Immunotoxins as Teratogens
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Environmental exposure to certain drugs, chemicals, radiation, and viruses can cause abnormal fetal development. A single teratogen can cause malformations of multiple body systems. Conversely, multiple teratogens can cause abnormal development of the same system. This leads to speculation that there may be some underlying mechanism in common to most teratogens. If such a mechanism could be established, it might be possible to develop a more rapid and accurate assay for potential teratogens. This paper explores the hypothesis that immunotoxicity may be a common marker for many established teratogens.

The immune system is a frequent target organ of toxic insult following chronic or acute exposure to environmental chemicals, therapeutic drugs**,** abused drugs or radiation. Interaction of the immune system with these xenobiotics may result in undesirable effects of three principal types: 1) immunosuppression; 2) immune deregulations (autoimmunity); and 3) immunologic response to the xenobiotic (allergy). *(NTP Annual Plan 1986)* The health implications of these immune dysfunctions are increased risk of infectious diseases; development of neoplasia; autoimmune disorders and allergies. *(Berlin et* al**.** *1987)*

An analysis of current research on immunotoxins also suggests that prenatal exposure to xenobiotics can result in a fourth type of adverse outcome - teratogenesis. New research in developmental immunotoxicology is exploring the possibility that one teratogenic outcome of prenatal exposure to immunotoxins may be impairment of the developing fetal immune system.*(NTP 1988)* Children born with dysfunctional immune systems are at increased risk of allergies, chronic infections, autoimmune disease, learning problems and/or childhood cancer.

Immunologically active agents can be divided into immunodepressants and immunostimulants, but a more appropriate term would be immunomodulators since both immunodepressants and immunostimulants can produce paradoxical immune effects. In fact, exposure to an immunodepressive xenobiotic may first be manifested by a form of immune hyperactivity since downregulatory cells may be more sensitive than helper-inducer immunocytes. *(Spreafico 1987)*

Evidence that immunosuppressive agents may be teratogenic can be found as far back as the early sixties in research on thalidomide, the popular sedative which caused a worldwide epidemic of children with phocomelic limbs and other serious birth defects. Hellman and his co-workers were able to demonstrate that thalidomide was able to suppress immunological responses to transplanted tissue. A number of other chemical compounds such as aminopterin and methotrexate as well as radiation were also reported to have this immunosuppressive effect. These agents were generally teratogenic in mammals. It was observed, even in this early research, that immunosuppressive agents usually inhibit the cell divisions in growing tissues and that this effect is consistent with a teratogenic action as well as an immuno-toxic response. *(Niilson 1962)*

The possibility of a consistency in the teratogenic effect of immunotoxins can be further explored in research on a broad range of xenobiotics which are immunotoxic and teratogenic in mammals including: lead, mercury, polybrominated biphenyls (PBBs), polychlorinated biphenyls (PCBs), diethylstilbestrol (DES) and other estrogenic compounds, ethylene glycol monomethyl ethers, diphenylhydantoin (Dilantin), antihistamines, pesticides, alcohol and marijuana and tetrachlorodibenzo-p-dioxin (TCDD).

Lead and Mercury - Studies have shown that human lead exposure has been related to immunosuppression manifested as increased susceptibility or severity of infection. *(Hadden 1986)* Although heavy metals like lead and mercury have been reported to be cytotoxic to numerous cell types, they are also able to induce allergic hypersensitivity. Any metal known to produce an allergic response may be a promoter of autoimmunity. Research has suggested that lead and mercury-induced immunomodulation can cause autoimmune disease. (Law*rence 1986)*Animal studies have demonstrated that lead induced immune reactivity can also enhance the growth of tumors. *(Lawrence 1986)*

