Autoimmune Disorders: Light at the End of the Tunnel?
Autoimmunity, one of three major mechanisms of ‘inappropriate’ immunity
What are autoimmune diseases?

The ability of the immune system to discriminate between 'self' and 'non-self' is a fundamental requirement for life.

The existence of self-tolerance prevents the individual’s immune system from attacking normal cells and tissues of the body.

A breakdown or failure of the mechanisms of self-tolerance results in Autoimmunity.
Autoimmune Diseases

In autoimmunity, an immune response to self results in tissue injury. Autoimmune disorders are a diverse group of conditions, which occur due to abnormal stimulation and signaling within the immune system. "Self" versus "non-self" recognition is altered.

- There are ~80 different autoimmune diseases.
- Women are at 2.7x greater risk.
- Autoimmune diseases fit into Type II, III, and IV hypersensitivity-induced responses.
- Autoimmune diseases are not mediated by IgE (Type I hypersensitivity) antibodies.
How common are autoimmune diseases?

The prevalence values depend on the genetic background of the studied populations, on the geographical area, sizes of the populations, and definitions of the parameters that are being considered as positive signs of a disease.

Autoimmune diseases involve a multigenic predisposition.

For example, an individual who has an identical twin with SLE has a much higher frequency of developing SLE than a member of the general population (27-54% vs 0.1%)
How common are autoimmune diseases?

Cumulative data obtained from many different comprehensive epidemiological studies in the past 50 years estimate that the prevalence of autoimmune diseases is at the range of 3-9%.

Some autoimmune diseases are rare, while others, such as Hashimoto's disease, affect many people.

Fortunately, most diseases cause minor inconveniences and are not life threatening (e.g., Psoriasis, Vitiligo).

Many autoimmune diseases co-occur at greater than expected rates within proband patients and their families; this does not appear to be a uniform phenomenon across all diseases.
### Recent Prevalence Data for Autoimmune Diseases, by Geographic Area

<table>
<thead>
<tr>
<th>Disease</th>
<th>Rate per 100,000</th>
<th>Study Area</th>
<th>Rate per 100,000</th>
<th>Study Area</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital-based Data</strong></td>
<td></td>
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<tr>
<td><strong>Denmark</strong></td>
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<tr>
<td>Systemic lupus</td>
<td>32</td>
<td>US, Spain, Greece</td>
<td>34-150</td>
<td>Saudi Arabia</td>
<td>19</td>
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<td>Celiac disease</td>
<td>50</td>
<td>Greece, Netherland, Iceland, Italy</td>
<td>180-350</td>
<td>Iran, Tunisia</td>
<td>140-280</td>
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<td></td>
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<td>Finland</td>
<td>740-1000</td>
<td>Brazil, Argentina</td>
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<td>1900</td>
<td>Turkey</td>
<td>900</td>
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<tr>
<td>Multiple sclerosis</td>
<td>182</td>
<td>US, Canada, Italy, Greece, France</td>
<td>177-358</td>
<td>Brazil, Argentina</td>
<td>4-20</td>
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<td></td>
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<td>Norway, Portugal</td>
<td>121-200</td>
<td>Jordan, Iran, Israel</td>
<td>11-62</td>
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<td>46-50</td>
<td>Japan</td>
<td>13</td>
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<tr>
<td>Myasthenia gravis</td>
<td>18</td>
<td>Greece, Estonia, Croatia, UK, Sweden</td>
<td>8-15</td>
<td>Colombia</td>
<td>3</td>
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<td></td>
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<td></td>
<td>8-15</td>
<td>Curacuo &amp; Aruba</td>
<td>7</td>
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<tr>
<td>Sjögren disease</td>
<td>48</td>
<td>UK, Slovenia, Greece</td>
<td>3500</td>
<td>China</td>
<td>330-770</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>381</td>
<td>France, Hungary, UK</td>
<td>310-810</td>
<td>Thailand, China</td>
<td>120-280</td>
</tr>
<tr>
<td><strong>Hospital and non-Hospital-based Data</strong></td>
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<tr>
<td><strong>Europe, North America, Australia, New Zealand</strong></td>
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<tr>
<td><strong>Asia, Middle East, Caribbean, South America</strong></td>
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</tbody>
</table>
Main causative factors of autoimmune diseases

- **Genetic predisposition** - Many genetic loci affect the predisposition to autoimmune disease. Many autoimmune diseases show association with specific Major Histocompatibility Complex (MHC) genes.

