(Immunology 1) Hypersensitivity and Allergy Notes
10th February 2011

Learning Objectives:
- Outline the mechanisms by which IgE, antibodies, immune complexes and T cells can cause tissue damage and inflammation (the four types of hypersensitivity), giving examples of the clinical syndromes associated with each
- Outline the factors underlying the development of atopic/allergic diseases
- Describe the important clinical features of asthma, hay fever, allergic eczema and anaphylaxis
- Briefly describe the approach to investigation and management of patients with these disorders

Hypersensitivity Reactions:- Are ‘appropriate’ immune responses to viruses, bacteria, fungi and parasites. Such reactions are important as they:
- Are required to eliminate pathogens
- May be concomitant tissue damage as a side effect, but as long as the pathogen is eliminated quickly, the damage will be minimal and repaired easily.

It involves antigen recognition by antibodies and cells of the immune system.

Hypersensitivity reactions occur when immune responses are mounted against:
- **Harmless foreign antigens** (allergy, contact hypersensitivity)
- **Autoantigens** (autoimmune diseases)
- **Alloantigens** (serum sickness, transfusion reactions, graft rejection)
- **Infectious agents** (that are not cleared and lead to chronic immune mediated damage)

Inflammation
This is the body’s response to injury.
- It is a rapid attempt to bring the body’s defences to the site of injury.
- It is a common feature of all hypersensitivity reactions.
- Immune molecules and cells migrate to sites of injury and/or infection.
- Features:
  - Local dilatation, increased blood flow
  - Increased vascular permeability
    (Caused by C3a, C5a, histamine and leukotrienes)
  - Inflammatory mediators and cytokines
    (IL-1, IL-2, IL-6, IL-8, TNF and chemokines)
  - Inflammatory cells infiltrate and cause tissue damage
    - Chemotaxis (Cell trafficking)
    - Neutrophils, macrophages, lymphocytes and mast cells
    - Cell activation
- Signs:
  - Redness
  - Heat
  - Swelling
  - Pain

Hypersensitivity Reactions Classifications:
Classified by Gell & Coombs:
- **Type I**: Immediate Hypersensitivity
- **Type II**: Antibody-Dependent Cytotoxicity
- **Type III**: Immune complex Mediated
- **Type IV**: Delayed Cell Mediated

This is an artificial classification – hypersensitivity is usually a mixture of mechanisms
- Types I, II and III depend upon the interaction of an antigen with an antibody
- Type IV (delayed) involves T-Cell recognition

Type I (Immediate Hypersensitivity)
- Anaphylaxis
- Asthma
- Rhinitis
  - Seasonal
  - Perennial (lasting more than 3 seasons)
- Food Allergy

Primary (1°) Antigen Exposure
Primary (1°) Antigen Exposure
- IgE Antibody Production
- IgE binds to mast cells and basophils

Secondary (2°) Antigen Exposure
- More IgE Antibodies are produced
- Antigens form cross-bridges with IgE on mast cells/basophils
- Leading to degranulation of mast cells and the release of mediators

Type II (Antibody-Dependent Hypersensitivity)
Clinical presentation depends on target tissue
- Organ-Specific Autoimmune Diseases
  - Myasthenia Gravis (Acetylcholine Receptor Ab) – Autoimmune neuromuscular disease leading to muscular weakness
  - Glomerulonephritis (Anti-glomerular basement membrane [GBM] Ab)
  - Pemphigus Vulgaris (Ab to epithelial cell cement)
- Autoimmune Cytopenias (blood cell destruction)
  - Haemolytic anaemia
  - Thrombocytopenia
  - Neutropenia
- Haemolytic Disease of the newborn (Rhesus Ab)
- Drug Allergies
- Hyper-acute Graft Rejection
- Transfusion Reactions
- Pernicious Anaemia (Intrinsic Factor-blocking Abs)
- Idiopathic Urticaria (Abs against IgE receptor)

Mechanism
- Antibody interaction with cell surface Antigen
- Complement Activation
  - Cell Lysis
  - Mast Cell Activation
- Inflammation
  - Attraction of Cytotoxic Cells
  - (Neutrophils, Eosinophils, Monocytes, Killer Cells)

Tests for Ab-Dependent Hypersensitivity
- Test for specific autoantibodies
Test for specific autoantibodies
- Organ and Non-Organ Specific
- Immunofluorescence
  - Tissue Slide + Serum + Fluor Detector à Micro
- For identified antigens – ELISA

