Lecture Notes on IMMUNOTOXICITY

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First edition

Lecture Notes

On

Immunotoxicity

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To:

My brother Yousef.

Dr Abdulla M. Elahwel

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PREFACE

This handbook is written for junior and senior medical doctors who will find many articles useful for everyday work especially the interaction of the normal immune system with different medicines and supplements. These interactions include good and bad effects. The book is divided into several chapters, first one introduces in brief the anatomy and physiology of the immune system, following chapters explain disorders in the immune system following exposure to different poisons, finally the last chapter explains the interaction between food and immune system.

Abdulla M. Elahwal

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ABBREVIATIONS

- 2-acetyl-4(5)- tetrahydroxybutylimidazole (THI)
- Cell-Mediated immunity (CMI)
- Central nervous system (CNS)
- Cutaneous drug reactions (CDRs)
- Delayed-type hypersensitivity (DTH)
- Epigallocatechin-3-gallate (EGCG)
- Erythema Multiforme (EM)
- Extrinsic allergic alveolitis (EAA)
- Human immunodeficiency virus (HIV)
- Humoral-Mediated immunity (HMI)
- Hydrogen peroxide (H2O2)
- Immunoglobulins (Ig)
- Interferon (IFN)
- Interleukin (IL)
- International Contact Dermatitis Research Group (ICDRG)
- Jun N-terminal kinase (JNK)
- Lipopolysaccharide (LPS)
- Lymphocyte proliferation test (LPT)
- Lymphokine-activated killer (LAK) cell
- Major histocompatibility complex (MHC)
- Myeloid differentiation factor 88 (MyD88)
- Nasal lavage (NAL)

- Nitro blue tetrazolium (NBT)
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Nuclear factor-α B (NF-α B)
- Pathogen-associated molecular patterns (PAMPs).
- Phytohemagglutamin (PHA)
- Polyunsaturated fatty acids (PUFAs)
- Polyvinyl chloride (PVC)
- Red blood cell (RBC)
- Stevens-Johnson syndrome (SJS)
- Systemic lupus erythematosus (SLE)
- T-cell antigen receptor (TCR)
- T-helper/inducer cells (CD4)
- Toll-like receptors (TLRs)
- Toxic epidermal necrolysis (TEN)
- Toxic Epidermal Necrolysis (TEN)
- T-suppressor/cytotoxic cells (CD8)
- Tumor necrosis factor (TNF)
- Zinc (Zn)

CHAPTER I:

Normal immune system

CHAPTER I

NORMAL IMMUNE SYSTEM

The main function of the immune system is to presume the integrity of the living organism. It is responsible for identifying "self and non-self" antigen and hence, defending the body against foreign invaders.

Anatomy of the immune system

Although the immune system operates throughout the body, the cells of the immune system are organized into specific structures. These are classified as central (bone marrow and thymus) and peripheral (lymph nodes, spleen and mucosa-associated lymphoid tissue).

I. Central lymphoid tissue

1. **Bone marrow:** All cells of the immune system are derived from the bone marrow.

2. **Thymus:** Thymus gland is situated in the anterior mediastinum. The gland enlarges during childhood but after puberty it undergoes a process of involution. However, it continues to function throughout life. Histologically, the gland is formed of an outer cellular cortex and an inner cellular medulla. Immature lymphocytes enter the cortex, proliferate, mature and then pass to the medulla from which they enter the circulation. During the process of maturation, T-lymphocytes develop the important attribute known as self-tolerance.

II. Peripheral lymphoid tissue

1. **Lymph nodes:** These are small bean-shaped structures lying along the course of lymphatics and are aggregated in the neck, axilla, groins and para-aortic regions.

    a. **Cortex** The cortex is formed mainly of B-lymphocytes arranged in follicles, which called primary lymphoid follicles. Activated B cells occupy the center of the lymphoid follicle (germinal center) and the follicle is then called secondary follicle. Activated B-lymphocytes within the germinal center change to centrocytes and centroblasts, which pass to the medullary sinuses and change to immunoblasts. Immunoblasts, which divide and produce a clone of T cells responding to a specific antigen. The

paracortex contains also interdigitaling cells, which act as antigen presenting cells.

b. **Medulla:** It is formed of large blood, medullary cords (rich in plasma cells and macrophages) and medullary sinuses.

2. **Spleen:** The spleen acts as both part of the immune system and as a filter. It is formed of

   a. **Red pulp:** Designed to facilitate the removal of old or damaged red blood cells.

   b. **White pulp:** Consisting of T-cells, B-cells and accessory cells similar to those of the lymph nodes.

3. **Mucosa-associated lymphoid tissue:** Mostly found in the mucosa of gastrointestinal tract, respiratory tract and urogenital tract.

   Gut-associated lymphoid tissue comprises the following

   a. Tonsil and adenoid (Waldeyer's ring).

   b. Peyer's patches

   c. Lymphoid aggregates in appendix and large intestine.

   d. Lymphoid tissue accumulating with age in the stomach.

   e. Small lymphoid aggregates in the esophagus.

   f. Diffusely distributed lymphocytes and plasma cells in the lamina propria of the gut.

4. **Liver:** The walls of hepatocytes, which from the masses of liver lobules, are penetrated by vascular sinusoids lined by endothelial cells and special reticuloendothelial cells, called Kupffer cells, which have immune system function. Intrahepatic circulation of blood is basically through both the portal vein system and the hepatic artery. Sixty per cent of hepatic blood flow is through the portal vein of the liver thus plays a pronounced role in host resistance mechanisms and antigen detection.

Physiology and components of the immune system

T-cells

Stem cells that enter the thymus gland are rapidly divide, acquire their antigen specificity and are selectively deleted if they bear any self-reactivity. The "educated" daughter cells, termed thymus-derived or T-lymphocytes which leave the thymus and travel to other lymphoid tissues. Murine T-lymphocytes possess both the Thy-1 marker and the T-cell antigen receptor (TCR)-CD3 complex, and fall into two major classes, either T-helper/inducer cell expressing CD4 or T-suppressor/cytotoxic cells, which display CD8. The majority of lymphocytes in the peripheral blood and lymph nodes and about one half of the cells in the spleen are T-cells, when stimulated, T-cells produce cytokines. These are soluble mediators synthesized by cells of the immune system that bind to specific receptors or target cells and modulate cell function in immunological reactions.

Types of T cell

A. Helper T cells

Most immune responses require the action of these cells, which play a central coordination role in both humoral and cellular immunity.

B. Cytotoxic T cells

Cytotoxic (killer) T cells are the only T lymphocytes that directly attack and kill other cells. They are responsive to cancer cells, cells of transplanted tissues and organs and host cells that are infected with viruses, intracellular parasites and bacteria.

C. Suppressor T cells

As the pathogen is defeated and disappears from the tissues, suppressor T cells release lymphokines that inhibit T cell and B cell activity. Suppressor T cells may also help prevent autoimmune disease.

B-Cells

In contrast to T-lymphocyte maturation, the development of lymphocytes capable of synthesizing and secreting antibody (immunoglobulin) molecules in mammals is thought to occur in several sites, including the bone marrow, spleen and mucosal-associated lymphoid tissues (MALTs). Following activation by antigen or antigen-activated

T-helper cells and lymphokines, B-cells proliferate and terminally differentiate to antibody-producing plasma cells, which turn over rapidly and are replenished by newly differentiated cells.

B-cells express surface antigen-combining receptor molecules, which are of identical specificity to the immunoglobulins they synthesize and secrete five different types of immunoglobulins IgM, IgG, IgA, IgD, and IgE. These proteins are composed of two separate types of polypeptide chains joined by disulfide linkages, termed the heavy and light chains because of differences in their relative molecular masses. In addition to surface immunoglobulin, B-cells display receptors for Fc regions of immunoglobulin molecules, major histocompatibility complex (MHC) Class II molecules, receptors for complement proteins, and the CD4 molecule, which plays an essential role in the contact between B- and T-cells.

Macrophages

Stem cells also give rise to mononuclear phagocytes of the myeloid series, of which the macrophage is the primary cell type. Immature macrophages leave the bone marrow and are found in the lymphoid organs, liver, lungs, gastrointestinal tract, central nervous system, serous cavities, bone, synovium and skin, and differentiate within these sites. Macrophages are attracted to microbes by the gradient of foreign molecules emanating from them, a process called chemotaxis. Upon contact, the macrophage can engulf the microbe or chemicals (e.g. heavy metals) (Fig. 1), process and present the derived antigen via its major histocompatibility complex (MHC) molecules to T cells, and secrete cytokines (e.g., IL-1, TNF-alpha, IL-12), degradative enzymes, complement components, reactive oxygen intermediates and coagulation factors. Macrophages readily infiltrate tumors and provide one of the mechanisms of host defence against malignancies.

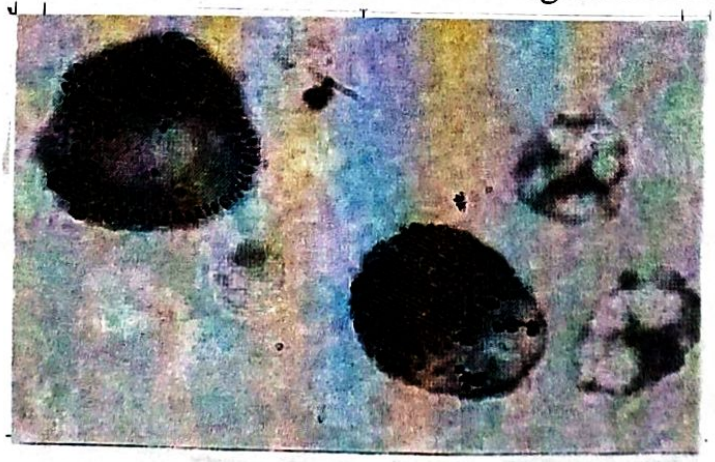

Fig. 1 Alveolar macrophages with ingested particles in metal workers.

Mast cells

Mast cells are derived from precursors in the bone marrow that migrate to specific tissue sites to mature. While they are found throughout the body, they are most prominent in the skin, the upper and lower respiratory tract, and the gastrointestinal tract. In most organs mast cells tend to be concentrated around the small blood vessels, the lymphatics, the nerves and the glandular tissue. These cells contain numerous cytoplasmic granules that are enclosed by a bilayered membrane. There appear to be two different populations of mast cells in humans, based on the presence or absence of certain proteolytic enzymes, notably tryptase and chymase. Mast cells found in the skin and connective tissue have both enzymes, while those in the alveoli, bronchial and bronchiolar regions, and mucosa of the small bowel contain only tryptase.

Mast cells may be activated by antigen-specific IgE bound to high affinity receptors, antigen-specific IgE bound to low affinity IgG receptors or through complement receptors. Following activation, mast cells release preformed mediators such as histamines and generate newly formed mediators such as tumor necrosis factor (TNF)-alpha and leukotriene C4.

Basophils

Basophiles represent approximately 1% of the white blood cells in peripheral blood. They have a half-life of about 3 days. They respond to chemotactic stimulation and tend to accumulate in inflammatory reactions. Basophiles have high affinity IgE receptors, as do mast cells. Cross-linking of surface-bound IgE by a multivalent specific allergen causes changes in the cell membrane and signal transduction that result in the release of mediators from the cytoplasmic granules. These preformed mediators include histamine, many other potent mediators, and proteolytic enzymes. Release of these substances from mast cells and basophiles is responsible for the early phase symptoms seen in allergic reactions, which occur within 30 to 60 minutes after exposure to the allergen.

Eosinophils

Eosinophils represent 2-5% of the leukocytes. Polymorphonuclear eosinophils resemble polymorphonuclear neutrophils, with the difference that they contain large red granulations (eosin staining) and crystals, which may also be traced in the expectorates of asthmatic patients (Charcot-

Leyden crystals). Eosinophil counts are increased, especially in allergic reactions, but they also act as a defence against certain parasites, in chronic inflammatory phenomena, and perhaps also in the defence against cancer. Like neutrophils, they do not return to the bone marrow from which they originate, but are eliminated via mucosal surfaces.

Immunoglobulins

IgG

IgG represents 75% of the total immunoglobulins in humans. IgG2 and IgG4 cross the placental barrier. Thus, at birth, a baby temporarily carries IgG of its mother, which lasts for 4-6 months. IgG intervenes in infections by means of opsonization and it can neutralize toxins. IgG appears especially following a secondary immune response, i.e., after a second encounter with antigen. The secretion of IgG is modulated by collaboration between B- and T-lymphocytes. IgG is strongly opsonizing for macrophages and polymorphonuclear cells possessing receptors for the Fc portion of IgG. Antigenic analysis of IgG myelomas revealed further variation and showed that they could be grouped into four isotypic subclasses now termed IgG1, IgG2, IgG3 and IgG4. The differences all lie in the heavy chains, which have been labeled gamma1, gamma2, gamma3 and gamma4, respectively.

IgA

IgA represents 10-15% of the human serum immunoglobulin pool, where it occurs as a monomer of the regular immunoglobulin four-chain unit, in contrast to secretory IgA, which mainly occurs in dimeric form. It has direct combination with and neutralization of pathogenic microorganisms in the gut and respiratory tract.

IgM

IgM represents about 10% of immunoglobulins. IgM antibodies are pentamers (5 units), the monomeric units being fixed by a J chain. They are also known as macroglobulins or heavy globulins. IgM is the first to appear in an immune response, and is the predominant antibody isotype in the early phase of humoral immunity. As it has a short life span, its presence points out to a recent infection (e.g., in toxoplasmosis).

IgD

This is normally present in minute concentrations in blood and other body fluids. It is readily detected on the surface of many early B cells in conjunction with IgM.

IgE

The plasma level of IgE in normal individuals is low. The IgE level is commonly increased in patients suffering from Type I allergies. It is a cytophilic Ig, i.e., it fixes to the surface of certain cells, especially mast cells and basophiles. It does not fix complement. IgE occurs predominantly in perivascular tissues where mast cells are localized. The binding of IgE with an antigen specific to this IgE on the mast cell membrane provokes the release of mediators from mast cell granules (degranulation).

Types of immunity
Humoral-Mediated immunity (HMI)

Electrophoretically, five major classes of human immunoglobulins can be separated these classes are IgM, IgA IgG, IgE and IgD. Each immunoglobulin class is synthesized by a separate population of B cells. B cells recognize an antigen and divide repeatedly; most of the daughter cells differentiate into plasma cells, which synthesize antibodies specific to that antigen. Plasma cells release their antibodies, which bind to the antigen, render it harmless, and tag it for destruction by other agents. Some B cells differentiate into memory cells, which provide lasting protection against further exposure to the same pathogen.

Cell-Mediated immunity (CMI)

T cell lymphocytes develop in the thymus gland where they acquire antigen receptor and divide into subpopulation of cells with distinctive functions. These populations of T-cell are recognized by their different wall surface markers. T lymphocytes involve four types

1. Cytotoxic (killer) T cells, which carry out the attack.
2. Helper cells, which promote cytotoxic T cell action and other defense mechanisms. The helper cells also known as CD4. They have a glycoprotein on their surface called CD4.

3. Suppressor cells, which limit the attack and keep the immune system from running out of control. Cytotoxic and suppressor cells are collectively known as CD8.
4. Memory T cells, which are descended from the cytotoxic cells and are responsible for memory in cellular immunity.

Consequences of immunosuppression/ immunodeficiency

The major consequence of immunodeficiency or impaired immune responsiveness is failure of protection of the host by antibody or effector cells directed against specific target antigens. Antibody and effector cells are essential for a protective effect against infectious and toxic agents that can cause destructive tissue injury and disseminated infections (Buckley, 1992). An impaired immune response also limits the response to protective vaccines that normally build adequate levels of cellular and antibody protection against infectious agents. Selective impairment of immune responsiveness in some instances may also lead to hypersensitivity states due to dysregulation. This effect could also result in autoimmune disease by promoting recognition of self-antigens, and hyper-responsiveness with increased antibody and effector cell production. Increased potential for the development of neoplasia and disseminated malignancies, especially those of the lymphocytic tissues, may occur with impaired immune surveillance.

The duration of immunodeficiency states might be transient or long lasting, depending on the severity and site of the specific xenobiotic effect. The immune impairment that results from continued specific drug therapy with immunosuppressive agents or human immunodeficiency virus (HIV) infection are the only examples of long-lasting acquired immunodeficiency in humans. Acquired deficiency of immune function as a result of xenobiotics or radiation have shown the marked capacity for self-restoring activity of the immune system, so that once an offending agent has been cleared from the body the various cellular components return to a normal state.

Classification of immune reactions

The four major types of hypersensitivity are

Type I anaphylactic, immediate reaction.
Type II cytotoxic reaction.
Type III immune complex reaction.
Type IV delayed or cell-mediated reaction.

Sometimes a fifth type of hypersensitivity is added, i.e., Type V stimulatory hypersensitivity.

1. Type I hypersensitivity

The distinguishing feature of Type I hypersensitivity is the short time lag, usually seconds to minutes, between exposure to antigen and the onset of clinical symptoms. The key reactant in Type I or immediate sensitivity reactions is IgE. Antigens that trigger formation of IgE are called atopic antigens, or allergens. Atopy refers to an inherited tendency to respond to naturally occurring inhaled and ingested allergens with continual production of IgE. Patients who exhibit allergic or immediate hypersensitivity reactions typically produce antigen-specific IgE in response to a small concentration of antigen. IgE levels appear to depend on the interaction of both genetic and environmental factors.