- **Gender** - Hormonal influences, especially sex hormones. In specific autoimmune diseases (SLE, MS), females are more commonly affected.

- **Environment** - Infections, especially viral, stress conditions, etc.
Susceptibility to Autoimmunity

- The best evidence for genetic factors in autoimmunity comes from identical twin studies.
- High concordance in twins suggests shared genetic or environmental factors.
- If a disease is restricted to monozygotic twins then genetic factors are important.
- In insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis, MS, and SLE, about ~20% of monozygotic twins show concordance, compared with <5% in dizygotic twins.
Autoimmune responses are mediated by the adaptive immune system

- Adaptive immune responses are mediated by lymphocytes
- Primary cells of the lymphatic system, also circulate in blood
- They respond in an antigen-specific manner
- They are ~30% of all blood leukocytes (white blood cells).
- Each lymphocyte has a unique antigen (Ag) receptor
- Are inactive until they meet a pathogen and undergo activation
- Memory of the adaptive immune response is provided by the lymphocytes
The adaptive immune system

The humoral response involves interaction of B lymphocytes (B cells) with antigen (Ag) and their differentiation into antibody-secreting plasma cells. The secreted antibody (Ab) binds to the antigen and facilitates its clearance from the body.

The cell-mediated responses involve various subpopulations of T lymphocytes (T cells) that recognize antigen presented on self-cells. T helper (T_H) cells respond to antigen by producing cytokines. Cytotoxic T (T_C) cells respond to antigen by developing into effector cytotoxic T lymphocytes (CTLs), which mediate killing of altered self-cells (e.g., virus-infected cells).
Self-tolerance depends on the concerted action of a variety of mechanisms that operate at different sites and stages of development.

**Central tolerance**
Central deletion of newly formed T and B lymphocytes in the thymus and bone marrow.

**Peripheral tolerance**
Cellular inactivation of adult lymphocytes, by ‘weak’ signaling that occur in the absence of costimulatory molecules.

**Regulatory cells**
Treg-mediated suppression of cytokine production.

**Acquired tolerance**
Immune system's adaptation to external antigens, such as the tolerance to fetal antigens during pregnancy. In adults, by repeated administration of very large doses of antigen, or small doses that are below the threshold required for stimulation of an immune response.
### Mechanisms by which infectious agents can break self-tolerance

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Disruption of cell or tissue barrier</th>
<th>Molecular mimicry</th>
<th>Superantigen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect</strong></td>
<td>Release of sequestered self antigen; activation of nontolerized cells</td>
<td>Production of cross-reactive antibodies or T cells</td>
<td>Polyclonal activation of autoreactive T cells</td>
</tr>
<tr>
<td><strong>Example</strong></td>
<td>Sympathetic ophthalmia</td>
<td>Rheumatic fever Diabetes Multiple sclerosis</td>
<td>Rheumatoid arthritis</td>
</tr>
</tbody>
</table>

**Immunobiology, Janeway et al., 4th Ed. Fig. 13.39a, p. 530 (5th, Fig. 13.42a)**
Antibody Structure

Ag-binding site

light chain

Ag-binding site

hinge region

heavy chain

light chain

Ag = antigen
Ab = antibody
V = variable domain
C = constant domain
H = Heavy chain
L = Light chain
S-S = disulfide bond

Fc portion of the Ab
Antibody molecules recognize and interact with small antigenic determinants (epitopes).

The specific site of an antigen that binds to an antibody is called an antigenic determinant or epitope.

Most antigens have a variety of epitopes that generate a number of different antibodies that are called polyclonal.

An immune response to a single epitope by one type of Ab producing cells is termed monoclonal.
Molecular mimicry

An antibody molecule that reacts against a specific epitope on a foreign antigen can cross-react against a similar epitope on a self protein.
Rheumatic fever can occur following *Streptococcus* infection due to formation of cross-reactive Abs that respond against heart, joints, skin, and brain tissue.
A role for IFNγ in autoimmunity

Thyroid cells do not normally express HLA class II molecules

IFN-γ receptor

Thyroid epithelial cell

Activated T cells recognize thyroid peptides presented by HLA class II and induce autoimmune thyroid disease

IFN-γ produced during infection or non-specific inflammation induces HLA class II expression on thyroid cells

IFN-γ

HLA class II molecules

Thyroid epithelial cell

Autoimmune thyroid disease
Autoimmune Diseases

Organ specific autoimmune diseases:

Usually affect a single organ and the autoimmune response is directed against antigens within that organ.

e.g.: Type I diabetes mellitus, Goodpasture’s syndrome, multiple sclerosis, Grave’s disease, Hashimoto’s thyroiditis, autoimmune pernicious anemia, myasthenia gravis, autoimmune Addison’s disease, vitiligo.

