科技资料

Immunotoxicity of Metals and Immunotoxicology

International Programme on Chemical Safety (UNEP-ILO-WHO) • Commission of the European Communities • International Commission on Occupational Health • Federal Ministry for Environment, Nature Conservation and Nuclear Safety; Federal Health Office, Federal Republic of Germany

IMMUNOTOXICITY OF METALS AND IMMUNOTOXICOLOGY

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PLENUM PRESS • NEW YORK AND LONDON

Library of Congress Cataloging-in-Publication Data

Immunotoxicity of metals and immunotoxicology / edited by A.D. Dayan ... [et al.].
p. cm.
"Proceedings of an international workshop organized with the assistance of the Federal Health Office of the Federal Republic of Germany and the Fraunhofer Institute for Inhalation Toxicology and Aerosol Research held November 6-10, 1989, at the Fraunhofer Institute and the Medical High School, Hanover, Federal Republic of Germany"--T.p. verso.
Includes bibliographical references and index.
ISBN 0-306-43679-5
1. Immunotoxicology--Congresses. 2. Immune system--Effect of metals on--Congresses. I. Dayan, Anthony D. II. Germany (West). Bundesgesundheitsamt. III. Fraunhofer-Institut für Toxikologie und Aerosolforschung (Hannover, Germany)
RC582.17.I45 1990
616.97'071--dc20 90-14178
CIP

Proceedings of an international workshop organized with the assistance of the Fraunhofer Institute for Inhalation Toxicology and Aerosol Research and the Hanover Medical High School, held November 6–10, 1989, in Hanover, Federal Republic of Germany

Publication No. EUR 12764 (EN) of the Commission of the European Communities, Scientific and Technical Communication Unit, Directorate-General Telecommunications, Information Industries and Innovation, Luxembourg

International Programme on Chemical Safety, IPCS Joint Symposia, No. 15

ISBN 0-306-43679-5

Plenum Press is a division of
Plenum Publishing Corporation
233 Spring Street, New York, N.Y. 10013

Printed in the United States of America

PREFACE

Considerable scientific and political interest has been expressed, paralleling public concern about the effects of chemicals on the immune system and the implications of those effects for health. Coupled with speculation about the magnitude and extent of the problem is discussion of needs for predictive testing and regulatory control measures.

The first international seminar on the immunological system as a target for toxic damage was held in Luxembourg in 1984. It was organized by the International Programme on Chemical Safety (United Nations Environment Programme-International Labour Office-World Health Organization) and the Commission of the European Communities with the support of the US Environmental Protection Agency and the National Institute of Environmental Health Sciences (USA) and the participation of the International Society of Immunopharmacology. In view of the perceived importance of immunotoxicity, it was considered necessary to organize a follow-up meeting.

Thus, an international workshop on the immunotoxicity of metals and immunotoxicology was held in Hanover, Federal Republic of Germany, on 6-10 November 1989. It was organized jointly by:

- the International Programme on Chemical Safety - a cooperative programme of the United Nations Environment Programme, the International Labour Office and the World Health Organization
- the Commission of the European Communities' Health and Safety Directorate
- the International Commission on Occupational Health, through its Scientific Committee on the Toxicology of Metals
- the Federal Ministry for Environment, Nature Conservation and Nuclear Safety, Bonn
- the Federal Health Office of the Federal Republic of Germany, Berlin (West) and
- the Fraunhofer Institute for Inhalation Toxicology and Aerosol Research, Hanover.

The workshop took place at the Fraunhofer Institute and the Medical High School in Hanover. There were 100 participants drawn from 18 countries, with a range of scientific backgrounds, who were able to share experience and opinions.