Both lead and mercury are acknowledged teratogens. *(NJDH 1986)* Studies of children with prenatal exposure to high lead levels have demonstrated impairment in verbal processing and performance and sustained attention. Mercury is also teratogenic to the developing brain and can cause growth deficiency, blindness**,** deafness, microcephaly and poor muscle tone. Impaired immune function may be a delayed effect of prenatal exposure to methyl mercury. Disastrous effects on the unborn were documented in Minamata Bay, Japan when mothers consumed fish from mercury contaminated waters; in Iraq when 6,530 people ate mercury-treated seed grain and in New Mexico when animals fed on the contaminated seed grain were eaten by humans. *(Smith 1982)*

Polybrominated biphehyls (PBBS) PBBs are flame-retardants used in clothing manufacture. In 1973, PBBs were introduced into the food chain in Michigan when they were accidentally substituted for a food supplement in feed for livestock. The effects of this contamination first became evident in the farm animals: cows, chickens and sheep that suffered severe wasting disease, abortions and deformed offspring - calves born with holes in their heads; lambs with no hind legs and deformed faces.

When these PBB poisoned animals were inadvertently consumed by farm families and later customers of their products, men, women and children began to report symptoms of PBB toxicosis: blinding headaches, digestive problems, skin eruptions, inexplicable weight loss, fatigue, decreased resistance to infection, chest pains, decreased libido, nervousness, sleep disturbances, visual problems, irritability, memory problems, aching muscles and joints and decreased tolerance to alcohol. An epidemic of miscarriages and abortions was also reported in some rural communities. *(Egginton 1977)*

Symptoms in both animals and humans first appeared after stress. PBBs are stored in the fat-soluble tissues of the body. As long as the toxin was quiescent in the fat it appeared to do little harm, but as soon as the fat was mobilized to cope with stress PBB began to devastate the system.

Paradoxically, the sicker animals usually had the lowest levels of PBB in their bodies. These animals had gotten rid of most of the PBB through milk production and calving. They were showing the effects of the damage that the chemical had done to their systems. The healthier looking animals still had more of the PBB in their tissues.

In humans, there were great variations of PBB levels within families and no apparent relationship between the levels of PBB in a person's tissues and the severity of symptoms. There seemed to be vast differences in the way people's bodies react to toxins. *(Egginton 1977)*

Subsequent testing of the PBB-affected human population demonstrated immunological disturbances including depressed T-cell numbers, abnormalities in cell-mediated immunity, increased null cells and Ig levels. *(Hadden 1986)*

Polychlorinated biphenyls (PCBs) PCBs, compounds used as heat transfer media and plasticizers, have become a ubiquitous cause of environmental contamination. In animals, PCB immunotoxicity has been correlated with increased susceptibility and mortality from viruses, bacteria and parasites. Widespread human toxicity occurred after consumption of PCB contaminated rice oil in Japan and China. Immunotoxic effects included chloracne, decreases in serum Ig levels and impaired cell mediated immunity with decreased T cell numbers and function as well as increased susceptibility to respiratory infection. *(Hadden 1986)* PCBs are also probable cancer-causing agents in humans with evidence of an association between PCBs and skin cancer. *(NJDH 1986)*

Follow-up studies of children exposed in utero to PCB have been reported by several researchers. Rogan and colleagues studied over 100 Taiwanese children conceived in the 5 years after their mothers had been poisoned by PCBs and their contaminants, the polychlorinated dibenzofurans. The children had a significant excess of ectodermal defects and developmental delays. In the U.S., studies have reported that at the upper end of exposures in the general population, there is evidence of motor impairment in newborn infants, motor delay in 6 and 12 month olds and impaired visual recognition memory in 7 month olds. *(Rogan 1989)*

Diethylstilbestrol (DES) - DES is a synthetic non-steriodal compound that has estrogenic activity. It was used for over thirty years as a treatment to prevent miscarriage. In 1971, DES was linked to cervical and vaginal carcinomas in the female children of treated mothers. DES has also been used as a growth promoter in poultry and meat production and was linked to episodes of breast enlargement in young children who ate contaminated meat in Puerto Rico and Italy.

