Hypersensitivities

HYPERSENSITIVITIES (autoimmunity, alloimmunity, allergy):
Hypersensitivity is an inappropriate immune response misdirected against the host’s own tissues (autoimmunity), or directed against beneficial foreign tissues such as transfusions or transplants (alloimmunity), or it can be exaggerated responses against enviromental agents (allergy). They are classified as: type I (IgE mediated); type II (tissue specific); type III (immune complex mediated) & type IV (cell mediated) reactions (immediate, min / hrs, or delayed, hrs / days). The most rapid immediate hypersensitivity reaction, anaphylaxis, occurs within minutes of reexposure (can lead to CV shock).

Type I, Ag reacts with mast cell’s IgE & elicits degranulation. Type II, caused by complement mediated lysis, opsonization and phagocytosis, Ab-dependent cell-mediated cytotoxity, & modulation of cellular function. Type III, caused by formation of immune complexes deposited in target tissues where they activate complement cascade, generating chemotactic fragments that attract neutrophils. Type IV, caused by specifically sensitized T-cells to kill target cells directly or to release chemokines that activate other cells, such as macrophages.

Hypersensitivity is an inappropriate immune response
# Relative Incidence and Examples of Hypersensitivity Diseases

<table>
<thead>
<tr>
<th>Ag target</th>
<th>Type I (IgE – mediated)</th>
<th>Type II (tissue specific)</th>
<th>Type III (immune complex)</th>
<th>Type IV (cell mediated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy environmental Ag</td>
<td>++++ Hay fever</td>
<td>+ Hemolysis in drug allergies</td>
<td>+ Gluten (wheat) allergy</td>
<td>++ Poison ivy allergy</td>
</tr>
<tr>
<td>Auto-immunity, self-Ag</td>
<td>+ May contribute to some type III reactions</td>
<td>++ Autoimmune thrombocytopenia</td>
<td>+++ Systemic lupus erythematosus</td>
<td>++ Hashimoto thyroiditis</td>
</tr>
<tr>
<td>Alloimmunity, another's Ag</td>
<td>+ May contribute to some type III reactions</td>
<td>++ Hemolysis disease in the newborn</td>
<td>+ Anaphylactic response to IgA, if IgA is not made</td>
<td>++ Graft rejection</td>
</tr>
</tbody>
</table>

**Hypersensitivity is an inappropriate immune response**

## Hypersensitivities

- **Mechanisms**
  - Antigenic targets

- **Infection**
  - Infectious microorganism defense mechanisms infection and injury clinical manifestations countermeasures

- **Immune Deficiency**
  - Clinical presentation primary deficiency secondary deficiency evaluation and care replacement therapy

- **Stress Response**
  - General adaptation synd. neuroendocrine control role of immune system

- **Aging**
  - In general, and its effect on specific endocrine organs, as an example

Hypersensitivity is an inappropriate immune response
## Hypersensitivities

### IMMUNOLOGIC MECHANISMS OF TISSUE DESTRUCTION

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Time</th>
<th>Ab</th>
<th>Cell</th>
<th>C* (e.g.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE-mediated</td>
<td>Immediate</td>
<td>IgE</td>
<td>Mast cell</td>
<td>No</td>
</tr>
<tr>
<td>II</td>
<td>Tissue specific</td>
<td>Immediate</td>
<td>IgG, IgM</td>
<td>Macrophage in tissue</td>
<td>Yes</td>
</tr>
<tr>
<td>III</td>
<td>Immune complex</td>
<td>Immediate</td>
<td>IgG, IgM</td>
<td>Neutrophils</td>
<td>Yes</td>
</tr>
<tr>
<td>IV</td>
<td>Cell mediated</td>
<td>Delayed</td>
<td>none</td>
<td>Lymphocytes, Macrophages</td>
<td>No</td>
</tr>
</tbody>
</table>

(* Participation of complement)

