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Environmental Influences on the Immune System and Allergic Reactions

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Environmental interactions with the immune system may result in two types of adverse outcomes: immunodeficiency and immunopathology. Serious immunodeficiency most commonly results from ionizing radiation or as a recognized side effect of iatrogenic drug therapy, usually cancer chemotherapy. At present there is little basis for believing that biologically significant suppression of immune competence in man results from more subtle interactions with environmental agents. On the other hand, environmentally triggered immunopathology is a source of considerable morbidity and mortality. Additional research is needed in the following areas: (a) basic mechanisms of immunopathological reactions; (b) development of methods for accurately implicating or excluding immunological mechanisms in the etiology of hypersensitivity states; (c) development of methods for assessing in advance the potential immunogenicity of new industrial chemicals and occupational allergens; (d) identification of the risk factors which predispose to immunopathological outcomes when individuals are exposed to sensitizing chemicals or other "natural" allergens.

Introduction

The immune system allows an organism to discriminate "self" from "non-self." In a broad sense, an individual's environment may be defined as the sum of experiences which are "non-self." The immune system provides the individual with a specific memory of past environmental interactions. In addition, homeostatic effector mechanisms within the immune system protect the individual from potentially deleterious environmental interactions. These mechanisms are best understood with regard to the protective immunity induced by exposure to infectious agents. The immune system also provides a triggering mechanism for inflammatory processes which result in isolation and elimination of noxious foreign substances or damaged host tissue. It may also play an important role in constant surveillance for and elimination of neoplastic growths.

Environmental interaction with the immune system may result in undesirable effects of two principal types. If environmental hazards succeed in damaging the immune system functionally, a relative state of immunodeficiency may result. Immunodeficiency, if severe, can be life-threatening in that an important biological defense system is rendered inactive. Occasionally, the immune system, designed by evolution to be of overall benefit to the individual, is nevertheless capable of mediating harmful pathological processes. The particular circumstances which favor the development of self-destructive immunopathology are largely unknown. Whereas severe immunodeficiency states are uncommon, immunopathological processes are known or suspected to play a role in a large number of disease states.

This presentation attempts a limited review of significant aspects of environmentally-induced immunodeficiency and immunopathology. It does not attempt analysis of every conceivable environmental interaction with the immune system, but rather focuses upon interactions which meet three requirements: (1) the environment-immune system interaction is common enough to have potential impact on the public health; (2) there remain unanswered research questions of crucial importance to the development of solutions which may ameliorate the problem; and (3) the problem is not likely to be dealt with by other members of the Task Force.

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Effects of Environmental Agents on Immunologic Competence

Physical and Chemical Agents

It has been long recognized that appreciable doses of ionizing radiation may result in immunodeficiency states of various degrees. The effects of nonionizing electromagnetic radiation including microwave transmission are less well studied. At present there is no reason to suspect that the routine use of roentgenography in medicine or dentistry or radiation exposure from appliances such as color television sets and microwave ovens can induce significant states of immunodeficiency. This is not to say, however, that there are no undesirable biological effects resulting from these exposures.

Chemical toxins such as benzenes and toluenes can produce various degrees of bone marrow suppression which occasionally may be irreversible. Severe bone marrow aplasia is often accompanied by some degree of immunodeficiency, depending upon the age of the individual and the spectrum of bone marrow-derived cells affected. In most cases, the hemopoietic deficit is paramount and responsible in large part for the associated morbidity and mortality. Not all individuals are equally susceptible to the effects of such chemical toxins; the basis for susceptibility or resistance is unknown.

Drugs of a variety of types can induce immune-deficient states. The best examples of this are the antineoplastic drugs which possess generalized cytotoxicity, in which effects the cellular elements of the immune system share. In general, rapidly proliferating cells are affected to a greater degree, and long-lived small lymphocytes which carry immunologic memory may be relatively spared. The malignant process for which the drug is given is the chief concern. In patients "cured" by cancer chemotherapy, persistent immunological deficits are rare, suggesting that the immunodeficiency state is temporary. The same is true of patients given immunosuppressive drugs in order to render them tolerant to a homograft. In this case, some degree of immunological incompetency of the host is the desired effect achieved by drug administration.

