

Allergy: The price paid for longevity and social wealth?

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Soon after German reunification, von Mutius et al¹ found that atopic sensitization was markedly more frequent in West German children than in their peers in East Germany (37% vs 18%). Although asthma rates were also higher in West Germany, the East German children had higher rates of bronchitis. Differences in unmeasured environmental exposures were believed to be responsible for the differences in allergy (and bronchitis) rates in these 2 ethnically similar populations. Five years after unification, allergy rates had gone up in East Germany, and allergic sensitization rates had equalized in the eastern and western regions of the country, presumably because of an increase in exposures associated with westernization of East Germany.² In this issue of the *Journal of Allergy and Clinical Immunology*, von Hertzen et al³ report a similar west-east disparity in childhood allergic sensitization, hay fever, and eczema, with higher rates of allergy among Finnish children from Pitkaranta district compared with their counterparts in the adjacent Russian communities in Karelia. Wheeze rates were similar in the 2 communities, but although wheeze was associated with allergy and asthma diagnosis among the Finns, wheeze was not associated with allergy among their Russian counterparts.

Although von Mutius et al¹ have demonstrated temporal trends leading to equalization of allergy rates between West and East Germany, the generational differences in allergic sensitization point to possible widening of the gap in sensitization rates between Finland and a neighboring region of Russia. Whereas Finnish sensitization rates were lower in mothers compared with those in children,

Russian rates were higher in mothers compared with those in children. Conclusions drawn from the comparison of maternal and child allergy rates must be tentative and tempered by understanding that comparison of rates in populations of differing age (and, for some, of differing sex) has limitations as a tool for evaluating temporal trends in allergy. Temporal trends are more effectively explored through prospective study or through the repeating of cross-sectional surveys of disease rates in same-aged populations at 2 or more points in time. Nevertheless, the generational differences in allergy suggest that temporal changes in environmental exposures might be partially responsible for a possible widening of differences in allergic sensitization between Finnish and Russian children.

What environmental changes have occurred over the past 20 or more years that might account for that widening gap in allergy prevalence? Increased microbial exposure through infection or change in diet might be partly responsible for the lower allergy rate in Russian children. Many investigators have tested and reviewed the hygiene hypothesis, first proposed by Strachan.⁴⁻⁸ He suggested that with the decrease in family size, a decrease in early childhood exposure to infectious diseases might be responsible for the increased rates of hay fever and allergy.⁴ This hypothesis has been broadened to consider exposures from farms,⁵ raw milk and fermented foods,⁹ pets, and parasites¹⁰ as sources of infection, microbial components, or high doses of allergen¹¹ that might protect against allergy. Early-life microbial exposures through farming, animals, or infection is hypothesized to modify innate immune and/or T regulatory cell behavior, leading, in part, to down-regulation of production of proinflammatory cytokine secretion by T_H2 (and perhaps also by T_H1) lymphocytes.⁷

In the article by von Hertzen et al,³ parental farming and indoor pets, as well as parental history of atopy and sex, were all cross-sectional predictors of atopic sensitization in multivariate models (see Table E3 in von Hertzen et al³). As with all cross-sectional studies, it is not known whether the exposure to farming or pets preceded the development of allergy. Moreover, parental farming and having pets did not explain the difference in the 3-fold between-country difference in allergy rates that remained after adjustment for these factors. It is possible that the between-country differences might be further explained by better delineation of differences in what farming represented in Russia compared with Finland. Nevertheless,

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it is likely that unmeasured factors other than farming are in great part responsible for the differences in atopy between children from these 2 neighboring countries.

In Russia the unfortunate worsening of health and social services that accompanied the dissolution of the USSR might, in part, be responsible for the lowering of allergic sensitization in children through increased microbial exposure. The study by von Hertzen et al⁵ was carried out in 2003 among children born between 1987 and 1996, during the height (1992-1994) of major mass Russian outbreaks of childhood diseases, including diphtheria, measles, mumps, and rubella.¹² In a Centers for Disease Control and Prevention report on emerging infectious disease in Russia, Netesov and Conrad¹² review the unfortunate history of that time. In the former Soviet Union, diphtheria was controlled through vaccination. In the early 1990s, the government began policy recommendations and mass media advertising against diphtheria vaccination,¹³ leading to an almost 30-fold increase in the disease rate by 1994. Despite a reverse in policies reducing vaccination rates, the mumps rate continued to increase after the outbreaks in the early 1990s, in part because of insufficient funds for the first and second vaccine and because the vaccine might have degraded during delivery or storage because of inadequate conditions. Long-term trends in acute gastrointestinal infections have been harder to document, although dysentery rates were 37% higher in 1998 compared with 1997. Acute hepatitis B and C rates have increased steadily in the 1990s, and half of the patients have been young, 11 to 30 years of age.¹⁴ Tuberculosis rates increased 70% between 1990 and 1995. Studies from other countries provide suggestive but by no means conclusive evidence that exposure to acute childhood infections, such as measles,¹⁵ or to mycobacterial¹⁶ infections might protect against allergy.

