may be other explanations of their findings that may be just as likely but are less easily supported by experimental results. For instance, it has been found by Olivetti et al. (2) that poor antenatal care of the mother increases the likelihood of the development of atopy in the child, giving an odds ratio (4.7) that is considerably higher than that (1.45) found regarding neonatal care in the study by Montgomery et al. The possible existence of a link between the types of antenatal and neonatal care emphasizes the need for caution in the interpretation of the results presented by Montgomery et al.

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References

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