Non-organ specific disorders:

Affect multiple organs and are usually associated with responses against self-molecules widely distributed throughout the body.

e.g.: SLE, Rheumatoid arthritis, scleroderma, Primary Sjogren’s syndrome, polymyositis.

Immunobiology, Janeway et al., 5th Ed. Fig. 13.2, p. 504
Two types of autoimmune diseases

<table>
<thead>
<tr>
<th>organ-specific</th>
<th>non-organ-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>brain</td>
<td>Muscle</td>
</tr>
<tr>
<td>multiple sclerosis</td>
<td>myasthenia gravis</td>
</tr>
<tr>
<td>thyroid</td>
<td></td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td></td>
</tr>
<tr>
<td>Primary myxedema</td>
<td></td>
</tr>
<tr>
<td>thyrotoxicosis</td>
<td></td>
</tr>
<tr>
<td>stomach</td>
<td>kidney</td>
</tr>
<tr>
<td>pernicious anemia</td>
<td>SLE</td>
</tr>
<tr>
<td>adrenal</td>
<td>skin</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>pancreas</td>
<td>joints</td>
</tr>
<tr>
<td>insulin-dependent diabetes mellitus</td>
<td>rheumatoid arthritis</td>
</tr>
</tbody>
</table>
### Organ-specific
- Hashimoto’s thyroiditis
- primary myxoedema
- thyrotoxicosis
- pernicious anemia
- autoimmune atrophic gastritis
- Addison’s disease
- premature menopause (few cases)
- insulin-dependent diabetes mellitus
- stiff-man syndrome
- Goodpasture’s syndrome
- myasthenia gravis
- male infertility (few cases)
- pemphigus vulgaris
- pemphigoid
- sympathetic ophthalmia
- phacogenic uveitis
- multiple sclerosis
- autoimmune hemolytic anemia
- idiopathic thrombocytopenic purpura
- idiopathic leucopenia
- primary biliary cirrhosis
- active chronic hepatitis (HBsAg negative)
- cryptogenic cirrhosis (some cases)
- ulcerative colitis
- atherosclerosis
- Sjogren’s syndrome
- rheumatoid arthritis
- dermatomyositis
- scleroderma
- mixed connective tissue disease
- anti-phospholipid syndrome
- discoid lupus erythematosus
- systemic lupus erythematosus (SLE)

### Non-organ-specific

Autoimmune disease may be classified as organ-specific or non-organ-specific depending on whether the response is primarily against antigens localized to particular organs, or against widespread antigens.

*Immunology, Roitt et al., 5th Ed. Fig. 28.3, p. 368*
Autoimmune responses are initiated in the same way as normal adaptive immune responses.

A self antigen is recognized on the target tissue by effector lymphocytes.

Tissue damages can be mediated by effector mechanisms of both T and B lymphocytes (antibodies).

In contrast to a regular immune response, an autoimmune response persists since the antigens cannot be permanently removed.
Why is MHC involved in susceptibility to autoimmune diseases?

- Autoimmune responses are mediated by T cells.

- T cells recognize Ags only when displayed by MHC molecules on the surface of antigen presenting cells.

- Some Human Leukocyte Antigen (HLA; human MHC) types preferentially bind self-antigens which can then be presented to T cells.
MHC class I and class II molecules
**T cell recognition**

$T_H1$ and $T_H2$ cells recognize antigen presented by MHC class II molecules.

On recognition of antigen on infected macrophages, $T_H1$ cells activate the macrophage, leading to the destruction of the intracellular bacteria.

When $T_H2$ cells recognize antigen on B cells, they activate them to proliferate and differentiate into Ab-producing plasma cells.

