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Environmental Contaminants and the Immune System

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Evidence continues to accumulate on the modulating effects of environmental contaminants (such as organochlorines, oxymetholone, lead, cadmium, mercury and gallium arsenide) on immunity (Lewis et al 1996; Lawrence & McCabe, 2002, Karmaus et al 2005; Dietert & Piepenbrink 2006; Mishra 2009; Ohsawa 2009). The immune system appears especially sensitive to environmental contaminants such as lead and cadmium (Dietert & Piepenbrink 2006; Fowler 2009), and while lead exposure at low and moderate levels does not produce overt cellular cytotoxicity, the immune-associated health effects are a result of an impaired regulation of cell function, such that its detection and understanding requires the use of more sensitive indicators of immune function such as biomarkers (Karmaus et al. 2005; Duramad et al. 2007).

Understanding how specific environmental agents impair both immune function and the ability of the immune system to elicit protective immune responses becomes essential given the commitment of many funding bodies and agencies to eradicate vaccine-preventable infectious disease through the use of national immunization programs and other access programs in children such as through the Bill and Melinda Gates Foundation funded GAVI Alliance Prevenar vaccination program in Rwanda (GAVI 2009). This understanding is even more necessary given that children's immune systems have been recognized as being potentially more susceptible to environmental exposures (Kovarik & Siegrist 1998).

Lead, and to a lesser extent cadmium, have been the most extensively studied in understanding how heavy metals impair immune function. While the overall effects of lead on antibody production appears to be minimal, if lead dosage and exposure are sufficient it can lead to depressed total antibody levels. More importantly low-level lead exposure skews antibody isotype production eliciting a more significant health risk. In effect, lead results in switching of B lymphocytes from producing IgM and IgG antibody isotopes critical in conferring protection against infectious agents to IgE associated with allergic and hypersensitivity responses (Basaran & Undeger 2000) and especially among children (Karmaus et al. 2005; Sun et al 2003; and Lutz et al 1999).

However, it is the T lymphocyte subset that appears to be the most sensitive to the toxic effects of lead and cadmium, and to some extent gallium arsenide. While gallium has a very specific role in inducing a defect in the early antigen-processing

(Lewis et al. 1996), lead inhibits antigen presentation through inhibiting specific T lymphocytes (Th1) stimulation while promoting presentation to Th2 lymphocytes (McCabe and Lawrence, 1991; Ohsawa 2009). By either mechanism, the overall effect of lead and gallium is to skew the immune response away from making protective antibody responses against specific pathogens and may impair the ability of a child with even low lead-exposure levels to make an adequate immune response to a vaccine. Immune responses are known to be influenced by specific genes (eg, Vβ and Km(1)) that have been associated in some populations with increased susceptibilities to bacteria such as *Haemophilius influenzae* type b, pneumococcus, and meningococcus (De Inocencio et al 1995; Lenoir et al 1988). That lead and mercury have been shown to bias usage of specific genes is of concern in populations already struggling with high vaccine-preventable disease rates and underlying genetic factors of susceptibility (Heo et al. 1997). Lead clearly plays a critical role in the disruption of the critical Th1/Th2 lymphocyte balance necessary to maintain host resistance to infectious disease.

Further, the production of a critical cytokine, interferon-γ, that is essential in the ability to initiate and maintain protective immune responses and that has been recently demonstrated in young children under 3 years of age in Thailand and the Philippines to be associated with vaccine-induced protection against influenza (Forrest et al 2008), has been shown to be significantly impaired by lead and mercury exposure (Lee and Dietert, 2003; Lawrence & McCabe 2002). Other cytokines important in eliciting protective responses are also significantly affected, such as interleukin(IL)-12 and IL-2. Both being significantly down-regulated to levels known to be inadequate for effective host resistance (Singh et al. 2003).

One of the leading effects of lead is the suppression of the ability to induce delayed type hypersensitivity (DTH) responses upon exposure to a new antigen. Essentially, to elicit a protective immune response requires the induction of a DTH response to recruit lymphocytes and other cells to the site of the deposition of the antigen or vaccine. This impairment is the oldest of the known effects of lead on the immune responses first reported by Muller et al (1977).

This brief synopsis covers only part of what is know about the underlying mechanisms of immune dysfunction associated with even low levels of environmental contaminants with the review by Dietert and Piepenbrink (2006) providing an extensive summary of the current level of knowledge.

However, what is evident is that while a lot of the literature has focused on the effects of materials such as lead on the induction of hypersensitivity reactions (eg, asthma, skin rashes, etc.) and autoimmune disease, that the same underlying immune dysfunctions also has a critical impact in the effective implementation of routine pediatric vaccination programs and their likely effectiveness in communities involving even low levels of environmental heavy metal contaminants.

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