Estrogens, particularly DES, may have significant immunosuppressive effects *(Hadden 1986)*DES has been shown to have immunotoxic effects on some components of the human immune system. The. natural killer cell system which is a primary defense against tumors and viruses is the most susceptible to DES. *(Kalland 1986)* The National Toxicology Program has reported altered immune function and resistance to infectious agents in mice exposed to DES. *(NTP Annual Report* 1985) Clinical observations on the prevalence of susceptibility to infectious agents during pregnancy also indicate an effect of female sex steroids on the human immune system.

In addition to being a transplacental carcinogen, DES has also been associated with malformations of the genitalia in both male and female children exposed in utero. DES daughters have shown cellular and structural abnormalities in the vagina, cervix, uterus and Fallopian tubes. Studies have also confirmed abnormalities of the reproductive tract in DES sons such as undescended testicles and benign cysts. (DES *Action 1986)*

It has been noted that the developing immune system is more susceptible to toxic effects in general and that this holds true for the effects of DES. In the mouse, exposure of the immature immune system to DES leads to persistent impairment of the immune system, particularly decreased natural killer cell activity. (Kalland *1986)*

Diphenylhydantoin (Dilantin) Evidence is accumulating that this anti-seizure medication may have significant immunosuppressive effects. *(Hadden 1986)* National Toxicology Program studies in mice exposed to diphenylhydantoin demonstrated a selective effect on immune function resulting in depressed serum IgA levels and altered bone marrow function. Researchers are trying to correlate these findings with the IgA deficiency and increased sinuopulmonary infection that occurs in humans on long-term diphenylhydantoin treatment *(NTP 1984)*

A number of reports have suggested a relationship between diphenylhydantoin and the development of lymphadenopathy, lymphoma and Hodgkins Disease. There have also been reports of malignancies such as neuroblastoma occurring in children whose mothers received diphenylhydantoin during pregnancy. (PDR *1988)*

In addition to having immunosuppressive effects, diphenylhydantoin is also teratogenic to the developing fetus and has been associated with an increased incidence of congenital malformations, such as cleft lip/ palate and heart malformation, and a pattern of congenital malformations called Fetal Hydantoin Syndrome. The sequence of abnormalities in children whose mothers took diphenylhydantoin during pregnancy includes prenatal growth deficiency, microcephaly and mental deficiency. *(PDR 1988)*

Antihistamines - Antihistamines are**,** by the very nature of their pharmacological activity, immunosuppressant. An allergic reaction occurs when a foreign antigen activates T-cells passing through the site of the allergic response. These activated T-cells stimulate B-cells to produce high levels of IgE antibodies. At the same time, the T-cells release chemotactic factors which attract basophils into the affected tissue. The basophils, bind with the newly produced IgE and when these cells come in contact with the allergen, they release stores of histamine, heparin and other mediators amplifying the allergic response. Antihistamines block the effects of histamine on blood vessels and smooth muscle, thus they help to suppress the body's reaction to a foreign antigen.

Standard adverse reaction warnings on most antihistamines include many symptoms which are also characteristic of chemically-induced immune dysfunction: rash, photosensitivity, fatigue, dizziness, disturbed coordination, insomnia, tinnitus, paresthesia, neuritis, blurred vision, headache, gastrointestinal problems, hemolytic anemia, thrombocytopenia and so on. Like other

immune modulators, antihistamines can also produce the paradoxical effects of sedation in some people, restlessness and excitation in others. *(PDR 1988)*

Doxylamine succinate, an antihistamine in a number of over-the-counter products as well as the controversial morning sickness remedy Bendectin, has been associated with a statistically significant increase in acute nonlymphoblastic leukemia in children whose mothers took Bendectin for eleven weeks or more during pregnancy. *(Robinson et al 1988) In* 90-day chronic toxicity studies at the National Toxicology Program, doxylamine was associated with toxic lesions of the livers and parotid glands of mice and rats. (NTP *1986)*

Bendectin has been associated with limb reduction defects, heart defects, oral clefts and other serious birth defects in animal and human studies. *(ABDC 1988)* Other antihistamines, diphenhydramine (Benadryl), meclizine and cyclizine have also been associated with birth defects in animal and human studies.

