

Chapter 2

The Immune System and immunotoxicity

The Immune System and immunotoxicity

INTRODUCTION

Each day, the human body must defend itself against a battery of foreign substances (e.g., bacteria and viruses), as well as against elements from within (e.g., cancer cells). This protective capacity arises, for the most part, from our immune system, which can generally distinguish what is “self” from what is “nonself,” or foreign. The stark statistics of acquired immune deficiency syndrome (AIDS), for example, demonstrate the importance to human health of an appropriately functioning immune system.

The immune system is a complex, highly regulated, cooperative effort among several types of cells, cell products, tissues, and organs. It is not an isolated system, but operates in concert with other systems within the body (e.g., endocrine, central nervous, and cardiovascular). Any particular stimulus to the immune system results in a complex series of events, and any single response can have a number of consequences. Similarly, perturbations that primarily affect other body systems can cascade, resulting in an effect on the immune system.

This chapter briefly describes the principal components of the immune system and the general consequences that stem from perturbations to it. This chapter also briefly explores one of the practical considerations of immunotoxic substances and humans: Who is at risk?

Only the most basic and broad concepts of immunology are presented in this chapter. Current knowledge about the immune system is presented in several sources (4,19,22). Similarly, a detailed description of toxicological effects on the immune system is beyond the scope of this report but is presented elsewhere (7,10,11,18,27,28).

COMPONENTS OF THE IMMUNE SYSTEM

Cells are the basic structural unit of living organisms. They are the smallest components of plants and animals that are capable of carrying on all essential life processes.

A single cell is a complex collection of molecules with many different activities, all integrated to form a functional, self-assembling, self-regulating entity, although cells in different organs carry out different functions.

Several types of cells comprise the human immune system, as do units of cells and tissue, i.e., organs. Together these cells, tissues, and organs respond to challenges to the immune system. This section briefly describes the major components of the immune system; a later section examines how these elements coordinate to mount an immune response.

Antigens and Antibodies

Elements that are capable of eliciting an immune response are called antigens. Humans are exposed to antigens primarily through inhalation, direct skin contact, or ingestion. Antigens include, but are not limited to, chemical compounds and micro-organisms. And, while antigens are generally substances “foreign” to – i.e., originating outside — the human body, in some instances, the immune system will perceive a normal, self component of the body as foreign and mount an immune reaction against it. Several types of cells can react with antigens, depending on the exact nature of the particular antigen.

One response to antigen stimulation results in the production of proteins called immunoglobulins, or antibodies. Antibodies have binding sites that are specific for, and complementary to, the structural features of the antigen that stimulated their formation. Antibodies formed by a sheep, for example, in response to injection of human hemoglobin (the antigen) will combine with human hemoglobin and not an unrelated protein such as human growth hormone.

By combining specifically with antigens, antibodies can neutralize substances, such as toxins. Antibodies also facilitate the elimination of bacteria and viruses to which they are bound by recruiting other components of the immune system (e.g., macrophages and complement).

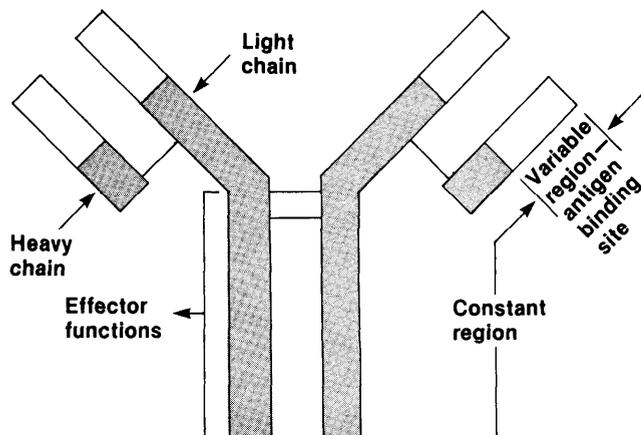
(Complement activation is a rapid, complex process that is activated by antigen-antibody complexes to destroy cells, bacteria, or viruses, or cause inflammation.)

The basic unit comprising antibodies consists of four protein chains—two identical light chains and two identical heavy chains. Heavy chains can vary in type, and the type of heavy chain in a particular antibody determines the subclass— i.e., IgM, IgA, IgD, IgG, or IgE—of antibody. These protein subunits are linked in a fixed and precise orientation to form a “Y”-shaped molecule (figure 2-1). The forked end of the antibody contains two variable regions, the sites of the molecule that recognize and bind with the specific antigen. To accommodate the many antigens that exist, these variable regions differ from molecule to molecule. The other end is nearly identical among all antibodies and is known as the constant, or effector, region. The constant region is not responsible for antibody binding specificity, but has other functions, including promoting efficient attachment of the antigen-antibody complex by certain cells and activation of the complement cascade.

