ABSTRACT

Environmental contaminants include the potentially toxic metals lead, cadmium and mercury; the chlorinated pesticides mirex, toxaphene and hexachlorobenzene; chlorinated dioxins and furans; polyaromatic hydrocarbons; and polychlorinated biphenyls. While many of these chemicals are resistant to degradation in the natural environment, they dissolve readily in oils and thus accumulate in the fatty tissues of fish, birds and mammals. Human exposure is predominantly through the ingestion of contaminated food. An array of toxic effects including effects on the immune system have been described in experimental animals and in humans accidentally exposed to these chemicals. Such studies suggest that the immune system of the developing fetus and the newborn is particularly vulnerable to the toxic effects of chemicals. To fully appreciate the magnitude of risk these chemicals pose to children's health, there is a need for additional carefully focussed epidemiologic and mechanistic studies.

The Impact of PCBs and Dioxins on Children's Health: Immunological Considerations

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Since the 1940s there has been an alarming increase in the industrial production and widespread use of synthetic and potentially toxic chemicals and metals. Many of these chemicals are resistant to degradation which allows them to persist in the environment for a long time and to migrate widely using natural atmospheric and water transport mechanisms.[1] These properties, combined with inadequate disposal or destruction methods, have resulted in considerable contamination of many ecosystems throughout the world.[2]

The presence of persistent toxic chemicals in the environment has raised serious concerns among government regulators and the public at large regarding their potential effects on human health, especially those relating to the developing immune system of the fetus and infants. These concerns have been addressed, over the years, by several regulatory agencies at the national and international levels and proposed initiatives and guidelines have been issued regarding "safe" levels of chemicals in the food and water.[3,4]

In particular, attention has been focussed on health effects due to the polychlorinated biphenyls (PCBs), dioxins and dibenzofurans. These ubiquitous chemical mixtures are resistant to decomposition in the natural environment; they dissolve readily in oils and in the fatty tissues of fish, birds and mammals and are, thus, accumulated by living organisms at all levels of the food chain.[5] Human exposure to these contaminants is mainly through the consumption of food, particularly fish caught in contaminated waters, and to a much lesser extent through coming in contact with contaminated water.[2]

Experimental animal data and epidemiologic investigations in humans indicated that these chemicals produce a variety of toxicities leading to an array of clinical and pathological manifestations.[6,7] Chemical-induced toxicities include effects on the immune system which may lead to diminished resistance to infectious agents.[7] Data derived from experimental animal studies and epidemiologic studies of humans occupationally exposed to organochlorine pesticides indicated that humans are at increased risks for cancers of the lymphopoietic and hematopoietic systems suggesting that the 'immune surveillance' mechanisms may be compromised.[8,9]

This article presents a brief review of data on the potential adverse effects of environmental contaminants, mainly PCBs and dioxins, on the immune system of children and proposes potential areas of research that would require further consideration.

The immune system

The immune system consists of many organs and tissues strategically positioned in anatomically defined peripheral lymphoid organs and tissues throughout the host's body. It contains a large number of structurally and functionally different cell types including the mononuclear phagocytic cells and the natural killer cells which are members of the innate or natural immunity, and the T and B lymphocytes and their subsets which are responsible for the development of acquired immunity. The origin of these cells is the pluripotent stem cell found in the bone marrow.[10]

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Acquired immunity is functionally divided into cell-mediated immunity and humoral or antibody-mediated immunity. Cell-mediated immunity refers to the branch of the immune system whose multiple functions are performed via lymphocytes and phagocytic cells with the antibody playing a subordinate role (Table I). Humoral immunity is mediated through antibodies, the product of the B-lymphocyte which upon activation trasforms into the antibody-producing plasma cell.[10]

Exposure to a foreign agent sets in motion a number of tightly regulated events resulting in activation, proliferation and differentiation of the various cells of the immune system. These cells are in constant communication with one another via either cell surface contact or via cytokines produced by such cells.[11] The ultimate function of this cascade of events is to safeguard the host from foreign invaders.