Hypersensitivity is an inappropriate immune response
### Hypersensitivities

#### SAME EXAMPLES OF AUTOIMMUNE DISORDERS

<table>
<thead>
<tr>
<th>System disease</th>
<th>Organ or tissue</th>
<th>Probable self-Ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves disease</td>
<td>Hyperthyroidism</td>
<td>TSH-R in thyroid gland</td>
</tr>
<tr>
<td>Hashimoto disease</td>
<td>Hypothyroidism</td>
<td>Thyroid cell surface Ag, TG</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Pancreas</td>
<td>Islet cell, Ins, Ins-R in β cell</td>
</tr>
<tr>
<td>Addison disease</td>
<td>Adrenal hypofunction</td>
<td>Surface Ag, microsomal Ag</td>
</tr>
<tr>
<td>Male infertility</td>
<td>Tests</td>
<td>Surface Ag in spermatzoza</td>
</tr>
<tr>
<td>Neuromuscular tissue</td>
<td>Neural tissue</td>
<td>Surface Ag of nerve cells</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Neuromuscular junction</td>
<td>Ach-R, striations skeleton/cardiac m.</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Heart</td>
<td>Cardiac Ag that react w/Strap-Ag</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>Ulcerative colitis</td>
<td>Colon</td>
</tr>
<tr>
<td></td>
<td>Pernicious anemia</td>
<td>Stomach</td>
</tr>
<tr>
<td>Connective tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Joints</td>
<td>Collagen, IgG</td>
</tr>
<tr>
<td>Systemic Lupus</td>
<td>Multiple sites</td>
<td>Ag in nuclei, organells, EC matrix</td>
</tr>
<tr>
<td>Renal system</td>
<td>Glomerulonephritis</td>
<td>Kidney</td>
</tr>
<tr>
<td>Renal glomerulonephritis</td>
<td>Kidney</td>
<td>Multiple immune complexes</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>Goodpasture disease</td>
<td>Lung, kidney</td>
</tr>
<tr>
<td>Goodpasture disease</td>
<td></td>
<td>Basal membrane, alveoli, glomeruli</td>
</tr>
</tbody>
</table>

Hypersensitivity is an inappropriate immune response
### Hypersensitivities

#### CAUSES OF CLINICAL ALLERGIC REACTIONS

<table>
<thead>
<tr>
<th>Typical allergen</th>
<th>Mechanism</th>
<th>Clinical manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingestants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foods</td>
<td>Type I, II, III</td>
<td>Gastrointestinal allergy</td>
</tr>
<tr>
<td>Drugs</td>
<td>Type I, II, III</td>
<td>Urticaria, immediate drug reaction, hemolytic anemia, serum sickness</td>
</tr>
<tr>
<td>Inhalants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollen, dust, molds</td>
<td>Type I, III</td>
<td>Allergic rhinitis, bronchial asthma</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>Types I, III</td>
<td>Allergic bronchial Aspergilosis</td>
</tr>
<tr>
<td>Thermophilic actinolysetes*</td>
<td>Types III, IV</td>
<td>Extrinsic allergic alveolitis</td>
</tr>
<tr>
<td>Injectants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Types I, II, III</td>
<td>Immediate drug reaction, hemolytic anemia, serum sickness</td>
</tr>
<tr>
<td>Bee venom</td>
<td>Type I</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Type III</td>
<td>Localized Arthus reaction</td>
</tr>
<tr>
<td>Serum</td>
<td>Types I, III</td>
<td>Anaphylaxis, serum sickness</td>
</tr>
<tr>
<td>Contactans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poison ivy, metals</td>
<td>Type IV</td>
<td>Contact dermatitis</td>
</tr>
</tbody>
</table>

(* an order of fungi that is stimulated to grow by warmth)

Hypersensitivity is an inappropriate immune response
Hypersensitivities – Type I

MECHANISM OF TYPE I
IGG – MEDIATED REACTION:

First response to an allergen stimulates B-lymphocytes to mature into plasma cells that produce IgE, which is adsorbed to the surface of mast cell by binding to specific Fc-R to “sensitize” it.

In a 2nd exposure, allergens cross-link surface bound IgE causing degranulation.

The initial phase is characterized by vasodilation, vascular leakage, and smooth muscle spasm or glandular secretions, usually within 5-30 min after Ag exposure.

The late phase occurs 20-8 hr later without additional exposure to Ag and results from infiltration of tissue with inflammatory cells, like eosinophils, neutrophils, and basophils.