Cells

In recognizing and reacting to substances it perceives as foreign, the immune system, or lymphoid system, involves several different cell types. Most of these cells are commonly referred to as white cells, or leukocytes. Fig-

Figure 2-1 – Structure of an Antibody Molecule



SOURCE: Office of Technology Assessment, 1991.

ure 2-2 presents one simple classification scheme for white cells.

An exhaustive description of each type of cell involved in an immune response is beyond the scope of this report. Rather, this section provides short descriptions of only the principal cell types—lymphocytes and macrophages—to serve as background for the following section, which describes the interaction of these cell types, and for chapter 3, which discusses how scientists test for immunotoxicity by measuring perturbations in these cell populations. Table 2-1 lists additional cell types that have immunological importance.

B Cells

A particular subclass of lymphocytes, called B lymphocytes or B cells, recognizes antigens as foreign substances and responds by producing antibodies specific for a given antigen. Antigen-antibody mediated reactions are known as humoral immunity. Once a B cell has been activated by an antigen, it is committed to producing antibodies that bind to the specific antigen. B cells arise from precursors in the bone marrow (as do all other lymphoid and blood cells). These cells, like macrophages (described in following section), play important roles in antigen processing, one sequence of events necessary to trigger antibody production and other immune responses.

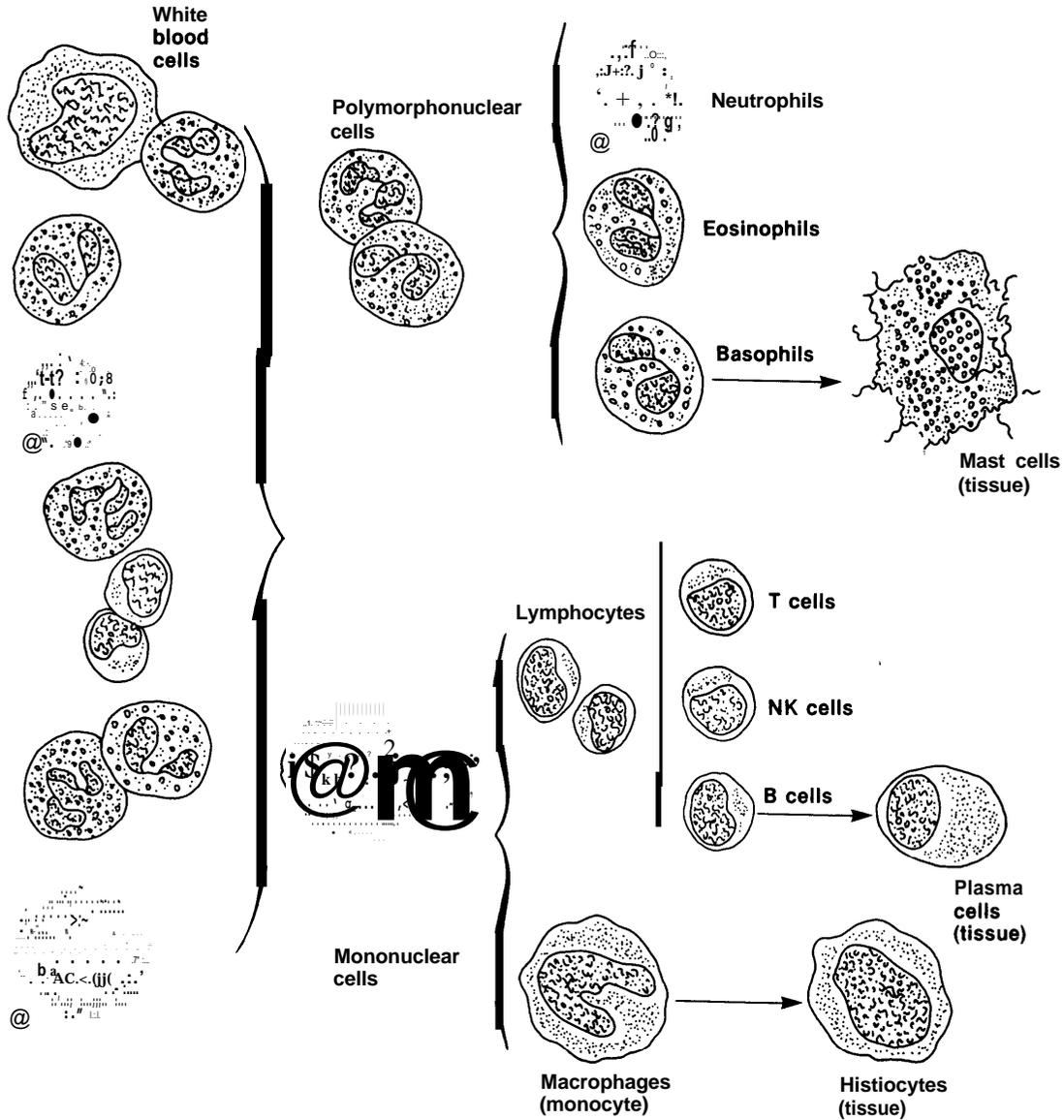
A distinguishing feature of the outer surface of B cells is the presence of surface antibodies. These surface markers, along with surface markers on other cells of the immune system (box 2-A), play critical roles in the activation and