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*Janeway et al., Immunobiology, 4th Ed., Garland Publishing, 1999, Fig. 1.30 (5th; Fig. 1.31, 2001)*
The genetic organization of the major histocompatibility complex (MHC) in humans and the mouse

Janeway et al., Immunobiology, 4th Ed., Garland Publishing, 1999, Fig. 4.19
The human MHC genes are highly polymorphic

Numbers above the bars indicate the number of known alleles for the specific gene in the Caucasoid population

Janeway _et al._, Immunobiology, 4th Ed., Garland Publishing, 1999, Fig. 4.21 (5th; Fig.5.12, 2001)
Expression of MHC alleles is co-dominant

The MHC is so polymorphic that most individuals are likely to be heterozygous at each locus.

Janeway et al., Immunobiology, 4th Ed., Garland Publishing, 1999, Fig. 4.22. (5th; Fig. 5.13, 2001)
HLA-linked autoimmune diseases

Relative Risk - Ratio of antigen frequency in disease population to frequency in control population
The statistical association between an autoimmune disease and a specific HLA gen is expressed as the relative risk. Relative risk is the ratio between the incidence of the disease among carriers of the gene in question and the incidence among non-carriers.
## Association of autoimmunity with HLA

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA allele</th>
<th>Relative risk</th>
<th>Sex ratio (♀:♂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B27</td>
<td>87.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>B27</td>
<td>10</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>DR2</td>
<td>15.9</td>
<td>~1</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>DR2</td>
<td>4.8</td>
<td>10</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>DR3</td>
<td>3.7</td>
<td>4–5</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>DR3</td>
<td>2.5</td>
<td>~1</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DR3</td>
<td>5.8</td>
<td>10–20</td>
</tr>
<tr>
<td>Type I insulin-dependent diabetes mellitus</td>
<td>DR3/DR4</td>
<td>~25</td>
<td>~1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>DR4</td>
<td>4.2</td>
<td>3</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>DR4</td>
<td>14.4</td>
<td>~1</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>DR5</td>
<td>3.2</td>
<td>4–5</td>
</tr>
</tbody>
</table>
Classification of autoimmune diseases

Autoimmune diseases can also be classified based on the immune mechanism which leads to the autoimmune response. There are three known mechanisms, also termed immunological hypersensitivity, that can induce autoimmunity.

- **Type II** - Cytotoxic/Stimulating (IgG/IgM-mediated)
- **Type III** - Arthus or Immune complex (IgG/IgM, immune complex-mediated)
- **Type IV** - Delayed type hypersensitivity (T cell-mediated delayed responses)

Some autoimmune diseases have multiple types of immunological hypersensitivity.
Type II hypersensitivity-induced autoimmune diseases
Anti-cell surface antigen autoantibodies

- Binding of autoantibodies to cell surface molecules can lead to cell destruction (Type IIA), or to stimulation or inhibition of cell activities (Type IIB).
Autoimmune diseases due to type II hypersensitivity

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Autoantigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Rh blood group antigens, I antigen</td>
<td>Destruction of red blood cells by complement and phagocytes, anemia</td>
</tr>
<tr>
<td>Autoimmune thrombocytopehria purpura</td>
<td>Platelet integrin gpIIb/IIa</td>
<td>Abnormal bleeding</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>Non-collagenous domain of basement membrane collagen type IV</td>
<td>Glomerulonephritis, pulmonary hemorrhage</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Epidermal cadherin</td>
<td>Blistering of skin</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Streptococcal cell wall antigens Antibodies cross-react with cardiac muscle</td>
<td>Arthritis, myocarditis, late scarring of heart valves</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>Thyroid-stimulating hormone receptor</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Progressive weakness</td>
</tr>
<tr>
<td>Insulin-resistant diabetes</td>
<td>Insulin receptor (antagonist)</td>
<td>Hyperglycaemia, ketoacidosis</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Insulin receptor (agonist)</td>
<td>Hypoglycaemia</td>
</tr>
</tbody>
</table>

Cellular destruction

- by cross-reactions

Cellular activation

Cellular inhibition

Cellular inhibition

Cellular activation

*Immunobiology, Janeway et al., 4th Ed. Fig. 13.1, p. 490 (5th, Fig. 13.1)*
Type IIA hypersensitivity-induced autoimmune diseases

Anti-cell surface antigen autoantibodies that induce cell cytotoxicity

• Initiated by the production of autoantibodies (IgM/IgG).

• Induced by autoantibody binding to intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (adsorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen).

