

dependence. The CARS will not fulfill all the needs of such children, but it is clearly a realistic and important first step in this direction for Brazil.

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Asthma in early life: is the hygiene hypothesis correct?

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Since the original studies in the late 1980's there have been literally hundreds of birth cohort studies that have purported to document the role of respiratory infection and genetic susceptibility in the development of early life asthma, including the paper in this issue looking at wheezing in southern Brazil and explain the results based on the hygiene hypothesis.¹

As originally formulated by Strachan, the hygiene hypothesis suggested that younger siblings had less hay fever than their older siblings because they had more frequent infections and hence less allergy.² Von Mutius, and others have popularized this hypothesis, as the explanation for the asthma epidemic.³ In my view, there is substantial contradictory data to suggest that both the hygiene hypothesis

itself, and its ability to explain the asthma epidemic are not correct.

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- Point 1: Although there is an ecologic relationship between the decline in all infections and the rise of T helper 2 (Th2) diseases, the hygiene hypothesis does not explain why T helper 1 (Th1) autoimmune diseases have increased over the same time frame as the Th2 diseases.

- Point 2: As pointed out by Platts-Mills, and others, the decline in infections diseases is a result of antibiotics, better housing, better water, and this decline antedated by many years the epidemic of both Th1 and Th2 autoimmune diseases.⁴

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- Point 3: There is ample evidence that the lungs of children susceptible to both asthma and respiratory infection are abnormal BEFORE any infection occurs. Thus, lung damage is not simply the result of the infectious process.^{5,6}
- Point 4: There is no evidence that there has been any real decrease in the number, incidence, or type of viral respiratory infections over the 30-year period that asthma prevalence has risen.
- Point 5: All of the phenomenon of the autoimmune disease epidemic could be explained by a factor that has been changing over the 40-year period that autoimmune disease has increased, which could be associated with infection occurrence and with both Th1 and Th2 autoimmune disease.
- Point 6: The hygiene hypothesis cannot explain the high rates of asthma among the urban poor in the USA and other industrialized countries.
- Point 7: The hygiene hypothesis cannot really explain the association of the asthma epidemic with industrialization and the urban rural gradient in disease risk.

In my view, vitamin D deficiency in pregnant women and their offspring is the likely explanation for most of what we have seen in the rise in early life asthma incidence and prevalence.⁷⁻¹⁰ It explains the association with infection because vitamin D deficiency is associated with increased occurrence and severity of infection. It explains why the lungs are abnormal before infection because in animal models of vitamin D deficiency lung development is abnormal. It explains urban-rural and black-white differences in asthma prevalence and the differences in prevalence between industrialized and rural countries because these trends mirror the epidemiologic trends in vitamin D deficiency. Trends that have been exacerbated by the elimination of cod liver oil supplementation during pregnancy and early childhood, by greater time spent indoors, and by increased use of sunscreen.

What is needed to test the hypothesis that the real cause of the asthma epidemic is vitamin D deficiency in pregnant women and their offspring, not changes in infection rates? First, observational studies with careful measurement of exposure are necessary. To do this food frequency questionnaires, sun exposure questionnaires, and vitamin D levels need to be performed in birth cohort studies and in follow-up of children. It is likely given that close to 70% of all pregnant

women are vitamin D deficient, that these observational studies may have a considerable null bias. Ultimately randomized controlled trials of immune sufficient doses of vitamin D given to pregnant women compared to multivitamins will be necessary to test this hypothesis. Trials such as this are currently under design in various places worldwide and we await their results with interest.

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