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Hypersensitivities
mechanisms
antigenic targets

Infection
Infectious microorganisms, defense mechanisms, infection and injury
clinical manifestations
countermeasures

Immune Deficiency
clinical presentation
primary deficiency
secondary deficiency
evaluation and care
replacement therapy

Stress Response
general adaptation syndrome
neuroendocrine contribution
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(A) Angioedema
(B) Allergic urticaria. Skin lesions with raised edges developed in min-hr with resolution after 12 hr.

Hypersensitivity is an inappropriate immune response.
Hypersensitivities – Type II

MECHANISM OF TYPE II
TISSUE SPECIFIC REACTION:
Ab binds to Ag in cell surface and destroys or prevents the cell from functioning by:

(A) Complement mediated lysis (RBC target is depicted in this figure)
(B) Phagocytosis by macrophages in the tissue
(C) Neutrophil mediated destruction of the RBC
(D) Ab dependent cell-mediated cytotoxicity (ADCC), or
(E) Modulation or blocking the normal function of receptors by antireceptors antibodies

C1, complement component C1
C3b, complement fragment produced from C3, which acts as opsonin.
Hypersensitivities – Type III

MECHANISM OF TYPE III IMMUNE COMPLEX MEDIATED REACTION:

1. Immune complex form in the blood from circulating Ag and Ab and
2. are deposited in certain target tissues
3. The complexes activate complement through C1 and generate fragments that are chemotactic for neutrophils
4. The neutrophils attached to the IgG and C3b in the immune complexes and
5. release a variety of degradative enzymes that destroy the healthy tissues.

Hypersensitivity is an inappropriate immune response
Hypersensitivities – Type IV

MECHANISM OF TYPE IV CELL MEDIATED REACTION:

Antigens from target cells stimulate T-cells to differentiate into T cytotoxic cells (Tc) which have direct cytotoxic activity, and T helper cells (Th) which produce cytotoxins (mainly interferon gamma) that activate macrophages.

The macrophages can attach to targets and release enzymes and reactive oxygen (O2) species that induce apoptosis of the target.

Hypersensitivity is an inappropriate immune response
Hypersensitivities – targets

**Hypersensitivities**
- mechanisms
- antigenic targets

**Infection**
- infectious microorganism defense mechanisms infection and injury clinical manifestations countermeasures

**Immune Deficiency**
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**Stress Response**
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**Hypersensitivity is an inappropriate immune response**

**DEVELOPMENT OF ALLERGIC CONTACT DERMATITIS:**
Left: development of allergy to poison ivy. The primary contact with the Ag sensitizes (produce reactive T cells) the individual but does not produce a rash (dermatitis). The secondary contact activates a Type IV cell-mediated reaction that causes dermatitis.

Right: contact dermatitis caused by a delayed hypersensitivity reaction leading to vesicles scaling of the sites of contact.

**catechol molecules**
- skin proteins

**T cells → T memory cells**
- 7 – 10 days
- no dermatitis
- 1 – 2 days
- cathecols combined with skin proteins
- dermatitis

**PRIMARY CONTACT**

**SECONDARY CONTACT**

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Hypersensitivities – targets

ABO BLOOD TYPES:
The relationship of antigens and antibodies associated with the ABO blood groups.
(A) The surface of RBC of individuals with blood group A have A antigen carbohydrate and their blood have IgM antibodies against the B antigen.
(B) The surface of RBC of individuals with blood group B have B antigen carbohydrate, and their blood contain IgM antibodies against the A antigen.
(C) The surface of RBC of individuals with blood group AB have both A and B antigens, and their blood have antibodies to neither A nor B antigens.
(D) The surface of RBC of individuals with blood group O have neither A nor B antigens, and their blood contains antibodies to both A and B antigens.

Hypersensitivity is an inappropriate immune response

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(D) The surface of RBC of individuals with blood group O have neither A nor B antigens, and their blood contains antibodies to both A and B antigens.
HUMAN LEUKOCYTES ANTIGENS (HLA): The major histocompatibility complex (MHC) is located in chromosome 6 and contains genes that code for class I antigens and class III proteins (e.g., complement proteins and cytokines).