Anaphylaxis

Anaphylaxis is the most severe type of allergic response, as it involves multiple organs and may be fatal. Anaphylactic reactions are typically triggered by glycoproteins or large polypeptides. Smaller molecules, such as penicillin, are haptens that may become immunogenic by combining with host cells or proteins. Typical agents that induce anaphylaxis include venom from insects in the Hymenoptera family, drugs such as penicillin, and food such as seafood or egg albumin.

2. Type II hypersensitivity (Antibody-dependent cytotoxic)

Type II hypersensitivity reactions are caused by **IgG** and **IgM** antibodies directed towards cell surface antigens. These antigens may be altered self-antigens or heteroantigens. Such antibodies, bound to the cell membrane, can activate inflammatory phagocytes by Fc receptor triggering. These phagocytes will then try to kill or to inactivate their target, as they would kill a microorganism. If they are unable to phagocytose the whole cell, they will cause cell damage by secreting oxygen radicals and by generating inflammatory mediators such as arachidonic acid metabolites (prostaglandins and leukotrienes) from their cell membrane.

3. Type III hypersensitivity (Immune complex)

It is mediated by IgG or IgM, stems from the formation of large amounts of antigen-antibody complex throughout the body. Some

complexes become trapped in the basement membrane under the endothelium of blood vessels and trigger intense inflammation. Type III reactions are involved in acute glomerulonephritis and in systemic lupus erthematoses. Both diseases are autoimmune.

4. Type IV - delayed-type hypersensitivity

It is skin reactions, which take more than 12 h to develop after antigen application. The classical Type IV reaction is the tuberculin reaction, which reaches its maximum 24-72 h after the intradermal injection of mycobacterial extracts. This delayed type skin reaction to intradermally injected protein is characterized by a pronounced induration reflecting a dense mononuclear cell infiltrate. Since it became clear that antigen-specific T-cells are responsible for these reactions, the term Type IV reactivity has been used not only in relation to delayed-type hypersensitivity (DTH) reactions in the skin, but also to T-cell-mediated inflammatory reactions in other tissues. In addition, other T-cell-mediated reactions, such as those to infectious agents or tumour antigens, which are rather protective than hypersensitive, are regularly described as Type IV reactions.

5. Type V stimulatory hypersensitivity

Stimulatory hypersensitivity occurs when antibodies binding to a cell surface molecule cause inappropriate stimulation of the cell. Normal feedback inhibition will then fail. An example is Graves' disease (exophthalmic goitre), in which autoantibodies to the thyroid-stimulating hormone receptor on thyroid cells stimulate the production of excessive amounts of thyroid hormone, resulting in disease.

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CHAPTER II:

Immunotoxicity

Chapter II

IMMUNOTOXICITY

Immunotoxicity refers to any adverse effect on the structure or function of the immune system, or on other system as a result of immune system dysfunction. An effect is considered adverse or immunotoxic if it impairs humoral or cellular immunity needed by the host to defend itself against infectious or neoplastic disease (immunosuppression) or it causes unnecessary tissue damage (autoimmunity, hypersensitivity, or chronic inflammation).

This definition incorporates the concept that the immune system is in complex balance that includes interactions with other systems (e.g. nervous and endocrine) that may utilize or be affected by the same biological medicators or poisons (e.g. neuropeptide and steroid hormones). Change in an immune function or level of immunological mediator may not necessarily appear as an adverse effect, as in imunostimulation. Caution must be exercised in such cases, because a non-specific enhancement of the immune response that might be interpreted as a beneficial effect may result in suppression of specific immunity against a particular infection.

Normal functioning of the immune system prevents serious illnesses, such as infections and tumors. Immunotoxicology represents abnormalities in the immune system produced by exposure to chemicals and drugs. One consequence of dysfunction of the immune system is partial or complete immunosuppression, resulting in reduced defences against these conditions.

Allergy is another type of adverse effect on health produced by harmful immune responses following exposure to certain chemicals. The initial exposure results in the state of allergic sensitization, in which the immune system is primed to respond inappropriately on subsequent exposure to the same agent, and allergy is the functional disorder caused by that response. The best-known types of allergic response affect the skin, i.e., allergic contact dermatitis and atopic eczema, and the airways, i.e., asthma and allergic rhinitis, but any tissue in the body may be affected.

Allergic responses usually occur to foreign antigens, although self-antigens may sometimes be the targets of damaging immune responses. This is known as autoimmunity and may occur because the self-antigens have

been modified by chemicals or because the latter have adversely affected the control mechanisms that normally prevent autoimmune reactions.

Both allergic and autoimmune disorders may be caused by the responses of the immune system to substances of low (e.g., transition metals and simple organic compounds) or high relative molecular mass (e.g., proteins, including food components). The harmful reactions may occur at the site of exposure or systemically. The genetic make-up of the individual may be one predisposing factor.

Laboratory Assessment of immunotoxicity

A variety of immunlogic assays are available to investigate the effects chemicals and drugs on the immune system. Information concerning immunotoxic effects of drugs and chemicals can be used to explore the risk to humans in some instances. Immune alteration can be expressed as an enhancement or suppression of the immune function, or no demonstrable effect. Immune enhancement could result in autoimmunity, hypersensitivity disease, or allergy states. Immune depression can result in increased incidence of infections and neoplasia. The immune cells can be easily isolated and their functions studied in vitro assay systems.

Tier I Immunotoxicity Assay

Tier I testing provides high sensitivity for detection of immunotoxicants, but it lacks the specificity of the Tier II assay. The basic testing panel includes immunopathology, cell-mediated immunity, humoral-mediated immunity, and non-specific immunity. Complete blood counts with cell differentials help screen for the neutropenias and lymphopenias, commonly seen from immunosuppressive drugs and chemicals. Normal complete blood count and differential do not exclude immunotoxicity. Hemoglobin concentration and total RBC count are also part of this test. The weights of lymphoid organs are an important part of immunotoxicology screening. The individual organ weights are usually compared in an organ to-body weight ratio. Alteration of these normal ratios serves as an indicator of immunotoxicity and immune dysfunction. The organs typically studied are the thymus, spleen, and lymph nodes.

Tier II Immunotoxicity Assay

Tier I testing consists of a general screening panel of immune assays. Tier II testing is a comprehensive evaluation which includes in depth analysis of HMI and CMI functions, as well as host resistance. Tier II tests are restricted to confirmation of the initial screening or to exploring the mechanism of immune dysfunction. Tier II assays include examination of macrophage phagocytosis, bactericidal activity, macrophage enzyme levels, and macrophage cytolysis of tumor cells; quantification of T cell subpopulations using monoclonal antibodies; host resistance to infections and tumors; quantification of lymphokines; granulocyte function by nitro blue tetrazolium (NBT) testing; and bone marrow examinations.

TYPES OF HYPERSENSITIVITY DISEASES

I. Type I hypersensitivity diseases

A. Occupational asthma

Occupational asthma may be defined as asthma initiated by an agent inhaled at work. The inhaled agent has "switched on" asthma, and this is an example of a response induced by an identifiable environmental agent

1. **Biological materials:** Exposure to materials of biological origin occur in a wide variety of occupations. These include farming, the handling, storage, transport and processing of agricultural products such as grains and beans.

2. **Synthetic chemicals:** Exposure to the synthetic chemicals, which cause occupational asthma, occur in many different settings.

    a. Isocyanates are widely used and exposure occurs during their manufacture and in the production of polyurethanes.

    b. Acid anhydrides are used as curing agents in the manufacture of epoxy and alkyl resins.

Occupational asthma induced by protein allergens is invariably associated with atopy and with the presence of specific IgE antibody. In contrast, occupational asthma induced by chemical allergens is not restricted to atopic individuals and is not always associated with the presence of demonstrable IgE antibody. For both forms of asthma, the inflammatory

response in the respiratory tract is similar and characterized by T-lymphocyte and eosinophil infiltration.

The immunopathology of occupational asthma has the characteristic features of airway smooth muscle contraction, edema, and fluid accumulation, resulting presumably from the local release by mast cells of inflammatory mediators such as histamine and leukotrienes. Reactive chemicals capable of stimulating IgE response seem able to bind covalently to tissue proteins to form stable conjugates. The eosinophilia associated with allergen-induced respiratory reactions is influenced markedly by cytokines and, in particular, by interleukin-5.

Chemical causes of occupational asthma

Many different chemicals encountered at work can stimulate the hypersensitivity response and cause asthma. The more prevalent causes are shown in Table 1.

Table 1. Examples of occupational chemical respiratory allergens

Isocyanates
Diphenylamine-4,4'-diisocyanate
Hexamethylene diisocyanate (HDI)
Isophorone diisocyanate (IPDI)
Naphthalene-1,5-diisocyanate
Toluene 2,4-diisocyanate (2,4 TDI)
Toluene 2,6-diisocyanate (2,6 TDI)
Amines
Acid anhydrides (Dimethyl ethanolamine, Tetrachlorophthalic anhydride and Trimellitic anhydride)
Abietic acid (Glutaraldehyde)
Aminopenicillanic acid
Iso-nonanoyl sulfonate oxybenzene
Aminocephalosporanic acid
Methyl-2-cyanoacrylate
Ampicillin
Alpha-Methyldopa
Azocarbonamide
Phenylglycine acid chloride
3'-hydroxymethylacetophenone diacetate
Benzylpenicillin
Cephalexin
Chlorhexidine
Styrene
Complex platinum salts
Ethyl cyanoacrylate
Tylosin and Natural rubber latex

Atmospheric pollutants and asthma

There is evidence that air pollutants are involved in exacerbating asthma. Certain air pollutants have the potential to stimulate bronchoconstriction or airways inflammation. Exposure to SO_2 is associated with chest tightness and bronchoconstriction, with the concentration required to induce a response being dependent upon the degree of hyperresponsiveness. The effects of SO_2 may be augmented in the presence of other pollutants. It has been reported that the sensitivity of mild asthmatics to SO_2 is increased by prior exposure to ozone (O_3). Ozone is an oxidant pollutant that reacts rapidly with tissue components. It is formed by photochemical reactions involving oxides of nitrogen and organic molecules and occurs with other photochemical oxidants and fine particles in the complex mixture called "smog".

The use of bronchoalveolar lavage (BAL) as a research tool has afforded the opportunity to sample lung and lower airways after exposure to O_3 and to ascertain the extent and course of inflammation and its constitutive elements. The bronchoalveolar lavage studies have clearly demonstrated that O_3, even at very low concentration, causes increases in numbers of neutrophils, and a variety of other constituents of bronchoalveolar lavage fluid, some with potential inflammatory properties such as prostaglandin E_2, fibronectin, elastase and IL-6. Inflammation was also detected in the upper airways of O_3-exposed subjects as shown by an increase in neutrophils and other inflammatory indicators in the nasal lavage (NAL) fluid. Both nasal lavage fluid and bronchoalveolar lavage fluid from non-asthmatic subjects exposed to O_3 have been shown to contain the mast cell marker tryptase. Bascom et al. (1990) suggested that O_3-induced inflammation might share certain features of the response observed in subjects with allergic rhinitis challenged with allergen.

Particulate air pollutants, especially fine particles derived from combustion sources, are also of interest although there have been few controlled exposure studies outside those involving acid aerosols. Bioaerosols, to which an asthmatic is sensitized, are well known to exacerbate asthma. Studies in mice have demonstrated that diesel exhaust particles facilitate the induction of allergy. Chemicals adsorbed to the diesel exhaust particles, as well as carbon particles with very little chemicals on them appear to enhance the allergic immune response.

Predisposing factors of occupational asthma

1. **History:** The development of specific immunological responses and asthma usually occurs within a short period (1-2 years) from initial exposure to an occupational allergen. For those who survive this period, the risk of subsequently becoming sensitized is low. There is limited evidence that the amount of exposure experienced during this period is important.

2. **Atopy:** This is the development of IgE antibody to common environmental allergens such as grass pollens, house dust mite and cat fur, and is usually identified by skin prick test. It is associated with an increased risk of developing IgE antibody and asthma to some, but by no means all cases of occupational asthma.

3. **Cigarette smoking:** It exerts an important influence on the risk of developing occupational asthma, probably through an adjuvant effect on IgE production. IgE antibody production and asthma develop considerably more frequently in tobacco smokers compared to non-smokers exposed at work to many proteins and poisons including green coffee beans, acid anhydrides and complex platinum salts.

Diagnosis of occupational asthma

Accurate and early diagnosis of occupational asthma is important so that patients can avoid further exposure to the cause of their asthma and minimizes the risk of development of chronic asthma.

1. History

The characteristic history is the development of asthmatic symptoms (which may occur after the end of the working day, in the evening or night time) after an initial symptom-free interval. These improve when away from work (at weekends or holidays) and recur on return to work, often deteriorating during the workweek.

2. Serial peak expiratory flow measurements

Asthma can be confidently attributed to an agent inhaled at work when measurements of lung function reproducibly deteriorate during periods at work and improve during absence. Determination of airway

caliber for this purpose is most conveniently made by serial self-recording of serial peak expiratory flow during a period of several weeks, which ideally includes a long weekend or holiday period.

3. Immunological investigations

Evidence of IgE-mediated responses to low molecular weight poisons (usually conjugated to human serum albumin) can be obtained from skin prick and serological test. Such tests are diagnostically important where the development of IgE antibody bears a close relationship to the development of asthma and is not simply an unrelated consequence of exposure, or due to cross-reacting antigen binding to IgE antibody stimulated by other environmental allergens. These criteria have not been demonstrated for many occupational agents, but have been shown for asthma caused by laboratory animals, acid anhydrides and complex platinum salt.

4. Inhalation tests

The provocation of an asthmatic reaction by the specific occupational agent in a controlled inhalation test remains, for many, the gold standard against which other diagnostic tests for occupational asthma should be judged. It remains an essential part of the investigation and demonstration of new causes of occupational asthma, and an important tool where other methods of investigation have proved inadequate to provide a confident basis for future management advice. The aim in an inhalation test is to produce the exposure in the work place to a single agent and to provoke reproducibly an asymptomatic but significant asthmatic response.

B. Rhinitis and conjunctivitis

Rhinitis and conjunctivitis are common allergic inflammatory conditions induced by hypersensitivity to environmental allergens affecting the nasal (rhinitis) and/or conjunctival mucosa (conjunctivitis).

Rhinitis, characterized by one or more of the symptoms of nasal congestion, rhinorrhea, sneezing and itching, is defined as the inflammation of the lining of the nose due to increased vascular permeability, sensory nerve stimulation, and vasodilation with sinusoidal pooling plus edema formation. These responses are due to mediators released from the mucosal mast cells, and histamine is a major participant. The symptoms of allergic conjunctivitis consist of redness, lacrimation, itching and burning of the conjunctiva.

Rhinitis and conjunctivitis caused by contact with chemicals

Allergic rhinitis and conjunctivitis caused by contact with chemicals is less common than by contact with proteins. The prevalence is unknown. The scope of the problem is probably underestimated. Upper respiratory tract hypersensitivity involving the nose often coexists with asthma, conjunctivitis, bronchitis, and occasionally with contact dermatitis, allergic alveolitis or fever.

Occupational chemicals may be haptens, allergens, mediator-releasing or pharmacological agents and irritants. Eliciting agents that sometimes are shown to induce an immediate-type IgE-mediated hypersensitivity include anhydrides, metallic salts, dyes, diisocyanates and antibiotics. In many, but not all, workers with trimellitic acid-induced rhinitis and asthma, specific IgE antibodies and positive skin tests can be found, suggesting Type I and Type III allergic mechanisms.

In isocyanate workers with rhinitis, conjunctivitis, asthma, bronchitis, chronic obstructive lung disease, cutaneous reactions or fever, 26% had positive skin-prick tests and in 14% specific IgE antibodies could be detected after conjugation of isocyanates with serum albumin. In the majority of cases with occupational rhinitis, conjunctivitis and asthma caused by platinum salts, a Type I hypersensitivity was proved by skin tests, *in* vitro histamine release and passive cutaneous anaphylaxis. In textile workers exposed to reactive dyes, who had respiratory complaints, skin-prick tests and patch tests were positive. It is thought that these small molecule chemicals are haptens that combine with proteins to form antigenic determinants.

Rubbing of the eyes after handling detergents or other chemicals may provoke a contact conjunctivitis. Positive patch tests are found to chemicals such as antibiotics, thiomersal, benzalkonium chloride, solutions for contact lenses, and metallic salts. In these cases Type IV hypersensitivity seems to be the primary allergic mechanism.

