Review article

Immunotoxicology: suppressive and stimulatory effects of drugs and environmental chemicals on the immune system

A discussion*

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Abstract. The fundamental characteristic of the adaptive immune system which has evolved in the vertebrates is the ability to recognise, and subsequently destroy, "foreign", and potentially harmful, antigens. The selective advantage which the immune system confers is the capacity to resist infectious, and possibly malignant, disease. It has been apparent for many years that individuals in whom immune function is impaired, due either to a congenital defect or to other factors such as treatment with certain immunosuppressive drugs, exhibit an increased susceptibility to infection and, in some cases, an elevated risk of developing at least some forms of malignancy. There is an increasing awareness from rodent studies that a variety of drugs and environmental chemicals have the potential to unintentionally impair components of the immune system. Risk assessment, based upon data from chemically induced changes in one or more parameters of immune function, is, however, dependent upon a knowledge of the functional reserve of the immune system. One of the objectives of the meeting from which this report derives was to examine what sources of information are available, and what experimental protocols can be employed, to permit accurate evaluation of immunological reserve. Although, under normal circumstances, the immune system selectively and specifically recognises foreign antigen, it is clear that the potential to recognise "self" is present and that in certain circumstances this potential is realised. Antibodies directed against normal tissue antigens have been shown to be associated with, and in some instances the presumptive cause of, "autoimmune" disease. There is a growing list of drugs and chemicals which are capable of eliciting autoantibodies and pathological autoimmune reactions. A second purpose of this meeting and of this report was to review the current state of knowledge regarding drug- and chemical-induced autoimmunity.

Key words: Autoimmunity—Environmental chemicals—Drugs—Immunosuppression—Immunostimulation

Introduction

There is a growing awareness that a variety of chemicals have the potential to influence the functional activity of
the immune system. Induced changes in immunological status can be broadly divided into those in which immune function is impaired and those in which tissue-damaging allergic or autoimmune responses are initiated. The purpose of the meeting from which this report is derived was two-fold, firstly to examine what sources of information are available for determining the relationship between impairment of immune function and altered host resistance to infectious and/or malignant disease, and secondly to explore the current state of knowledge regarding the potential of drugs and chemicals to induce autoimmunity.

Chemically-induced impairment of immune function

During the last decade the field of immunotoxicology has attracted considerable attention and there now exists substantial literature, a review of which reveals that a variety of chemicals are able to impair the functional integrity of the immune system of rodents. Evaluation of the toxicological significance and human health implications of data obtained from experimental studies in rodents requires, however, a careful consideration of a number of factors. From a purely practical point of view it is relevant to consider whether there exist chemicals which, under certain conditions of exposure, are selectively immunotoxic, and would therefore escape detection in routine toxicological analyses. Although it is not unreasonable to suppose that selective immunotoxins exist, there are few examples in the literature. It is also pertinent to address the question of whether perturbations in immune function are reversible, and here again little information is available. Perhaps the major problem posed by experimental immunotoxicity studies is the relevance of quantitative or qualitative changes in one or more components of the immune system to the functional activity of the integrated mechanisms of host defence and the ability to resist infection and malignant disease. Of direct relevance to the relationship between empirical observations of dysfunction following chemical exposure and the integrity of host defence mechanisms is the extent to which the immune system possesses a functional reserve. There are two avenues of investigation which might be expected to yield information of value in assessing the functional reserve of the immune system. Firstly, in experimental systems, it is possible to examine directly the relationship between chemically induced perturbations of immune function and the ability to resist challenge with transplantable tumours and/or pathogenic micro-organisms. A second, and in our opinion, currently under-valued, source of information is available from the clinical and laboratory examination of congenital and acquired immune deficiency disorders in man.

The immune system as a target for toxicity

The ability of an organism to respond to foreign material is phylogenetically ancient and can be traced back to the protozoa and coelenterates. Such mechanisms of host resistance clearly offer important evolutionary advantages and in man there exist a number of “natural” (non-specific) defence mechanisms, such as the action of scavenger phagocytic cells, which play an important role in resistance to infectious disease. In addition to such natural protective mechanisms there has, in the vertebrates, evolved an exquisitely sensitive adaptive immune system in which there is a specific recognition of, and response to, foreign antigens. The cardinal features of the mammalian adaptive immune system are memory, specificity and the capacity to distinguish between self and non-self. It is the lymphocyte which plays a pivotal role in adaptive immune responses and which exhibits the properties of antigenic specificity, immunological memory and the ability to distinguish foreign, and potentially harmful, antigens from those normally expressed in the organism. Lymphocytes are clonally distributed with respect to antigenic specificity and each clone of lymphocytes possesses a unique membrane receptor for antigen. On primary exposure to foreign material those clones of lymphocytes which express complementary membrane receptors recognise and respond to antigenic determinants. The response comprises both division and differentiation. The induced prolifera-

![Diagram of immune system response to antigen](image-url)