INFECTION:
Bacteria injure cells by producing exotoxins (enzymes that damage host plasma membranes or inactivate enzymes critical to protein synthesis), and endotoxins (activate the inflammatory response and produce fever). In septicemia, endotoxins release vasoactive enzymes that increase blood vessel permeability, hypotension, and septic shock.

Viruses may low protein synthesis, disrupt lysosomal membranes, form inclusion bodies where synthesis of viral nucleic acid occurs, fuse with cells to produce giant cells, alter antigenic properties of the host cell, and transform host cells into cancerous cells.

Fungi cause mycosis that occurs as yeasts (spheres) or molds (filaments or hypheae). They release toxins and enzymes that are damaging to tissue.

Most infections might be bacterial, viral or fungal in origin.
### Classes of Human Infectious Micro-organisms

<table>
<thead>
<tr>
<th>Class</th>
<th>Size</th>
<th>E.g. Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td>20-30 nm</td>
<td>Measles, Hepatitis B, Pneumonitis</td>
</tr>
<tr>
<td>Bacteria</td>
<td>0.8-15 μm</td>
<td>Staphylococcal wound infection, Cholera, Streptococcal pneumonia</td>
</tr>
<tr>
<td>Chlamidia</td>
<td>20-1000 nm</td>
<td>Trachoma</td>
</tr>
<tr>
<td>Rickettsiae</td>
<td>300-1200 nm</td>
<td>Rocky Mountain spotted fever</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>125-350 nm</td>
<td>Mycoplasma pneumonia</td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>1-10 μm</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Fungi</td>
<td>2-200 μm</td>
<td>Tinea pedis (athlete's foot)</td>
</tr>
<tr>
<td>Protozoa</td>
<td>1-360 μm</td>
<td>Giardiasis</td>
</tr>
<tr>
<td>Helminths</td>
<td>3 mm – 10 m</td>
<td>Trichinosis</td>
</tr>
</tbody>
</table>

Most infections might be bacterial, viral or fungal in origin.
### PATHOGENS THAT DIRECTLY CAUSE TISSUE DAMAGE

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Produce exotoxins</strong></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>Tonsilitis, Scarlet fever</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Boils, toxic shock syndrome, food poisoning</td>
</tr>
<tr>
<td>Corynbacterium diphteriae</td>
<td>Diphtheria</td>
</tr>
<tr>
<td>Clostridium tetani</td>
<td>Tetanus</td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td>Cholera</td>
</tr>
<tr>
<td><strong>Produce endotoxins</strong></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Gram-negative sepsis</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>Meningitis, pneumonia</td>
</tr>
<tr>
<td>Salmonella typhi</td>
<td>Typhoid</td>
</tr>
<tr>
<td>Shigella</td>
<td>Bacillary dysentery</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Wound infection</td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td>Plague</td>
</tr>
<tr>
<td><strong>Cause direct damage by invasion</strong></td>
<td></td>
</tr>
<tr>
<td>Variola</td>
<td>Smallpox</td>
</tr>
<tr>
<td>Varicella zoster</td>
<td>Chicken pox, shingles</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Polyvirus</td>
<td>Poliomyelitis</td>
</tr>
<tr>
<td>Measles virus</td>
<td>Measles, subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Influenza</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Cold sores</td>
</tr>
</tbody>
</table>

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**Infection - defense**

- **Infection**
  - Infectious microorganism defense mechanisms infection and injury clinical manifestations countermeasures
  - **Hypersensitivities**
    - Mechanisms antigenic targets

- **Immune Deficiency**
  - Clinical presentation primary deficiency secondary deficiency evaluation and care replacement therapy

- **Stress Response**
  - General adaptation synd. neuroendocrine control role of immune system

- **Aging**
  - In general, and its effect on specific endocrine organs, as an example

