Minireview

Xenobiotic-induced Immune Alterations: Implications in Health and Disease


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Immune function may be significantly altered following occupational, inadvertent or therapeutic exposure to chemically diverse xenobiotics. The environmental chemicals like pesticides, halogenated hydrocarbons, polychlorinated dibenzofurans, organic solvents, asbestos, silica, heavy metals etc. may interact with both cellular and humoral components of the immune system which can result in altered immune status that in turn may lead to decreased resistance to infection, certain forms of neoplasia or in some cases exacerbate allergy or autoimmunity. Recent advances in pharmacogenomics and toxicogenomics have contributed a lot to delineate the mechanism of interaction of xenobiotics with the biological system at the cellular and molecular level. However, detection of immune changes on exposure to immunotoxic agents is highly complex, especially in humans due to several confounding factors like age, sex, race gender, co-existence of disease, food habits, smoking etc. Thus, establishing a quantitative relationship between immunotoxicological data and risk assessment, following xenobiotic exposure is still a challenge. The present article reviews the immune alterations caused by exposure to variety of xenobiotics, and their implications in health and disease.

Keywords: Xenobiotics, Pesticides, Disease, Autoimmunity, Immunotoxicity

Introduction

A xenobiotic (Greek, xenos “foreign”; bios “life”) is a compound that is foreign to a living organism. The experimental, epidemiological and other evidences suggest that exposure to such toxic environmental chemicals can lead to serious adverse health effects. The immune system is especially vulnerable to detrimental effect of xenobiotics and immunotoxicity can result in reduced resistance towards infection, generation of tumours that escape immune surveillance or increased incidence of autoimmune disorders. Studies on experimental animals and humans have shown that exposure to pesticides, heavy metals, solvents, halogenated and aromatic hydrocarbons etc. can adversely affect the function of immune system. Therapeutic administration of immunostimulating agents can have detrimental effects and few environmental chemicals that have immunostimulating properties (beryllium, silica, hexachlorobenzene) can have clinical consequences. Besides, a variety of other factors like polymorphisms in xenobiotic-metabolizing enzymes, nutritional status, age, gender etc. can also substantially alter susceptibility to xenobiotics.

Current trend is to understand in detail the molecular mechanisms of interaction of the xenobiotics with the biological system, which ultimately lead to various pathological states. The mechanistic analysis of cellular responses to xenobiotics requires the functional characterization of changes in both gene and protein expression. The ability to study changes in both genes and proteins in vitro and in vivo has become accessible with the development of molecular tools such as microarrays, siRNA, recombinant protein expression and viral gene delivery. The present article reviews the immune alterations caused by exposure to pesticides, heavy metals and other xenobiotics, their pathophysiological implications in health and disease and also briefly discusses the avenues for future research in this area.

Exposure to environmental toxins

Multiple chemical load comes from daily exposure to chemical compounds in our indoor and outdoor air, food and water. Xenobiotics like pesticides are now an all pervasive and almost an inescapable part of our environment. The widespread and often indiscriminate use of these toxic chemicals have created global health concern, particularly because an
estimated 85-90% of pesticides applied do not reach their intended target organisms\textsuperscript{7}. The persistence and extreme stability of certain groups of pesticides are ultimate source of contamination at dietary level. The pesticide residues have been detected in ground water, dairy products, vegetables, fruits and even spices\textsuperscript{8-10}. The hazards from pesticides is higher in developing countries, where their use is poorly regulated and many class-I pesticides (extremely hazardous) that are banned or strictly controlled in developed world are freely available in places not having resources for their safe use\textsuperscript{11}. Besides, in many countries agrochemicals are not handled or stored using even the prescribed minimal safety standards and protective clothing often proves to be too expensive or impossible to wear in hot and humid climate. Studies have revealed the presence of significant amounts of different pesticides and their metabolites in human body fat, blood and milk in different populations across the globe\textsuperscript{12-14}.