Pathophysiology

Allergens transported by the air come into contact with the mucosal surface. Contact with mast cells or basophiles leads to IgE-dependent activation and degranulation of mast cells. Preformed mediators stored in the granules (e.g., histamine, tryptase) are released rapidly and elicit

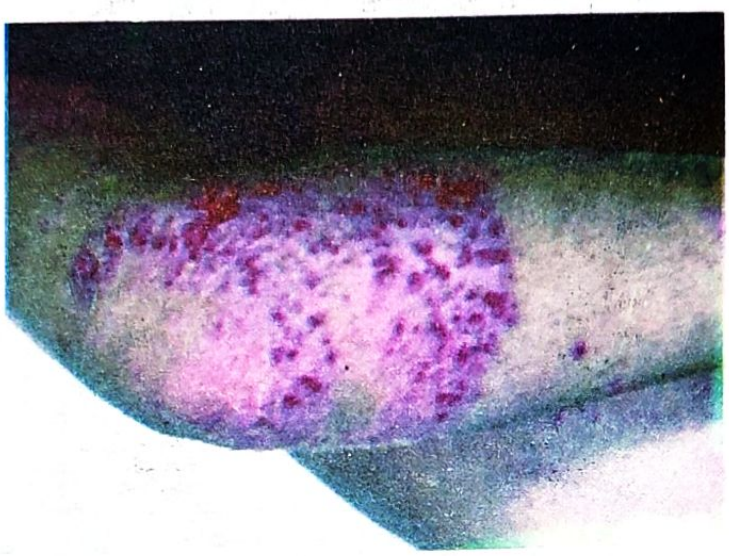
immediate symptoms. Other mediators are eluted slowly (e.g., heparin) or are synthesized de novo (e.g., prostaglandins, leukotrienes). Afferent nerve stimulation may provoke an axon reflex, and the release of neuropeptides (Substance P, Tachykinins) may amplify this reaction.

Mediators that are released slowly induce a late- phase reaction after 6 to 12 h, which results in local accumulation of inflammatory cells including CD4+ T-lymphocytes, eosinophils, Basophiles and neutrophils. These cells and mast cells release cytokines and proteins (e.g., eosinophil basic proteins) that perpetuate the reaction. Inflammatory cytokines (e.g., IL-4) may selectively recruit eosinophils by increasing the expression of adhesion molecules on the vascular endothelium. The eosinophil can cause epithelial denudation, mucus secretion and histamine release. Both eosinophil and neutrophil infiltrates are inhibited by corticosteroids.

C. Atopic Eczema (Atopic Dermatitis)

Atopic Eczema (Atopic Dermatitis) is an inflammatory skin disease, characterized by an itchy, erythematous, poorly demarcated skin eruption (Fig. 2). It is believed to be multifactorial. Recent interest has focused on the role of airborne allergens (house dust mites, pollen, animal dander), outdoor pollution and climate. In Atopic Eczema, the patient is much troubled by itching skin; there is a history of chronic or chronically relapsing dermatitis, worst on the flexures, which are excoriated and there is a family or personal history of atopy. This is the typical picture of Atopic Eczema, though some of the features may be absent.

In any discussion of pathogenesis, family history is important because Atopic Eczema is part of the atopic syndrome that includes genetically determined such as extrinsic bronchial asthma, allergic rhinitis, allergic conjunctivitis and gastrointestinal allergy. Important laboratory indices are blood and tissue eosinophilia and antigen-specific IgE bound to mast cells in skin (intracutaneous challenge) or peripheral blood (serological assays).



D. Urticaria

Urticaria may be defined as an eruption of short-lived red oedematous swellings of the skin, associated with itching. Angioedema is the corresponding tissue reaction of urticaria occurring deeper in the subcutaneous tissue (Fig. 3). Urticaria lasts less than 24 hour, although new lesions may continue to arise. In contrast, angioedema is characterized by deep, skin-colored swelling, most commonly of the lips or eyes that may last for several days. It may occur with urticarial lesions or arise independently.

Urticaria usually involves degranulation of mast cells and release of histamine. Many different elicitors have to be considered. Allergy due to a reaction between a specific antigen and a mast cell-fixed IgE antibody is only one mechanism. Pseudo-allergic reactions, toxic effects and viral infections play a major role.

If acute urticaria persists, it is called chronic urticaria. Wheals may be circular, polycyclic or figured. Itching is almost always present in patients with urticaria but is inconsistent in angioedema.

Fig. 3 Angioedema with marked swelling of the upper lip.

Skin previously involved by wheals or angioedema looks entirely normal apart from occasional purpura or other signs of trauma due to scratching. The mucous membranes are frequently involved including the tongue, soft palate and pharynx. Although discomfort and breathing difficulty may occur, fatalities are almost exclusively associated with hereditary angioedema. Acute urticaria may be associated with systemic anaphylactic symptoms (wheezing, dyspnoea, syncope, abdominal pain, vomiting). Occasionally acute urticaria may merge into serum sickness, arthritis, fever, proteinuria). Common causes of allergic acute urticaria include ingestion of penicillin, shellfish, soft fruit and nuts.

Urticaria of immunological origin may arise rapidly (often less than 60 minutes) at the site of contact of the skin or mucous membranes with a specific substance.

Contact urticaria may also be of non-immunological origin, and there are frequent instances in which the mechanism is uncertain. When an immune mechanism is involved, the final common pathway is probably the same. Contact urticaria of immunological origin involves IgE-mediated hypersensitivity. In non-immunological examples, the offending substance may evoke histamine release directly from cutaneous mast cells. Such substances include ammonium persulfate and cinnamaldehyde.

E. Anaphylaxis

Anaphylaxis means a severe systemic allergic reaction. No universally accepted definition exists because anaphylaxis comprises a constellation of features, and the argument arises over which features are

essential features. A good working definition is that it involves one or both of two severe features respiratory difficulty (which may be due to laryngeal edema or asthma) and hypotension (which can present as fainting, collapse, or loss of consciousness). Other features are usually present. The confusion arises because systemic allergic reactions can be mild, moderate, or severe. For example, generalized urticaria, angioedema, and rhinitis would not be described as anaphylaxis, as neither respiratory difficulty nor hypotension potentially life-threatening features is present.

An allergic reaction results from the interaction of an allergen with specific IgE antibodies, bound to Fc receptors for IgE on mast cells and Basophiles. This leads to activation of the mast cell and release of preformed mediators stored in granules (including histamine), as well as of newly formed mediators, which are synthesized rapidly. These mediators are responsible for the clinical features. Rapid systemic release of large quantities of mediators will cause capillary leakage and mucosal edema, resulting in shock and asphyxia. The common causes of anaphylaxis are food (e.g. Peanuts, Tree nuts, Fish, Shellfish, Egg, Milk and Sesam), Bee and wasp stings, Drugs Antibiotics (e.g. penicillin, Intravenous anaesthetic drugs, Aspirin, Non-steroidal anti-inflammatory drugs, Intravenous contrast media, and Opioid analgesics) and Latex rubber.

II. Type II hypersensitivity diseases

Pathogenic Type II reactions may occur towards autoantigens, alloantigens (in blood transfusions), infective agents and drugs or chemicals, as described above. These immune reactions may cause corresponding disorders, i.e., autoimmune diseases, transplantation/ transfusion reactions or drug-induced haemolytic reactions.

Some drugs or their metabolites are chemically reactive agents that readily bind to cells and tissues. Such drugs, present on the cell membrane of blood cells, are obvious targets for pathogenic Type II reactivity.

The most frequent allergic reaction occurs with penicillin and its relatives. Benzylpenicillin is a small molecule with a relative molecular mass of 372.47 and with a highly reactive beta-lactam ring, which may bind to amino groups on proteins (carrier), forming covalent conjugates. The formed penicilloyl hapten is considered as the major determinant in penicillin allergy. Although penicillin is able to induce all types of hypersensitivity reactions (IgE-, immune complex- or T-cell-mediated),

haemolytic anaemia with penicillin-specific IgG antibodies reacting with penicillin-coated erythrocytes is a typical example of Type II reactivity.

Interestingly, the specificity of drug-induced antibodies is often much broader than would be expected from the penicillin example. Ultimately, drugs trigger Type II reactivity without being involved in the final destructive reaction. In addition to hapten-specific antibodies, drugs can induce antibodies to metabolites, to drug-carrier combinations or to the carrier alone, resulting in clear-cut autoimmune reactivity. D-penicillamine is a classical example of a drug inducing autoimmunity, but chemicals such as mercury and gold are also able to induce autoimmunity.

The mechanism by which drugs can induce autoantibodies is by presenting the hapten in or on their autoreactive B-cells, which are normally present at very low frequencies without being activated, can trigger hapten-specific T-cells to help them (the B-cells) differentiate into antibody-producing plasma cells. Although the induction of the disease is drug-dependent, the Type II effector reaction towards autologous targets may be drug-independent. Hence, in this case the induced autoimmune disease would continue after the exposure to the drug had ceased.

A- Autoimmune haemolytic anemia

In drug-specific haemolytic anaemia, drug-specific B-cells present the drug to drug-specific T-cells. Activation of T- and B-cells now induces the B-cell to become a plasma cell, producing drug-specific antibodies. Eventually these antibodies lead to destruction of haptenized erythrocytes, while normal cells remain intact.

In drug-induced autoimmune haemolytic anaemia, an autoreactive B-cell ingests and processes erythrocyte membranes, including the haptenized parts. Normally, autoreactive B cells exist but do not become activated by lack of appropriate stimulating T-cells. If drug-specific T-cells are present, however, these B-cells, presenting haptenized peptides may become activated and differentiate into autoantibody-producing plasma cells. These antibodies may induce haemolysis of all erythrocytes in a drug-independent manner.

When drugs, like penicillin, bind covalently to red blood cells, these drug-specific antibodies bind to the cells and induce their elimination by phagocytosis in the spleen. The induction of high titres of penicillin IgG

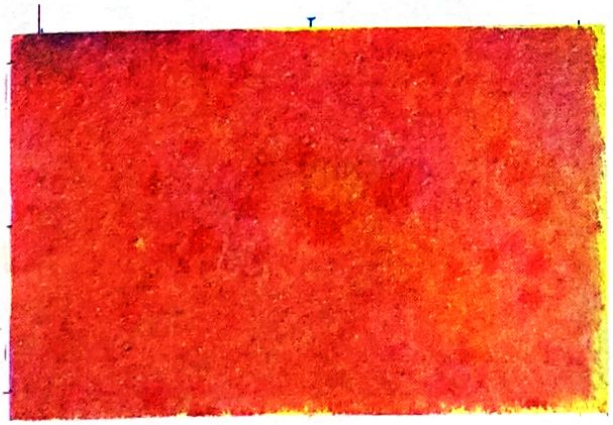
antibodies typically occurs upon intramuscular administration, rather than upon intravenous penicillin therapy. On the other hand, relatively high intravenous doses of penicillin are required to make the erythrocytes susceptible to immune-mediated haemolysis. Thus, most patients with penicillin-induced haemolytic anemia have received large doses of drug over a protracted period. After discontinuation of therapy the haemolysis quickly resolves and the antiglobulin test becomes negative within weeks.

Some drugs appear to be able to induce true autoimmune haemolytic anaemia, with Rhesus antigens as the most common targets of the red cell antibodies. While several drugs have been reported to provoke red cell autoantibodies, alpha-methyldopa is the best-studied example. Only after prolonged therapy anti-red cell autoantibodies (IgG anti-Rh) are formed. Upon withdrawal of the drug the antibody titres usually decline and haemolysis ceases.

If soluble drug-specific antibodies are present, they may form immune complexes with administered drugs and fix complement. The complexes are then adsorbed by erythrocytes resulting in lysis. Strictly speaking, this haemolysis is caused by Type III reactivity.

B- Autoimmune thrombocytopenic purpura

Autoimmune or idiopathic thrombocytopenic purpura (ITP) is another example of a Type II reaction involving destruction of self-antigens. This disease is characterized by shortened platelet survival and the presence of antibody bound to platelets. It can be classified as acute, intermittent or chronic, depending on the severity and frequency of the symptoms (Fig. 4).



Drug-associated idiopathic thrombocytopenic purpura appears to be of two types acute, immune-mediated syndromes caused by drug-dependent antibodies and insidious, dose-related toxic effects. Quinine is by far the most common cause of immune-mediated thrombocytopenic purpura. The characteristic presenting features of quinine-associated thrombocytopenic purpura are the sudden onset of nausea, vomiting, diarrhea (occasionally bloody), fever, and chills occurring several hours after quinine ingestion. Sepsis is a common initial, incorrect diagnosis. Patients may have severe mental status abnormalities, even coma.

In addition to the signs of thrombocytopenic purpura, leukopenia, disseminated intravascular coagulation, and liver function abnormalities may occur, all of which can be caused by quinine sensitivity. These syndromes are caused by quinine-dependent antibodies to epitopes on multiple cell types. Plasma exchange treatment appears to be effective.

Quinine is also one of the most common drugs that can cause isolated thrombocytopenia. In patients with isolated thrombocytopenia, the absence of anemia and any other systemic symptoms and signs exclude consideration of thrombocytopenic purpura. However, one important case report describes a patient with Quinine-induced isolated thrombocytopenia who developed thrombocytopenic purpura following a subsequent exposure to quinine. This observation is consistent with the development of only quinine-dependent antiplatelet antibodies causing the initial episode and the subsequent development of quinine-dependent antibodies to multiple tissues causing the systematic disorder of thrombocytopenic purpura.

Ticlopidine and Clopidogrel have also been reported to be associated with thrombocytopenic purpura. In patients with Ticlopidine-associated thrombocytopenic purpura, the Ticlopidine had been taken for less than 2 weeks in 15% of patients and less than one month in 80% of patients. In the largest report on Clopidogrel-associated thrombocytopenic purpura, the onset of thrombocytopenic purpura was 3-14 days after beginning Clopidogrel in 10 of 11 patients. However since 2 of the 11 reported patients had recurrences of thrombocytopenic purpura without re-exposure to clopidogrel, the initial drug association may have been coincidental.

C- Pemphigus and pemphigoid

Pemphigus is the term used to describe a group of diseases that have in common superficial blistering of the skin and mucous membranes (Fig.5).

It is a type II reaction in the skin. These organ specific autoimmune skin diseases have been linked to antibodies directed against specific proteins found in human skin. Removal of these antibodies by plasmapheresis reduces disease activity and transfer of positive sera to mouse and monkeys can induce pemphigus-like lesions.

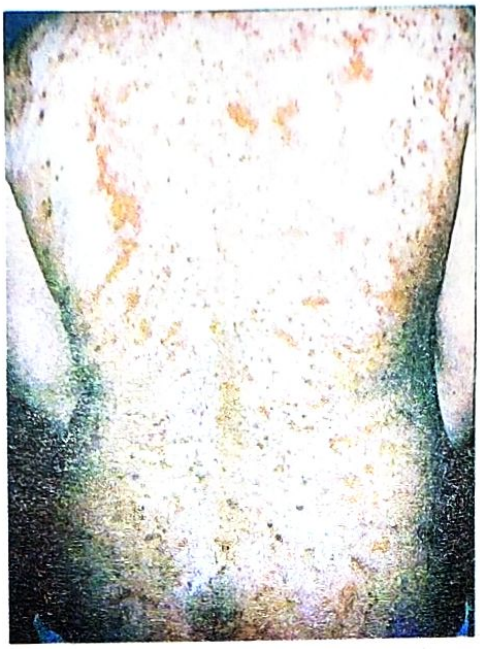


Fig. 5 Pemphigus.

Drugs may play a precipitating role in pemphigus. Penicillamine-D, thiopronine, ampicillin, rifampicin, phenylbutazone, captopril, pyrazolon, enalapril and piroxicam can all induce pemphigus. It would appear that the presence of certain chemically reactive groups in the drugs, in addition to the pemphigus susceptibility genes in the patient, predispose for drug-induced pemphigus. Sulfhydryl groups (-SH), present in D-penicillamine, and active amide groups (-CO-N-), typically present in enalapril, are held responsible for the acantholytic effects in human skin cultures. In the group of penicillin and cephalosporins, this active amide group is probably more important for the induction of pemphigus than the sulfhydryl group.

D- Myasthenia gravis

Myasthenia gravis is an autoimmune disease that is mediated by IgG antibodies directed to the acetylcholine receptors in the postsynaptic membrane of the muscle. The number of receptors can be considerably reduced by complement-mediated lysis and accelerated internalization. Additionally, the residual receptors may be blocked by autoantibodies directed to the acetylcholine binding site, thus leading to further impairment

of the transmission from nerve to muscle. As a consequence, the disease is characterized by weakness and fatigue of the striated muscles. In some patients only few muscles are affected; a well-known localized form of the disease is ocular myasthenia.

In young patients with myasthenia gravis (40-50% of patients, usually female) the thymus is an important site of autoantibody production and T-cell activation. Within the hyperplastic thymus, formation of lymphoid follicles can be observed, with germinal centers surrounded by T-cells. As therapeutic treatment, in addition to immunosuppression, thymectomy is beneficial in these patients, since a substantial source of both antigen and antibody-producing plasma cells is thus removed. On the other hand, in late onset (usually male) patients (15-20%), the thymus is rather atrophic and autoantibody production by thymic cells is relatively low. In another minority of patients (15-20%) thymoma may develop. In this last group of patients, autoantibodies to striated muscles are typically found in addition to the acetylcholine receptor autoantibodies.

Like pemphigus, myasthenia gravis can be induced by a number of drugs. D-penicillamine, used for treatment of rheumatoid arthritis, has been most frequently reported as a trigger for myasthenia gravis. A few other drugs are suspected of inducing myasthenia gravis; among them are thiopronin and chloroquin. Drug-induced myasthenia is characterized by frequent involvement of facial and oropharyngeal muscles.

III. Type III hypersensitivity diseases

Extrinsic allergic alveolitis

Extrinsic allergic alveolitis (EAA) is usually defined in pathological terms as a granulomatous inflammatory reaction which predominantly involves the gas-exchanging parts of the lung and which is the outcome of a specific immunological response to an inhaled substance. The vast majority of reported cases have been caused by inhaled organic dusts, but a few cases have been attributed to inhaled isocyanates. No reported case has been validated by biopsy evidence of the characteristic pathological appearances; cases have been identified on the basis of

a. Characteristic clinical history.
b. Changes on chest radiograph.

c. Pattern of functional change following controlled isocyanate inhalation.

d. Proportions of cells received at bronchoalveolar lavage.