Table 2-1—Major Cells Classes of Immunological Importance

Primary effector cells
B lymphocytes
T lymphocytes
NK cells
Antigen presenting cells
B lymphocytes
Macrophages/monocytes
Follicular dendritic cells
Interdigitating dendritic cells
Langerhans cells
Endothelial cells
Accessory cells
Neutrophils
Basophils and mast cells
Eosinophils
Platelets

SOURCE: Office of Technology Assessment, 1991.

Figure 2-2-White Cells



SOURCE: Office of Technology Assessment, 1991, adapted from S. Sell, *Basic Immunology: Immune Mechanisms in Health and Disease* (New York, NY: Elsevier, 1987),

regulation of the immune system. Surface immunoglobulins define the specificity of the response for that B cell and help trigger the production of antibodies by that cell.

T Cells

A second broad group of lymphocytes are T cells. Like B cells, T cells arise from precursors in the bone marrow, but must circulate to the thymus for maturation. Similarly, they have characteristic cell surface markers and can

specifically recognize antigen if it has been processed and presented to them by other cells of the immune system. Based on functional and other criteria, T cells can be divided into several major subpopulations (table 2-2).

T cells can be viewed as the “master regulators” of the immune system (22). In addition to their required interaction with B cells to produce antibody, various T cell types are responsible for cell-mediated immunity, a class

Box 2-A – Cell Surface Receptors of the Immune System

Outer surfaces of all cell types are not smooth, but are imbedded with components called receptors. Hundreds of cell receptor types allow cells to attach to other cells, communicate, bind, or transport drugs from the exterior to a cell's interior, and perform an array of additional functions. Three families of cell surface receptors are "signature" markers for the immune system and regulate the interactions of cells activated during immune responses: the immunoglobulin and immunoglobulin-like family, including antigen receptors on B and T cells; the "integrin" family, which plays an important role in adhesion and migration of immune cells; and the "selectins," which are important for the regulation of certain immune cells at sites of inflammation.

Researchers have begun to unravel how receptors interact with other cells, tissues, and organs of the immune system, and with tissues and organs of other systems. They are also beginning to understand the genetic basis for subtle, genetically based variations in receptors among individuals.

Certain receptors and receptor subclasses are clearly linked to specific immune functions and reactions. This knowledge makes it easy to track these cell types in individuals, to measure how they might differ in the population, and perhaps, to correlate changes or differences with immunoresponsiveness, including susceptibility to disease or a particular toxicant. For example, two immune system receptors on T cells called CD8 and CD4 differentiate cytotoxic/suppressor T cells from helper T cells. Blocking both receptors in laboratory experiments prevents signaling that a "proper" immune response should be mounted, and a 100-fold higher concentration of antigen is necessary to induce a response.

Because the perturbations of many immunotoxicants might take place by alterations of an immune system receptor, or disruption of communication between receptors, understanding immune system cell surface receptors—their structures, functions, and interactions—will likely be important to developing refined immunotoxicity tests. For example, toxicants might exist that block the signaling process. A validated immunotoxicity test to specifically measure signal interruption might be a sensitive and useful tool. Similar tests could be developed based on understanding of integrins and selectins. Such developments, however, are not on the immediate horizon.

SOURCE: Office of Technology Assessment, 1991, based on T.A. Springer, "Adhesion Receptors of the Immune System," *Nature* 346:425-434, 1990.

of immune responses that does not depend on antibody production. T cells can be cytotoxic, i.e., directly kill cells that are expressing a specific antigen. T cells (and macrophages and natural killer (NK) cells) produce a variety of protein molecules, called cytokines, but they do not produce antibodies.

Cytokines serve as messengers that transmit signals between cells to control and modulate an immune response. For example, some cytokines recruit other cells to participate in and augment an immune response. Some stimulate B cells to produce antibodies. Others suppress the immune reaction or ensure that the system focuses on the antigen and does not run rampant in a nonspecific attack that would damage host tissue. Cytokines are produced in extremely small amounts – on the order of parts per billion – and act locally at the site of their release. The interferon are examples of cytokines.

Macrophages

Macrophages (literally "large eaters") are the largest cell type in the immune system and play a central role in the immune system's response to a foreign agent. Macrophages invade sites of inflammation and serve to clear the sites of cellular debris; they are also particularly effective in phagocytizing, or ingesting, infecting organisms.