Marijuana and Alcohol - Abuse of marijuana or alcohol has been shown to contribute to impaired immune function and lowered resistance either directly or indirectly through an abnormal life style and malnutrition. *(Dean 1984)* Both substances have also been associated with adverse effects on the unborn. A pattern of congenital malformation called Fetal Alcohol Syndrome has been identified in the children of chronically alcoholic women. FAS may include growth and mental deficiency, microcephaly, short palpebral fissures and other anomalies of the skeleton and heart. *(Smith 1982)* Marijuana use during pregnancy has been associated with an increased risk of childhood acute nonlymphoblastic leukemia. *(Robinson 1989)*

Glycol Ethers - Ethylene glycol monomethyl ether (Methyl Cellusolve) and 2-ethoxyethanol (Cellusolve) are widely used industrial solvents for paint, inks, nitrocellulose, pigments and leather finishes.

Immunological studies of solvent-exposed workers have shown a decrease in overall T-cells; a decrease in T-4 helper cells; and increase in natural killer cells and an increase in human B-lymphocytes. Similar changes in lymphocyte subpopulations are found in states of immunodeficiency and immunogenetic forms of aplastic anemia. *(Denkhaus 1986)*

Bone marrow injury has been reported in a study of lithographers exposed to glycol ethers.*(Cullen 1983)* A syndrome called Chemically Acquired Immunodeficiency has also been reported in Silicon Valley workers exposed to glycol ethers. This pattern of illness includes abnormal T-cell function; flu-like symptoms; multiple allergic reactions to ink, perfume, gasoline, heating fuel and household chemicals; repeated infections; depression; gastrointestinal complaints; chronic headaches and fatigue; concentration, learning and memory difficulties and reproductive problems including miscarriage. *(Spake 1986)*

NIOSH recommends that Methyl Cellusolve and Cellusolve be regarded in the workplace as having the potential to cause adverse reproductive effects, including toxic effects to the unborn if the mother is exposed during pregnancy. Even at the permissible exposure limits, these two

glycol ethers produced damage to the reproductive systems of two species of test animals including testicular wasting, male infertility, and birth defects in the offspring of mothers exposed during pregnancy. *(UAW 1986)* Since thymic atrophy has been observed in animals exposed to glycol monomethyl ether, the National Toxicology Program has started studies to examine the consequences of exposure to this chemical during the development of the fetal immune system. *(NTP 1986)*

Dioxin - 2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin (TCDD) is the prototype for certain isomers from several classes of halogenated aromatic compounds. Toxic responses to TCDD in animals include teratogenesis, wasting and thymic atrophy. Immunological studies have shown depressed antibody response, cell-mediated immunity and lymphoproliferative responses in association with increased susceptibility to pathogen and tumor challenge particularly in neonates of exposed mothers. *(Hadden 1986)*

Studies in various animal and cell culture models indicate that TCDD's actions seem to focus on two target systems, the skin and the thymus resulting in altered patterns of growth and differentiation. This suggests that TCDD may be altering similar regulatory events in both cell targets. *(Greenlee 1986)*

In culture, TCDD can suppress the formation of granulocyte-macrophage colonies and plaque forming cells. TCDD can also suppress proliferating cells of the immune system, including hematopoietic stem cells and B cells in adult mice. *(Tucker 1986)* Rodents exposed to TCDD during the perinatal period of immune system development have exhibited immunosupression characterized by thymic atrophy, suppressed-cell mediated immunity and increased susceptibility to infections. *(Greenlee 1986)*

Studies of workers seventeen years after accidental exposure to dioxin have reported immune system alterations including increases in antinuclear antibodies and immune complexes in the peripheral blood of exposed workers and a significant increase in the number of natural killer cells. *(Jennings ET al, 1988)*

Immunologic tests of dioxin-exposed residents of Quail Run Mobile Home Park in Missouri also revealed immune alterations characterized by a decreased ability to react to challenge with specific antigens. Clapp suggested that these findings indicate an association between long-term exposure to dioxin and depressed cell-mediated immunity. (Clapp *et al. 1990)*