Typically, patients present with a history of recurrent episodes of breathlessness associated with systemic symptoms of fever, malaise and chills. A few (but only a minority of reported cases) have had abnormal chest radiographs. In the majority of cases the diagnosis has been made by the response to inhalation testing or the pattern of cells recovered at bronchoalveolar lavage. Inhalation testing provoked the changes of an "alveolar reaction" with proportionate reduction in forced expiratory volume in 1 second (FEV_1) and forced vital capacity accompanied by a neutrophil leucocytosis and fever. The cells recovered at bronchoalveolar lavage have, as is characteristic of Extrinsic allergic alveolitis (EAA), shown an increase in the proportion of lymphocytes.

In some cases IgG antibody to a human serum albumin conjugate of the relevant isocyanate has been identified in serum. The outcome of EAA caused by isocyanates has been little reported, but most cases, even if showing significant functional impairment at the time of diagnosis, would seem to have no permanent residual disability after avoidance of isocyanate exposure. Environmental organic chemicals like toluene diisocyanate and trimellitic anhydride, but also inorganic compounds, as chromium and nickel are known sometimes to cause pulmonary disease.

IV. Type IV hypersensitivity diseases

A- Chronic beryllium disease

Chronic beryllium disease is a systemic disorder with primary manifestations in the lungs. The pathogenic beryllium compounds include metallic beryllium, beryllium alloys and beryllium oxide fume. Inhalation of low levels of beryllium dusts or salts over months to years is associated with a chronic interstitial pulmonary granulomatous disorder clinically similar to sarcoidosis. The skin manifestations of beryllium disease consist of contact dermatitis and subcutaneous granuloma formation with occasional ulceration.

The concept that the granulomas of chronic beryllium disease are T-cell-mediated immune granulomas is supported by the following observations

a. Beryllium (i.e., the antigen) persists in the lung for long periods.

b. Large numbers of T-cells and non-caseating granulomas are present in the lung.

c. In response to beryllium salts, lung and blood T-cells proliferate and release lymphokines in vitro, a parameter also used diagnostically to distinguish beryllium disease from sarcoidosis.

d. Intradermal administration of beryllium salts induces a local granulomatous response in these individuals.

In chronic beryllium disease, the lung T-cell population is predominantly of the CD4+ phenotype. These CD4+ T-cells, compared to blood T-cells from the same individual or compared to T-cells from normal individuals, exhibit increased proliferation in response to beryllium. The T-cells are activated, expressing HLA class II molecules and IL-2R and releasing IL-2.

Analysis of T-cell lines and T-cell clones of individuals with this disease has confirmed that the beryllium-induced response is antigen-specific and that all the responder cells are CD4+ T-cells.

In an epidemiological study of groups exposed to the combustion products of coal containing a high concentration of beryllium, Bencko et al. (1980) found elevated levels of IgG and IgA and increased concentrations of autoantibodies (anti-nuclear and anti-mitochondrial antibodies).

B- Systemic autoimmune diseases

Several organ-specific autoimmune diseases such as pemphigus and pemphigoid and myasthenia gravis have been discussed above. Many of the major rheumatological disorders are autoimmune in nature. Although systemic lupus erythematosus (SLE) can be ranked under Type III immune complex disorders, for other autoimmune diseases this categorization is less clear-cut.

Inherent properties of poisons inducing autoimmunity

A variety of medicinal drugs with a relative molecular mass of less than 1000 can elicit systemic hypersensitivity reactions and autoimmune disorders in susceptible individuals at low incidence. Chemical agents, drugs in particular, with a documented potential to induce autoimmune disorders such as SLE, belong to different chemical classes. These include,

among others, derivatives of aromatic amines, hydrazines, hydantoins, thioureylenes, oxazolidinediones, succinimides, dibenzazepines, phenothiaines, sulfoamides, pyrazolines, amino acids, amines, halothane, mercuric chloride, gold preparations, occupational or environmental chemicals such as tri- and perchloroethylene and vinyl chloride. Environmental nitrophenols have been suggested to be able to elicit or perpetuate human autoimmune disorders. Many of these compounds are heterocyclic and contain at least one aromatic group, suggesting that particular chemical entities may favour induction of immune dysregulation.

From a pharmacological point of view, the majority of autoimmune disease-inducing drugs are beta-adrenergic-receptor-blocking compounds, drugs acting on the central nervous system (CNS), anti-thyroid agents and anti-infective agents. In view of the tight functional connectivity between immune, nervous and endocrine systems, which is at least partially affected by shared receptors and mediators among the systems, it is possible that CNS drugs modulate immune responses by acting at these receptors or inducing common mediators.

Lupus-inducing compounds have the capacity to be oxidized by the extracellular myeloperoxidase-H_2O_2 system of activated neutrophils, despite their chemical and pharmacological heterogeneity.

Allergic contact dermatitis

Allergic contact dermatitis is considered to be the most frequent pathological manifestation of Type IV reactivity. In allergic contact dermatitis, T-cells are sensitized to proteins, environmental agents and chemicals, entering the body via the skin. Repeated exposure to such chemicals results in persistent eczematous inflammatory reactions at the site of allergen contact. Although allergic contact dermatitis can be regarded as a prototype of delayed-type hypersensitivity, the sensitization process for chemical contact allergens, which already starts in the most superficial layers of the skin, is very special.

1. Hand eczema

Allergic contact dermatitis on the hands is therefore both a common disease and costly for the society, and it can imply significant socioeconomic consequences for the individual. In a survey of 564 cases of

permanent disability caused by skin diseases, 222 of the 564 were caused by allergic contact dermatitis of the hands (Fig. 6).

Frequent causes of allergic hand eczema are nickel, chromate, rubber additives preservatives, and fragrances. It can be acute or chronic, and it can be located on either the dorsal or volar surfaces, or only on the fingers. It can also present as a diffuse dermatitis. Spread to the face and forearms are common.

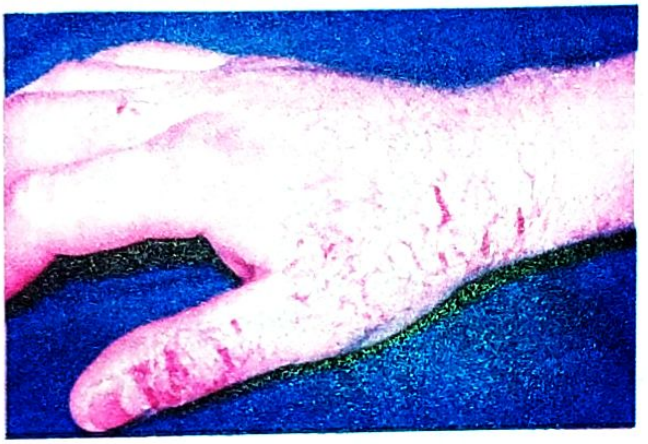


Fig. 6 Hand Eczema.

2. Facial dermatitis

The face is second to the hands in the frequency of allergic contact dermatitis. The exposure can be direct to airborne allergens or indirect by contact with allergens transferred from the hands to the face. Acute allergic contact dermatitis in the face is often dramatic with severe edema particularly of the eyelid regions. Chronic cases frequently show patchy dermatitis even if the allergen is uniformly spread on the face. Cosmetics, particularly fragrances, are the most common causes of facial dermatitis. Allergic contact dermatitis from medicaments (e.g., eye drops) (Fig. 7) and airborne occupational dermatitis are seen. Severe edema of the eyelids is a common pattern of plant dermatitis. Facial dermatitis causes distress to the individual because of pain, itching and disfiguration.

3. Other types of dermatitis

Shoe dermatitis is located in the skin area in direct contact with the offending material, most frequently chromate-tanned leather, rubber and glues.

Allergic contact dermatitis from textiles gives a characteristic clinical pattern with dermatitis in areas where textiles are in close contact with the skin on the trunk and extremities (Fig. 8). The offending sensitizers are textile dyes and formaldehyde-releasing textile resins.

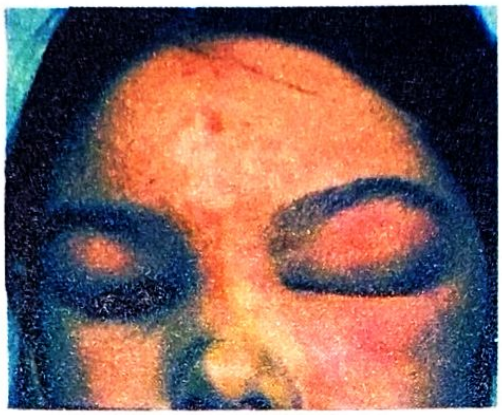


Fig. 7 Facial Contact dermatitis.

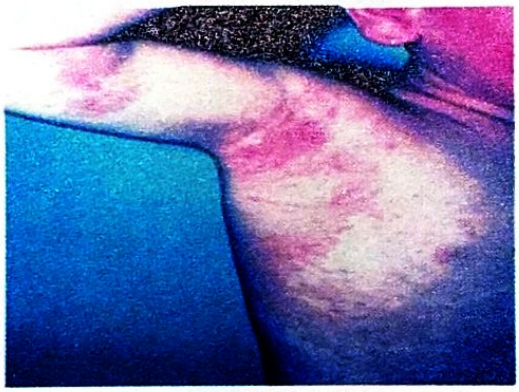


Fig. 8 Allergic contact dermatitis.

4. Allergic contact urticaria

Contact urticaria is an immediate wheal reaction in the skin caused by vasodilatation, with subsequent edema (Fig. 9). Contact urticaria can either be allergic or non-allergic. In the non-allergic types chemical causes a degranulation of the mast cells without involvement of the immune system. The allergic types are mediated via IgE bound to specific receptors on the mast cells and basophil lymphocytes in the skin. The clinical types are similar with urticaria localized at the contact site. Generalized anaphylactic reactions are rare. Both organic and inorganic substances have now been described as causes of allergic contact urticaria.

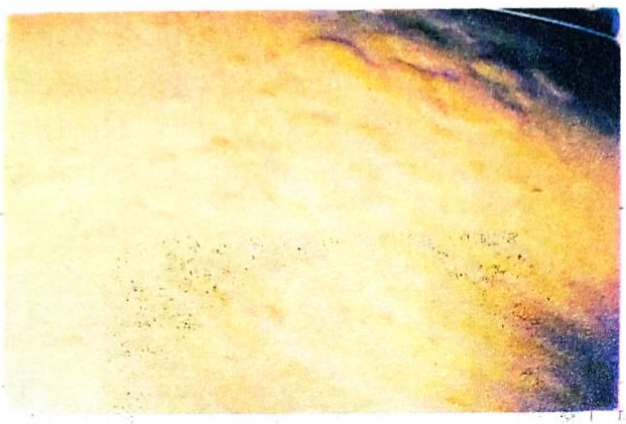


Fig. 9 Urticaria.

Contact urticaria is a frequent occupational disease among individuals handling animals and animal products. Allergic contact urticaria from proteins in rubber latex is a frequent and troublesome problem among workers, particularly health personnel, due to widespread use of rubber gloves. A sensitization frequency of 2.8 to 10.7% has been reported in health personnel. Individuals occupationally sensitized to rubber latex proteins can develop anaphylactic reactions if exposed to rubber gloves as patients.

Allergic contact dermatitis as an occupational disease

Occupational skin diseases are defined as skin diseases either wholly or partly caused by the patient's occupation. The epidemiology of occupational skin diseases, which mostly comprise contact dermatitis of the hands, is known from population and cross-sectional studies of specific occupational groups.

Skin diseases comprise between 20 and 40% of all occupational diseases, depending on geographical area. Approximately one-third is caused by allergic contact dermatitis and the rest mainly by irritant dermatitis. The principal occupational contact sensitizing chemicals are listed in Table 2. The common high-risk occupations for allergic contact dermatitis, modified from Rycroft (1995), are given in Table 3. The prevalence of occupational contact dermatitis in these occupations varies from a few percent up to 15%.

Table 2 Main allergens related to occupational exposure.

Allergens	Sources of exposure
Acrylates	Adhesives; bone cement; dental products; UV-curing lacquers, etc.
Amine	Hardeners/curing agents for epoxy resin.
Chromate	Cement; leather; pigments
Cobalt	Paints/lacquers.
Colophony	Adhesives; dental products; paper; tin solder, etc.
Epoxy resin	Adhesives; paints; electric insulation
Isocyanates	Adhesives; paints; fillings; polyurethane foams.
Nickel	Coins; nickel plated objects; contaminated oils, etc.
Paraphenylenediamine	Hair dyes; rubber additive.
Plastics/resins	Adhesives; paints; fillings, containers, etc.
Rubber additives	Rubber gloves; rubber tubing; washers, etc.

Table 3 High-risk occupations for allergic contact dermatitis.

Adhesives/plastics workers	Horticulturalists
Agriculturalists	Leather tanners
Cement casters	Painters
Glass workers	Rubber workers
Graphic workers	Textile workers
Hairdressers	Tilers
Health care workers	Wood workers

Diagnostic methods

1. Patch testing

The aim of patch testing is to diagnose contact sensitization to environmental chemicals. The patch test was introduced in 1896 by the Swiss dermatologist Jadahsson. The technology is a biological test where contact allergy is proved by re-exposing the skin to the specific chemical under occlusion on a skin area of 0.5 cm^2 on the upper back for 2 days. A positive test is a reproduction of the clinical disease showing redness, infiltration and eventual vesicles. Standardization has taken place, particularly influenced by the Scandinavian and later the International Contact Dermatitis Research Group (ICDRG). The test should only be performed using standardized test materials. All patients are primarily tested with the Standard series including the most frequent sensitizing chemicals

such as metals, preservatives, fragrances, rubber additives and topically used medicaments. Testing is frequently supplemented with substances present in the patient's private or occupational environments. Specially trained staff is necessary to obtain high quality outcome of the procedure.

Sensitization can be quantified according to the degree of positive patch test reaction (+ to +++), patch test concentration threshold defined by dilution series, and finally by the "Use test". In the latter test the individual is exposed to the chemical simulating normal use. The outcome of patch testing defines whether contact allergy is present or not.

The frequency of positive patch test reactions in the general population. The allergens causing positive reactions most frequently in eczema patients were nickel, fragrance mixes, cobalt chloride, colophony and balsam of Peru. For the general population, nickel and thiomersal were the most common causes of positive patch test reactions. Contact sensitization is generally more frequent among patients investigated at dermatological centers than it is in the general population.

2. In vitro testing

Several attempts have been made to develop in vitro methods for testing contact sensitization. In vitro tests, in particular the lymphocyte proliferation test (LPT), using patient-derived white blood cell samples, can be of considerable value in answering specific scientific questions, e.g., on the involvement of allergen-specific T-cells or on potential cross-reactivity patterns between allergens.

3. Assessment of exposure

To establish the diagnosis of allergic contact dermatitis, the outcome of patch testing needs to be combined with a detailed exposure history. Both domestic and work-related exposures need to be elucidated. Factory visits are valuable but rarely done. The most common contact allergens are metals, preservatives, rubber additives, perfumes and medicaments. The main sources of exposure to contact allergens can be divided into groups of substances, products or use categories. Exposure to allergens occurs under many circumstances, such as occupational, domestic work, hobby and leisure time activities, topical medicaments, cosmetics, personal care products, clothing and shoes.

Treatment and prevention of allergic contact dermatitis

The treatment of allergic contact dermatitis requires medical intervention. It usually involves the controlled use of emollients or corticosteroids as well as prevention of further exposure to the offending allergen.

1. Primary prevention

In the 1960s an epidemic of contact dermatitis from dishwashing products occurred in Scandinavia. The epidemic was resolved by the concerted action of dermatologists and manufacturers. Extensive chemical analysis combined with animal predictive testing, identified highly sensitizing sultones to be present in some products. It was determined that these specific chemicals occurred as an impurity in the manufacturing process, when temperature control was not strictly maintained. The evaluation of the problem led to a solution, and there have been no recurrences.

There are examples of exposure to hapten concentrations being legally regulated in an attempt to prevent contact sensitization. There is a complex European Union regulation on cosmetic products, forbidding certain substances and regulating others, i.e., preservatives, by a concentration limit.

Since the 1950s, chromate in cement has been known to be one of the main causes of allergic chromate dermatitis among construction workers. At the start of the 1980s the Scandinavian countries added ferrosulfate at a low concentration to cement to reduce the hexavalent chromate to trivalent chromate. The idea of this initiative was that the trivalent chromate is not absorbed, or only to a minor degree, through human skin, and therefore the risk of primary sensitization from this salt is significantly less than from hexavalent chromate.

Nickel is a common contact allergen on a global scale. This allergy is caused by intimate skin contact with metal alloys, releasing nickel when exposed to human sweat. Under simulated use conditions, some alloys release high amounts and other alloys low amounts of nickel.

2. Secondary prevention

The cornerstones of the secondary prevention of allergic contact dermatitis (elicitation of contact dermatitis) are based on sufficient diagnostic procedures and patient information systems. The availability of standardized patch test materials is essential. Furthermore, it is crucial that it is possible for the doctor to inform the patient where exposure to the specific allergen can be expected. Edman (1988) found that the prognosis for patients sensitive to topical medicaments depended upon whether the patients were able to follow the doctor's advice on the occurrence of sensitizers in different products. Later studies have shown that patients with contact allergy to formaldehyde often continued to be exposed to formaldehyde. When a careful investigation was made, formaldehyde exposure could be demonstrated in nearly all the patients, which seemed to be decisive for the prognosis of their hand eczema.