Macrophages do not produce antibodies. Instead, they are involved in the first step leading to induction of an immune response. A macrophage ingests and nonspecifically processes antigen, and then presents the processed antigen on its cell surface so that it can be recognized by specific antigen reactive cells. Such antigen presentation and processing—which is linked to genetic elements (3,12,17,24,29) – is a critical part of the induction of both humoral and certain cell-mediated

Table 2-2—Major Functions of T Cells

Abbreviation	Function
T ₀ ~	T cells responsible for "delayed-type hypersensitivity y." After reacting with antigen, T ₀ cells release cytokines that can kill target cells in vitro (cytotoxins) and activate macrophages, inducing inflammation.
T _h	T helper cells assist in humoral immunity, i.e., antibody production. They are required if a B cell is to produce antibody. One characteristic feature of helper T cells is a surface marker called CD4.
T _k	Often referred to as killer T cells, or cytotoxic lymphocytes, this subclass of T cells, after being specifically sensitized, directly interacts with target cells to kill them in vitro. They are distinguished from NK cells by the requirement for sensitization and cell surface markers.
T _s ~	T cells that serve to control immune responses by producing factors that can act on both B cells and T _h cells. Suppressor T cells can be distinguished from helper T cells because they exhibit a signature molecule referred to as CD8.

SOURCE: Office of Technology Assessment, 1991.

immune responses. (B cells also process antigens.) Macrophages also produce important cytokines that regulate overall immune responsiveness.

NK Cells

Another lymphocyte subclass is natural killer cells, or NK cells. NK cells derive from the bone marrow, but their exact relationship to B cell and T cell precursors remains to be elucidated. NK cells share some properties of T cells and macrophages, but also share several surface characteristics with B cells.

NK cells do not play a central role in antigen-specific antibody responses, but are critical components of general, nonspecific immune defenses. In vitro, NK cells lyse, i.e., kill, several types of tumor cells and virus-infected cells, and thus are believed to be important in the body's defense against viruses or cancer. Additionally, these cells likely play an important role in immunity to certain bacterial and parasitic infections.

Organs

Several organs are responsible for the development and maintenance of a functioning immune system (figure 2-3), which complicates making assessments of immunotoxicity. Changes in the circulatory or lymphatic

systems, for example, can affect any number of organs. Strictly speaking, however, lymphoid organs are the principal organs of the immune system (22). A lymphoid organ is a compartmentalized collection of lymphocytes, macrophages, and other immune cells. It may be part of, or mixed among, cells of another organ. Lymphocytes also circulate freely through the blood and lymphatic vessel network.

Bone marrow, the thymus, and even the fetal liver, in part, are lymphoid organs. In humans (and most other species), bone marrow is the predominant organ from which lymphoid cells originate. Some of the cells that develop in the bone marrow complete their maturation before entering circulation. Others, however, must undergo further differentiation in other organs (e.g., the thymus).

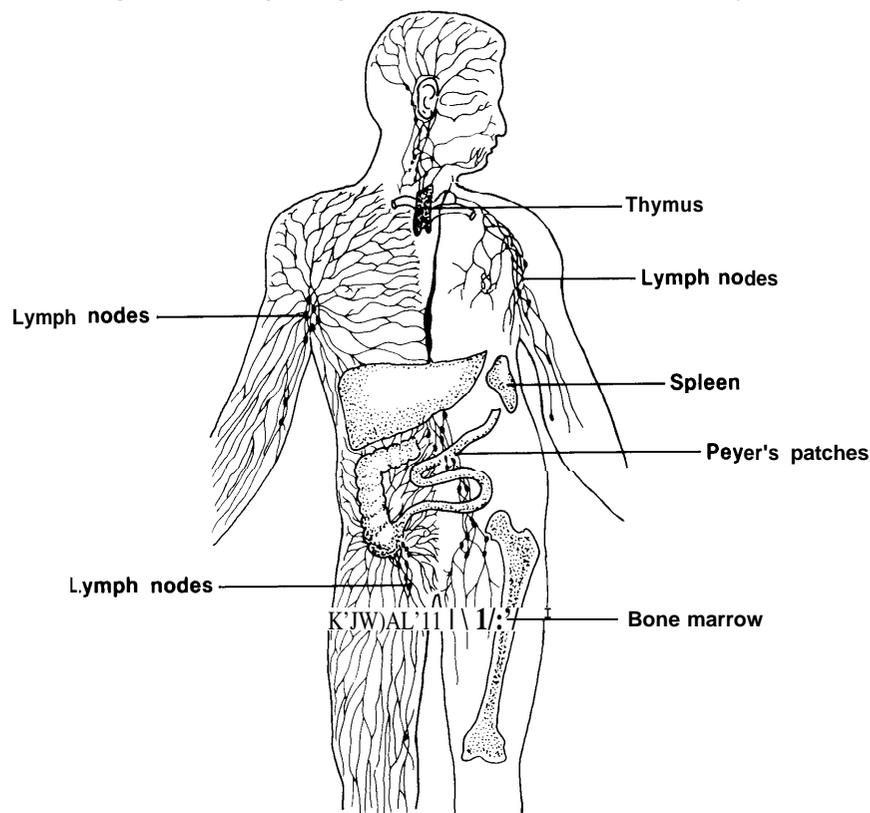
The spleen and lymph nodes are lymphoid organs that clear the blood of infectious organisms and serve as repositories for antibody-producing cells. Tonsils, the appendix, and Peyer's patches (small aggregates of cells in the intestine) are also lymphoid organs. Local collections of tissue within both the gastrointestinal tract and bronchus play a role in certain immune responses—gastrointestinal lymphoid tissue is thought to play an important role in immunity to infectious agents entering the body through the mouth, for example.