Metals, a major category of globally distributed pollutants, are notable for their wide environmental dispersion, their tendency to accumulate in select tissues of the human body, and their overall potential to be toxic, even at relatively minor levels of exposure. They may be inhaled as dust or fume (tiny particulate matter, such as the lead oxide particles produced by the combustion of leaded gasoline). Some metals can be inhaled as vapors (e.g., mercury vapor in the manufacture of fluorescent lamps) or be ingested involuntarily through food and drink. The amount that is actually absorbed from the digestive tract can vary widely, depending on the chemical form of the metal and age and nutritional status of the individual\textsuperscript{15}.

Human beings at the top of the food chain are more vulnerable to health effects, as ingestion of toxic chemicals is several folds higher through the process of biomagnification\textsuperscript{16}. Recent studies indicate that certain population groups may be more susceptible to toxic effects of xenobiotics\textsuperscript{17,18} because certain characteristics of the sub-population may result in greater exposure.

Interaction of xenobiotics in biological systems

Xenobiotics can interact with the biological system in a number of ways. If two chemicals that act at a common site such as a receptor or an enzyme, their actions may be additive, if both activate the target or occlusive, if one activates and the other binds without activating or with a slow dissociation constant\textsuperscript{19}. However, many effects are more complex and act through some combination of altering gene expression, changing levels of intracellular concentrations of ions, altering cellular metabolism or production of cellular regulators. Under these circumstances, the effect of mixtures is more difficult to predict. In fact, only a few chemicals have a single cellular target and most of them act at multiple sites on different cell types or in some cases even at multiple targets within the same cell types. There may be quite different actions on the kidney, liver, and brain, each with a different disease-related outcome. The actions at each of these sites depend on the presence of genes, receptors, and cellular regulators in the specific cell types\textsuperscript{20}. Moreover, the organisms are often exposed to multiple xenobiotics that may have synergistic effects. Thus, systematic studies are essential to study the interactions of simultaneous exposure to different xenobiotics with the biological system.

Xenobiotics-induced immune alterations: Pathophysiological implications

The immune system has evolved to counter challenges to the integrity of self from either the microorganisms or the cells that have escaped the organism’s control mechanism\textsuperscript{21}. The fact that xenobiotics can impair the function of immune system has led to progress in immunotoxicology over the last two decades. Immunotoxic effects of xenobiotics include: histopathologic effects in immune tissues and organs, cellular pathology, altered maturation of immunocompetent cells, changes in B and T cell sub-populations, and functional alterations of immunocompetent cells\textsuperscript{22}. Compounds that adversely affect the immune system are some drugs, pesticides, solvents, halogenated and aromatic hydrocarbons, and metals; ultraviolet radiation can also be immunotoxic\textsuperscript{23}. The pathophysiology of the immune system, including the variable susceptibility of its components, alterations to the lymphoid organs, and the reversibility of changes are important for understanding the impact of immunotoxicity.

Pesticides

The intricate balance that is the hallmark of immune system shows vulnerability to any chemical, including pesticides that can cause structural and functional alterations to the system. Experimental studies on human cell cultures and laboratory animals have provided strong evidence that many pesticides
are immunotoxic. Important changes in host immunity may occur after acute or chronic pesticide exposure. Pesticides can target both humoral and cellular component of the immune system and these changes correlate closely with altered host resistance to the pathogens.

Organochlorine compounds like DDT, chlordane, aldrin, lindane etc. though less acutely toxic than organophosphate pesticides, have greater potential for chronic toxicity. Administration of 200 ppm DDT or its metabolites in the diet for 5 weeks suspends generation of both humoral and cell-mediated immune response to ovalbumin. Aldrin and dieldrin reduce mouse resistance to viral infection through effects on macrophages. Chlordane and heptachlor have been found to affect the developing immune system. Administration of 300 ppm of hexachlorocyclohexane (HCH) in the diet for 30 days suppresses the ability of splenocytes to proliferate in response to mitogen to generate a CTL response in mice. Alteration of immune function and increased incidence of infections have been reported in infants of populations exposed to organochlorines.