In risk assessment of chemicals, the focus was initially on acute clinical toxicity, but the effects that may occur at lower doses, such as some of the immune-mediated effects, have more recently been of increasing concern. This workshop represented the first systematic coverage of immune-related effects of metals and their compounds. The objectives of the workshop of which this volume is the proceedings were to:

(i) review and evaluate data on metal-induced effects on the immune system in humans and animals, including autoimmune phenomena and immunologically induced hypersensitivity,

(ii) compare data on the effects of the same chemical in humans and experimental animals,

(iii) review the results of monitoring for effects on the immune system of metals in human populations,

(iv) review the current status of predictive test methods for effects on the immune system, and

(v) review histopathological changes in the immune system in experimental animals following exposure to chemical immunotoxicants and their relevance for predicting risk in human populations.

At the workshop, 29 formal presentations stimulated detailed discussions in plenary sessions and led to the formation of ad-hoc working groups. Some of these examined and discussed histopathological material and slides and new techniques that have been developed for evaluating the histopathology of the immune system. Reflecting the priorities identified, the working groups reviewed the immunotoxicology of metals, including hypersensitivity, autoimmunity, human studies and monitoring, and predictive testing. The members of the workshop concentrated on the need for defining dose-effect, dose-response relationships for metals and metallic compounds that induce immunologically mediated effects, and discussed the value of screening/predictive tests in rodents as well as the requirements for conducting appropriate epidemiological studies.

The conclusions and recommendations of their discussions are contained in the report of the workshop.

Many people assisted in the work associated with the organization and running of the workshop, in addition to those who contributed papers, and we are grateful to all of them for a most successful cooperation which brought together an impressive interdisciplinary spectrum of knowledge. Finally, the local organization at the Fraunhofer Institute and Medical High School provided a firm basis for successful international cooperation in a field of science of growing importance.

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LIST OF ABBREVIATIONS AND ACRONYMS USED

AHTR, autoimmune hypersensitivity-type response
AIDS, acquired immunodeficiency syndrome
ALN, auricular lymph node
ALNA, auricular lymph node assay
ANA, antinucleolar antibody
BAL, bronchoalveolar lavage
BN, Brown-Norway
BSA, bovine serum albumin
CBD, chronic beryllium disease
CBETC, bis(ß-carbobutoxyethyltin) dichloride
ConA, concanavalin A
CY, cyclophosphamide
DBTC, di-*n*-butyltin dichloride
DETC, di-*n*-ethyltin dichloride
DHR, delayed hypersensitivity reaction
DHTR, direct hypersensitivity-type response
DMTC, di-*n*-methyltin dichloride
DNCB, dinitrochlorobenzene
DOTC, di-*n*-octyltin dichloride
DTH, delayed-type hypersensitivity
EDTA, ethylenediaminetetraacetic acid
ELISA, enzyme-linked immunosorbent assay
GBM, glomerular basement membrane
GN, glomerulonephritis
GPMT, guinea-pig maximization test
GVH, graft-*versus*-host
ICGN, immune complex glomerulonephropathy
IDDM, insulin-dependent diabetes mellitus
IFN, interferon
Ig, immunoglobulin
IL, interleukin
KLH, keyhole limpet haemocyanin
LPS, lipopolysaccharide
LTT, lymphocyte transformation test
MEST, mouse ear swelling test
MGC, minimal glomerular changes
MGP, membranous glomerulopathy
MHC, major histocompatibility complex
MIF, migration inhibition factor
MLR, mixed lymphocyte reaction
NK, natural killer
NOD, non-obese diabetic
OS, obese strain
PALS, periarteriolar lymphocyte sheath
PCA, passive cutaneous anaphylaxis
PCA, plaque-forming cell assay