• Mediated by a) complement activation and cell lysis, b) NK cell and macrophage activation that lyse the cells directly or following phagocytosis, respectively.
In diseases, such as autoimmune hemolytic anemia, Abs specific for cell-surface antigens can destroy cells.
Drug-induced autoimmune hemolytic anemia

Drug (P=Penicillin)-modified red blood cells induce the production of antibodies, because the bound drug makes the cells look foreign to the immune system. Upon binding of these antibodies, the red blood cells become more susceptible to lysis or phagocytosis. Onset is dependent on the presence of specific antibodies.
Goodpasture’s Syndrome
Anti-glomerular basement antibody disease

- A disease caused by autoantibodies binding to basement-membrane antigens of the kidney glomeruli and the alveoli of the lungs.
- Complement activation leads to direct cell damage and inflammation due to the release of complement chemotactic factors (C5a).
- Damage to the kidney and lung basement membranes leads to progressive kidney damage and pulmonary hemorrhages.
- Death ensues several months after the onset of disease.
- Biopsies of patients reveal linear deposits of IgG and C3b along the basement membranes.
Goodpasture’s Syndrome

Fluorescent anti-IgG staining of a kidney biopsy of a patient with Goodpasture’s syndrome reveals deposits of IgG autoantibodies along the glomerular basement membrane.

Mechanism of tissue damage in Goodpasture’s Disease:
Deposition of IgG Abs in the kidney glomeruli, activation of complement and recruitment of inflammatory cells.

This Figure is similar to: Immunobiology, Janeway et al., 4th Ed. Fig. 13.10, p. 499 (5th, Fig. 13.12)
**Type IIB hypersensitivity-induced autoimmune diseases**

Some autoimmune Abs can cause abnormal physiological responses without cell/tissue injury

*Stimulating or blocking anti-cell-surface receptor autoantibodies*

- Initiated by the production of autoantibodies (IgM/IgG).
- Abs binding to a cell surface receptor stimulate the receptor by mimicking the action of the natural ligand.
- Abs binding to a cell surface receptor block the receptor and prevent its interaction with its natural ligand.
- Abs cause abnormalities in tissue function with no tissue damage or inflammation.
Autoimmune diseases caused by autoantibodies against cell-surface receptors

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Antigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ disease</td>
<td>Thyroid-stimulating hormone receptor</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Progressive weakness</td>
</tr>
<tr>
<td>Insulin-resistant diabetes</td>
<td>Insulin receptor (antagonist)</td>
<td>Hyperglycemia, ketoacidosis</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Insulin receptor (agonist)</td>
<td>Hypoglycemia</td>
</tr>
</tbody>
</table>

These antibodies produce different effects depending on whether they are agonists (which stimulate) or antagonists (which inhibit) the receptor. Note that different autoantibodies against the insulin receptor can either stimulate or inhibit signaling.
Thyroid cells are stimulated by TSH binding to its corresponding receptor. Abs to the TSH receptor, present in the serum of thyrotoxicosis (Graves’ disease) patients, bind to the receptor in a similar manner, thereby delivering a comparable stimulus to thyroid cells, leading to overproduction of thyroid hormones.
Graves’ Disease: Serum from autoimmune disease patients can transfer the same disease to experimental animals

When humans, mice and rats, share an autoantigen, the transfer of Abs from an affected human can cause the same symptoms in an experimental animal.

For example, Abs from patients with Graves’ disease frequently produce thyroid activation in rats.
In Myasthenia gravis autoantibodies inhibit receptor function

Autoimmune Abs inhibit ligand binding to receptors.

A. Under normal circumstances, acetylcholine released from stimulated motor neurons at the neuromuscular junction binds to acetylcholine receptors on skeletal muscle cells, triggering muscle contraction.

B. Myasthenia gravis is caused by autoantibodies against the alpha subunit of the acetylcholine receptor. Binding of autoantibodies to the receptor does not activate it but causes receptor internalization and degradation. As the number of receptors on the muscle is decreased, the muscle becomes less responsive to acetylcholine.
Antibody-mediated autoimmune diseases can appear in the newborn of affected mothers as a consequence of transplacental antibody transfer.

In pregnant women, IgG Abs cross the placenta and accumulate in the fetus before birth. Babies born to mothers with IgG-mediated autoimmune disease frequently show symptoms similar to those of their mother during the first few weeks of life. Fortunately, there is little lasting damage as the symptoms disappear along with the maternal Abs. In Graves' disease, the symptoms are caused by Abs against the thyroid-stimulating hormone receptor (TSHR). Children of mothers making thyroid-stimulating Abs are born with hyperthyroidism, but this can be corrected by replacing the plasma with normal plasma (plasmapheresis), thus removing the maternal Ab.