Unlike the immune system in adults which under normal circumstances is functionally mature, the immune system of the neonate and newborn is still at its developmental stage and thus is considered to be functionally immature in some respects. The elegant work of Zola and his colleagues[12] has recently shown that there are distinct differences in the expression of cell-surface receptors and the types of cytokines produced between the neonate and the adult human. This may explain the observed immaturity of certain functions of the lymphocytes during early infancy.

Due to the functional immaturity of the infant's immune sytem, a significant level of protection against microbial infections is derived by the transplacentally transmitted maternal IgG antibody and by immunologic factors found in the breastmilk.[13]

Unfortunately, transplacental and breastmilk transfer are also venues through which several of the environmental contaminants, including PCBs and dioxins, find their way to the fetus and the neonate. Studies in which nonhuman primates have been used as the experimental animal model indicated that there is a correlation between the levels of PCBs in the dam's fat and the levels in the milk of a lactating dam.[14] Approximately 30% of the body's PCB burden can be eliminated via lactation resulting in a net increase of the offspring's chemical burden.[15,16]

Animal studies

The recently completed studies in nonhuman primates indicated that chronic *in utero* exposure to low levels of PCBs had profound effects on several parameters of the immune system of the adult and infant monkeys. Among these there was a significant decrease in the monkey's ability to respond to an antigenic challenge which may lead to diminished resistance to microbial infection.[17-19]

Another multigeneration reproductive/immunotoxicity rat study by Tryphonas[20] involved feeding Sprague-Dawley rats lyophilized salmon from Lake Ontario, which contains high levels of contaminants, and from the less-contaminated Lake Huron. The first (F1) and second (F2) generation pups which were exposed *in utero,* through lactation and through the ingestion of fish-containing diets up to 13 weeks of age, were examined for immunologic effects. Results indicated that the leukocyte numbers in the peripheral blood and in the spleen of the F2 generation male rats fed the Lake Ontario fish diets were lower compared to those fed the Lake Huron fish diets. This effect was due to a parallel shift in the T-helper/inducer subset of T lymphocytes.

Human studies

Shifts in T lymphocyte subsets similar to those observed in experimental animals have also been noted in the infants of Inuit people in Northern Quebec.[21] The Inuit people are known to consume large amounts of marine mammal food. Consequently their blood contains high PCB and dioxin levels. In this study, the effects of environmental contaminants in breastfed vs bottle-fed infants were investigated. Quantitative analysis of the T lymphocyte subsets was performed in these babies at 3, 6 and 12 months. The authors reported that the T-helper/T-suppressor-cytotoxic cell ratios were lower in the breastfed infants at 6 and 12 months of age, suggesting that the increased levels of these chemicals in the breastfed infant may be responsible for the observed downward shift in the T-cell subsets. However, these results should be interpreted with caution due to the normally large biological variability observed among individuals and on a day-to-day basis for a given individual without overt clinical consequences. Thus, further evaluation using more direct indicators of immune function, such as incidence of infection and antibody levels to common childhood diseases, would be required.

TABLE I
Functional Features of Cell-mediated Immunity

- Cell-mediated immunity against fungi, viruses and bacteria;
- Delayed-type hypersensitivity reactions;
- Rejection of tumours and foreign tissue such as transplants;
- Allogeneic (e.g., graft vs. host) diseases.

Another study by Swain[22] was primarily designed to investigate reproductive/neurobehavioural effects of contaminants in infants of fish-eating populations. In this cohort, the levels of PCBs in the mother's milk correlated positively with the number of fish meals consumed by the mother. It was also reported that the incidence of infections in infants born to mothers who consumed fish from Lake Michigan correlated with the levels of PCBs in the maternal blood, suggesting that the immune system of these infants may have been affected by PCBs.

A significant decrease in the levels of B lymphocytes which are the progenitors of the antibody-producing plasma cells, was observed in children born to mothers living in the dioxin-contaminated Times Beach in the Missouri area.[23] However, the incidence of infections in these children was not monitored and the clinical significance of this finding is not known.