Cytokines, the important regulators of immune function play a crucial role in activation, proliferation and differentiation of lymphocytes. A particular cytokine may be differentially altered in response to pesticide exposure depending on the class of pesticide, duration of exposure and interaction with other host factors. Recent study from our laboratory has show that serum IL-2, IL-4 and TNF-α levels are significantly raised with decrease in IFN-γ level in lindane poisoning cases as compared to healthy controls (Table 1). Investigating such changes in cytokine profile may help to evaluate specific health risk caused by acute or chronic lindane exposure in human population. The significant decrease in IFN-γ levels could enhance the chances of infections occurring in poisoning cases. The IL-2 and TNF-α increase may result from a mechanism to compensate for the decrease in IFN-γ after pesticide exposure. TNF-α is also associated with the activation of repair mechanisms, following xenobiotic damage. Thus, determination of serum cytokines in pesticides exposure could provide test systems for evaluation of chemical safety and susceptibility to pesticide-induced immunotoxicity.

A number of studies have been carried out to assess the effects of organophosphates on the immune system. Sub-chronic malathion exposure induces differential degrees of humoral and cell mediated immune suppression in experimental animals.

Exposure to paraoxon has been shown to inhibit production of IL-2 by rat splenocytes. Administration of single high dose of methyl parathion in mice elevates the humoral immune response with no effect on delayed type hypersensitivity (DTH) reaction. The effects of impurities in organophosphate pesticides on immune system have been studied. Majority of the studies have been conducted with O,O,S-trimethyl phosphorothioate (OOS-TMP). Following acute, non-toxic doses of OOS-TMP, the generation of both cell-mediated and humoral immunity is blocked, following in vivo and in vitro exposure to antigen.

The immune system may be a sensitive target for many carbamate pesticides. Exposure of sub-chronic doses of propoxur in rats has been found to suppress both humoral and CMI responses. The humoral immune response is also suppressed after inhalation of carbaryl, but not after oral or dermal exposure. Intraperitoneal administration of aminocarb also suppresses humoral immune system, whereas inhalation has no effect. Very little information is available regarding the effect of pyrethroids on the immune system. Acute and subchronic administration of cypermethrin has been found to suppress humoral immune function in experimental animals. Exposure of mice to supercypermethrin (a pyrethroid pesticide) inhibits humoral response only, after administration at doses that result in mortality in some mice.

Little data are available on the effects of herbicides on the immune system (Table 2). Oral administration of 100 mg/kg/day atrazine for 3 days to rats decreases the number of WBC, but has no effect on lymphoid organ or serum immunoglobulin levels. A decrease in the number of single and double positive thymocytes, with no effect on splenic or lymph node population has been reported after propanil.

<table>
<thead>
<tr>
<th>Cytokine&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Normal subjects (n = 20)</th>
<th>Lindane poisoning cases (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>16.3 ± 2.39</td>
<td>45.13 ± 6.34&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IL-4</td>
<td>0.79 ± 0.09</td>
<td>1.86 ± 0.42&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>TNF-α</td>
<td>7.25 ± 0.82</td>
<td>31.17 ± 3.73&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>2.96 ± 0.57</td>
<td>1.18 ± 0.15&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Values are given as absolute mean of serum cytokine concentration (pg/mL) ± SD

<sup>b</sup>Significantly different from normal subjects (P <0.05)
Effect on humoral immune response

<table>
<thead>
<tr>
<th>Pesticide model</th>
<th>Animal</th>
<th>Dose and duration of exposure</th>
<th>Reported effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDT</td>
<td>Mouse</td>
<td>100 ppm for 4 weeks</td>
<td>Antibody titre to SRBC (↓)</td>
<td>63</td>
</tr>
<tr>
<td>Endosulfan</td>
<td>Rat</td>
<td>10 and 20 ppm For 8-22 weeks</td>
<td>Antibody titre to TT (↓)</td>
<td>81</td>
</tr>
<tr>
<td>Malathion</td>
<td>Rat</td>
<td>20, 50 or 100 ppm/day3-12 weeks</td>
<td>Serum IgG (↓), Secondary PFC response (↓)</td>
<td>24</td>
</tr>
<tr>
<td>Propoxur</td>
<td>Rat</td>
<td>10, 30, 90 mg/kg Bw for 30 days</td>
<td>Antibody titre to SRBC (↓)</td>
<td>37</td>
</tr>
</tbody>
</table>