PFC, plaque-forming cells
PHA, phytohaemagglutinin
PLN, popliteal lymph node
PLNA, popliteal lymph node assay
PPD, purified protein derivative
PUFA, polyunsaturated fat
PWM, pokeweed mitogen
RAST, radioallergosorbent test
SAFA, saturated fat
SAT, sodium aurothiomalate
SLE, systemic lupus erythematosus
SRBC, sheep red blood cells
STZ, streptozotocin
TBM, tubular basement membrane
TBTC, tri-*n*-butyltin chloride
TBTF, tri-*n*-butyltin fluoride
TBTO, bis(tri-*n*-butyltin) oxide
TCDD, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin
TCR, T cell receptor
Th, T helper
TMA, trimellitic anhydride
TNF, tumour necrosis factor
TPhTA, triphenyltin acetate
TPhTC, triphenyltin chloride
TPhTH, triphenyltin hydroxide
TPTC, tripropyltin chloride
Ts, T suppressor
Ts-Ab, antibody suppressing T cells
VAA, vitamin A acetate

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INTRODUCTION

IMMUNOTOXICITY OF METALS AND IMMUNOTOXICOLOGY

Report of an International Workshop held in Hanover, Federal Republic of Germany on 6-10 November 1989

INTRODUCTION

Immune response has been recognized, but not understood, for centuries. The role and function of the immune system in response to infection was perceived approximately a century ago. The hypersensitivity reaction was understood at the beginning of this century, but the recognition of autoimmune disease is comparatively recent, dating from the mid-1950s. The explosion of knowledge of the structure and function of the immune system owes most to the introduction of organ transplantation, which started, on a practical basis, at much the same time. It was found that the immune system could be modulated as a whole or in parts by chemicals used therapeutically. Observations that some non-therapeutic xenobiotic chemicals also had immunomodulatory properties raised interest in the potential risk that many biologically active chemicals might have direct primary or secondary effects on the immune system or that the system itself might mediate toxicity in other systems and organs.

The effects of chemicals, including drugs, on the human immune system are of interest to international organizations, governmental authorities, clinicians, occupational health professionals, pathologists, immunologists, toxicologists, industries, workers, consumers and other interest groups. In risk assessment of chemicals, the focus was initially on acute clinical toxicity, but effects that may occur at relatively low doses, including several of those mediated by the immune system, have become of increasing concern. Although many chemicals have been shown experimentally to cause disturbances in components of the immune system, the mechanisms and their clinical significance are not well understood. The current status of predictive testing in animals and humans for immunotoxic effects *in vitro* and *in vivo* indicates that further methods and techniques for evaluation of test results must be developed. The use of immunological assays in the monitoring of the health status of populations should be pursued and developed.

The Workshop participants discussed the following topics:

(i) the immune system and immunotoxicology,

(ii) immunotoxicity of metals,

(iii) hypersensitivity induced by metals,

(iv) autoimmunity,

(v) studies of effects on the human immune system of occupational and environmental exposures to chemicals, and

(vi) laboratory investigations of immunotoxicity.

Immunotoxicity of Metals and Immunotoxicology, Edited by A. D. Dayan *et al.*, Plenum Press, New York, 1990

THE IMMUNE SYSTEM

The primary function of the immune system is to protect the organism against infection. The development of immunology followed the observation that certain infections and molecules, perceived as foreign, confer a highly specific immunity to reinfection, an observation utilized by Jenner some 200 years ago to introduce vaccination against smallpox. The normal immune response is characterized by its memory, by which a subsequent challenge with a specific stimulus provokes a more vigorous but well regulated response. The cellular and molecular basis for these characteristics has unfolded progressively over the past thirty years.

The immune system is a dynamic and complex organ system which can be the target of chemically induced toxicity. The discipline of immunotoxicology deals with toxic manifestations resulting from chemical interaction with the immune system. Since the discipline is in its infancy, its terminology is still evolving. Clear definitions and standardization of terms (e.g., hypersensitivity, immunotoxicant, immunoenhancement) are essential to facilitate interaction and to avoid confusion among the diverse groups of scientists working within the discipline.

In addition to the inherent interactions between components of the immune system, there is also interplay between these components and those of other organ systems. Neuroendocrine interactions with the immune system are increasingly recognized as important in delineating primary and secondary immunotoxic effects of chemicals.