**Most infections might be bacterial, viral or fungal in origin**
PATHOGENS THAT INDIRECTLY CAUSE TISSUE DAMAGE

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produce immune complex</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Kidney disease</td>
</tr>
<tr>
<td>Malaria</td>
<td>Vascular deposits</td>
</tr>
<tr>
<td>S. Pyogenes</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>Kidney damage in secondary syphilis</td>
</tr>
<tr>
<td>Most acute infections</td>
<td>Transient renal deposits</td>
</tr>
<tr>
<td>Produce autoantibodies</td>
<td></td>
</tr>
<tr>
<td>S. Pyogenes</td>
<td>Rheumatic fever</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Cause cell – mediated immunity</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Mycobacterium leprae</td>
<td>Tuberculoid leprosy</td>
</tr>
<tr>
<td>Lymphocytic choriomeningitis virus</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>Lyme arthritis</td>
</tr>
<tr>
<td>Schistosoma mansoni</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Herpes stromal keratitis</td>
</tr>
</tbody>
</table>

Most infections might be bacterial, viral or fungal in origin.
### EXAMPLES OF MECHANISMS USED BY PATHOGENS TO RESIST THE IMMUNE SYSTEM

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect on immunity</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Destroys or blocks</strong></td>
<td>Make toxins</td>
<td>Staphylococcus, Streptococcus</td>
</tr>
<tr>
<td></td>
<td>Make anti-oxidant</td>
<td>Mycobacterium sp., Salmonella thyphi</td>
</tr>
<tr>
<td></td>
<td>Make proteases digest IgA</td>
<td>Neisseria gonorrhoea, Haemophilus influenza</td>
</tr>
<tr>
<td></td>
<td>Make “Fc-R” like surface molecules that bind Ab</td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td></td>
<td>Kill phagocyte, block chemotaxis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blocks phagocytosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blocks kill by O2-radicals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Promotes bacterial attachment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blocks complement activation &amp; Ab functioning as opsonins</td>
<td></td>
</tr>
<tr>
<td><strong>Mimics self-antigens</strong></td>
<td>Make surface Ag as self-Ag</td>
<td>Group A streptococcus (M prot), Mycoplasma pneumoniae (red cell Ag)</td>
</tr>
<tr>
<td></td>
<td>Pathogen resembles own tissue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Forms Ab against self-Ag leading to hypersensitivity disease</td>
<td></td>
</tr>
<tr>
<td><strong>Change antigenic profile</strong></td>
<td>Undergo Ag mutation or activate genes that change surface molecules</td>
<td>Influenza, HIV, some parasites</td>
</tr>
<tr>
<td></td>
<td>Immune response delayed because of failure to recognize new antigen</td>
<td></td>
</tr>
</tbody>
</table>

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Immune deficiencies

DEFICIENCIES IN IMMUNITY:

Failure of mechanisms of self-defense. It can be congenital (primary, fail lymphocyte development) or acquired (secondary to disease or other physiological failure). Its hallmark is propensity to unusual or recurrent severe infections.

Most defects of cell-mediated responses are fungal / viral, while humoral / complement defects elicit bacterial infection. Severe Combined Immunodeficiency (SCID) is a total lack of T-cell function & severe (partial/ total) lack of B-cell function.

Congenital thymic aplasia or hypoplasia is characterized by complete or partial lack of T-cell immunity, and parathyroid (hypocalcemia) and cardiac anomalies.

Defects in B-cell function span from lack of B-cell maturation to selective immunoglobulin deficiency (e.g. IgA).

AIDS is an acquired dysfunction caused by a retrovirus that infects and destroys CD4 lymphocytes (Th cells).

Immune deficiency is a failure of mechanisms of self-defense.

<table>
<thead>
<tr>
<th>EXAMPLES OF PRIMARY DEFICIENCIES IN IMMUNITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classification</strong></td>
</tr>
<tr>
<td>B-lymphocyte deficiency</td>
</tr>
<tr>
<td>T-lymphocyte deficiency</td>
</tr>
<tr>
<td>Combined deficiency</td>
</tr>
<tr>
<td>Complement deficiency</td>
</tr>
<tr>
<td>C6</td>
</tr>
<tr>
<td>Phagocyte deficiency</td>
</tr>
</tbody>
</table>

Immune deficiency is a failure of mechanisms of self-defense.
### EXAMPLES OF PRIMARY DEFICIENCIES IN IMMUNITY