Effect on cell-mediated immune response

<table>
<thead>
<tr>
<th>Pesticide model</th>
<th>Animal</th>
<th>Dose and duration of exposure</th>
<th>Reported effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDT</td>
<td>Rat</td>
<td>50 and 100 ppm for 6-22 weeks</td>
<td>LMI (↓)MMI (↓)</td>
<td>82</td>
</tr>
<tr>
<td>Lindane</td>
<td>Rat</td>
<td>20 ppm for12-22 weeks</td>
<td>LMI (↓)MMI (↓)</td>
<td>66</td>
</tr>
<tr>
<td>Malathion</td>
<td>Rat</td>
<td>20, 50 or 100 ppm/day3-12 weeks</td>
<td>LMI (↓) MMI (↓)</td>
<td>83</td>
</tr>
<tr>
<td>Propoxur</td>
<td>Rat</td>
<td>10, 30, 90 mg/kg Bw for 30 days</td>
<td>LMI (↓) MMI (↓)</td>
<td>36</td>
</tr>
</tbody>
</table>

(↓), Decrease; SRBC, sheep red blood cell; PFC, plaque forming cell; TT, tetanus toxoid; LMI, leucocyte migration inhibition; MMI, macrophage migration inhibition

Table 3—Effect of propoxur and melatonin on immune and oxidative stress markers in rats

<table>
<thead>
<tr>
<th>Treatment (mg/kg bw)</th>
<th>Antibody titre (−log₂)</th>
<th>PFC/10⁶ splenic cells</th>
<th>MDA (nmol/ml)</th>
<th>GSH (mg/gHb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8.01 ± 0.5</td>
<td>2600 ± 340</td>
<td>2.90 ± 0.19</td>
<td>2.25 ± 0.14</td>
</tr>
<tr>
<td>Propoxur</td>
<td>5.00 ± 1.0ᵃ</td>
<td>1150 ± 400ᵇ</td>
<td>3.82 ± 0.22ᵃ</td>
<td>1.10 ± 0.05ᵇ</td>
</tr>
<tr>
<td>Melatonin</td>
<td>8.50 ± 1.0ᵇ</td>
<td>2800 ± 315ᵇ</td>
<td>2.88 ± 0.14ᵇ</td>
<td>2.00 ± 0.17ᵇ</td>
</tr>
<tr>
<td>Propoxur + melatonin</td>
<td>7.50 ± 0.5ᵇ</td>
<td>2200 ± 250ᵇ</td>
<td>3.00 ± 0.13ᵇ</td>
<td>2.18 ± 0.20ᵇ</td>
</tr>
</tbody>
</table>

Significantly different from “control and “propoxur-treated group; (P <0.001)

Heavy metals

Heavy metals including lead, cadmium and mercury etc are capable of altering the immune response in laboratory animals and humans. The workers with elevated blood lead levels (30-90 µg/100 ml) have shown increased suppressor cell activity, lowered lymphocyte proliferation after mitogen stimulation in vitro, decreased IgA concentrations in saliva, lowered complement C3 levels⁴⁶, and an enhanced prevalence of respiratory infection. Although the immunotoxic effects of cadmium, lead, and mercury have been reported in experimental animals both in vivo and in vitro, the data on the effects of heavy metals on the human immune system are scanty and refer mainly to occupational exposure⁴⁷. These studies nevertheless provide evidence that at least mercury and lead affect the immune system. Significantly decreased levels of serum IgG and IgA, but not IgM, IgD, or IgE have been reported in workers occupationally exposed to metallic mercury vapours for 20 years in comparison with unexposed controls⁴⁸. The workers exposed to mercury in dental amalgams have shown increased levels of IgE and increased incidence of asthma and development of contact dermatitis. In addition, total lymphocytes, CD4, and CD8 levels have found to be higher in exposed subjects than in controls⁴⁹. More than one mechanism appears to operate in immunotoxicity due to metals. Defect in B cell function and impaired accessory cell function or deficient complement system have been implicated⁵⁰. Lead as well as cadmium are sulphhydryl alkalyting agents with high binding affinity for cellular and sulphhydryl groups. They modulate membrane bound thiols and thus alter the lymphocyte function⁵¹. The augmentation of T and B cell responsiveness stated as above could precipitate autoimmunity.
Miscellaneous xenobiotics