Immunotoxic effects of chemicals may also depend upon the immunogenetic make-up of the host; this is well established in studies in laboratory animals. Variation in susceptibility to chemical immunotoxicity observed in outbred animals and humans may thus, in part, be due to genetically based differences. Certain species and strains of laboratory animals, for example, are predisposed to developing autoimmune responses following exposure to specific chemicals. In humans in whom environmental agents induce autoimmune responses, an association with a specific major histocompatibility complex (MHC) haplotype has been described in some cases.

The uniqueness of the immune system relative to other organ systems as a target for chemical toxicity starts with the antigen component, which is required to elicit an immune response. This requirement imparts an additional level of complexity in designing immunotoxicity studies. Assessment of chemically mediated immunotoxicity cannot be based upon any single morphological or functional parameter; however, since it is not practical to evaluate all immunologically relevant parameters in a single toxicity or immunotoxicity study, the challenge facing immunotoxicology is to identify the most important predictive parameters and to suggest a practical approach to assessing immunotoxicity. The problem is further complicated by the immunological redundancy and/or reserve which may be characteristic of the immune system and which may be an important determinant of response following exposure to immunotoxic chemicals. Further understanding of the concepts of redundancy and reserve is required, particularly in relation to the extrapolation of experimental data on immunotoxicity to humans. Molecular methods, including the use of gene probes (e.g., for measuring lymphokine/cytokine mRNA) may also provide a means for the early identification of suspected immunotoxic effects of chemicals.

IMMUNOSUPPRESSION

Disordered function of the immune system can give rise to increased susceptibility to infection, to neoplasia, to a variety of hypersensitivity states and to autoimmune disease. Increased susceptibility to infection and certain forms of neoplasia are a consequence of immune system suppression, while hypersensitivity reactions result from excessive stimulation; autoimmune disease may involve elements of both stimulation and suppression of the immune system. The realization that the immune system can be both stimulated and suppressed by chemicals, drugs and environmental chemicals led in the last decade to the rapid development of immunotoxicology. Potentially immunosuppressive chemicals may be encountered in the general environment in the form of pollution, as food contaminants and

as a result of occupational exposure. In humans, a congenital deficiency of B lymphocytes, and hence of plasma cells, gives rise to agammaglobulinaemia and failure to produce antibodies against common bacterial infections. A deficiency of immunocompetent T lymphocytes, as in thymic aplasia, increases susceptibility to infection with microorganisms to which normal individuals are resistant and to a rapidly fatal outcome following infection with common viruses such as measles and chicken pox. The highly complex immune system may be impaired by a variety of extraneous factors, including certain viral infections and chemical agents. The retrovirus, human immunodeficiency virus, by its effect on CD4+ T lymphocytes gives rise to deficient cellular immunity manifested by a variety of opportunistic infections seen in acquired immune deficiency syndrome (AIDS). Studies of this virus have provided fresh insights into the functioning of the immune system. Although infectious agents are often implicated in the etiology and pathogenesis of autoimmune disease, available circumstantial data point to the likelihood that environmental chemicals may well be another set of important etiological factors in these complex disorders.

Immunosuppression has been induced with a variety of chemotherapeutic agents to enable the grafting of tissues and organs into genetically dissimilar hosts; however, such drugs suppress not only the immune response to the graft but also other immune responses. Cytotoxic drugs used in the treatment of cancer and ionizing radiation also give rise to immunosuppression. Transplant recipients who have been immunosuppressed have an increased incidence of certain cancers, in particular of lymphomas; and secondary cancers are also more common in patients treated with cytotoxic drugs.