<table>
<thead>
<tr>
<th>Classification</th>
<th>Deficiency</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-lymphocyte deficiency</td>
<td>In bone marrow</td>
<td>Recurrent bacterial infection</td>
</tr>
<tr>
<td></td>
<td>In class switch</td>
<td>Mild GI, respiratory infection</td>
</tr>
<tr>
<td></td>
<td>No B-cells, no Ab made</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limited or no IgA only</td>
<td></td>
</tr>
<tr>
<td>T-lymphocyte deficiency</td>
<td>In thymus</td>
<td>Recurrent viral/fungi infect.</td>
</tr>
<tr>
<td></td>
<td>To a specific Ag</td>
<td>Recurrent and disseminated infection with Candida</td>
</tr>
<tr>
<td></td>
<td>No T-cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No T-cell response to Candida</td>
<td></td>
</tr>
<tr>
<td>Combined deficiency</td>
<td>In B and T cells</td>
<td>Various recurrent infections</td>
</tr>
<tr>
<td></td>
<td>Interaction of B,T, APC</td>
<td>Various recurrent infections</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>Various recurrent infections</td>
</tr>
<tr>
<td></td>
<td>No cell / humoral immunity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No class I or II MHC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytoskeletal, defect, low IgM</td>
<td></td>
</tr>
<tr>
<td>Complement deficiency</td>
<td>C3</td>
<td>Recurrent bacterial infection</td>
</tr>
<tr>
<td></td>
<td>Little or no C3 produced</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C6</td>
<td>Recurrent disseminated infection with Nisseria</td>
</tr>
<tr>
<td></td>
<td>Little or no C6 produced</td>
<td></td>
</tr>
<tr>
<td>Phagocyte deficiency</td>
<td>Neutrophils</td>
<td>Recurrent bacterial infection</td>
</tr>
<tr>
<td></td>
<td>Lack of neutrophils</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacterial killing</td>
<td>Recurrent bacterial infection sensitive to O2 radicals</td>
</tr>
<tr>
<td></td>
<td>Lack of O2 radicals produced</td>
<td></td>
</tr>
</tbody>
</table>

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**Stress - general**

- **Hypersensitivities**
  - Mechanisms
  - Antigenic targets
- **Infection**
  - Infectious microorganism defense mechanisms
  - Infection and injury clinical manifestations countermeasures
- **Immune Deficiency**
  - Clinical presentation primary deficiency secondary deficiency evaluation and care replacement therapy
- **Stress Response**
  - General adaptation syndrome
  - Neuroendocrine control role of immune system
- **Aging**
  - In general, and its effect on specific endocrine organs, as an example

The alarm reaction includes increased Cortisol, Epi, and Nepi secretion.

*The stress axis is the main inhibitor of the immune system.*
THE STRESS RESPONSE

- Adrenal gland
- Nerve signal
- Kidney
- ACTH
- medulla
- cortex
- Glucocorticoids (cortisol)
- Adrenaline (epinephrine)
- Liver releases glucose
- Increased HR, breathing rate, and blood sugar

Stress - general

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The stress axis is the main inhibitor of the immune system.
The stress response

**Stressor**
- Central nervous system
- Hypothalamus

**CRH**

**Sympathetic nervous system**
- Neurogenic Y (NP)
- Noradrenaline
- Epinephrine
- Blood pressure
- Increased heart rate
- Increased force and rate of cardiac contraction
- Increased glucose uptake in skeletal muscle and adipose tissue
- Increased glucose synthesis
- Decreased glucose output
- Increased circulating free fatty acids
- Increased appetite
- Increased energy intake
- Stress - general adaptation syndrome

**CRH**
- Neurogenic Y (NP)
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- Increased appetite
- Increased energy intake
- Stress - general adaptation syndrome

**Posterior pituitary**
- ADH (vasopressin)
- TSH (thyroid-stimulating hormone)
- ACTH (adrenocorticotropic hormone)
- Cortisol

**Anterior pituitary**
- ADH (vasopressin)
- TSH (thyroid-stimulating hormone)
- ACTH (adrenocorticotropic hormone)
- Cortisol

**Immuno-suppression**
- Anti-inflammatory
- Enhanced humoral immunity

**Humoral immunity**
- Protects against multicellular parasites, extracellular bacteria, some viruses, soluble toxins, and allergens.