In recent years, increasing use has been made of immunosuppressive drugs in perilous clinical disorders where chronic immunopathological mechanisms are suspected. Such disease states include rheumatoid arthritis and systemic lupus erythematosus, both commonly considered "autoimmune" diseases. It has recently become appreciated that excessive activity of a subset of lymphocytes whose normal function is to suppress or regulate the overall immune response may be an important mechanism in some "autoimmune" states, and in some immunodeficiency diseases as well. Immunosuppressive chemotherapy aimed specifically at this hyperactive lymphocyte population may be more extensively employed in future medical therapy.

The effects of immunosuppressive drugs on various arms of the immune system has been studied but the general basis for their efficacy is still poorly understood. For example, the role of partial immunosuppression in the beneficial antiinflammatory effects of high doses of corticosteroids is still unknown. In addition, antimicrobial drugs such as rifampin and amantadine, which were not designed to achieve immunosuppression, have, nevertheless, been found to have significant influences on immune competence. No doubt other drugs with unexpected side effects affecting the immune system will be developed in the future, and these may be of benefit in selectively altering immune capabilities in medical disease states where this may appear desirable. In general, however, drug effects on the immune system are routinely studied as part of the vigorous requirements for new drug applications. Whether drugs now commonly in use, including patent medications, are capable of altering immune capabilities in certain individuals has not been systematically evaluated, but currently there seems no reason to suspect that this presents a significant problem.

Increasing evidence raises the possibility that chronic, subclinical exposure to certain chemicals of environmental concern such as heavy metals and halogenated hydrocarbons may depress immune responsiveness and in some cases increase susceptibility to infectious agents in experimental animals (*1*). The relevance of these observations for human disease is currently unknown but deserves further exploration.

General Pollutants and Psychosocial Stress

Experimental studies of "dirty" environments using laboratory animals have failed to demonstrate any adverse effect of such environments on either the development of the immune system, its degree of competence, or the decline of immune capability with age (*2*). In fact, some animal studies have suggested that "dirty" environments actually facilitate antibody formation, presumably by some form of adjuvant effect (*3*). The influence on immune competency of social factors such as overcrowding and other types of psychological stress has been the subject of psychosomatic research (*4*). In general such research has shown that stressed animals are more

susceptible to a host of biological insults including infections and neoplasms. Whether these biological effects can be explained totally on the basis of impairment of immunological competence seems unlikely but warrants further study.

Research Needed

With regard to the ability of environmental agents to induce immunodeficiency, there are not, in the opinion of this author, general lapses in knowledge which warrant major project-directed efforts. We are aware that drugs, chemicals, ionizing radiation, and stress in sufficient quantity will impair immune function. This knowledge has been exploited in some medical circumstances to render beneficial effects. More subtle influences of environmental agents on immune capability, though quite conceivable and perhaps even likely, do not at this time appear to impair the biological fitness of most individuals. The resiliency of the immune system to environmental stress appears to be great, as might be expected since its principal evolutionary function is to protect the individual from environmental insults. Nevertheless, studies of the effect of chronic low-dose exposure to environmental agents on immune responsiveness should be pursued in carefully selected areas. Such areas include studies of physical and chemical agents, including drugs for which there is some indication of selective toxicity for the immune system, and evaluation of clinical states of increased susceptibility to infection or increased incidence of cancers of multiple origin where the possibility of environmental induction exists (e.g., "epidemics" of multiple infections or neoplastic diseases in industrial settings.)

Environmentally-Induced Adverse Immunological Reactions

Scope of the Problem

Immunopathological mechanisms contribute substantially to human mortality and morbidity. The circumstances under which the immune system can inflict pathological damage are myriad (*5*). The pathological process may be relatively organ-specific (e.g., allergic asthma, contact dermatitis) or multisystem (e.g., anaphylaxis, immune complex disease). Apparently, no tissue is entirely safe from immune-inflicted damage. Even the central nervous system and the anterior chamber of the eye, long thought to be relatively isolated from immunologically competent cells, now clearly can be the site of immunopathological damage. Which tissue or organ system is affected by immunopathological mechanisms depends upon numerous factors. Among these are the route of entry and distribution of the antigen, the metabolic state of the organism, overall immunological competence, and in many cases factors which have not been clearly identified.