Effect of drugs on immune system

Drugs can cause release of intracellular mediators by activation of complement through the alternative pathway, or they may act directly without involvement of the immune system (anaphylactoid reaction). Often, the antigen has not been identified. Conversely, the antigen basis of penicillin allergy is clearer than for most other drugs and this is used as an instructive model.

Manifestations of drug-induced immunotoxicity

Immune reactions associated with drug therapy can affect virtually every organ

1. Dermatological manifestations Rash may be one of a variety of types, from localized contact dermatitis or angio-oedema to diffuse urticaria or widespread macular or popular rash. When secondary to bone marrow effects, purpura may be found. The skin is the most commonly affected.

2. Hematological manifestations may affect the circulating blood (e.g. haemolytic anaemia) or any cellular components in the bone marrow (e.g. eosinophilia, thrombocytopenia, agranulocytosis or pancytopenia).

3. Hepatic manifestations may occur as cholestatic or hepatic jaundice.

4. Renal manifestations may occur as oliguria or nephritic syndrome.

5. Pulmonary manifestations affect the bronchi (e.g. bronchospasm) or the parenchyma (e.g. eosinophilic infiltrates).

In many instances, the reactions are not confined to one organ, although maximum physiological disturbance may be so focused; for example, renal failure from interstitial nephritis requires specific medical treatment but may be associated with rash, pyrexia and possibly eosinophilia.

The severity of the reaction can also vary, ranging from acute, life-threatening anaphylaxis to a mild rash requiring no specific therapy. Even dermatological reactions vary in the degree of incapacitation, which they incur, and some, such as purpura, can herald a potentially life-threatening situation.

Features suggestive of drug induced immunotoxicity

1. Prior contact with the same substance or one of similar chemical structure.
2. Reaction occurring with doses which are small in relation to the therapeutic dose.
3. No dose-response effect.
4. Reaction unrelated to pharmacological effects.
5. Other manifestations of allergy occurring concurrently.
6. The reaction affects only a minority of the exposed population.

These features may be difficult to elucidate and none is specific for a hypersensitivity state.

Diagnosis of drug induced immunotoxicity

1. History of drug intake.

2. Skin prick tests: They are probably safer than intradermal tests. It is essential that suitable concentrations and appropriate controls be used. They have been successfully used in identifying allergy to pencillins and muscle relaxants.

3. Patch tests: It must be carefully controlled to help distinguish irritant from immunological effects. The various in vitro tests can be specific if the correct antigen is chosen. Rechallenge with the drug, using a small test dose, can be very useful in selected circumstances. Together with measurements of the various markers of an immune reaction, specific information is obtainable.

4. Sequential approach To investigating whether a drug reaction is immunological in origin, it involves

   a. Screening for non-specific evidence of an immunological reaction.

   b. Studying with appropriate specific tests.

   c. Perfoming a controlled rechallenge with monitoring of immunological markers.

Management of drug induced immunotoxicity

Life-threatening reactions need emergency treatment with adrenaline, corticosteroids and life-support systems as indicated. Other supportive measures may be necessary in some instances, such as severe thrombocytopenia or haemolytic anemia, and appropriate organ functions should be monitored until they return to normal.

Withdrawal of the drug is logical, even in mild reactions. The patient must be informed and instructed to inform other clinicians in future, before any therapy is prescribed. Carrying or wearing an alerting message is desirable for patients who have experienced severe immediate reactions, particularly to common or emergency drugs.

Drug-induced immune mediated hepatic injury

Drug-induced immune mediated hepatic injury is an adverse immune response against the liver that results in a disease with hepatitic, cholestatic or mixed clinical features. Drugs such as halothane, tienilic acid, dihydralazine and anticonvulsants trigger a hepatitic reaction and drugs such as chlorpromazine, erythromycins, amoxicillin-calvulanic acid, sulfonamides and sulindac trigger acholestatic or mixed reaction. Unstable metabolites derived from the metabolism of the drug may bind to cellular proteins or macromolecules leading to a direct toxic effect on hepatocytes.

Protein adducts formed in the metabolism of the drug may be recognized by the immune system as neoantigens. Immunocyte activation may then generate autoantibodies and cell-mediated immune response, which in turn damage the hepatocytes. Cytochromes P 450 are the major oxidative catalysts in drug metabolism and they can form a neoantigen by covalently binding with the drug metabolite that they produce. Autoantibodies that develop are selectively directed against the particular cytochrome isoenzyme that metabolized the parent drug.

The hapten hypothesis proposes that the drug metabolite can act as a hapten and can modify the self of the individual by covalently binding to proteins. The danger hypothesis proposes that the immune system only responds to a foreign antigen if the antigen is associated with a danger signal, such as cell stress or cell death. Most clinically overt adverse hepatic events associated with drugs are unpredictable and they intermediate (1 to 8 weeks) or long latency (up to 12 months) periods characteristic of hypersensitivity reactions. Immune-mediated drug-induced liver disease always disappears or becomes quiescent when the drug is removed. Methyldopa, minocycline and nitrofurantoin can produce a chronic hepatitis.

Poisons-induced Autoimmune diseases
Systemic lupus erythematosus

SLE is predominantly a disease of young women (9:1 female to male ratio) and is commoner amongst certain ethnic groups. Clinically, the disease manifestations include arthritis, serositis, photosensitivity, oral ulceration, malar rashes, recurrent thromboses, glomerulonephritis and central nervous system involvement, e.g., epilepsy, psychoses. Serologically, SLE is characterized by autoantibody production to nuclear components such as anti-nuclear antibodies, antibodies to double stranded DNA and antibodies to extractable nuclear antigens.

The majority of cases of SLE are idiopathic but certain drugs are known to cause SLE in genetically predisposed individuals. Many drugs reported to be associated with drug-induced lupus e.g. procainamide, ticlopidine and hydralazine have been studied in detail. Clinically, drug-induced lupus is similar to idiopathic lupus, but there are one or two striking differences. For example, serositis and pleuro-pulmonary involvement is much commoner in drug-induced lupus, whereas renal disease and central nervous system disease is less common in comparison to idiopathic lupus. Serologically, anti-nuclear antibodies and antibodies to both single-stranded

and double-stranded DNA are found in both drug-induced and idiopathic lupus, but it is uncommon to find very high levels of anti-DNA antibodies in drug-induced lupus.

Antibodies directed against certain components of histone are thought to be characteristic of drug-induced lupus. Although anti-histone antibodies may commonly be found in idiopathic lupus, they react to the H1 and H2B subunits of histone. In drug-induced lupus, the specificity appears to be against the H2A-H2B dimer in procainamide-induced lupus, or against H3 and H4 in hydralazine-induced lupus.

The exact mechanisms by which drugs can induce lupus remain unknown and a number of possibilities are being considered. It may be that the ability of both procainamide and hydralazine to bind polynucleotides in vitro may render DNA and/or histones antigenic. A more specific mechanism has been suggested whereby drugs interfere with the normal process of methylation of DNA. Following DNA replication, cytosine residues are methylated at the 5-position by the enzyme DNA methyltransferase. Failure of methylation of regulatory sequences is associated with gene expression, whereas methylation is associated with suppression of gene transcription. Thus, DNA methylation is a mechanism regulating gene expression.

Studies have shown that procainamide- and hydralazine-treated human T-cells show evidence of hypomethylation. In particular, procainamide is capable of reversibly inhibiting T-cell DNA methyltransferase in a dose-dependent manner. Furthermore, these T-cells become autoreactive in response to procainamide and hydralazine.

Scleroderma in relation to environmental and drug exposure

Scleroderma (progressive systemic sclerosis) is a multisystem connective tissue disease of unknown etiology. It is commoner in women and is characterized by widespread, diffuse sclerosis affecting the peripheral vasculature, skin, gastrointestinal tract, heart and muscle. Raynaud's phenomenon is a very common early feature, and pulmonary and renal involvement may be serious and life threatening.

Scleroderma-like conditions (pseudoscleroderma) and scleroderma have been associated with a variety of drugs (e.g. Pentazocine, Cocaine, Diethyl proprion, Bleomycin, Carbidopa, L-5-hydroxytryptophan, and

Fenfluramine HCl), chemical and environmental agents (e.g. Toluene, Benzene, Xylene, Aromatic mixes e.g., white spirit, Vinyl chloride, Trichloroethylene, Perchloroethylene, Naphtha-n-hexane, Epoxy resins, Metaphenyl-enediamine and Urea formaldehyde foam insulation).

Silicone breast implants

Tenenbaum et al. (1997) showed the existence of a relationship between the level of anti-polymer antibodies in the serum and the severity of clinical complications (related to connective tissue) in silicone breast implant recipients. Although these antibodies were not directed against silicone polymers this might be the first objective marker to be used as a diagnostic feature in silicone breast implant patients. Smalley et al. (1995 & 1997) reported on a lymphocytic response to silica (silicon dioxide) similar to that for silicone (polysiloxane polymer), a silicon derivative, and present in silicone breast implant material; in silicone breast implant patients and their children.

Toxic oil syndrome

This epidemic started in May 1981 when large numbers of patients in the Madrid industrial area suffered acute respiratory illnesses that did not respond to antibiotics. The etiological agent was identified as being rapeseed oil that had been denatured with 2% aniline. Oleyl-anilide proved to be an excellent marker for case-related oil specimens although the precise nature of the etiological agent has never been described.

Eosinophilia-myalgia syndrome

Hertzman et al., 1990 reported a case-control study that firmly linked the consumption of possibly contaminated L-tryptophan from one source with the eosinophilia-myalgia syndrome. L-tryptophan was widely used as a non-prescription food supplement by health conscious individuals for a wide variety of minor ailments.

The clinical features resembled those of toxic oil syndrome. Laboratory investigations consistently showed an eosinophilia early in the disease course, although this diminished spontaneously even when the patients continued to be ill. The main factor in treatment was the avoidance of further ingestion of L-tryptophan. Glucocorticoids were used widely and helped the myalgias and reduced the eosinophil count, but there was often

a recurrence of symptoms on stopping the steroid treatment, and progression to chronic disease was not altered.

Vinyl chloride disease (occupational acro-osteolysis)

Vinyl chloride (CH_2=CHCl) is a combustible colorless gas at room temperature that is used in the manufacture of a variety of plastics. These patients developed paraesthesia of the fingers, cold sensitivity, Raynaud's phenomenon, pseudoclubbing of the fingers, skin edema and thickening of the fingers, hands and forearms, and chest X-ray changes. The risk of development of symptoms was related to cumulative exposures over time and work practices but was not related to handling the finished polyvinyl chloride (PVC) product.

Vinyl chloride is a cause of non-cirrhotic portal hypertension and angio-sarcoma of the liver.

The skin changes of vinyl chloride disease resemble morphoea clinically and histologically, and vascular changes were often present with luminal narrowing of the digital arteries and subtotal occlusion of these vessels. The most dramatic radiological change is acro-osteolysis seen in the terminal phalanges of the fingers; a transverse lytic band is seen across the distal phalangeal shaft. Ward et al. (1976) reported immunological abnormalities in vinyl chloride disease including polyclonal increases of IgG, cryoglobulins, evidence of complement activation and low titre anti-nuclear antibodies. Vascular endothelial, medial and sub-intimal deposits of IgG, C3, C4 and fibrin/fibrinogen were seen on histology of small and medium-sized arterioles. Reduced T-cell and modestly increased B-cell numbers were also observed.

Systemic Vasculitis environmental factors and drugs

Various drugs are associated with hypersensitivity reactions and the most common mechanism is an immune-complex-mediated vasculitis. Drugs account for approximately 10-20% of dermal vasculitis (Fig. 10). The cutaneous lesions most commonly seen include palpable purpura, although urticarial lesions may be seen in 10%. They usually occur symmetrically on the lower limbs extending to the thighs and buttocks. In Mullick's series of 30 patients, 19 had disseminated vasculitis with other organ involvement, including renal disease, synovitis, pleuropulmonary and cardiovascular

disease with coronary vessel vasculitis and cardiac failure. More than 80% of patients had constitutional features such as fatigue, malaise and fever.

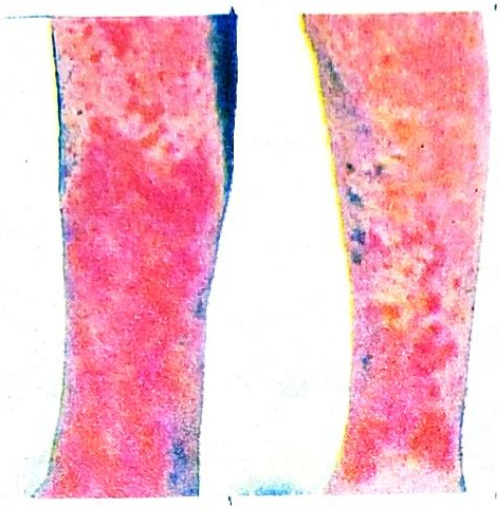


Fig. 10 Vasculitis

Morbilliform Reactions

Morbilliform rashes are common CDRs characterized by primary skin lesions of fine pink macules and papules that may become confluent. Typically, lesions begin on the trunk and pressure-bearing areas and progress symmetrically to cover large areas of the body. Lesions usually begin within 1 to 2 weeks of starting a medication and fade 1 to 2 weeks following cessation. Histological examination reveals a lymphocytic interface dermatitis with vacuolar changes at the dermal-epidermal junction and papillary dermal edema and eosinophils. Dyskeratotic cells may be found along the dermal-epidermal junction. Because CDRs, particularly morbilliform reactions, are so common and because they may be seen with many different classes of medications, identification of the causative agent can be a significant challenge.

Roujeau and Stern (1994) describe several criteria that may be helpful in defining a CDR

1. Other causes for the eruption, such as viral exanthema, should be excluded.
2. A temporal relationship between drug use and onset of the rash should exist.
3. Improvement should be noted following drug cessation.
4. Reactivation upon rechallenge of the drug should be noted.

5. The cutaneous reaction is known to be associated with the drug in question.

A careful history and research into the causative agent will allow prompt withdrawal of the offending agent and can prevent a patient from being falsely labeled with multiple drug allergies. There is some evidence that certain individuals are more likely to develop reactions to multiple medications, but a "multiple drug allergy syndrome" has not been clearly established.

Fixed Drug Eruption

Fixed drug eruption represents a unique CDR pattern characterized by skin lesion(s) that recur at the same anatomic site(s) upon repeated exposures to an offending agent. Most commonly, the skin lesion is a dusky erythematous macule and is usually found on the lips and genitalia, although any skin or mucosal surface may be involved. The skin lesions may be associated with a burning sensation and may be present in multiple numbers or progress to the development of central vesicles and bullae, particularly after the repeated use of an agent. The skin findings may be associated with nonspecific constitutional symptoms, including fever, malaise, nausea, and vomiting.

Fixed drug eruption usually occurs within hours of administration of the offending agent. Most commonly implicated are sulfa medications, barbiturates, and tetracycline. Certain medications also appear to have a predilection for certain anatomic locations (e.g., tetracyclines genitalia). Histology demonstrates a mixed inflammatory infiltrate of lymphocytes, neutrophils, and eosinophils at the dermal-epidermal junction. The epidermis contains necrotic keratinocytes. Melanin-containing macrophages in the dermis and chronic epidermal changes including acanthosis, hypergranulosis, and hyperkeratosis may be seen in older lesions.

The differential diagnosis of fixed drug eruption includes erythema multiforme (EM), as well as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in cases of disseminated or bullous fixed drug eruption. In contrast to fixed drug eruption, recurrent lesions in EM tend not to recur in the sites of previous involvement. Unlike SJS and TEN, mucous membrane involvement is not a consistent finding in fixed drug eruption.

Fixed drug eruptions resolve spontaneously without scarring a few weeks after onset, usually with residual post-inflammatory pigmentation.

A non-pigmenting variant of fixed drug eruption was described by Shelley and Shelley (1987). In this variant, which is most common following the use of pseudoephedrine, lesions resolve spontaneously without evidence of post-inflammatory pigmentation.

A careful history of previous drug exposures and skin lesions is integral in identification of the causative drug. Provocation testing with oral rechallenge of smaller doses of the suspected agent is the best method to determine with certainty the source of a fixed drug eruption. In cases of bullous or disseminated fixed drug eruption, however, oral challenge may be potentially dangerous. Patch tests, scratch tests, and intracutaneous testing may be helpful if positive, but are less reliable means of testing. When possible, patch testing should be performed at the site of previous eruption in conjunction with a vehicle to aid in drug absorption.

Erythema Multiforme (EM)/Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

The spectrum of severe cutaneous reactions, EM, SJS, and TEN, are the most feared of the cutaneous drug reactions. TEN occurs exclusively as a result of drug exposure and mortality reaches nearly 30%. An epidemiologic survey in France from 1981 to 1985 of private dermatologists, hospital dermatology, burn, intensive care, and infectious disease units estimated the prevalence of TEN to be 1.5 cases per million per year.

Constitutional symptoms are more common with TEN, but both TEN and SJS patients may present with fever that precedes the mucocutaneous eruption by 1 to 3 days. The mucocutaneous findings of both SJS (Fig. 11) and TEN progress rapidly over hours to days. Lesions of the gastrointestinal and respiratory tract are not uncommon in these reactions, the latter of which may be a significant source of mortality. Conjunctival involvement may result in synechiae, persistent photophobia, visual impairment, or complete blindness.