Immunobiology, Janeway et al., 4th Ed. Fig. 13.15, p. 503 (5th, Fig. 13.17)
Type III hypersensitivity-induced autoimmune diseases
IgG/IgM immune complex-mediated disease

- The autoantigens are soluble and upon interaction with autoantibodies form soluble immune complexes.

- Occur when antigen-antibody complexes that are not adequately cleared by immune cells accumulate, giving rise to an inflammatory response and attraction of leukocytes.
Autoimmune Diseases due to Type III Hypersensitivity

Some common autoimmune diseases classified by immunopathogenic mechanism

<table>
<thead>
<tr>
<th>Syndrome</th>
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<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DNA, histones, ribosomes, snRNP, scRNP</td>
<td>Glomerulonephritis, vasculitis, rash</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid factor IgG complexes</td>
<td>Arthritis</td>
</tr>
</tbody>
</table>
Mechanisms of tissue injury in SLE

- Production of small immune complexes
- Deposition in blood vessel walls, basement membranes
- Renal glomerulus and other organs
- Activation of phagocytes
- Tissue damage
SLE is the most commonly known autoimmune disorder. This characteristic “butterfly” rash is made worse by exposure to sunlight. Lupus is a potentially fatal autoimmune disease that strikes 1 in 2,000 Americans and 10 times as many women as men.
Pernicious anemia

Described by Addison in 1849: fatigue, macrocytic anemia in well nourished individuals

Cause: Autoimmune destruction of parietal cells by autoantibodies to parietal cells and/or presence of autoantibodies to intrinsic factor. It results in B12 malabsorption.

Prevalence: 1.9% of the elderly have PA (2.7% women, 1.4% men; 4.3% in Black women)

Increased incidence in American blacks, Northern Europeans

Often associated with other antibodies, e.g. anti-thyroglobulin in Hashimoto's thyroiditis
**normal**

- **stomach**
  - **diet**
  - **B₁₂ absorbed from gut**

<table>
<thead>
<tr>
<th>IF</th>
<th><strong>B₁₂</strong></th>
</tr>
</thead>
</table>

**pernicious anaemia**

- **stomach**
  - **diet**
  - **parietal cell secretion**
  - **plasma cell secretion**

<table>
<thead>
<tr>
<th>IF</th>
<th><strong>B₁₂</strong></th>
</tr>
</thead>
</table>

**B₁₂ not absorbed**
Type IV hypersensitivity-induced autoimmune diseases

T cell-mediated delayed-type hypersensitivity diseases

• Specific autoreactive T cells

• Direct damage to target cells by cytotoxic T cells
Autoimmune Diseases due to Type IV Hypersensitivity

Insulin-dependent diabetes mellitus (IDDM)
The insulin producing β cells in the pancreatic islets are selectively destroyed.
Type I diabetes is a T cell-mediated disease in which the islets cells (β cells) of the pancreas are attacked and killed. The antigen recognized is not known, but there is a very large correlation with the expression of the DR3/4 HLA types. The culprit appears to be a variant of the linked DQ-beta gene lacking a charged aspartic acid at position 57.

Diabetic autoimmunity is characterized by self-reactive B and T lymphocytes that target a set of proteins expressed in pancreatic cells. Proinsulin (PI), IA2, GAD65 and 67, and islet cell autoantigen of 69 kDa (ICA69) are the major examples. These target self-Ags are not islet cell specific, and neither is diabetic autoimmunity; signs of celiac and thyroid autoimmunity are fairly common in patients, and diabetes-prone NOD mice develop signs of thyroid and Sjögren’s disease.

- Disease affects 0.2% of the population.
- Caused by an autoimmune attack on the pancreas.
- Directed against the insulin-producing β-cells located in spherical clusters called the islets of Langerhans.
- The autoimmune response destroys the β-cells – results in decreased insulin production, leading to elevated levels of blood glucose.
- Islet cell destruction occurs by waves of immunological attack.
- Initial infiltration of activated CD8+ T cells (CTL), which destroy the islet cells by direct lysis.
- A local increase in IFN-g, TNF-a and IL-1 occurs as a consequence of the response.
- The initial infiltration of CD8+ T cells and the activation of macrophages – referred to as insulitis.
- The cytokine release further activates infiltrating CD4+ T cells.
- Together, both CD4+ and CD8+ T cells destroy remaining islet cells by DTH mechanisms.
- Involves both cytokine release and the effect of lytic granules released by activated macrophages.
- Autoantibodies to surface antigens on islet cells contribute to cell destruction by antibody-dependent cell-mediated cytotoxicity (ADCC).
- The abnormalities in glucose metabolism result in serious metabolic problems, including ketoacidosis and increased urine production.