Gell and Coombs (*6*) have proposed a classification of immunopathological mechanisms (see Table 1). This classification ignores much of what has been learned in recent years concerning the intricacies of the mechanisms, particularly the variety of mechanisms by which thymus-derived lymphocytes may inflict tissue injury. The classification also oversimplifies by omitting the complex interactions of these mechanisms which often amplify or attenuate one another. Rarely is one of these mechanisms operative in total isolation from the others. Nevertheless, the classification is useful didactically in categorizing the principal mechanisms now known by which the immune system can inflict injury.

A single environmental agent may be capable of initiating any or all of these mechanisms. A ready example of this is provided by allergic drug reactions. An immunological response against penicillin may result in anaphylaxis or urticaria (type I) in one patient, hemolytic anemia (type II) in a second patient, serum sickness (type III) in another, and contact dermatitis (type IV) in yet another patient. The variables that determine which pathological process is manifest in given individuals are poorly understood.

Furthermore, it becomes important to appreciate that, while an immune response to a foreign antigen is necessary, it is not in and of itself sufficient for the initiation of immunopathological processes. This is again well illustrated from studies of penicillin hypersensitivity (*7*). We now know that the vast majority of patients who receive penicillin drugs respond immunologically to the drug–protein complexes which normally form under physiological conditions; yet only a very small percentage of those who respond immunologically to penicillin administration exhibit any adverse reaction to the drug. There appear to be, therefore, individual risk factors, some of which are unrelated to the ability to engender an immune response against penicillin, which may be principal determinants of risk of immunopathological reactions to the drug. Except for the minimal influences of age and atopic status, the individual risk factors which predispose to penicillin allergy are unknown. Penicillin hypersensitivity provides our best studied example of sensitization by small molecular weight drugs and chemicals. With regard to other drugs, most industrial and oc-

Table 1. Classification of immunopathological reactions

Gell and Coombs type	Description	Mechanism(s)	Clinical examples
I	Anaphylactic hypersensitivity (reaginic allergy)	IgE mediated non-cytotoxic mediator release from basophilic leukocytes and tissue mast cells	Anaphylaxis Urticaria "Extrinsic" asthma Allergic rhinoconjunctivitis
II	Cytolysis or cytotoxic damage	Complement mediated injury involving antibodies (IgM and IgG) and any cell with iso-antigen	Rh hemolytic disease of the newborn Interstitial nephritis Some drug-induced cytopenias Goodpasteur's syndrome
III	Immune complex	Complement-mediated inflammatory response initiated by soluble antigen–antibody complexes (mainly IgG)	Serum sickness SLE nephritis Drug fever Some glomerulonephritis
IV	"Delayed" or cellular hypersensitivity	Injury directly (cytolysis) and indirectly (lymphokines) from sensitized small lymphocytes and macrophages	Contact dermatitis Tuberculin hypersensitivity Allograft rejection Tumor immunity

cupational allergens, and infectious agents little or nothing is known of the risk factors for immunopathology. This is in contradistinction to certain "natural" aeroallergens such as pollens, animal danders, fungi, and organic dusts where an inherited constitutional substrate commonly called "atopy" is a major but not the sole predisposing factor (*8*).

In summary, the problem of sensitivity to environmental agents is more complex from the point of view of preventive medicine than it initially appears. It is not, as originally assumed, simply a matter of identifying and minimizing exposure to those environmental agents which are immunogenic in man. Since only a small number of those patients who respond immunologically to an environmental agent will suffer any ill consequences from that encounter, it becomes necessary to focus upon the risk factors which predispose to actual immunopathology. These may be either environmental factors (e.g., the intensity and duration of exposure to the environmental agent) or individual risk factors endogenous to the organism (e.g., genetic factors controlling immune responsiveness, metabolic processing of antigen, and the "atopic" diathesis; coexisting disease states, metabolic aberrations, etc.).