Clapp also reported a study of 48 children from Seveso, Italy who were heavily exposed to dioxin. Their lymphocyte responses to selected allergens were significantly higher than the controls. (Clapp *ET al, 1990)*

Malignancy is one possible outcome of chemical and viral immunosuppression. Higher rates of sarcomas and non-Hodgkin's lymphoma have been previously reported in seriously immunodepressed individuals such as AIDS patients and renal transplant patients. *(Zahm,1988)*Hardell reported a significantly increased rate of soft-tissue sarcomas in

populations exposed to dioxins in a case-control study. *(Hardell 1990)* A panel of scientists has recently reported a statistical association between TCDD contaminated Agent Orange exposure and the development of non-Hodgkin's lymphoma, soft-tissue sarcoma, chloracne and other skin disorders; early liver disease and porphyria cutanea tarda, a metabolic disorder in Vietnam veterans. (AOSTF *Report* 1990)

The Agent Orange panel also said there was enough evidence to suggest an association between Vietnam veterans' TCDD exposure and the development of Hodgkin's Disease, neurological and psychological problems, immunological abnormalities, a large number of cancers, reproductive difficulties and developmental problems in the veterans' children *(AOSTF Report 1990)*

Epidemiological surveys have reported an association between paternal TCDD exposure and increases in several categories of birth defects in children including neural tube defects, heart defects and oral clefts. The Ranch Hand Study reported a doubling of birth defects in the children of Agent Orange exposed veterans. *(Ranch Hand 1986)* None of these studies, however, has measured the prenatal effects of TCDD which may be the most prevalent in veterans' children, i.e. the effects of TCDD on the development of the immune system.

A report by the National Information System for Vietnam Veterans at the University of South Carolina has analyzed developmental disabilities in over 1,500 children of Vietnam veterans' served by the project to date. The most commonly reported conditions can be grouped into the area of immune response disorders including persistent skin rashes, multiple allergies, infections, chronic fevers, asthma, attention deficit disorders and learning disabilities. *(Smith 1990)*

This apparent pattern of skin and immune system disorders seems consistent with information gained from animal models indicating that the skin and immune system are target organs for TCDD. Even the reported increases in learning and attention problems can be related to possible immunological dysfunction.

A 1987 report to Congress on learning disabilities stated that research on the prenatal immune system may be important for understanding learning disabilities because of evidence in animals that prenatal immune disorders can affect brain development and result in behavior comparable to what is observed in learning disabled children. *(LD Report to Congress 1987)* In separate and collaborative studies, Galaburda and Geschwind have postulated a relationship between diseases of the immune system and learning disabilities. *(Galaburda 1985,* Geschwind 1985) Lahita has reported that 35% of the male offspring of mothers who suffer from the autoimmune disorder lupus have forms of learning disabilities or cognitive problems like stuttering, delayed speech or autism. Lahita said that this was the first study to show that learning and cognitive problems in children may be linked to both the development of the immune system and to intrauterine effects. *(Lupus Footnotes 1989)*

Pesticides - The category pesticides includes insecticides, herbicides and fungicides. Since "cide" means to kill, it is readily apparent that these agents are lethal to various forms of life -- insect, plants and fungi. That this lethality may also extend to humans is becoming increasingly apparent especially in the area of damage to the immune system. Symptoms of a pesticide-

weakened immune system include: skin rashes, nausea, fatigue, depression, leukemia, frequent infections and fever.