Going against the hypothesis that the west-east differences in allergy prevalence are related to failure to immunize and increased rates of childhood infectious disease is the absence of striking differences between Finnish and Russian children in the reported prevalences of immunization and infection. The reported immunization rates were 100% in both regions. Is this reporting bias, or is this accurate? Were a higher proportion of Russian children vaccinated later in childhood after already being exposed to measles, mumps, rubella, or diphtheria? The reported rate of "contracted infections" is only slightly higher among the Russian children, but these data are retrospective and collected without virologic-microbiologic or clinical confirmation of diagnoses. Crowded housing and poor sanitation in Russian communities might have led to increased infection exposure, despite small families and few siblings, but living conditions are not detailed in this report. Parental-reported parasitic disease is higher among the Russian children in this study, but a follow-up prospective study design including parasitologic evaluation would be needed to assess whether parasitism contributed to protection against allergy in these children. To more fully measure differences in environmental exposures and conditions, the investigators would have to apply different

epidemiologic tools, both in terms of questionnaires and biologic sampling. It seems unlikely that the children in this region of Russia were spared the decrease in living conditions and the outbreaks in infections that occurred in other parts of their country in the 1990s after the dissolution of the USSR. As the authors report, the average life expectancy among Russians in Karelia is 10 to 14 years less than the life expectancy among Finns.

Probiotic diets, including diets with vegetables spontaneously fermented by lactobacilli, have been hypothesized to alter gut flora and protect against allergy.⁹ In a study of 9- to 18-year-old children in Russia and the United States in 1996, mean intakes of all nutrients except magnesium were significantly higher among US children.¹⁷ Traditional food-frequency questionnaires might not be ideal for evaluating probiotic dietary intake. Although it is possible that the Russian children in this study had a higher intake of fermented foods, this would have to be specifically investigated. If the Finnish children had joined others in western society, it is also possible that their allergy risk was upregulated by increased ingestion of snacks full of trans fatty or n-6 fatty acids, which have been considered as risk factors for allergy or asthma in observational and intervention studies.¹⁸

Environmental exposures likely led to the predominance of atopic wheeze in Finland and nonatopic wheeze in Russia. This finding was only partially explored by the investigators. The rate of parental smoking was 39% in Russia and 3.8% in Finland, and although undocumented, it is likely that a significant proportion of the older teenagers in Russia were also smoking. Although the relation of smoking to allergy is controversial, the relation of smoking to wheeze is well proved and might partially account for the nonallergic wheezing in the Russian children. Moreover, if the Russian children encountered more infections and higher levels of endotoxin and other respiratory irritants, these exposures could also have increased wheeze risk while reducing allergy risk. The authors also suggest that wood smoke exposure might also be higher in Russia. Studies of other populations of children have documented increases in wheeze with poorly ventilated wood smoke or gas stove exposures.¹⁹ Reduced fetal growth and low birth weight have been proposed as risk factors of small airways and wheeze.²⁰ In Northwest Russian infants cigarette smoking, poor housing conditions, maternal stress, and maternal alcohol consumption were shown to be independent determinants of reduced fetal growth (birth weight and ponderal index).²¹

Is allergy the price that communities have to pay for their increased standard of living? High rates of allergy and high allergic asthma morbidity in the urban United States contradict the assertion that all disadvantaged situations are likely to be protective against allergy.²² However, Russian children in Karelia are likely exposed to the components of poverty that reduce their life expectancy but protect against allergy. As physicians and scientists, our goal is to isolate the components within complex exposures related to farming or other sources of microbial exposure that might in packaged and nontoxic form reduce

allergy risk in susceptible children. At the same time, we aim to work toward the general improvement of child health and to identify behaviors and social policies that would protect children both from allergy and also from early childhood infections that are associated with serious acute and chronic morbidity.

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