**Cellular/humoral immunity**
- Protects against intracellular bacteria, fungi, protozoa, and several viruses.

**Stress response**
- General adaptation syndrome
- Neuroendocrine control of immune system

**Aging**
- General, and its effect on specific endocrine organs, as an example

**CRH – Mast cells – Histamine axis on Th1 / Th2 balance, and cellular/humoral immunity:**

Humoral immunity protects against multicellular parasites, extracellular bacteria, some viruses, soluble toxins, and allergens. Cell immunity protects against intracellular bacteria, fungi, protozoa and several viruses.

*The stress axis is the main inhibitor of the immune system.*
Humoral immunity protects against multicellular parasites, extracellular bacteria, some viruses, soluble toxins, and allergens. Cell immunity protects against intracellular bacteria, fungi, protozoa and several viruses.

CRH – Mast cells – Histamine axis on Th1 / Th2 balance, & cellular / humoral immunity:

- Increased acute inflammation allergic reaction
- Decreased cellular immunity allergic reaction
- Increased humoral immunity (Th2 shift)
- B lymphocytes (Ab) eosinophils, mast cells

**Stress - neuroendocrine**

- Hypersensitivities
  - mechanisms
  - antigenic targets
- Infection
  - Infectious microorganism
  - defense mechanisms
  - infection and injury
  - clinical manifestations
  - countermeasures
- Immune Deficiency
  - clinical presentation
  - primary deficiency
  - secondary deficiency
  - evaluation and care
  - replacement therapy

**Stress Response**
- general adaptation synd.
- neuroendocrine control
- role of immune system

**Aging**
- in general, and its effect on specific endocrine organs, as an example

The stress axis is the main inhibitor of the immune system.
Health outcome determinants in stressful life situations is moderated by numerous factors. Whether a life – challenged individual experiences distress or illness depends on the subject's appraisal of the event and the coping strategies used during the stressful period. Models (A) and (B) reflect possible outcomes in stressed healthy and symptomatic individuals. Model (C) illustrates the dynamic clinical setting in which the diagnosis of a serious illness and subsequent medical interventions may be perceived as stressful challenges & have potential detrimental influences on physical outcome.

The stress axis is the main inhibitor of the immune system.
Although it is doubtful that a single theory would explain all the mechanisms of aging, three of them have retained their appeal:

1. Cellular changes produced by genetic and environmental lifestyle factors

Cells are damaged during replication from the inside (e.g. DNA, proteins) or from the outside (e.g. ionizing radiation). Cells might also be programmed to age and thus have a finite life span in which to replicate. For example, it has been suggested that an intrinsic genomic program progressively slows or shut down physiological events (e.g. mitosis).

Experiments do not support that aging is the result of somatic mutations.

Accumulation of altered proteins in aging may result from an increased production or a decreased ability of aged cells to degrade their cellular proteins, or both.
2.- Changes in cellular regulatory, or control mechanisms, especially in cells of neuro-endocrine, immune, & central nervous system

A genetic program for aging is encoded in the brain and is controlled and relayed to peripheral tissues through hormonal and neuronal agents.

Possible neuro-endocrine mechanisms include:
(1) increase hormonal degradation; (2) decreased rate of hormonal synthesis/secretion; and (3) decreased target-organ sensitivity related to number of cellular receptors for hormonal ligands, ligand receptor binding, or ligand internalization.

Immune mechanisms have been suggested since:
(1) immune function declines with age; (2) this decline is related to some diseases (e.g. cancer); and (3) number of auto-antibodies increase with age.

Three non-exclusive theories of aging supported by experimental data

Aging in general

Hypersensitivities
- mechanisms
- antigenic targets

Infection
- infectious microorganism
- defense mechanisms
- infection and injury
- clinical manifestations
- countermeasures

Immune Deficiency
- clinical presentation
- primary deficiency
- secondary deficiency
- evaluation and care
- replacement therapy

Stress Response
- general adaptation syndrome
- neuroendocrine control
- role of immune system

Degenerative extracellular and vascular alterations

Extracellular factors affecting aging include binding of collagen; increase in free radicals’ effect on cells; structural alterations of fascia, tendons, ligaments, bones and joints; and peripheral vascular disease, particularly arteriosclerosis.