IMMUNE RESPONSES

Immune responses can be divided into two categories: nonspecific and acquired. Nonspecific, or innate, immunity involves those cells (e.g. macrophages and natural killer cells) and processes (e.g., complement activation) that do not depend on exposure, followed by reexposure, to antigen. Generally, nonspecific immune responses represent the body's first line of defense and involve a generic, innate reaction to foreign substances. Acquired, or adaptive, immunity is characterized by antigen specific processes.

There are two broad classifications of acquired immunity that are commonly referred to as humoral immunity and cell-mediated immunity. Both require the coordination of multiple cell-types of the immune system. And, while one type of immune response can sometimes dominate after exposure to a particular antigen, for the most part, both play roles when foreign substances are presented. This section briefly describes the interac-

Figure 2-3 –Major Organs and Tissues of the Immune System



SOURCE: Office of Technology Assessment, 1991, adapted from S. Sell, *Basic Immunology Immune Mechanisms in Health and Disease* (New York, NY: Elsevier, 1987).

tions involved in the two classes of acquired immune responses to provide a background for how perturbations in immune responses can be measured.

As mentioned previously, the immune system functions principally to protect the body. Under some circumstances, however, control mechanisms can be compromised and the immune system turned against the body, causing harm. Conditions that arise when this occurs vary from mild discomfort to fatal disorders. Thus, this section also examines pathological immune responses.

humoral Immunity

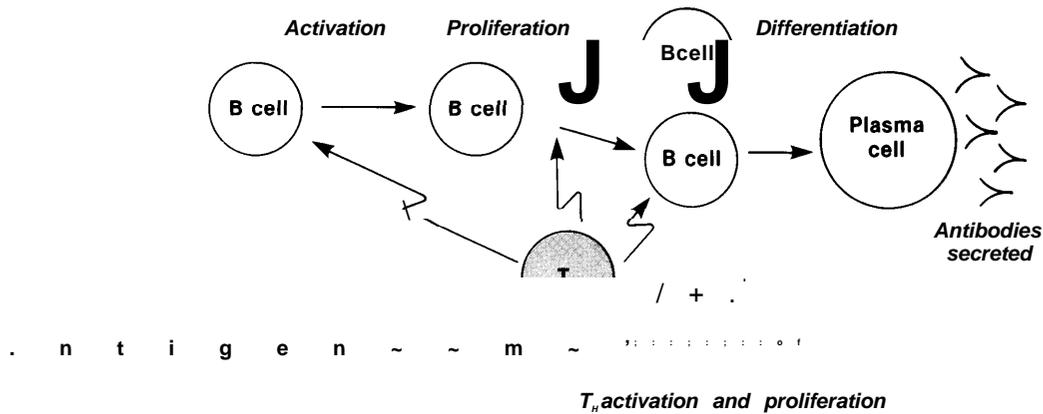
The production of specific antibodies in response to exposure to a foreign substance is called humoral immunity. humoral immunity can be particularly important in protecting the body against certain biological agents.

As illustrated by figure 2-4, three types of immune cells typically interact during optimum immunoglobulin production. A toxic substance that blocks any step can disrupt this response in a measurable fashion.

First, an antigen presenting cell, often a macrophage, must process the foreign substance. Macrophages perform this reaction nonspecifically, and in doing so concentrate the antigen as well as release factors that facilitate subsequent B and T cell cooperation. Second, T helper cells interact with the antigen-presenting cell to produce chemical signals, cytokines (interleukins), that stimulate B cells and additional T cells. Finally, the B cell can mature into an antibody producing cell, also called a plasma cell.

This series of reactions is antigen-specific. Each different antigen elicits a unique antibody and there are a

Figure 2-4 – Generation of Antibody Forming Cells



T-helper (T_h) cells

**Antigen
processing cells**

SOURCE: Office of Technology Assessment, 1991, adapted from K. White, Medical College of Virginia, Richmond, VA, 1990.

large number of antigens against which antibodies can be produced. Additionally, the immune system has a "memory" whereby re-presentation of a familiar antigen results in a slightly different, accelerated immune response. Both B and T cells are involved in immune memory.