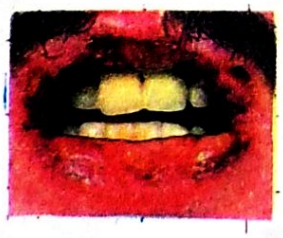


Fig. 11 Stevens-Johnson Syndrome.

Skin biopsy may be helpful in excluding other bullous dermatoses. Some authors believe that EM due to non-drug causes should be considered a distinct entity from more severe drug-induced SJS and TEN. EM is characterized by a dense dermal inflammatory cell infiltrate and keratinocyte necrosis In contrast, TEN shows complete epidermal necrosis and a sparse mononuclear cell infiltrate.

If a severe cutaneous reaction is suspected, immediate withdrawal of all potential offending agents is the most effective mode of therapy. Patients with extensive involvement should be cared for as a "burn patient" with fluid resuscitation, infection control measures, and nutritional support in a hospital burn-unit setting.

Antibiotics, particularly sulfonamides (Fig. 12) and penicillins, are traditionally implicated in many cases of severe drug reactions, but Roujeau's (1987) survey of drug eruptions in France from 1981 to 1985 found that NSAIDs had emerged as the more common cause of TEN. This was attributed in part to the availability of several new NSAIDs after 1980.

Fig. 12 Hypersensitivity reaction to sulfonamides.

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CHAPTER III:

Examples of poisons affecting immune system

Chapter III

EXAMPLES OF POISONS AFFECTING IMMUNE SYSTEM

Antinflammatory Drugs

1. Corticosteroids

They alter transiently the number of circulating leukocytes e.g. neutrophilia and lymphocytopenia. The total number of circulating T cells are markedly decreased but B cell numbers are modestly reduced. Among the T cell subsets, number of CD4 cells is reduced to a great extent than are numbers of CD8 cells.

2. Aspirin

It has long history of use and it the most common salicylate. It inhibits prostaglandins by inhibiting cyclooxygenase. In addition, it inhibits a variety of neutrophil and monocyte functions, such as aggregation, degranulation and superoxide anion production.

Cytotoxic Drugs

Cytotoxic drugs are a group of chemicals with pharmacologic property of killing cells capable of self-replication. These drugs were originally introduced into clinical medicine for anticancer therapy. The lymphocytotoxic activities of these can be related to their toxicities for cells in specific phase of the mitotic cycle.

Cytotoxic drugs are divided into 3 groups

Group I This group includes modes of therapy that exert their maximum immunosuppressive activity when administered just before the antigen and are less effective if used after the immunologic challenge. Included in this group are corticosteroids, irradiation, and nitrogen mustard.

Group II This group includes drugs that show immunosuppressive properties only if administered in the period immediately following the antigenic challenge. This group includes azathioprine and methotrexate.

Group III This group includes drugs that show inhibitory activity if administered either before or after antigenic stimulation, although these

compounds show greater suppressive activities if used after the immune challenge (e.g. cyclophosphamide).

1. Azathioprine: This compound is a phase-specific drug. It acts by competitive enzyme inhibition to block synthesis of inosinic acid, the precursor of purine compounds adenylic acid and guanylic acid. Therefore, the major effect is to impair DNA synthesis. This results in a decreased rate of cell replication and explains the phase-specific action of the drug. It inhibits T cells responses compared with those resulting from activation of B-lymphocytes. Nevertheless, both cell-mediated and humoral responses can be suppressed. In addition, it is effectively reduce the numbers of circulating natural killer cells, which responsible for antibody- dependent cell- mediated cytotoxicity.

2.Cyclophosphamide: It is an alkylating agent causing pronounced suppression of humoral antibody responses. Also, It causes inhibition of IgG and IgM antibody responses without significant changes in T cell responses. The effect of cyclophosphamide on cell-mediated immune responses is extremely variable. The cytotoxic effects of cyclophosphamide are primarily due to its ability to bind and cross-link DNA chains. It may also, react and alter the function of other intracellular macromolecules.

3.Cyclosporin: It alters selectively the immunoregulatory activities of helper T cells without affecting suppressor T cells, B-lymphocytes, granulocytes, or macrophages. Furthermore, it acts by impairing cellular functions without killing target lymphocytes. It acts as an immunosuppressant by blocking an early phase of a developing immune response. The principal targets of this drug are CD4 (helper T) lymphocytes. It may also function as an immune inhibitor by impairing the ability of activated helper T cells to respond to interleukin-2.

4.Mycophenolate mofetil: is a new cytotoxic drug whose active metabolite, mycophenolic acid, blocks the action of insine monophosphate dehydrogenase, resulting in inhibition of purine synthesis. Mycophenolic acid has an anti-proliferative effect on T and B lymphocytes and also inhibits the glycosylation of cell surface adhesion proteins.

Antibiotics and Antifungal Drugs

1. **Amikin:** decreases the response of IgM and IgG to sheep red blood cells.
2. **Cefaclor:** increases the response of IgM.
3. **Cefotaxime:** decreases the response of IgM and IgG to sheep red blood cells.
4. **Cephalexin:** causes delayed type hypersensitivity reaction.
5. **Clindamycin:** suppresses polymorphonuclear leukocytes phagocytosis.
6. **Metronidazole:** causes chills, suprapubic pain, fever, erythema and maculopapular rash.
7. **Streptomycin:** suppresses the response of antibodies to sheep red blood cells.

Antiparasitic Drugs

1. **Niridazole:** a potent suppressor of cell mediated immunity.
2. **Praziquntel:** The most important anti schistosomal compound in current use. It affects the humoral immunity of the host.
3. **Levamisole:** augments the activity of the cytotoxic T cells.

Antigraft rejection Drugs

FK 506 causes inflammation and skin hypersensitivity.

Anesthetic Drugs

1. **Halothane:** Single exposure to halothane decreases the resistance to tumors antibody response and alters lymphocyte subpopulations and lymphoproliferative responses.

2. **Ketamine:** After 24 hours from intramuscular injection, the cellular mediated immunity depressed. It may cause suppression of Natural Killer Cell Activity and Promotion of Tumor Metastasis.

Cardiovascular Drugs

1. **Clonidine:** Clonidine suppresses Plasma and Cerebrospinal Fluid Concentrations of TNF-α during the peri-operative Period.

2. **Hydralazine and procainamide:** They may induce Lupus erthematosis.

Drugs of abuse

1. Morphine: It releases histamine from sensitized cells and depresses natural killer cells.

2. Cocaine: It decreases intestinal lamina propria IgA cells, CD8 splenocytes, splenocyte interferon production and antibody response.

3. Fentanyl: reduces the splenic natural killer cell activity.

4. Alcohol: depresses humoral immunity. It suppresses neutrophil chemotaxis and decreases the number of T lymphocytes.

5. Tetrahydrocannabinol: suppresses immunity by decreasing interferons, tumor necrosis factor, interleukin-6 and interleukin-12. The ultimate outcome of these effects may be an enhanced susceptibility to infectious disease, cancer and AIDS.

Nervous system Drugs

1. **Alprazolam:** It increases the activity of natural killer cells and lymphocytic proliferation.
2. **Carbamazepine:** It depresses humoral and cellular immunity.
3. **Naloxone:** It may cause anaphylaxis.
4. **Chlorpromazine:** suppresses the response of antibodies to sheep red blood cells.
5. **Mepivacaine:** causes type II hypersensitivity reaction.

Steroid Hormones and related Drugs

1. **Testosterone:** may increase release of histamine and increase CD8 T cells number.
2. **Progestrone:** may increase histamine release.

Cigarette smoking

It increases interleukin 4 and decreases the level of serum IgE.

Immunomodulators

They are biological response-modifying compounds that affect the immune response in either positive or negative fashion. Although

immunosuppressive drugs and some therapeutic uses of gamma globulin can be included in this definition.

Augmenting the host's natural immune response to viruses by the administration of exogenous cytokines such as interferon-α is a strategy increasingly employed in antiviral therapeutics. Enhancing the release of endogenous cytokines is, however, an alternative approach. The imidazoquinolinamines imiquimod and resiquimod have demonstrated potency as inducers of IFN-α and other cytokines both in vitro and in vivo.

A. Compounds derived from bacteria

1. Complete Freund's adjuvant

It contains mycobacterial derivatives and has been used as adjuvant to boost humoral immune responses.

2. Bacillus Calmette-Guerin (BCG)

It has been extensively studied in the treatment of certain malignancies (e.g. malignant melanoma). It stimulate T and B- lymphocytes and natural killer cell function and to augment interleukin-1 production.

B. Compounds derived from Eukarytotic organisms

1. Thymic Hormones

They include thymosine, thymulin, thymopentin and thymostimulin. They have demonstrated immunostimulatory actions. They have clinical benefit in a variety of viral infection including hepatitis and Zoster. They increase CD4 CD8 T cell ratios.

2. Cytokines

They are generally subdivided into interferons, interleukins and colony- stimulating factors.

C. Biochemical agents

The best-known biochemical immunomodulator is levamisole, an imidathiazole compound. The mechanism of action is unknown and it exhibits no direct cytoxic activity. It is used as an adjunct in the treatment of colon cancer and has some benefit in treatment of infection (e.g. measles and influenza). Inosine pranobex delays the progression of AIDS.

Controversy exists, about its optimal dose, toxicity, use in combination with other drugs and overall benefit. Other immuno-stimmulatory drugs (e.g. polyribosinic agents and pyrimidinolones) probably act via their ability to induce the production of interferons.

Inhaled poisons affecting the immune system

1. Diisocyanates

The main occupational hazards caused by polyurethane chemicals are asthma and rhinitis, but contact dermatitis and urticaria may also develop.

2. Acrylates

Methacrylates are well-known contact sensitizers; cyanoacrylates have caused only few cases of contact allergy. Acrylates may also have other harmful health effects. Hand and finger symptoms and paraesthesiae have been reported among dental personnel preparing acrylates with their hands.

3. Acid Anhydrides

Anhydrides are low relative molecular mass chemicals that have been reported to cause immunologically mediated respiratory diseases. Contact urticaria and other skin symptoms have also been described. Some anhydrides, e.g., phthalic anhydride, have caused generalized urticaria, in connection with respiratory symptoms, after high exposure.

4. Solder flux

Solder flux causes symptoms of eye, throat and nose irritation. Lower respiratory tract symptoms, including cough and wheezing, also occurred.

5. Metal-polishing industry

The polishing process generates dust, containing fine particles of emery and metal, which are mainly composed of copper and zinc and constantly inhaled by the polishers. Occupational asthma was found to be confined to polishers. The polishers exhibited significantly greater reduction in various lung function parameters over the work shift, which was larger in

smokers than in non-smokers. The duration of exposure was directly correlated with acute fall in lung function.

Metals affecting the immune system

1. Mercury

There is evidence from studies that multiple exposures to inorganic mercury can lead to the production of antibodies against the glomerular basement membrane and results in an immunologically mediated membranous glomerular nephritis. This glomerular nephropathy is characterized by the binding of antibodies to the glomerular basement membrane, followed by the deposition of immune complexes in the glomerulus. There also is evidence from studies implementing several strains of both mice and rats that repeated exposures to inorganic mercury can lead to the deposition of immune complexes in the glomerular basal lamina, which leads to an immune complex glomerulonephritis. Whether mercury can induce an autoimmune glomerulonephritis in humans is not clear at the present.

2. Arsenic

Chronic arsenic exposures produced 2–10-fold elevation of serum interleukin-1ß, interleukin-6, and tumor necrosis factor-α levels, with greater increases seen by repeated injections than by oral exposure. Also, it elevates serum cytokines.

3. Arsine

Arsine is a war gas. Subchronic inhalation of arsine gas resulted in the following changes in immunity

1. Decreased percentage of splenic lymphocytes.
2. Decreased splenic T cells.
3. Decreased B cells.
4. Decreased activity of cytotoxic T lymphocytes.

4. Complex platinum salts

The complex platinum salt ammonium hexachloroplatinate is an essential intermediate in the refining of platinum, a corrosion resistant

metal used as a catalyst and in jewellery. Allergy to platinum salts in refinery workers was first reported in 1945. Subsequently, inhalation of ammonium hexachloroplatinate was shown to provoke asthmatic responses and to elicit immediate skin test responses in sensitized individuals.

5. Aluminum

Aluminum is the most abundant metal in the earth's crust. Contaminated drinking water, aluminum cans, containers and cooking utensils all are important sources of daily aluminum. The aluminum resulted in reduction in interferon production and splenic CD4 numbers.

SOLVENTS FECTING IMMUNE SYSTEM

Carbon tetrachloride

Carbon tetrachloride exposure resulted in marked suppression of both humoral and cell-mediated immune functions. Humoral immunity, as measured by the T-dependent antibody response to sheep red blood cells (SRBC), proved to be the most sensitive indicator of carbon-tetrachloride-induced immunotoxicity. Carbon tetrachloride was immunotoxic at all doses and there were no significant differences in the magnitude of immunosuppression between the routes of exposure.

Delaney & Kaminski (1994) studied the immunomodulatory activity of serum isolated from carbon tetrachloride-treated mice on T-cell-independent humoral immune responses. The results of the study suggested that carbon tetrachloride has bifurcating immunological effects. Exposure to carbon tetrachloride appears to suppress T-cell-dependent immune responses but enhance the activity of B-cells.

Pesticides and Insecticides

Pesticides and Insecticides have different effects on the immune system by different ways, which are elicited in the following table.

Pesticides and Insecticides	The effect on immune system
Chlordane	Defect in delayed hypersensitivity, enhancement of cell mediated immunity.
Dichlodiphenyltrichloroethane (DDT)	Decrease in lymphoid organ weights, decreased antibody response to antigens, increased delayed hypersensitivity to tuberculin, decreased neutrophil chemotaxis.
Dieldrin	Decreased antibody response, decreased host resistance to infectious agents.
Heptachlor	Decreased lymphoid organ weights
Lindane	Increased immunoglobulin concentrations, decrease in T lymphocyte proliferation.
Benzene hexachloride	Decrease in neutrophil chemotaxis.
Parathion	Decreased lymphoid organ weight.
Methyl parathion	Decrease in neutrophil chemotaxis.
Malathion	Decreased lymphoid organ weight, decrease in lymphocyte proliferation.
Chlorpyrifos	Decreased lymphocyte number, inhibited antibody and phagocytic responses.

Herbicides

1. **Rifit:** Causes significant reduction in body gain with leucocytosis. It also decreases the level of globulin in serum. Enlargement of the spleen and inflammatory changes in the gastrointestinal and respiratory tracts were found.

2. **Dioxin** suppresses cell mediated and humoral immunity. It reduces the number of CD8 cells Moreover, mediastinal lymph node cells failed to develop cytolytic activity and the production of interleukin (IL)-2 and interferon (IFN)-γ was suppressed.

Other poisons affecting immune system

a. Silica

Silica (quartz) is an important mineral dust, and a confirmed environmental pollutant, exposure to which is associated with the development of silicosis and other adjuvant diseases. The defense system has revealed that silica exposure can compromise host immuno-competence by altering both humoral and cellular immune responses.

b. Natural rubber latex

Populations at increased risk of developing natural rubber latex hypersensitivity include health care workers, rubber industry workers and subjects undergoing multiple surgical procedures, especially children with spina bifida and urogenital abnormalities. Prevalence figures for natural rubber latex allergy in studies using skin-prick tests range from 2.9 to 17% among hospital employees and are around 11% among glove-manufacturing workers.

RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH

a) Effective strategies to prevent the effect of poisons on the immune system should be employed, based on good information about the poison and its metabolites. Control of exposure should be the basis for preventing or minimizing the occurrence of effect of the immune disease.

b) There is urgent need to determine the cause of the increased frequency of the immune disorders.

c) The measurement of exposure of individuals and of populations may be difficult, but adequate assessment is essential to any analysis of the association between exposure and effect. The specific nature of immune responses represents a unique type of biomarker in studying past exposure, for example, by the use of skin patch or prick testing, complete blood count or assay of immunoglobulins to detect the disorder.

d) Worker surveillance systems, the quality of medical examination of workers and education of workers exposed to chemicals should be improved in order to reveal occupational immune-mediated diseases at an early stage. Relatively simple notification schemes for occupational disorders and post-marketing surveillance of medicines provide economic screening and alerting systems for immune diseases. Monitoring these disorders in the workplace is particularly valuable because exposure there is likely to be greater than anywhere else.

e) The efficacy and value of primary and secondary prevention and intervention strategies should be assessed at intervals using validated epidemiological techniques.

f) For allergic contact dermatitis, the available *in* vivo predictive models are of proven value for antigens of low relative molecular mass. The need is to discover how best they can be used to show the potency of allergens.

g) For allergic disorders of the respiratory tract, available *in* vivo test methods for substances of low relative molecular mass are promising, but their predictive value and specificity need to be

substantiated. For protein allergens, some animal test methods are being developed, but they require further evaluation using substances of known allergenic potential in humans.

h) The main method for avoiding occupational chemically induced autoimmune disease is the control of exposure. Pre-exposure assessment of those exposed to chemicals of immunomodulating potential should be considered in order to document any pre-existing features of connective tissue diseases. Strict adherence to guidelines to avoid or minimize exposure is advised, including the use of good occupational hygiene practices. Other risk factors such as smoking should be minimized and regular occupational medical examinations should be considered.

i) There is a need for investigation of the quantitative relationships between immune responses induced by chemicals and the severity of allergic reactions.

j) It is important to devise standard strategies for the clinical investigation and diagnosis of immune disorders.

k) Public health authorities, health professionals, the public and especially the workforce would benefit from better information about the occurrence, causes, clinical manifestations and consequences of different immune disorders.