HYPERSENSITIVITY

Immune responses, while designed to protect the individual against infection, are not always beneficial. An immune response may be inappropriate and excessive, giving rise to tissue damage. This may manifest as a type-I immediate hypersensitivity reaction, presenting commonly with urticaria, conjunctivitis, rhinorrhoea or bronchial asthma or rarely with anaphylactic shock, following exposure, for example, to insect bites, pollens, animal danders or house dust. Atopic subjects, prone to develop type-I hypersensitivity reactions, often have a family history of such disorders, although genetic factors can come into play only following the exposure to the environmental or occupational stimulus. Another common presentation is cell-mediated or delayed, type-IV hypersensitivity, manifesting with skin reactions following a variety of infections or skin contact with a wide variety of chemical agents encountered in plants, hair dyes, some drugs and in the working environment. Less common are hypersensitivity reactions characterized by cytotoxicity (type II), for example, when haemolytic anaemia, agranulocytosis or thrombocytopenia follows the administration of certain drugs. Also less common are immune complex-mediated reactions (type III) seen, for example, in allergic alveolitis, serum sickness and in some forms of glomerulonephritis.

The classification of hypersensitivity reactions as types I-IV, with reference to clinical criteria or experimental animal models, is still useful. More than one type of reaction could be manifested concomitantly, consistent with different, co-existing immune changes, all being part of a complex interaction of factors.

A number of laboratory methods are used to identify low-molecular-weight chemicals with potential to induce contact hypersensitivity reactions. Progress is being made in developing models to predict which chemicals are likely to induce anaphylactic responses after inhalation.

The guinea-pig is commonly used as an experimental animal for eliciting potential delayed-type hypersensitivity reactions, but testing is also carried out in mice. The latter include ear swelling tests and induction of lymphocyte proliferation. The advantage of the murine local lymph node assay for detecting contact allergens is its endpoint: this avoids the irrelevance of irritation or colour of the test compound. The popliteal lymph node assay (PLNA) in rodents is a possible screening test for identifying sensitizing chemicals. Recent screening of a wide variety of drugs and chemicals in the PLNA has revealed a good correlation with their potential to cause systemic autoimmune disease and contact dermatitis in humans. Predictive tests for the sensitizing chemicals as inhaled or ingested

allergens are being developed. Fundamental studies of suppressor cells and tolerance induction and of modification of metals by antigen-presenting cells are under way.

Procedures for studying hypersensitivity in humans are of two kinds - those which involve the individual directly, i.e., in-vivo testing, and procedures performed *in vitro* on donated blood samples. It is not possible at present to predict susceptibility to a primary immune response. Positive results indicate that sensitization has taken place, so that provocation testing is *a posteriori* in nature. Provocation tests include skin prick and scratch tests to evaluate type-I immediate hypersensitivity reactions, and patch tests in the evaluation of type-IV delayed hypersensitivity reactions. In addition, nasal challenge and bronchial inhalation tests are used in provocation testing for type-I hypersensitivity reactions. However, such testing procedures may enhance existing sensitization or even initiate sensitization. Patch testing with beryllium sulfate provides a good example of enhancement. In-vitro testing procedures include assay of histamine release from basophils and estimation of specific immunoglobulins, in particular specific IgE. Macrophage migration inhibition and lymphocyte transformation tests, however, can give both false-negative and false-positive results.

AUTOIMMUNITY

Immune responses can give rise to serious adverse health effects as a result of an autoimmune reaction. Here, the immune response is directed against one or more of the body's own constituents, with the formation of autoantibodies and unsuppressed autoreactive T cells. A wide spectrum of disease states may result, ranging from organ-specific diseases such as primary thyroiditis with myxoedema and type-I diabetes to non-organ-specific disorders, for example, systemic lupus erythematosus with widespread lesions and complex autoantibody formation. There appears to be an inherent predisposition for the development of autoimmunity; genes both linked and unlinked to the MHC are important.

The microsomal cytochrome P450 mono-oxygenase enzyme system, its possible involvement in the induction of autoimmune reactions and its possible role in the prediction of adverse immune reactions are also important.