In some cases, B cells can be stimulated, by certain antigens called T cell-independent antigens, to produce antibodies without the involvement of T cells. B cells can also be stimulated to proliferate in vitro by mitogens. Mitogen assays are used as a measure of immunotoxicity and are discussed in chapter 3.

One potentially adverse consequence involving antibody production is immediate-type hypersensitivity, a type of allergy response. (Some use the term allergy to refer only to immediate-type hypersensitivity, and not a second reaction, delayed-type hypersensitivity. This background paper uses allergy to denote both responses.) When immediate-type, or anaphylactic, reactions are initiated by certain antigens— e.g., pollens or animal dander— in certain individuals, mast cells (table 2-1, figure 2-2) release pharmacologically active substances (e.g., histamine, serotonin). These substances can induce a range of problems, including inflammatory changes in many tissues that result in hives and wheezing, or even abrupt changes in blood pressure. In some circumstances, such reactions can be life-threatening. The

predominant immunoglobulin involved in immediate-type hypersensitivity in humans is called IgE.

Cell-Mediated Immunity

As described previously in table 2-2, several sub-populations of T cells can be recognized physically and functionally. T cells, NK cells, and activated macrophages carry out the functions of the second broad category of acquired immune responsiveness, cell-mediated immunity. Again, the interaction of cells in cell-mediated immunity forms the basis for tests developed to assess potential immunotoxicants. Cell-mediated immune responses require antigen processing to specifically sensitize T cells. Table 2-3 summarizes the general types of cell-mediated immunity. Cell-mediated immunity is particularly important to transplantation rejection, tumor surveillance, and for protection against infectious agents.

Several different types of cell-mediated immune responses exist (8). One potentially adverse consequence of cell-mediated immunity is delayed-type hypersensitivity (DTH). Contact sensitization, such as poison ivy and other skin allergies resulting in inflammation and tissue damage, is a classic example of DTH. Another delayed-type hypersensitivity called cutaneous basophil sensitivity also involves the skin, but the predominant cell type involved differs from that for classic contact sensitivity

Table 2-3-Mechanisms of Cell-mediated Immunity

- Direct killing by sensitized T_H cells; the cells react directly with the target cells to lyse them (cytotoxic T lymphocyte activity).
- Indirect killing by sensitized T_H cells in combination with cytokines.
- Antibody-dependent cell-mediated cytotoxicity (ADCC) involves a type of lymphocyte without characteristic cell surface markers ("null cells") in combination with specific antibody.
- Direct killing by nonsensitized NK cells; the cells react directly with the target cells.
- Phagocytosis, i.e., digestion, of substances by macrophages.
- Release of cytokines.

SOURCE: Office of Technology Assessment, 1991; based on S. Sell, *Basic Immunology: Immune Mechanisms in Health and Disease* (New York, NY: Elsevier, 1987).

and the time lag between exposure and the reaction is shorter (1,8).

Autoimmunity

"Tolerance" is the term applied to the mechanisms that prevent the immune system from responding to its own—i.e., self or auto—antigens. Sometimes, however, tolerance to self antigens is lost, resulting in autoimmune reactions (table 2-4). When such situations occur, humoral immunity, cell-mediated immunity, or both can turn their destructive capabilities against the body, leading to tissue damage and/or inflammation. The presence of antibodies that react against self antigens (auto-antibodies) can sometimes be demonstrated in several autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, diabetes). But, the presence of autoantibodies is not inevitably associated with disease and, in fact, autoantibodies normally increase with age.

Autoimmune pathologies can be difficult to assess, but certain features are thought to be indicative of autoimmune phenomena. The induction of autoimmune events in a few discrete populations have been attributed to exposure of the individuals to certain toxicants (5,14,15).

WHAT IS immunotoxicITY?

As mentioned, immune responses are complex, multifactorial interactions with different consequences depending on the situation. In some instances, the immune response will be depressed or suppressed (table 2-5),

which can result in increased susceptibility to disease or tumor formation. Conversely, the immune system sometimes hyperreacts when presented with certain foreign substances, which can result in an allergic response, i.e., immunologic hypersensitivity, wherein the response is out of proportion to and more harmful than the initial threat of the substance. In some of these cases, the response can be the source of tissue damage, so that suppressing certain immune reactions actually reduces tissue injury. Finally, the immune system can become confused and fail to recognize the body's own components as "self" — i.e., the immune system treats a "self" substance as foreign and mounts an autoimmune response, which can result in certain characteristic pathologies.

For the purposes of this study, OTA defines *immunotoxicity* as an adverse or inappropriate change in the structure or function of the immune system after exposure to a foreign substance. Adverse effects can be manifest as immunosuppression, hypersensitivity, or autoimmunity.