Suppression of humoral immunity has been observed frequently after exposure to polycyclic aromatic hydrocarbons (PAHs), including benzo(a)pyrene, DMBA and 3-methylcolathrene. PAHs also suppress cell-mediated immunity. Most of PAHs also found to impair T-lymphocyte cytotoxicity and mixed lymphocyte responsiveness. Various mechanisms have been suggested for the immunosuppression due to PAHs. The immunosuppression may be due to parent compound or its metabolites, altered interleukin levels, a direct effect on transmembrane signaling or alteration in intracellular calcium mobilization. The association between changes in immunological parameters and host resistance and inhalation of particulate materials and oxidant gases is well established. For example, decrease in delayed-type hypersensitivity response, circulating T-cell numbers, and T-cell proliferation have been observed with and sometimes preceding asbestos-related diseases i.e. fibrosis, asbestosis, and mesothelioma. B-Cell response is increased, however, as evidenced by increased serum and secretory (primarily IgA) immunoglobulins. Natural killer (NK) cell activity is also altered after exposure to asbestos. In study of NK cell response in asbestos workers, it has been found that immune changes may occur independently of any early neoplastic process. Similarly, abnormal antibody production, decreased cell-mediated immune response, and decreased resistance to disease in subjects occupationally exposed to silica have been observed.

Certain organic solvents may also induce immune changes in humans. Exposure to benzene is associated with myelotoxicity and may lead to derangement of variety of immunological parameters. The mechanism of benzene-induced immunosuppression is still unclear. Benzene has potential to alter cytoskeletal development through inhibition of microtubule assembly. The polyhydroxy metabolite of benzene binds to sulphhydryl groups on the proteins that are necessary for the integrity and polymerization of microtubules. Such effect may alter membrane fluidity, which explains the sub lethal effect of benzene on lymphocyte function.

Factors affecting xenobiotic induced immunomodulation

The immune response, in general, depends on the successful interaction of the antigen with different cells like lymphocytes, macrophages and other accessory cells of the lymphoid organs. Many factors tend to complicate the assessment of immune competence. The important factors that affect modulation of antigenic response by xenobiotics are as follows:

Dose and duration of exposure

The immune effects may vary with the dose of the xenobiotics. Accidental acute dose exposure could have immunological consequences, while low exposure to chemicals may have minimal or no immunological effects. It is possible that high dose exposure may affect key cellular players of the immune system or aberrantly alter cytokine profile that subsequently determines the outcome of the immune responses. Lindane exposure at chronically high levels is found to affect cytokine levels in humans, which indicate severity of immunotoxicity. On the other hand, reports suggest that pesticides may be immunosuppressive at very low doses in which no other system toxicity is evident. The frequency and duration of exposure are important aspects of pesticide toxicity. Immunosuppression by some pesticides shows a dose-time relationship in experimental animals and nature of immunomodulation varies with duration of sub-chronic exposure. For example, DDT attenuates both primary and secondary humoral immune response in a dose-time dependent manner in mice exposed to 50 or 100 ppm DDT for 12 weeks. However, 3-8 weeks of exposure with 100 ppm DDT reduces secondary response without affecting the primary humoral immune response. The extent of alteration of humoral and cell mediated immune responses is affected differentially by various doses and duration of pesticide exposure. In short term exposure, the immunosuppressive effects are more pronounced in the secondary response than the primary. However, suppression of both primary and secondary antibody responses occurs after longer exposure duration. The effect of pesticides on secondary immune response is more time-dependent than on dose, suggesting a threshold susceptibility to exposure.

Poverty and nutritional status

People living in poverty may be more sensitive to xenobiotic exposure because of nutritional factors such as low body fat, micronutrient balance or protein deficiency. For example, protein deficiency enhances the immunosuppressive effect of sub-chronic (50 or 100 ppm) exposure to DDT in albino rats. Moreover, these animals maintained on 3% protein diet have also shown suppression in cellular and
humoral responses to antigen in dose dependent manner after exposure to DDT at dose levels that were not immunosuppressive in rats fed on 12 or 20% protein diet. Thus, there is a need to study the influence of different levels of dietary protein on immunotoxicity of the pesticides. In a recent study, we found that feeding (1 percent w/w) of ginger (Zingiber officinalis) for 4 weeks in rats attenuated the immunosuppressive effect of malathion and also appreciably reversed the malathion-induced changes in humoral and cell-mediated immunity (unpublished results).