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CHAPTER IV:

Food and immune system

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FOOD AND IMMUNE SYSTEM

In general, providing extra energy, multiple micronutrients, or moderately large doses of single nutrients improves immune function, and thus nutrition is regarded as an important determinant of the immune response. This understanding has developed out of the growth in the field of immunology from a descriptive science to one in which diverse immune phenomena can be coherently tied together and explained in precise structural and biochemical terms. The interdependency between the disciplines of nutrition and immunology was recognized formally in the 1970s when immunologic measures were introduced as part of the assessment of nutritional status. Today, protein-energy malnutrition is accepted as a major cause of immunodeficiency worldwide and the immune response is considered integral to the pathophysiology of many chronic diseases in which diet plays a major role in prevention or treatment.

Both the nutritional state and specific nutrients may affect the immune system directly (e.g., by triggering immune cell activation or altering immune cell interactions) or indirectly (e.g., by changing substrates for DNA synthesis, altering energy metabolism, changing physiologic integrity of cells, or altering signals or hormones). Knowledge of the impact of nutritional status on the functioning of the immune system has led to several practical applications, including the use of immunologic tests as prognostic indices in patients undergoing surgery and the use of immunologic methods to assess nutritional status and to determine the efficacy and adequacy of nutritional therapy. In addition, the role of specific nutrients or food in stimulating the immune response is being explored. New information should permit the development of uniquely designed feeding formulas or regimens with selected ingredients to optimize immune function in specific segments of the general and hospitalized populations. In the critical care area, several specific nutritional supplements have already been designed that are aimed at reducing the risk of infection and improving the recovery of immune function in immunocompromised patients.

Food contain various substances that can control the physiological functions of the body and modulating immune responses is one of the most important functions of food. Immune functions are indispensable for defending the body against attack by pathogens or cancer cells and thus play a pivotal role in the maintenance of health. However, the immune functions

are disturbed by malnutrition, aging, physical and mental stress or undesirable lifestyle. Therefore, the ingestion of food with immune-modulating activities is considered an efficient way to prevent immune functions from declining and reduce the risk of infection or cancer.

Food Capable of Improving Immune Functions in Healthy Individuals

Immune functions are not stable and usually fluctuate within fixed limits. In addition, various endogenous and exogenous factors can influence immune functions. Corticosteroids suppress a broad range of immune functions efficiently and exhibit anti-inflammatory activity. Malnutrition, aging, stress and undesirable lifestyle are also factors lowering immune functions. The elderly exhibit higher susceptibility to infection than the young, and delayed type hypersensitivity (DTH), antigen-specific antibody production, the proliferative response of T cells and the relative proportion of T cells decline with aging. Many kinds of physical and mental stress also disturb immune functions. For instance, a surgical operation exhausts patients and is accompanied by a decline in their DTH, and caregivers of dementia patients show a decrease in NK cell activity, antigen-specific antibody production and T cell proliferation on account of depression. Moreover, NK cell activity deteriorates under not only mental stress after divorce but also physical stress of heavy exercise. It is widely known that systemic malnutrition associated with a deficiency of protein and energy causes a decline in immune functions and results in susceptibility to infection. A deficiency in vitamins and minerals induces an attenuation of immune functions including phagocytic activity, NK cell activity, DTH, antigen-specific antibody production, and the proliferative response of T cells. In addition, NK cell activity and the proliferative response of T cells decline in patients with chronic fatigue syndrome.

The deterioration of immune functions possibly causes loss of health. A higher risk of infection is closely linked with low NK cell activity, and increased risk of mortality in the elderly after pathogenic infection is correlated with a decline in DTH. Bodily dysfunctions in chronic fatigue syndrome patients are negatively correlated with the proliferative response of T cells.

The immune functions in healthy individuals tend to be disturbed by various factors, and deterioration of health is closely connected with dysregulation of immune functions. On the other hand, it has been proposed that food-derived components can improve the immune functions in healthy

individuals. Vitamins, minerals, and fatty acids enhance delayed type hypersensitivity (DTH), vitamins and minerals enforce antigen-specific antibody production and vitamins, minerals and oligosaccharides increase T cells and augment their proliferative response. In addition, vitamins, minerals and lactic acid bacteria promote phagocytic activity and NK cell activity. The ingestion of these food not only normalizes immune functions but also reduces the incidence of pathogenic infection.

Food Capable of Improving Clinical Symptoms in Patients With Hypersensitivity

Immune reactions are usually evoked in response to externally derived hazardous antigens. However, in patients with hypersensitivity represented by immediate type allergy, immune reaction to non-toxic antigens and sometimes to the body's own molecules is induced. The causes of hypersensitivity are mainly genetic, but environmental factors, including air pollution, dietary components and residential conditions, also play an important role. As clinical condition and immune parameters change concomitantly in allergic patients, it is possible to observe the effects of food by measuring the immune parameters associated with allergic reactions.

Generation of pro-inflammatory cytokines and chemokines and expression of cell adhesion molecules are involved in the progression of allergic diseases including atopic dermatitis, pollinosis and allergic rhinitis. Levels of pro-inflammatory cytokines and chemokines increase and the expression of cell adhesion molecules is enhanced in allergic patients. Furthermore, eosinophils as well as mast cells secrete chemical mediators and worsen the clinical symptoms in the inflammatory areas.

When the immune parameters representing clinical symptoms characteristic of atopic dermatitis, pollinosis and allergic rhinitis normalize, the patients recover from allergic diseases. Therefore, normalization of these immune parameters by food is helpful in that allergic patients recover their health and persons with a predisposition to allergies may avoid falling ill. Parietaria extract, herbal extract and lactic acid bacteria have been found to suppress allergic diseases in human subjects as well as animal models.

An allergic reaction is a sequential immune response involving the processing and presentation of the allergen, activation of allergen-specific T and B cells, production of IgE against the allergen, and activation of mast

cells and eosinophils triggered by the allergen. Therefore, food-derived materials could prevent allergy by counteracting at least one step in the cascade of allergic reactions. It has been reported that a variety of food contain substances able to prevent an allergic reaction.

Food Capable of Improving Immune Functions in Subjects in an Immunocompromised State

Cancer patients are usually immunosuppressed and at high risk of infection due to a reduction of immune functions. Therefore, food capable of enhancing the immune responses of cancer patients with disturbed immune functions are valuable. Invading pathogenic bacteria or viruses are captured and killed by phagocytes such as neutrophils and macrophages, and NK cells recognize and lyse infected cells. Activated NK cells and T cells produce huge amounts of IFN-α, which further augments the anti-bacterial activity of macrophages.

Pathogens that have escaped capture by phagocytes or NK cells are incorporated and processed by professional antigen-presenting cells, which stimulate T cell clones expressing antigen receptors specific for pathogens. Activated antigen-specific T cells secrete various arrays of cytokines necessary for antibody production, and pathogen-specific antibodies play an important role in the exclusion of pathogens invading the airway, intestine and urinary tract. IgA secreted in the intestinal mucosa can neutralize toxins produced by pathogens and prevents diarrhea, and IgG circulating in sera is principally for defense against infection in the upper respiratory tract.

The incidence of infection increases and the aggravation of infectious diseases occurs when innate and acquired immune functions decline or are insufficient. Patients with undetectable levels of NK cell activity suffer frequent viral infections and the transfer of NK cells into suckling mice can render the recipient mice resistant to infection for murine cytomegalovirus. Patients with Gaucher disease, who were highly susceptible to serious bacterial infections, had macrophages with impaired anti-bacterial activity and the rate of infection among marrow transplant recipients 100–365 days after transplantation was negatively correlated with the total number of B cells and monocytes. On the other hand, several reports have shown that the improvement of depressed immune functions by ingesting food reduced infection rates and mitigated the severity of infectious disease. When assessing the anti-infectious capabilities of food,

phagocytic activity, NK cell activity, T cell number, production of antigen-specific antibodies and total IgG level can be regarded as useful parameters.

NK cells exhibit cytotoxic activity against not only infected cells but also cancer cells. IFN-α produced by activated NK cells suppresses the proliferation of cancer cells and activates cytotoxic T cells and macrophages. While NK cells kill cancer cells in an antigen non-specific manner, cytotoxic T cells recognize specific antigens of cancer cells for killing. Moreover, macrophages secrete molecules toxic to cancer cells and induce the apoptosis of cancer cells.

The proliferation and metastasis of cancer cells accelerate when immune functions are disturbed. It has been found that cancer patients have lower NK cell activity than healthy controls and persons with lower NK cell activity are subject to higher rates of cancer incidence, metastasis and aggravation of cancer. The macrophages infiltrating solid tumor have less phagocytic activity. On the other hand, when cancer patients ingest food capable of improving immune functions, the prognosis becomes much better. Based on the reports of clinical trials with cancer patients, phagocytic activity, NK cell number, T cell number, DTH and IFN-α production are all useful immune parameters for assessing the effect of food on prognosis after surgical operation for cancer. Moreover, it has been reported that NK cell activity deteriorates in AIDS patients, and branched chain amino acids, probiotics and vitamin A improves virus-triggered diseases.

Newborns exhibit immature immune functions and are vulnerable to pathogenic infection. Supplementation of vitamins in malnourished children and ingestion of probiotics in newborns enhance immune functions and prevent viral infection.

Mechanisms by which Food Influence Immune Functions

Food-derived substances incorporated into the body via various routes modulate immune functions. Taking into consideration that malnutrition or calorie restriction cause reduced activity in immune functions, nutritional condition is indispensable for the development of the immune system. Moreover, food-derived substances exhibit a special role in influencing immune functions.

The way that food-derived substances modulate immune functions is either indirect or direct. Comparative analyses of conventional and germ-

free animals revealed that indigenous intestinal microflora play a pivotal role in the development of host immune systems. Ingestion of probiotics stabilizes the intestinal microflora, and normalization of the intestinal microflora by probiotics could lead to modulation of the host immune system. In addition, probiotics such as lactic acid bacteria are recognized by specific receptors on the surface of phagocytic cells. Additionally, vitamins, minerals or fatty acids affect cellular functions by preserving the cell membrane or regulating gene expression after being incorporated into lymphocytes. One group of food represented by lactic acid bacteria stimulates innate immunity (phagocytic activity, NK cell activity), while other food, including vitamins and minerals, activate acquired immunity (T cell response, antibody production). However, as innate immunity and acquired immunity are closely linked, both groups of food may regulate both immune systems. It has been reported that various nutrients found in food exhibit anti-infectious functions.

Probiotics ingested may be partially digested in the gut and incorporated into M cells present in FAE, and then captured by dendritic cells or macrophages in the interfollicular area of PPs. These professional phagocytic cells hold various receptors on their surface capable of binding common structures of microbes, the pathogen-associated molecular patterns (PAMPs). Among the receptors for PAMPs, molecular structure and functions of TLRs (Toll-like receptors) have been recently unveiled. Ten TLR families (TLR1–TLR10) have been identified and ligands recognized by some TLRs have been determined. TLR2 recognizes peptidoglycans and lipopeptides as TLR4 does lipoteichoic acids and lipopolysaccharides. Moreover, the CpG oligonucleotides universally detected in bacterial DNA are recognized by TLR9. The signaling response to stimuli recognized by TLRs is mainly mediated by an intracellular adaptor molecule, MyD88 (myeloid differentiation factor 88). Thereafter, the nuclear transport of NF-α B (nuclear factor-α B) is stimulated and de novo synthesis of cytokines is induced. It has been proposed that stimuli through TLR2 activate both JNK (c-Jun N-terminal kinase) and ERK (extracellular signal regulated kinase) and induce production of IL-10, while stimuli through TLR4 activate JNK and induce production of IL-12.

Immune-modulating effects of amino acids such as glutamine and arginine have been evaluated. Ingestion of glutamine improved nitrogen retention and lowered incidence of bacteremia in patients with trauma, and enteral supplementation of glutamine-enriched diet enhanced the recovery of immune functions and reduced the length of hospital stay after surgical

operation in cancer patients. Glutamine is a nutrient for immune cells and acts as precursor for glutathione, which circumvents oxidant stress and improves cell-mediated immunity. Arginine is a substrate for synthesis of nitric oxide and improves helper T-cell numbers. Peri-operative feeding of arginine and n-3 polyunsaturated fatty acids (PUFAs) restored DTH and decreased infection rates in colorectal cancer patients.

Nucleotides are rich in food containing nucleic acid/nucleoprotein and supplementation of nucleotides is important for growth of infants. Addition of nucleotides increased the proportion of TCR bearing IELs through stimulating IL-7 production by IECs in mice, and ingestion of formula supplemented with nucleotides augmented NK cell activity and IL-2 production in human infants.

Vitamins and minerals exhibit important immune-modulating functions by entering cells and regulating gene expression. Vitamin A affects the differentiation of epithelial cells and inhibits IFN-α production by T cells at the transcriptional level, which results in stimulation of antibody-mediated immune responses. Vitamin C prevents the production of reactive oxygen intermediates and reduces DNA damage in immune cells. Moreover, vitamin C inhibits the transcription of NF-B, and down-regulates the production of pro-inflammatory cytokines. Vitamin E is also an anti-oxidant and exerts an anti-inflammatory effect. Vitamin E stabilizes the membrane of immune cells and enhances the binding of antigen-presenting cells and T cells.

Minerals prevent the oxidation of lipids in the cell membrane, which can reduce oxidative stress affecting immune cells. For instance, selenium is indispensable to the function of reducing enzymes such as glutathione peroxidase and thioredoxin reductase, and is needed to stimulate cell-mediated immune functions. Furthermore, zinc may be required for the translocation and binding of NF-B to DNA.

Long-chain PUFAs in food can modulate immune functions. Dietary n-3 PUFAs alter the lipid composition of the cell membrane and regulate the function of immune cells. Antigen-presenting cells from mice and humans fed n-3 PUFAs exhibited the capacity to suppress excessive activation of T cells. As a result, n-3 PUFAs can act as anti-inflammatory agents.

EXAMPLES OF FOOD AND CONSTITUENTS AFFECTING IMMUNE SYSTEM

Vitamin A

Retinoic acid (an active metabolite of vitamin A) has been capable of potentiating immunity. When combined with human recombinant interleukin-2 (IL-2), retinoic acid augmented lymphokine-activated killer (LAK) cell activity in both a dose- and time-dependent manner. Lin and Chu, 1990 suggests that, in addition to its use in chemoprevention of cancer, retinoic acid is of potential in adoptive immunotherapy lymphokine-activated killer (LAK) cell activity by retinoic acid.

Green tea

The natural green tea constituent may open up a new therapeutic avenue for young disabled adults with inflammatory brain disease by combining, on one hand, anti-inflammatory and, on the other hand, neuroprotective capacities.

Green tea has been claimed to exert anti-inflammatory properties through unknown molecular mechanisms. Dona et al., 2003 have shown that the most abundant catechin of green tea, (-) epigallocatechin-3-gallate (EGCG), strongly inhibits neutrophil elastase. EGCG exerts its action by the following evidences

1) Micromolar EGCG represses reactive oxygen species activity and inhibits apoptosis of activated neutrophils.

2) Dramatically inhibits chemokine-induced neutrophil chemotaxis in vitro.

3) Both oral EGCG and green tea extract block neutrophil-mediated angiogenesis in vivo in an inflammatory angiogenesis model.

4) Oral administration of green tea extract enhances resolution in a pulmonary inflammation model, significantly reducing consequent fibrosis.

Oral intake of green tea could act as an adjunctive therapy for prevention of transplant rejection in humans.

Food additives

There is little information about the effects of food additives on the immune system. An early study showed that the preservative methylparaben and the antioxidants butylated hydroxyanisole, butylated hydroxytoluene, and propylgallate suppress the in-vitro T-dependent antibody response, whereas vanillin and vanillic acid stimulate it.

The immunotoxicity of 'caramel color', which covers a large number of complex products used as food colorants, has been investigated. One of the compounds in this group, 2-acetyl-4 (5)- tetrahydroxybutylimidazole (THI) (caramel color III), has been found to be immunotoxic in rodents. THI induces a rapid reduction in the number of B and T cells in blood, spleen, and lymph nodes and morphological changes in the thymus of rats, with an increased number of mature medullary thymocytes and a decreased number of cortical macrophages. THI might reduce the migration of mature thymocytes into the periphery, as a decrease in the number of recent $ER4^+$ thymic emigrants was found in the spleens of exposed rats. Functional studies indicate changes in Th cell function, an increased capacity to clear the Gram-positive bacterium L. monocytogenes, and modulation of the activity of adherent splenic cells. It has been hypothesized that THI exerts an antivitamin B6 action by competing with pyridoxal 5'-phosphate for binding to the cofactor site of one or more pyridoxal 5'-phosphate-dependent enzymes.