In any of these reactions, the cells, tissues, and organs of the immune system can be activated, inhibited, destroyed, or their responses exaggerated. It is the demonstrated involvement of at least one or more of these components that defines whether a consequence results from an actual *immune response*. For example, the term allergy should be used only to denote the involvement of immune responses, but is often mistakenly used to describe other adverse reactions (box 2-B).

An array of biological, physical, and chemical substances can perturb the intricate balance of the immune system, and this complex system provides several target sites for immunotoxicants. OTA broadly defines *immunotoxicant* as a substance that leads to undesired effects on the immune system. The focus of this report is on immunotoxicants that are chemicals, although important information has been, and continues to be, learned from studies of biological substances.

Whether a substance causes an adverse effect on the immune system, which could be permanent or reversible, depends on many factors, including the nature of the substance, dose and exposure, route and extent of exposure, the presence of other agents, and an individual's sex, genetic predisposition, age, and state of health.

Table 2-4—Some Human Diseases in Which Autoantibodies Have Been Detected

Disease	Self-antigens (as defined by the autoantibodies involved or detected)
Guillan-Barré syndrome	Myelin and other components of the peripheral nerves
Hashimoto's thyroiditis	Cytoplasmic or microsomal thyroid antigen, thyroglobulin
Multiple sclerosis	Brain or white matter
Myasthenia gravis	Acetylcholine receptor at the neuromuscular synapsis
Progressive systemic sclerosis (scleroderma)	Various antigens in cell nuclei, especially nucleoli
Rheumatoid arthritis	Heart, muscle, joint, subcutaneous nodules, aggregated gamma-globulin
Systemic lupus erythematous (SLE)	Various nuclear antigens, especially double-stranded DNA, antigens on leucocytes and erythrocytes, liver, spleen, kidney, muscle

SOURCE: Office of Technology Assessment, 1991; adapted from E. Gleichmann, I. Kimber, and I.F.H. Purchase, "Immunotoxicology: Suppressive and Stimulator Effects of Drugs and Environmental Chemicals on the Immune System," *Archives of Toxicology* 63:257-273, 1989; and S. Sell, *Basic Immunology: Immune Mechanisms in Health and Disease* (New York, NY: Elsevier, 1987).

Table 2-5—Some Immunodeficiency Disorders

Disorder	Immunological defect
Acquired immune deficiency syndrome (AIDS) . .	Viral infection of certain T cells
Congenital thymic aplasia (DiGeorge syndrome)	Thymus absent or small; T cells absent or reduced
Severe combined immune deficiency disease (SCID; "Bubble Boy" disease)	Lack of T and B cells
X-linked hypogammaglobulinaemia (Bruton's disease)	Absence of B cells

SOURCE: Office of Technology Assessment, 1991; adapted from E. Gleichmann, I. Kimber, and I.F.H. Purchase, "Immunotoxicology: Suppressive and Stimulator Effects of Drugs and Environmental Chemicals on the Immune System," *Archives of Toxicology* 63:257-273, 1989.

Chapter 3 discusses what tests are currently employed to determine whether a substance is immunotoxic and describes immunotoxic substances and their effects.

immunotoxicANTS: WHO IS AT RISK?

While exposure to immunotoxic substances can occur anywhere to anyone, the opportunity to be exposed is greater for some populations of individuals than for others. Since immunotoxic effects have been described for some ambient and indoor air pollutants, some point out that the magnitude of individuals at risk could be tremendous (21). Yet others argue that while such effects have been described for indoor air pollutants, the levels of these chemicals would generally be low—probably below the threshold for response (2).

Nevertheless, certain discrete populations are probably at increased likelihood of exposure, more amenable for scientific research, or both. For example, observations of occupational exposures to toxic sub-

stances have contributed much of the data pertinent to immunotoxicological effects — i.e., hypersensitivity, autoimmunity, and immunosuppression. Similarly, immunosuppressive drugs can be viewed as prototype immunotoxicants, and so patients receiving such drugs to prevent transplant rejection can be observed. Consumers of cosmetics have also been examined to detect hypersensitivity to various agents.

Yet even among populations of individuals, not all of those exposed are affected. Certain individuals may be more susceptible to developing adverse reactions for a variety of reasons separate from mere exposure to the toxicant — even when dose and duration of exposure are similar for different individuals. For example, the person could be innately susceptible, i.e., be genetically predisposed. Age is another important factor in immunotoxicology, since the immune system is not completely functional at birth and might be more vulnerable to damage then. It also changes appreciably in older populations—generally to a less responsive level (26).