Pathological conditions

Compromised health status or pre-existing disease (i.e. skin disease or seizure disorder) may increase sensitivity to xenobiotic exposure. Chlorinated and organophosphate compounds may influence physiological and pathological conditions and may alter nutritional status and hepatic metabolism of other endogenous immunoregulatory substances. DDT increases susceptibility to leprosy infection in a dose-dependent manner, as revealed by enhanced bacillary growth in DDT exposed mice. Although it appears that the immunosuppressive effects of DDT could be one of the factors for increased growth of Mycobacterium leprae in normal mice, it is not known whether the pesticide itself could also enhance the multiplication of bacilli. Thus, more in vitro studies are required on the effect of DDT on growth of Mycobacterium leprae related mycobacteria, peritoneal macrophage activity and release of IL-2 by T-cells.

Age and gender

Exposure to xenobiotics does not affect all humans uniformly. Defined population groups may be more susceptible to toxic effects of pesticide exposure because of greater inherent sensitivity. Also certain characteristics of the sub-population may result in greater exposure. Pharmacokinetic differences in absorption, distribution, metabolism and excretion are the basis for most subpopulation differences in the pesticide sensitivity. Newborns may exhibit extreme quantitative differences in sensitivity to chemicals, as compared to adults. Although older people usually have higher levels of persistent chlorinated pesticides, scant research has been done that directly addresses pesticide sensitivity in geriatric populations.

Although it is not known whether both male and female mice are equally immunologically sensitive to pesticides, data on prenatal exposure to chlordane indicate that females may be more sensitive than males. Nevertheless it is also possible that males may be sensitive to other estrogenic chemicals, since estrogen receptors may be relatively unoccupied (unlike in female) which may facilitate action of environmental estrogens.

Previous or concurrent exposures

Individual sensitivity to xenobiotic exposure may be enhanced or diminished by simultaneous exposure to other chemicals. Pesticides frequently used indoors may synergistically interact with the materials that are in house dust. The PAHs commonly found in house dust increase the potency of chlorpyrifos to inhibit acetylcholine esterase by as much as 85% in vitro. It is likely that pesticide exposure occurs in combination with other agents such as solvents. People who are sensitive to solvents may be at increased risk for illness when exposed to low levels of pesticides. Further, impurities in the chemical formulation of individual particles may be more toxic than the original compound, e.g. malathion may be contaminated with O,O,S-trimethylphosphorothioate, a proven immunotoxicant.

Psychological stress

Stress is any internal/external stimulus capable of altering physiological homeostasis and the ability to cope with such stressful stimuli is a crucial determinant of health and disease. However, only a few studies are available on the interactions between environmental and emotional stressors in the regulation of immune responsiveness. A study in our laboratory evaluated the effects of different durations/intensities of restraint stress (RS) on DDT induced humoral responses in mice and it has been found that emotional stress may markedly enhance immunosuppressive effect of DDT at dose levels/treatment duration with no observed immunosuppression. RS may also markedly enhance the cell-mediated immunosuppressive effect of DDT at dose levels/treatment durations with no observed immune toxicity (unpublished results). Thus, testing of sub-toxic effects of DDT and other organochlorines on immune responses in relation to stress is important, since concomitant exposure to pesticide residues in the environment and to a variety of emotional stressors is highly probable. Therefore, evaluation of data from immunotoxicity studies in humans should also include consideration of emotional distress as a contributing factor.
Potential mechanisms of xenobiotic-induced immunotoxicity

Xenobiotics can interfere with many biological systems and affect the cellular functions including those of receptors, cell membrane transport and enzyme activation, but the mechanisms by which they cause immunotoxicity is still unclear. It is difficult to construct the actual sequence of molecular events occurring within cells of the lymphoid system and to determine specific sites for cellular-chemical interaction when organisms are exposed to xenobiotics. Certain xenobiotics may upregulate level of apoptosis in lymphocytes, which may account for immunosuppression. It has been suggested that cholinergic stimulation leads to suppression of PFC response during organophosphate exposure. Free radicals may also play an important role in immune regulation. Oxygen free radicals have many molecules and cellular targets in the immune system and selective depletion of T-lymphocytes, and decreased rosette formation and IL-2 production etc by these toxic species have been reported. Therefore, xenobiotic-induced oxidative stress may contribute to its immunotoxicity.  