The most immediately noticeable immune reaction to pesticide exposure is an increase in allergic reactivity often including multiple chemical hypersensitivity. People whose immunity is suppressed by pesticides may also be unable to fight off viral infections or may experience a reactivation of one or more of the herpes viruses. Immunological studies reveal that pesticide-exposure can cause a decrease in the number of B and Tcells. The ratio of T-4 to T-8 helper cells is often reversed similar to the immune abnormalities found in AIDS patients. *(Legro 1988)*

In Australia, approximately 400 of the 16,000 people who have been diagnosed with Chronic Fatigue Immune Dysfunction Syndrome (CFIDS) have been tested and found to have excessively high levels of chemical residues including pesticides in their bodies. *(Austin 1989)*CFIDS involves a pattern of symptoms including viral reactivation, immunological abnormalities, extreme fatigue, headaches, neurological and cognitive dysfunction, chronic sore throats and lymph node enlargement, muscle and join pain, neuritis, depression and mood swings and chronic infections.

The rate of cancers - non-Hodgkin's lymphoma, leukemia and testicular cancer is also increased in pesticide-exposed agricultural workers and their children. A recent study has also shown that children risk a higher incidence of acute leukemia if their parents use pesticides in the home or garden. *(Moses 1988)*

Pesticides may also be teratogenic to the developing fetus. A California study has reported a statistically significant increase in limb-reduction deformities in the children of mothers who lived in areas of high pesticide exposure. *(Schwartz 1988)* Two large chemical companies recently paid an out-of-court settlement to the family of a child born without any arms or legs. The mother had been exposed to teratogenic pesticides while working in the grape fields during pregnancy. *(Moses 1988)*

A body of research is growing daily to suggest that many other environmental agents in addition to those discussed in this paper can have adverse effects on the human immune system. Since many of these substances are ubiquitous in our environment, we would expect an epidemic of immune disease, cancer and birth defects. There is some evidence to believe this may already be happening. One in every three Americans will develop cancer in their lifetime. As many as twelve million Americans are estimated to have Chronic Fatigue Immune Dysfunction Syndrome. Over 15% of all children suffer minor or major birth defects according to the largest epidemiological study to date. It has also been reported that the birth defect rate has doubled in the last twenty-five years.

Yet, it is also clear that not everyone who is exposed to one of these potentially toxic agents will have an adverse outcome. There are obviously co-factors which can enhance the immunotoxic and teratogenic effects of xenobiotics. In an environmental health primer *(Enviro-Health Primer)* for seven counties in Florida, information is listed about suspected groups who may be

at high risk when exposed to environmental pollutants due to developmental processes, genetic conditions, nutritional deficiencies, diseases and behavioral activities.

Differences in genetic susceptibility are particularly important. For instance, the primer reports that among people of European ancestry, there are about 1 in 1,250 who are highly sensitive to the adverse effects of the broad category of anticholinesterase insecticides. Genetic vulnerability to hazardous chemicals has even become a condition for employment in the chemical industry which has been requiring genetic screening for such effects for the past fifteen years. *(Help Almanac 1981)*

Nutritional deficiencies may be another key co-factor. Children with vitamin A deficiency are more susceptible to the effects of DDT, hydrocarbon carcinogens and PCBs.

10% of women and 5% of men aged 30 to 60 who are deficient in dietary protein are at greater risk when exposed to DDT and other insecticides. *(Enviro-Health Primer)*

The teratogenic effects of environmental immunotoxins may also be modulated by genetic factors and diet. For instance, an animal study of the pesticide Dinoseb clearly showed that its teratogenic effect is correlated to the quality of the diet. *(Giavini et al,* 1989) Other research has suggested that susceptibility to the neurotoxic effects of thalidomide may be genetically determined. *(Kremer 1961)*

The prenatal and neonatal periods are characterized by immunoincompetence. Any toxic interference with the delicately balanced immune system during this period may have major consequences, much more so than in the adult. *(Shoham 1986)* Current research confirms that many immunotoxic agents also have teratogenic potential. One possible teratogenic outcome from prenatal exposure to immunotoxins may be impairment in the development of the immune system. This possible teratogenic outcome has not been addressed to any extent in current research nor has such an outcome been measured in any epidemiological studies of suspected immunotoxins to date. Since the consequences of immune incompetence include such serious outcomes as cancer, chronic illness, severe allergies and learning disabilities, it is critical that the new field of developmental immunotoxicology addresses these important issues as quickly as possible.

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