Prototypes of Environmental Sensitization

Environmental agents which can sensitize individuals for allergic (immunologic) responses fall into two major categories. First, large molecular weight foreign protein or carbohydrate substances may initiate an immune response directly; these substances are usually immunogenic but only occasionally allergenic. Examples of "complete" antigens which are highly immunogenic in man include bacterial and viral antigens, heterologous antisera, and biological pollens and spores. Many known factors contribute to the degree of immunogenicity of these substances; these include dose and frequency of exposure, degree of immunological "foreignness" (not-self), genetic factors within the host controlling immune recognition and responsiveness, and intrinsic physical-chemical properties of the antigen itself (*9*). Prototypes of the sensitizing mechanisms for these "complete" environmental antigens include the classic studies of experimental serum sickness in animals (*10*); and in man, the well studied examples of IgE-mediated pollenosis (allergic rhinitis and asthma) (*11*) and the industrial case of sensitivity to bacterial enzymes formerly added to some detergents (*12*).

Simple chemicals of molecular weight less than 1000 are generally not capable of eliciting an immune response in and of themselves. Only those drugs and chemicals which are capable of covalent linkage to carrier molecules (usually proteins) are immunogenic. Classic studies done many years ago have established that those chemicals which can covalently link to and thus "haptenize" autologous protein in host tissue are capable of sensitizing the host (*13*). Furthermore, the frequency of sensitivity observed *in vivo* is directly correlated with the protein reactivity of a chemical as demonstrated *in vitro*. The prototype for the immunogenicity of simple chemicals in man is penicillin hypersensitivity, where considerable immunochemical and clinical information had been acquired (*7*).

Categories of Offending Environmental Allergens

A large number of natural and man-made substances are capable of offending the human organism in a variety of ways. In fact, it is difficult to think of any environmental substance which cannot be toxic or noxious under certain circumstances. Even essential elemental ingredients such as oxygen can be toxic. When an individual becomes sensitive to a substance which most others tolerate at the same dosage with impunity, we correctly refer to this as "hypersensitivity." "Allergy" is understood by many laymen and professionals alike to be synonymous with hypersensitivity. Because of this semantic equation, numerous hypersensitivity states have been presumed without evidence to be immunologic in origin.

Table 2 presents a partial list of environmental allergens capable of inducing adverse reactions which may be mediated by immunological mechanisms. There are a large number of substances, particularly drugs (e.g., aspirin), which can elicit reactions in susceptible patients which appear clinically to represent allergic responses, but which are quite likely to have other nonimmunologic mechanisms. Making a clear distinction between immunologic and nonimmunologic mechanisms for adverse reactions to environmental agents is important, since the prophylaxis of these reactions as well as their management may depend heavily upon such knowledge.

Many "natural" substances which are potential allergens are essentially ubiquitous. Although exposure to plant pollens, fungal spores, and pollutant organic dusts may vary considerably in various locations, there are few geographic sites where susceptible individuals can avoid exposure to allergenic substances altogether. Allergic reactions to some of these materials (particularly pollens, fungi, and foods) are clinically associated with the "atopic" trait. However, other important risk factors are clearly involved and require exploration. Adverse effects associated with immunological responses to infectious agents, especially viruses, are clearly established in certain cases (e.g., subacute sclerosing panencephalitis), and suspected as contributing factors in others (various demyelinating diseases, and systemic lupus erythematosus). Whether less severe and more subtle consequences of viral and bacterial infections (e.g., bronchospasm in association with intercurrent viral infections; and cutaneous eruptions associated with numerous infectious states) are immunologically mediated requires further study.

Table 2. Some environmental allergens capable of inducing immunopathological states

"Natural" allergens	
Aeroallergens:	pollens, animal danders, organic dusts, fungal spores, infectious agents
Contactants:	poison ivy (oleoresin), infectious agents
Injectants:	stinging insect venoms
Ingestants:	foods, infectious agents including parasites
Occupational allergens	
Bird fancier's lung (serum proteins in droppings)	
Hypersensitivity pneumonitis due to variety of organic dusts	
Molds and particulates (e.g., cotton fibers)	
Industrial chemical allergens	
Detergent enzymes	
Heavy metal salts	
Toluene diisocyanate (TDI)	
Phthalic acid anhydride	
Piperazines	
Exoxy resins	
Soldering flux	
Polyvinyl chloride (PVC) fumes	
Drugs, patent medicine, food additives, cosmetics	
Penicillins	
Cepholosporins	
Quinidine	
Sulfonamides	
Antituberculous drugs	
Local anesthetics	
Phenolphthalein	
Antithyroid drugs	
Insulin	
Photosensitizing chemicals	
Fragrance chemicals	
Preservatives and stabilizers	
Food additives	