Occasional islet-reactive T cells are found in almost 10% of the general population, but <0.5% of these subjects are likely to develop overt diabetes.

Although it is uncertain what expands autoimmune T cell pools and what determines their tissue-destructive potential, access to islet target tissue has been suggested as a critical element in diabetes-prone hosts, despite availability of most relevant autoantigens in other tissues.

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### Some common autoimmune diseases classified by immunopathogenic mechanism

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<td>Brain invasion by CD4 T cells, weakness</td>
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Selective destruction of pancreatic $\beta$ cells in IDDM

The islets of Langerhans contain several cell types secreting distinct hormones. Each cell expresses different tissue-specific proteins. In insulin-dependent diabetes an effector T cell recognizes peptides from a $\beta$ cell-specific protein and kills the $\beta$ cell. Glucagon and somatostatin are still produced by the $\alpha$ and $\delta$ cells, but no insulin can be made.
Type I Diabetes

Islet of Langerhans in normal pancreas.

Islet of Langerhans from individual with insulin-dependent diabetes mellitus. Note the intense lymphocyte infiltration into the islet (insulitis).
Rheumatoid arthritis

Among the most serious and disabling types of arthritis, 2.1 million Americans live with rheumatoid arthritis.

About one out of seven Americans exhibit some form of arthritis.
Rheumatoid Arthritis

Th1 cells specific for an antigen in the joints

Lymphokine production

Accumulation of PMN and Mo

Autoantibodies

Rheumatoid Factor

Damage to cartilage

Joint destruction

Immune complexes
Rheumatoid arthritis

Rheumatoid arthritis (RA) affects peripheral joints and may cause destruction of both cartilage and bone. The disease affects mainly individuals carrying the HLA-DR4 variant of MHC genes.
Example of inflammation and the role of cytokines in RA

Tumor Necrosis Factor-alpha (TNFα):

• Released by macrophages

• Increases vascular permeability

• Increases adhesion molecule expression on blood vessel endothelium

• Increases MHC expression
Multiple sclerosis

• Some populations, such as Gypsies, Eskimos, and Bantus, never gets MS.

• For susceptible populations, if one person in a family has MS, that person’s first-degree relatives (parents, children, and siblings) have a 1-3% chance of getting the disease.

• Individuals with the HLA-DR2 variant of MHC genes are most susceptible to the disease.
A mouse model for MS:

Induction of EAE (experimental allergic encephalitis), a model for multiple sclerosis

Mice injected with myelin basic protein and complete Freund's adjuvant develop EAE and are paralyzed

The disease is mediated by myelin basic protein-specific TH1 cells

Disease can be transmitted by transfer of T cells from affected animal

![Diagram showing the process of EAE induction and disease mediation](Image)
At present, there is no cure for any of the autoimmune diseases.

What are the current optional treatments for autoimmune diseases?

1. Suppression of the immune response

This necessitates a delicate balance, controlling the disorder while maintaining the body's ability to fight disease in general.

The drugs most commonly used are anti-inflammatory corticosteroids.

Immunosuppressive drugs, such as Cyclosporin A (CsA), FK506, or rapamycin, which inhibit the production of IL-2, an essential T cell growth factor.
2. Immunotherapies

2a. Induction of T cell tolerance (by using altered peptide ligands).

2b. Cytokine-directed therapy, such as blocking of the tumor necrosis factor alpha (TNF-alpha).

TNF-alpha promotes the inflammatory response, which in turn causes many of the clinical problems associated with autoimmune disorders, such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, psoriasis.

Blocking TNF-alpha shows great promise as a new treatment for Rheumatoid arthritis.
3. Organ removal and hormone supplementation

- Removal of the thyroid in Graves’ disease (hyperthyroidism)
- T3 and T4 treatment in hypothyroidism
- Treatment with insulin in IDDM, a more complicated treatment since the requirement for insulin is variable.