Experimental data indicate that cytokines play critical roles in the pathogenesis of autoimmune diseases, but it is not clear what constitutes the initiating event for the induction of autoimmune disease. In experimental animal models, there is evidence that the T-cell cytokine interleukin 4 (IL-4) plays a rôle in the activation of autoreactive B cells through the induction of increased expression of class-II MHC antigens and consequent B-cell hyperactivity with increased production of IgE. Delineation of the role that interferon gamma (IFNγ) may play in the activation of autoreactive helper T cells, through the induction of aberrant expression of class-II MHC antigens on a target organ, was proposed for two examples of organ-specific autoimmunity (i.e., autoimmune thyroiditis and insulin-dependent diabetes mellitus). Comparisons between the experimental autoimmune models and human autoimmune diseases show a good correlation in the role that cytokines play in the progression of these diseases. There are possible exploratory and therapeutic applications (e.g., the use of anti-cytokine antibody) derived from an understanding of the role that cytokines play in autoimmune diseases.

Thus, experimental allogeneic diseases represent interesting tools for investigating the rôle of T cell-derived or macrophage-derived cytokines in the triggering of autoreactive B cells and for studying the effects of cytokine synergism or antagonism. These models may be particularly relevant for understanding autoimmune phenomena in humans.

IMMUNOTOXICITY OF METALS

When a metal ion enters a biological system, it does not travel as free metal, but combines with small or large molecules, such as proteins. The strength of the binding and the structure or fold of the protein then determine the shape (stereochemistry) of the combination and the ability of the immune system to recognize the metal-altered compound as well as the nature of the response.

Metals may affect the immune system in several ways; several metals can induce immunosuppression in experimental situations, although the mechanisms involved have not yet been elucidated. They may bind to autologous (self) proteins (constituents) and render them immunogenic; this is probably the case in metal-induced contact dermatitis. Metals may also induce true autoimmune manifestations, such as gold-induced autoimmune nephritis. There is some evidence from experimental models that heavy metals initiate a polyclonal activation of B cells requiring the activation of CD4+ T cells. Additional mechanisms, such as inhibition of suppression, must be considered.

Some of these immunologically-related effects are observed only in susceptible individuals. Susceptibility is, both in humans and animals, under the control of genes linked to the MHC (class-II genes) and of genes located outside this complex (sulfoxydator status). Strain differences in susceptibility to metal-induced immunotoxicity have been observed in rodents. Few data are available on immunosuppressive effects of metals in humans, and limited studies on lead-exposed workers and children have provided contradictory results.

Immunosuppression

A number of immunosuppressive effects of various organotin compounds have been demonstrated in animals. Of special interest are the selective thymic effects. A rapid metabolism of trisubstituted organotin compounds to disubstituted compounds can be assumed on the basis of similarities of the observed effects on the thymus. Both dialkyl- and trialkyltin compounds exert cytotoxic and cytostatic effects on several cell types, including thymocytes. A series of tri-alkyl-substituted compounds of tin exhibited a progression in effects on the thymus gland, with maximal activity for the propyl and butyl analogues and minimal activity for shorter and longer chain derivatives. It is likely that this cytotoxicity is of importance as an early event in the development of the thymotoxic effects of organotin compounds. Effects on cytokines have also been observed and may be of importance in explaining the systemic immunotoxicity of organotin. Other studies in animals show immunosuppressive effects of lead, mercury, cadmium, cobalt and organotins (see Table 1).

Table 1. Examples of metals which in specific chemical forms give rise to immunotoxic effects

A. Effects on specific immunity	
1. Hypersensitivity reactions (humans and animals)	
Type I	Chromium, cobalt, nickel, platinum
Type II	Gold
Type III	Gold, mercury
Type IV	Beryllium, chromium, cobalt, gold, mercury, nickel, zirconium
2. Autoimmune reactions (humans and/or animals)	Gold, mercury
3. Enhancement (humans and/or animals)	Selenium, zinc
4. Suppression (animals)	Cadmium, cobalt, lead, mercury, tin (organotin)
B. Effects on nonspecific immunity (animals)	
1. Enhancement	Manganese
2. Suppression	Cadmium, lead, mercury