Occupational and industrial allergens have been recognized with increasing frequency in recent years (*14*). Most commonly, these are aeroallergens and produce a pneumonitis usually designated extrinsic allergic alveolitis. Depending upon particle size and the intensity and duration of exposure, various organic dusts and their microorganismal flora can

stimulate an intensive immunological response in susceptible individuals. Most afflicted individuals have nonatopic backgrounds. The immunopathological mechanism is felt to be predominantly a type III, but the participation of a type IV process cannot be excluded. When extrinsic alveolitis occurs in atopic individuals, an additional IgE-mediated (type I) mechanism may also be of importance. In most of these disorders, the frequency of disease increases with increasing intensity of exposure, although other individual risk factors are clearly important. For example, still unexplained is why pigeon breeder's disease occurs in less than 5% of pigeon fanciers and why baker's asthma is a rarity among bakers.

Chemical allergens arising from industrial exposure usually inflict immunopathology upon only a small subset of workers who are hypersusceptible to the low dose exposure which is legally allowable in chemical plants. Since most immunological processes like toxicological ones are dose-related to some degree, it is not surprising that the establishment of maximum allowable concentrations to which industrial chemical workers can be legally exposed has resulted in significant reduction in morbidity. On the other hand, from 1 to 10% of industrial workers exposed to legally permissible levels of organic isocyanates will subsequently develop hypersensitivity reactions following low dose exposure to the chemicals (*15*). Similarly, a small group of highly susceptible workers becomes immunologically sensitive when exposed to numerous other industrial chemicals, including various synthetic resins, piperazine derivatives, penicillin salts, soldering fumes, heavy metal salts (especially platinum, beryllium, and chromium), industrial dyes, and many cosmetic and perfume ingredients (*16*). In almost all of these cases, it has been possible to identify a chemical which is highly protein-reactive and thought likely to be the principal offending allergen. When sensitized, many industrial workers cannot continue to tolerate even very low levels of further exposure. This has resulted in a considerable industrial medicine problem, one result of which has been an effort by industry to develop methods for identifying the hypersusceptible worker in advance (*17*). However, with very few important exceptions this has not yet become possible. Despite the absence of convincing evidence that an atopic background carries an increased risk of developing chemical sensitivity, it has become a common industrial practice to exclude such individuals arbitrarily from employment in industrial chemical industries.

Food preservatives and additives are clearly capable of inducing hypersensitivity reactions in susceptible individuals (*18*). Presently it seems doubtful that these are on the basis of immunologic reactions. However, additional study is needed not only of the mechanisms involved but of the susceptibility factors which predispose to these reactions.

Research Needed

Research on environmentally induced immunopathology must continue to be multifaceted. Where immunological mechanisms are implicated, the precise details of the pathological processes deserve exploration. Of greater short-range importance, however, would be the development of methods which would allow rapid assessment of whether a hypersensitivity reaction is mediated by an immunological mechanism. This becomes important in order to stimulate the search for alternative explanations in those cases of adverse reactivity where no immunological mechanisms can be implicated. As but one example, the study of aspirin sensitivity was long retarded by the unfounded assumption that the reactions were immunologic in origin. Now that this illusion has been removed, considerable progress is being made toward a better understanding of its biochemical basis.

For industrial and occupational hypersensitivity diseases, research efforts should be aimed at developing methods for predicting in advance the likely allergenicity of industrial chemicals so as to minimize from the very start worker and consumer exposure to these chemicals. Technical research is also needed to develop more effective and better tolerated methods of removing sensitizing chemicals from the inspired air of exposed employees. Considerable priority should also be given to identification of the individual risk factors which singly or collectively constitute the hypersusceptible state. It is now clear that immunological status (including an atopic background) is only one of numerous potential risk factors, and in most cases it may play a relatively minor role.

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