Fish oil (FO)

Dietary fish oil (FO), rich in (n-3) fatty acids, possesses potent anti-inflammatory properties in human and rodent autoimmune disease models. These properties likely involve changes in T-lymphocyte function, which indeed influences both the type and extent of immune response. The T-lymphocyte exerts its modulatory properties by proliferating in response to stimulation and producing various cytokines. Cytokines derived from the T-lymphocyte are categorized as Th-1 or Th-2. The Th-1 cytokines including interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor -α (TNF-γ) influence cell-mediated immunity, while the Th-2 cytokines, IL-4, -5, -6, and -10, regulate humoral or antibody-mediated immunity. Recently, dietary (n-3) fatty acids were found to modulate lymphocyte proliferation, cytokine production, signal transduction, and gene expression in healthy humans. Furthermore, other studies reported that dietary lipids also modulate immunoglobulin (Ig) production in both spleen

and mesenteric lymph node (MLN) lymphocytes from healthy rats. Specifically unsaturated fatty acids derived from vegetable oils enhance IgE production and inhibit IgG and IgM production by spleen or MLN lymphocytes. Indeed, the MLN play a pivotal role in intestinal immunity, whereas IgE is the primary mediator of the Type I hypersensitivity reaction to food allergens.

Alterations in both cell-mediated and humoral immunity occur with age in both elderly humans and aged rodents, thereby increasing the risk of developing autoimmune disease and cancer as well as both viral and bacterial infections. Many of these age-related changes involve defects in T-lymphocyte function, including a diminished proliferative response to mitogenic stimulation [i.e., concanavalin A (Con A)] and subsequent production of IL-2, a potent polyclonal T-lymphocyte mitogen, and alterations in Th-2 cytokine production in the blood and spleen. Cytokines can act directly on B-lymphocytes, promoting polyclonal activation and subsequent synthesis of antibodies such as IgG, IgE, IgM, and IgA. To date, the only known intervention to increase life span and abrogate some of the age-dependent immune abnormalities is energy restriction (R). Energy restriction (R) is defined as a 30–40% reduction in food consumption. The previous studies showed that R extended the life span of MRL/l pr mice by inhibiting the development and expression of the lymphoproliferative syndrome and by delaying the onset of autoimmune kidney disease in (NZB x NZW) F1 (B/W) mice Fernandes et al. 1994 also reported increasing the life span of B/W mice by feeding (n-3) fatty acid-enriched diets without R when compared to corn oil (CO) diet.

Carotenoids

Carotenoids represent a group of fascinating, abundant and widely distributed natural pigments. Carotenoids' possible role in reducing cancer in humans was first proposed by Peto et al. (1981). Since then, numerous epidemiological studies have suggested one or more Carotenoids from fruits and vegetables may decrease the incidence of major chronic diseases such as lung, breast and prostate cancers. Optimism about the anticancer activity of $^{\beta}$-carotene was dampened by recent studies that showed an increased incidence of lung cancer with β-carotene intake among high-risk populations of smokers and asbestos workers and no effect against cancer and heart disease.

The xanthophylls, lutein and zeaxanthin, are nonprovitamin A carotenoids and have specific biological functions in decreasing cancer development, in enhancing immune function and in protecting against age-related macular degeneration. For instance, mice fed high levels of lutein had slower growth of a transplantable mammary tumor. Furthermore, dietary lutein enhanced lymphocyte proliferation response. In humans, high dietary lutein is correlated with greater expression of estrogen receptors in breast cancer cells and consequently greater survival rates and better response to hormone therapy.

Lutein possesses potent antioxidant activity. In cultured cells, lutein is more effective than β - carotene in inhibiting the auto-oxidation of cellular lipids and in protecting against oxidant-induced cell damage.

Flavors

Flavors are mixtures of odorous molecules that can be extracted directly from natural food or can be synthesized in the laboratory after chromatographic and mass spectrographic analysis of natural products. In addition to the odorous molecules, flavors often contain nonvolatile compounds such as amino acids or salts that induce taste and/or somatosensory stimulation. Addition of flavors at optimal concentrations for the elderly (i.e., flavor enhancement) can improve food enjoyment and have a positive effect on food intake. For example, simulated chicken flavor can be added to chicken or chicken soup to provide a more intense "chicken" sensation. Flavor enhancement differs from more traditional methods of increasing odor and taste sensations such as spices, herbs and salt. Spices and herbs add different flavors to the food rather than intensify the chemosensory properties of the actual food. Because flavors are not spices, they do not irritate the mouth or stomach. Both the clinical and laboratory studies described below have found that flavor enhancement of food for the elderly can improve immunity, functional status and quality of life.

The immune and functional improvements (i.e., increased T and B cell counts and improved grip strength) occurred as a result of intensifying the flavor of some but not all food at a meal. Yet, flavor enhancement improved immunity and grip strength. Similar results were found in an additional study that used MSG and flavors to intensify both taste and smell simultaneously.

Zinc (Zn)

As a structural and/or functional component of numerous metalloenzymes and metalloproteins (Coleman, 1992), zinc (Zn) can affect many aspects of cellular metabolism, including physiological processes, such as immune function, antioxidant defense, growth and development. Therefore, an adequate supply of dietary Zn and the maintenance of Zn homeostasis are crucial for normal functioning of these systems. Primary mechanisms responsible for Zn homeostasis involve changes in Zn absorption and excretion in gastrointestinal tract and hepatic Zn storage and disposal. At the cellular level, metallothionein (MT) may be central to the homeostatic regulation of Zn metabolism.

Yogurt

Yogurt is defined as coagulated milk; it is obtained by lactic acid fermentation due to the presence of Lactobacillus bulgaricus and Streptococcus thermophilus in milk. The microorganisms of the final product must be abundant and viable. The belief that yogurt may be beneficial to health is centuries old. According to Persian tradition, Abraham owed his fecundity and longevity to the regular ingestion of yogurt; in the early 1500s, King Francis I of France was reportedly cured of a debilitating illness after eating yogurt made from goat's milk. Scientific interest concerning the health benefits of yogurt was sparked by Metchnikoff in the early 1900s. Metchnikoff proposed that the lactic acid microbes of fermentation must be antagonistic to the putrefying microbes of the gut, and, once introduced into the intestine, they would prevent the breeding of the noxious microbes, which required an alkaline environment. His hypothesis seemed confirmed by the fact that populations that regularly ate yogurt lived a very long time (e.g., Bulgaria, known for longevity). He experimented on himself and reported that his health, which was generally poor, improved with regular ingestion of a sour milk prepared with cultures of the Bulgarian lactic bacillus. Metchnikoff's enthusiasm about yogurt spilled over into the public, and doctors began recommending yogurt/sour milk as a hygienic food. Metchnikoff credited his relatively long life in part to the lactic bacilli in his diet, and hypothesized, "When people have learnt how to cultivate a suitable flora in the intestines of children as soon as they are weaned from the breast, the normal life may extend to twice my 70 years".

Recent studies have given support to Metchnikoff's theory that yogurt may indeed be beneficial to health. Studies show health effects ranging from increased digestibility of lactose to an increased immune response with the ingestion of a lactobacillus culture. Yogurt is widely accepted as a treatment for gastrointestinal distress. It is a good source of calcium for lactose-intolerant individuals, and has even been reputed to have hypocholesterolemic effects. Many recent studies have focused on the possible effect lactobacilli may have on the immune system and the ability to fight off an infection. Bloksma et al. (1979) found that in germ-free animals ingesting yogurt, there was a nonspecific increase of immunoglobulin (Ig)3G1, IgG2, IgG2a, IgG2b, and IgM antibodies. Stimulation of lymph follicles in the spleen of mice fed live cultures also led to an increase in IgG2a, but repeated experiments did not bear out this result.

It has been found that yogurt potentiates and accelerates the production and the release of interferon-γ (IFN-γ) by cells in culture, but whether the microorganisms can still potentiate this effect in vivo remains subject to debate. DeSimone et al. (1986) concluded that yogurt itself was not mitogenic, but that it possessed properties that potentiated IFN-γ production. Yogurt's bacteria may potentiate the production and the release of IFN- γ by immunocompetent cells and thereby modulate the host's immune response. Lactobaccili were found to adhere to lymphocytes in culture perhaps stimulating the release of IFN-γ. In an earlier study, an intriguing increase in the amount of IFN-γ produced occurred by stimulated cells from a group eating 450 g of live-active yogurt daily. Cells of groups consuming heat-killed yogurt or no yogurt (controls) did not produce a similar increase.

The few studies to date indicate that lactobacilli activate both a systemic and a local immune response. Locally, yogurt may enhance the immune response by increasing the percentage of B-lymphocytes and the phytohemagglutamin (PHA) and lipopolysaccharide (LPS)-induced proliferative responses of Peyer's patches in the intestine. In addition to the potentiating effects of the organism itself, the peptide products of the microorganism may possess immunomodulating activity, producing a systemic effect. Parker et al. (1984) identified a hexapeptide that is capable of exerting an anti-infectious immunostimulatory response on macrophages. Matar et al. (1996) found that the phagocytic activity of alveolar macrophages was increased in mice fed fermented milk; when mice were fed the hexapeptide itself, there was a significant increase in the resistance to pneumonia infection.

Immunity and lactation

Understanding how nutritional levels and body condition interact with immunocompetence is essential for understanding density-dependent effects in wild populations, particularly those affecting energetically expensive stages such as reproduction. If available resources limit immunocompetence, then trade-offs between investments in life-history components and investments in immunocompetence should be most evident at stages of maximum requirements (e.g., reproduction), particularly when resources are very limited. Lactation is the phase of reproduction in mammals demanding maximal nutritional resources. In addition, ruminants, such as deer, produce milk mainly from food ingested on a daily basis and not from body reserves. These findings suggest that lactation is the stage most likely to be affected by nutritional stress. Although ecological and epidemiological studies have shown a relationship between nutritional status, body condition, and immunocompetence at different population densities.

Increasing evidence indicates that immune defense is compromised by limiting access to resources, such as energy or protein. It is expected that this should be particularly the case during lactation. Although, as mentioned above, milk in ruminants is produced from food taken on a daily basis, it is well known that lactating cows can assume a negative protein balance during early lactation. However, the ability to mobilize tissue protein for milk production is small relative to the ability to mobilize fat. Protein body reserves are below 5% of total body protein in most mammals, and in cows, they could not support more than 20% of daily milk production for longer than 14 days. In contrast, when protein is not severely limiting but metabolizable energy intake is reduced, fat reserves are mobilized greatly to maximize milk production. This mobilization of fat can produce a compensatory response in deer lasting up to 4 wk under a sharp reduction in food availability.

Because newborns have impaired ability to produce antibodies and are more dependent on passively transferred immunity from the mother's milk than adults are, and because intestinal epithelium loses its ability to absorb intact macromolecules around 24 h after birth, colostrum is the main source of antibodies and immunity proteins for newborn calves. Immunoglobulins (Ig) in colostrum account for 70–80% of their protein content and are the result of selective accumulation from plasma Ig that starts several weeks before parturition. Thus, it is unlikely that food

restriction after calving would affect Ig content in colostrum. However, there are controversial findings suggesting that food restriction may affect calf absorption of such Ig. Protein from mature milk also contains 1–2% of Ig that appears to retain immunological activity in the intestine of the recipients. At least content of the most important Ig in milk, IgGs, is related to the serum levels of IgG in cattle mothers, whereas mortality rates of calves with low serum IgG are attributed to lack of IgG intake with milk.

Although, as mentioned above, most research on passive immunity transfer by milk intake has focused on Ig levels, humoral immunity is only one of the components of a complex system, which includes cell-mediated and other responses. Some authors have warned that single-variable studies suffer from an increased risk of erroneously concluding that no relationship exists between immunocompetence and life-history decisions (e.g., to reproduce, to grow).

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Glossary

Allergen - a substance that causes an inappropriate reaction by the immune system to normally harmless substances.

Allergy - A condition in which the body has an exaggerated (immune) response to a substance, like a vaccine. Also known as hypersensitivity.

Antibiotics - Medicines used to treat some bacterial diseases.

Antibody (Ab) - a protein molecule (also called an immunoglobulin) secreted by B cells in response to an antigen (Ag). When an antibody attaches to an antigen, it destroys the antigen.

Antigen - the portion of a foreign substance or germ that can cause the immune system to become active against it.

Antigen presenting cell (APC) - immune cells - such as b-cells, macrophages, and dendritic cells - that recognize foreign antigens, and present it to T-cells to initiate an immune response.

Autoantibody - an antibody that reacts against the body's own tissue.

Autoimmune disease - a disease that results when the immune system mistakenly attacks the body's own tissues. Examples: Rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes.

Bacteria - Tiny one-celled organisms present throughout the environment. Some bacteria cause disease (like diphtheria, tetanus, and typhoid fever).

B-cells (also called B lymphocytes) - a type of white blood cells that come from bone marrow and develop into plasma cells, mature B cells capable of producing antibody. Each b-cell is capable of making an antibody specific to the triggering antigen. The antigen trigger causing it to produce numerous plasma cells capable of manufacturing the antibody.

CD (clusters of differentiation)- As b-cells mature, they express different protein receptors on their surface. Some of these receptors can be used as treatment targets. These proteins or antigen markers are called Clusters of Differentiation (CD).

Chemokines are molecules released by pathogens and infected tissues that attract lymphocytes.

Complement - a series of blood proteins whose action "complements" the work of antibodies. Complement destroys bacteria, produces inflammation, and regulates immune reactions.

Cytokines are molecules released by cells to alter lymphocyte function.

IgA, immunoglobulin A - a type of antibody concentrated in mucous membranes and body fluids like tears, saliva, and secretions of the respiratory and gastrointestinal tract.

IgG, immunoglobulin G - the major antibody found in the blood that can enter tissues. It coats germs, helping other cells to seek and destroy them.

IgM, immunoglobulin M - an antibody that remains in the bloodstream where it can kill bacteria that enter the blood stream.

Immune response - reactions of the immune system to foreign substances.

Immune system - complex network of specialized cells and organs that has evolved to defend the body against attacks by foreign invaders.

Immunity - protection from disease-causing microbes or pathogens.

Immunoglobulins - a large family of proteins, also known as antibodies. There are five classes of immunoglobulins: IgA, IgM, IgG, IgD, and IgE.

Infection - a state in which microorganisms have taken residence and multiplied in body tissues.

Inflammation - an immune system reaction to stop the progression of disease-causing microbes, sometimes seen at the site of an injury. Signs of inflammation include redness, swelling, and heat.

Lymph nodes - small bean-shaped organs of the immune system, distributed widely throughout the body. They provide an environment where lymphocytes can receive initial exposure to foreign antigens (viruses, bacteria, fungi, etc.). This activates the lymphocytes to perform immune functions. Most lymph nodes form in clusters throughout the system, such as in the neck, armpit, and groin.

Lymphocytes - small white blood cells (B and T cells) that provide immune defense.

Macrophage - a large immune cell that gobbles microbes and presents antigens from the ingested pathogen to other immune cells. To further orchestrate an immune attack, macrophages send protein signals none as monokines.

MHC molecules - At the heart of immunity is the ability of immune cells to distinguish self from none self. So a fundamental question is how do immune cells do this? Is it by shape? Color? Scent?

As it turns out cell-to-cell communication is a touchy/feely thing, and that when immune cells bump into other cells in the night they grope for a specific molecule called the MHC. Your immune cells can tell by feeling for the distinctive structure of this molecule (it's protein signature) if it's one of your own ... so the correct MHC is a password for safe passage in your body. The diversity of the MHC molecule from one individual to another is sometimes referred to as polymorphism, and this diversity that's encoded onto each cell of your body is the reason transplanted tissue is typically rejected.

"One group of proteins encoded by the genes of the MHC are the markers of self that appear in almost all body cells. Known as class I MHC antigens, these molecules alert killer t cells to the presence of body cells that have been changed for the worse - infected with a virus or transformed by cancer - and that need to be eliminated."

"A second group of MHC proteins, class II antigens, are found on b cells, macrophages and other cells responsible for presenting foreign antigen to helper t cells. Class II products combine with particles of foreign antigen in a way that showcases the antigen and captures the attention of the helper t cells. "

Microbes - bacteria, fungi, or virus that invades the body. Also called a pathogen.

Molecule - The smallest physical unit made up of a chemical substance such as a protein or a fat. Molecules are the building blocks of a cell, and a gene determines how each molecule is produced.

Mucous membrane - The moist lining of certain body cavities such as the mouth.

Mutation - a change in a cell's DNA that may cause the cell to produce an abnormal protein.

Neutrophils - an important white blood cell that is both a phagocyte and a granulocyte abundant in the blood.

Phagocytes - large white blood cells that contribute to immune defense by engulfing microbes, such as bacteria and fungi, or other cells and foreign particles.

Side effect - An undesirable effect. (*adverse reaction.*).

Systemic - Affecting the whole body.

T cells (T lymphocytes) - white blood cells that either orchestrate the immune response (regulatory T cells) or directly attack infected or malignant cells (cytotoxic T cells).

Tolerance is a non-reactivity of the immune system to self.

Toxin - A poisonous substance produced by a living organism (e.g., a bacterium, a plant, or an animal). Some toxins can cause diseases, such as botulism and tetanus.

Tumor suppressor genes - genes that protect cells from cancer. They may put the brakes on accelerated growth, or initiate cell death when DNA damage is detected. DNA damage. The under expression of tumor suppression genes can lead to malignant behavior.

Vaccine - substance that contains parts of antigens from an infectious microbe. By stimulating an immune response (but not disease), it protects the body against subsequent infection by that organism.

Virus - A tiny organism that multiplies within cells and can cause disease. Measles, mumps, chickenpox, and hepatitis are diseases caused by viruses.

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Lecture Notes on IMMUNOTOXICITY

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