Increased cross-linking in ECF matrix leads to less elastin and soluble collagen, decreased cell permeability, dehydration, skin wrinkling, and skeletal muscle alterations (loss of contractility).

Free radicals from O2 resulting from oxidative cell metabolism damage tissue during aging. These include superoxide radical, hydroxyl radical and hydrogen peroxide.

Vascular deposition of lipids, Ca and plasma proteins due to alterations in ECF matrix affects vessel integrity, basal memb. thickening and smooth muscle alterations (e.g. arteriosclerosis).

Three non-exclusive theories of aging supported by experimental data
AGING, ITS EFFECTS ON SPECIFIC ENDOCRINE ORGANS:

Age-related endocrine changes include alterations in secretion, circulating levels, metabolism, and biologic activity of hormones. There is also a loss of circadian (a 24-hour period) control of hormone secretion. Although most glands decrease their levels of secretion, normal aging usually does not lead to a deficiency state.

The general changes in the endocrine glands that occur with older age include:

a) atrophy and weight loss with vascular changes,

b) decreased secretion and clearance of hormones, and

c) variable changes in receptor binding and intracellular responses.

Atrophy, hormone hyposecretion, and binding alterations are linked to aging

AGING, ITS EFFECTS ON SPECIFIC ENDOCRINE ORGANS:

For example, while adrenal cortex decreases its secretion of cortisol, negative feedback mechanisms maintain normal plasma levels. As thyroid function ebbs there is a decrease in T3-T4 which lead to a decrease in the metabolic rate and an unawareness of temperature (e.g. cold intolerance and hot days will not be noticed, thereby increasing the risk of heat stroke). A decrease in the secretion of GH causes a decrease in muscle mass and an increase in the storage of fat. Blood and tissue concentrations of many other hormones remain unchanged (e.g. TSH, thyroid hormones, ADH, PTH, prolactin, and glucocorticoids).

Despite unchanging hormone levels, some endocrine tissues become less responsive to stimulation. For example, there is less GH (growth hormone) and insulin secreted after a carbohydrate-rich meal or during a glucose tolerance test.

Peripheral tissues become less responsive to hormones, particularly glucocorticoids and ADH. The failure to produce enough cortisol can affect metabolism and the stress response. In addition, a decline in cortisol production will also reduce the anti-inflammatory and immunosuppressive qualities that they give. This means that the elderly are more prone to pain and infections.
Your third Case Study

SUMMARY:
You are presented with a 4-week-old Arab filly for depression, coughing and nasal discharge. The foal was born with no apparent problems. Immunoglobulin levels were checked and were normal. However, the foal has been unhealthy and seems to be repeatedly sick with skin and respiratory infection. On examination, the foal has a temperature of 38.8°C (102°F) (elevated), and a respiratory rate of 48 beats per min (elevated). On auscultation the foal has both crackles and wheezes (abnormal lung sounds). The capillary refill time (CRT) is prolonged, and the mucous membranes are darker pink than normal. The foal also has some abrasions and cellulitis in those areas of the skin.

TENTATIVE DIAGNOSIS:
LAB TESTS:
FINAL DIAGNOSIS:
TREATMENT:
A 4-week-old Arab filly with depression, coughing, and nasal discharge.

DEFICIENCIES IN IMMUNITY:
Failure of mechanisms of self-defense. It can be congenital (primary, fail lymphocyte development) or acquired (secondary to disease or other physiological failure). Its hallmark is propensity to unusual or recurrent severe infections.

Most defects of cell-mediated responses are fungal / viral, while humoral / complement defects elicit bacterial infection. Severe Combined Immunodeficiency (SCID) is a total lack of T-cell function & severe (partial/ total) lack of B-cell function.

Congenital thymic aplasia or hypoplasia is characterized by complete or partial lack of T-cell immunity, and parathyroid (hypocalcemia) and cardiac anomalies.

Defects in B-cell function span from lack of B-cell maturation to selective immunoglobulin deficiency (e.g. IgA).

AIDS is an acquired dysfunction caused by a retrovirus that infects and destroy CD4 lymphocytes (Th cells).