

CHAPTER 6

TOXICITY TO THE IMMUNE SYSTEM: A REVIEW

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1. INTRODUCTION

Immunotoxicology is defined as the study of events that lead to undesired effects as a result of interaction of foreign substances (e.g., xenobiotics) with the immune system. Toxic responses might arise when the immune system either (1) acts as a passive target of chemical insult, leading to a relatively broad-spectrum loss or potentiation of function; or (2) responds to the antigenic specificity of the chemical as part of a specific immune response. In the latter instance, a more limited population of antigen-specific immune cells is the initial target of the chemical interaction, with the potential for toxic responses to occur (e.g., in the skin or lungs), subsequent to the specific interaction between the chemical antigen (hapten) and host antibody or sensitized cells.

Chemically induced toxicity involving the immune system as the target may result in an increased incidence of infectious disease, the development of neo-

Abbreviations used in this chapter: AB, antibody; CMI, cell-mediated immunity; Con A, concanavalin A; CSA, cyclosporin A; CTL, cytotoxic T lymphocyte; CY, cyclophosphamide; DBCT, di-*n*-butyltin dichloride; DES, diethylstilbestrol; DOTC, di-*n*-octyltin dichloride; DTH, delayed-type hypersensitivity; ELISA, enzyme-linked immunosorbent assay; GVH, graft versus host; HMI, humoral mediated immunity; Ig, immunoglobulin; IL-1, interleukin 1; IL-2, interleukin 2; M ϕ , macrophage; MLR, mixed leukocyte response; MTD, maximum tolerated dose; NK, natural killer (cell); PBB, polybrominated biphenyls; PC, plasma cell; PCB, polychlorinated biphenyls; PFC, plaque-forming cell; PG, prostaglandin; PGE₂, prostaglandin E₂; SRBC, sheep red blood cells; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

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377

plasia, or autoimmune effects associated with immune dysregulation. The health consequences of exposure to chemicals that the immune system responds to as "nonself" (i.e., hypersensitivity) may be, *inter alia*, respiratory tract allergies to the specific substance (e.g., asthma, rhinitis) or allergic contact dermatitis to that substance, or autoimmune diseases in which the foreign substance modifies the host's tissue. Immunotoxicology is concerned with the identification and quantification of the components described above and with assessment of their importance in terms of human or animal health. In recent years, the science of toxicology has expanded along organ- or system-specific lines, to which are added studies on particular hazards.

The immune system is a highly regulated network of lymphoid cells requiring continued renewal, activation, and differentiation for full immunocompetence. The functions of the immune system include discrimination of self from nonself and defense against infectious micro-organisms and spontaneously arising neoplasia. Cell depletion, dysregulation, and functional deficits within this cellular network can result in a pathological process marked by altered responses to self- and nonself-antigens or increased susceptibility to infectious agents and tumor cells. It can therefore be easily appreciated that the immune system may be a frequent target organ for cytotoxic drug and nondrug chemicals. A large number of diverse compounds or their metabolites possess the capacity to induce autoimmunity or allergic responses in susceptible individuals (e.g., diisocyanates, penicillamine) (Table I). Conversely, immunosuppression has been well documented to occur following exposure of humans or animals to a wide range of chemicals (Table II), including inorganic pollutants, halogenated and nonhalogenated aromatic hydrocarbons, and therapeutic agents. Although several chemicals of occupational or environmental concern have produced immune modification in rodents and are suspected of producing similar effects in humans, in most cases rigorous clinical confirmation of altered immunological responsiveness is incomplete. Immunomodulatory activity (i.e., immunosuppression or immune enhancement) has been beneficially exploited in the development of anti-neoplastic agents and so-called biological response modifiers (BRMs) proposed for immunotherapy of immune deficiency and certain types of neoplasia.

The distribution of mononuclear phagocytes and lymphocytes throughout the body requires that they cope with the many xenobiotics (e.g., physical agents, chemicals, and drugs) that enter through the skin, blood, digestive tract, or pulmonary system. During the past decade, numerous studies have shown that exposure of rodents to chemicals or drugs by dosing protocols that did not cause overt toxicity often produced immune alterations sufficient to result in altered host resistance to challenge with infectious agents or neoplastic cells (Dean *et al.*, 1982, 1986b; Faith *et al.*, 1980; Vos, 1977). For certain environmental agents, the relevance of many of these rodent exposure studies to human health effects awaits further investigation. In the case of such drugs as cyclophosphamide, methotrexate, or cyclosporin A, the immune effects seen in rodents were comparable to immune alterations observed in the clinic (Dean *et al.*, 1987).