Two unfortunate instances of human exposure to PCBs and dibenzofurans have been reported:[25] one in Japan in 1968 which involved 1,600 individuals ranging in age from 4-24 years old[24] and a second episode in Taiwan in 1979 which involved 2,000 individuals.

A number of clinical manifestations typical of PCB poisoning as well as deaths, were recorded in the adult populations of both incidences.[26] Also a number of immunotoxic effects were noted including changes in cellular and humoral

immunity,[25,26] however, many of the immune abnormalities returned to normal after two years. Children born to the surviving mothers and who were exposed *in utero* and through breastmilk to the contaminants, were examined at school age for immunological effects. No abnormal values were detected for the immune parameters examined in any of these children. These surprising findings were attributed to the progressive elimination of contaminants from the body over the years, and to a potential reversibility of effects, a phenomenon observed in the adults as well.[26]

Studies have also been reported by Tognoni and Bonaccorsi[27] on the immune status of 44 children exposed to dioxin following an explosion at a herbicide factory in Seveso, Italy. While 20 of these children presented with chloracnae, a skin disorder characteristic of PCB and dioxin poisoning, no abnormalities were found in several of the immune parameters examined. However, in a subsequent study conducted six years after the explosion, a different cohort of dioxin-exposed children were reported to have a significant increase in blood lymphocyte numbers and in their lymphoproliferative activity upon mitogen stimulation as well as in serum complement protein levels, which correlated with the incidence of chloracnae. The ongoing registry which was set up to monitor the potential long-term effects on these children will undoubtedly assist in determining what the clinical significance of the observed immunologic effects would be.

The above studies reported effects on the immune system of children exposed to relatively high levels of these contaminants. However, a recently initiated study in the Netherlands investigated the effects of background levels of PCBs and dioxins on the immune system of breastfed vs bottlefed children.[28] The levels of dioxins in this country are reported to be twice the normal levels reported for North American populations. Correlations were made between PCB/dioxin levels in the mother's fat determined prenatally and postnatally, and leukocyte numbers in the infant's blood. Observations included: a higher prenatal PCB/dioxin exposure which was associated with an increase in the number of T lymphocytes bearing the T cell receptors of the gamma/delta type—the latter are normally very low in frequency in the normal population; increased total T lymphocytes and cytotoxic T cells at 18 months of age; and, a higher prenatal as well as postnatal PCB/dioxin exposure which was associated with lower monocyte and granulocyte counts at three months of age.[28]

While these findings suggested that the environmental contaminants studied may be immunosuppressive, no association was found between the levels of blood PCBs/dioxin and the incidence of infection, or the antibody levels to common childhood vaccines which are considered to be direct measurements of immune function. Thus, the clinical significance of the observed changes in leukocytes and T lymphocyte subsets is not clear at this point. Undoubtedly, the ongoing monitoring of disease status in these children will lead to a better understanding of the potential chemical-induced long-term effects on the immune system.

Future considerations

There is a need for additional well-designed epidemiologic studies which should include a battery of tests encompassing both quantitative and functional aspects of the immune system. In particular, there is a need for good correlative data between chemically induced changes in immune function measurements and changes in host resistance to specific disease. Until such correlations are established, interpretation of the observed shifts in lymphocytes and their subsets is only speculative.

In addition, there is a need to continue research activities towards elucidating the mechanisms of action of the various chemicals in experimental animal models. This is critical in interpreting and extrapolating data from experimental animals to humans and in understanding the relationship of immunocompetence to disease resistance.

CONCLUSION

The magnitude of risk certain environmental contaminants including PCBs and dioxins may pose to children's health remains to be established. However, data derived from experimental animals and epidemiologic studies indicated that the immune system is a target for toxic effects of environmental contaminants. Such data suggested that the fetus and the newborn are particularly at risk for the immunotoxic effects of environmental contaminants. Further research is required to determine the impact that long-term exposure to these chemicals will have on children's health.

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