A number of xenobiotics including mercury, iodine, vinyl chloride, organic solvents, silica, particulates, ultraviolet radiation, and ozone are associated with human autoimmune disease. In addition, xenobiotics may also exacerbate an existing autoimmune disease. Numerous mechanisms based on in vitro evidence and animal models have been proposed to explain how xenobiotics induce or enhance autoimmunity. These mechanisms can be broadly divided into three general categories. (i) inhibition of the processes involved in establishing tolerance by deletion, which could result in the release of newly generated autoreactive cells into the periphery, (ii) modification of gene expression in the cells participating in the immune response, permitting lymphocytes to respond to signals normally insufficient to initiate a response or allowing the antigen-presenting cells to abnormally stimulate a response. Abnormal gene expression can thus disrupt tolerance maintained by suppression or permitting activation of autoreactive cells, and (iii) modification of self-molecules, such that they are recognized by the immune system as foreign. Some mechanisms appear to be common to a variety of agents, and different mechanisms appear to produce similar diseases. However, evidences that any of these mechanisms are actually responsible for xenobiotic-induced human autoimmune disease are still largely lacking, and the possibility for numerous and as yet unidentified mechanisms also exists as shown in the Fig. 1.

Future challenges

i) Identification of risk factors that singly or collectively contribute to increased susceptibility to immunotoxic effects of xenobiotics

ii) Epidemiological studies in human populations are needed to establish the incidence of immune-related diseases, including immunosuppression, hypersensitivity, and autoimmunity associated with exposure to xenobiotics and to determine the impact of these effects on clinical diseases such as infections and cancer

iii) Development of models for studying the immunomodulating effect of xenobiotics during different stages of foetal development

v) To assess the possible role of heat-shock proteins in xenobiotic induced apoptosis and immunomodulation.

vi) Identification of dietary plant products that may act as immunostimulant to attenuate xenobiotic-induced immunotoxic effects.

Concluding remarks

Immune alterations by xenobiotics are crucial determinants of health and disease suggesting the need to investigate their potential risk and design precautionary measures. Due to obvious limitations in human studies, an understanding of these risks depends to a great extent upon the cellular and molecular events underlying xenobiotic-induced immune dysfunction in
Experimental animals. Such animal studies and our current knowledge about the pathogenesis of disease support the possibility that xenobiotic induced damage to immune system may be associated with a wide spectrum of diverse pathological conditions, some of which may be detectable after a long latency. Considering the widespread distribution and stability of certain xenobiotics in the biosystem, present data on adverse effects in humans appear to represent only tip of the iceberg. Risk to human health from xenobiotics should not be underestimated in any way and urgent steps should be taken to define factors that affect the evaluation of immune toxicity by environmental chemicals. The exact mechanism by which xenobiotics cause alterations in immune status is in many cases not clearly defined, but the close interactions between neurological and immunological functions provide many potential targets of toxicity. A better understanding of these interactions and more clearly defined end points in different species remains a priority for the future.

References
47. Valentino M, Rapisarda V, Santarelli L, Bracci M,
REFERENCES

63 Banerjee B D, Ramachandran M & Hussain Q Z (1986) *Bull Environ Contam Toxicol* 37, 433-440
78 Banerjee B D, Koner B C & Ray A (1997) *Environ Res* 74, 43-47
80 Rao T & Richardson B (1999) *Environ Hlth Perspect* 107, 737-742
81 Banerjee B D & Hussain Q Z (1987) *Bull Environ Contam Toxicol* 38, 435-441
82 Banerjee B D (1987) *Bull Environ Contam Toxicol* 39, 827-834