Box 2-B – "Allergy": Some Common Misperceptions

From an immunological standpoint, the term allergy refers to a normal immune response with deleterious consequences, such as allergic rhinitis, or hay fever (e.g., to grass pollen), or contact sensitivity (e.g., to poison ivy). True "allergies" occur when a human comes in contact with a substance that triggers a predictable response that involves certain components of the immune system. Immunological hypersensitivity, or allergy, is not due to an alteration of the immune system by a foreign substance per se, but is an inappropriate activation of the immune system. Two exposures, the first involving sensitization to the substance, are needed to demonstrate allergy.

"Allergy," however, is often improperly used to denote generic adverse reactions or susceptibilities. For instance, some persons develop, or are born with, an inability to produce the intestinal enzyme lactase. These lactase-deficient individuals are unable to breakdown the sugar lactose. For them, digestion and absorption of ordinary lactose-containing milk is quite troublesome and results in gastrointestinal distress. The symptoms, however, do not arise as a result of perturbations to the immune system. Rather, the problems stem from an intolerance, not an allergy, to the milk sugar lactose.

In contrast, some problems previously thought to be intolerances might be true immune reactions, or allergies — e.g., example the condition known as celiac sprue, where an individual has an adverse reaction to wheat. In this syndrome, the soluble protein of wheat flour, A-gliadin, induces a damaging inflammatory reaction to the epithelial layer of the gut leading to a malabsorption syndrome. Although once believed to be due to another enzyme deficiency, growing evidence indicates that A-gliadin shares significant structural homology with an adenovirus protein. As a result of earlier presensitization to the adenovirus protein, epithelial lymphocytes respond to the gliadin with subsequent adverse inflammatory effects — a true immune response, and hence a true allergic response.

SOURCE: Office of Technology Assessment, 1991.

Finally, the overall state of health is also important in determining immunotoxicity.

Genetic background, in particular, is an important consideration in evaluating both potential immunotoxicity and variation in toxic effects. For example, genetic bases could account for the differential ability of individuals to produce anti-inflammatory factors, which in turn would influence how a person would be able to mount and modulate an immune response to an offending agent (8). Likewise, although almost anyone can develop an allergy to a given substance, a distinct segment (15 to 20 percent (23)) of the population is clinically atopic, i.e., individuals who are unusually reactive to a variety of substances. Several genes have been identified that could influence this hyperreactivity (16), although specifics remain to be elucidated.

Not only is there a genetic basis for controlling the immune response to a particular antigen (as determined by histocompatibility or human leukocyte antigens (HLA), which present processed antigens (3,12,17,24,29)), but other genes are responsible for certain pharmacologic abnormalities that can predispose an individual to immune

dysfunctions, e.g., hyperreactivity to histamine or acetyl-methylcholine. The latter substance is used to detect people with hyperreactive airways that constrict and cause wheezing when exposed to antigen. Total IgE production—central to immediate-type allergic reactions—is regulated by genes (16). Persons could have genetic differences—singular or in combination—that might predispose them to allergies to certain environmental and occupational antigens (30). Certain HLA genes also are associated with increased risk of autoimmune diseases (13,20).

Finally, in addition to intrinsic factors, external risk factors are critical. Smoking and exposure to tobacco smoke, for example, are important external risk factors that must be accounted for in assessing potential immunotoxicity in humans (6). Another potential external risk factor is the presence of coincidental pulmonary infection at the time of exposure. The association of viral (but not bacterial) infection with triggering attacks of both childhood and adult onset asthma has been documented (9). Such infections can cause bronchial hyperreactivity that may even become permanent. It has been hypothesized that such an infection occurring in a worker

simultaneous with exposure to an industrial substance or environmental pollutant could result in an enhanced sensitivity to that substance. A different external factor, house dust mites, is a precondition for certain childhood asthmas (25).

SUMMARY AND CONCLUSIONS

A functioning immune system helps protect the human body from a vast array of chemical, physical, and biological foreign substances, as well as from problems that arise from within (e.g., tumor cells). Proper reaction to a stimulus requires the cooperation of several types of cells and organs, as well as feedback from other systems in the body.

Two broad types of immune responses exist: non-specific and acquired. The latter response involves two different types of reactions: humoral immunity and cell-mediated immunity. Humoral immunity is characterized by the production of antibodies that circulate in blood and lymph fluid. Cell-mediated immunity encompasses an array of responses that involve different cell types, but does not involve antibody production.

The complexity of the immune system makes it vulnerable to the effects of toxic substances on many fronts. Immunotoxicity, then, is any alteration in an immune response — suppression, hypersensitivity, or autoimmunity— resulting from exposure to a toxic substance.

The science of immunotoxicity, i.e., immunotoxicology, is complicated by several elements: the complex nature of the immune system, age of subject, genetic background, and external risk factors, such as smoking. Genetic factors account, in some instances, for variation in immune responsiveness to an antigen, and hence need to be assessed when evaluating potential immunotoxic effects of a substance.

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