Treatment for Ab-Dependent Hypersensitivity
- **Immunosuppressants** – steroids/cyclophosphamide
- Plasma Exchange
- Splenectomy
- IV Globulin

**Type III (Immune Complex Mediated Hypersensitivity)**
- Formation of **Antigen-Antibody Complexes**
- Deposition of complexes in a tissue
- **Complement** and cell recruitment/activation
- Activation of other cascades e.g. clotting
- Tissue damage (vasculitis)
- **Examples:**
  - Systemic Lupus Erythematosus (SLE)
  - Vasculitides (many different types)

**Type IV (Delayed Hypersensitivity Responses)**
- Chronic Graft Rejection
- GVHD
- Coeliac Disease
- Contact Hypersensitivity
- Tuberculosis
- Tuberculoid Leprosy
- (Asthma, Rhinitis and Eczema)

**Three varieties**
- Th1
- Cytotoxic
- Th2

**Mechanisms**
- Transient/Persistent Ag
- T-Cell Activation of macrophages, CTLs
- Much of the tissue damage is dependent on TNF
Hypersensitivity Reactions:

- Allergy is a type of hypersensitivity reaction.
- Types I, II and III are antibody-mediated – they are distinguished by the TYPE of antigen that they recognise.
- Type II reactions are directed to CELL SURFACE or MATRIX BOUND antigens.
- Type III is associated with the RECOGNITION OF SOLUBLE ANTIGENS.
- A number of allergies occur systemically (e.g. to penicillin)
- Asthma is caused by IgE binding to mast cells and by the induction of T-Cells which produces Th2 Cytokines

<table>
<thead>
<tr>
<th>Immune Reactant</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen</td>
<td>IgE</td>
<td>IgG</td>
<td>IgG</td>
<td>T_{H1} cells</td>
</tr>
<tr>
<td>Effector Mechanism</td>
<td>Mast-cell activation</td>
<td>FcγR{superscript} cells (macrophages, NK cells)</td>
<td>FcγR{superscript} cells (Complement)</td>
<td>Macrophage activation</td>
</tr>
</tbody>
</table>

### Allergy

- Common – the prevalence of atopy (immediate allergy) is 50% in young adults in the UK.
- Severity varies:
  - Mild (occasional) symptoms
  - Severe (chronic) symptoms
  - Life threatening anaphylaxis
- Risk Factors:
  - Genetic and environmental
- Common allergens include: Animal products, House Dust Mite Droppings, Pollens and Spores
- Around 80% of atopics have a family history
- It is POLYGENIC
  - Over 70 genes linked to asthma/atopy
  - Genes of IL-4 gene cluster (Chromosome 5) linked to raised IgE, Asthma and Atopy
  - Genes of IgE Receptor (Chromosome 11q) is linked to Asthma and Atopy
- Environmental Risk Factors
  - Age
    - Increases in children
    - Peaks in Teens
    - Reduces in adulthood
  - Gender
    - Asthma is commoner in males in childhood, commoner in females in adults
  - Family Size
    - Commoner in smaller Families
  - Infections
    - Early life infections protect against asthma
  - Animals
    - Early exposure to animals protects
Types of Inflammation in Allergy:

- **Anaphylaxis, Urticaria, Angioedema**
  - Type I Hypersensitivity (IgE Mediated)
- **Chronic Urticaria**
  - Type II Hypersensitivity (IgG Mediated)
- **Asthma, Rhinitis and Eczema**
  - Mixed Inflammation:
    - Type I Hypersensitivity (IgE Mediated)
    - Type IV Hypersensitivity (Chronic Inflammation)

Types of inflammation in allergy:

<table>
<thead>
<tr>
<th>Type I hypersensitivity</th>
<th>Type II hypersensitivity</th>
<th>Types I and IV hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>Chronic urticaria</td>
<td>Asthma</td>
</tr>
<tr>
<td>Urticaria</td>
<td></td>
<td>Rhinitis</td>
</tr>
<tr>
<td>Angioedema</td>
<td></td>
<td>Eczema</td>
</tr>
</tbody>
</table>

Expression of Disease Requires:

- Sensitisation to allergens – **primary response** (usually occurs early in life)
- Exposure to produce disease – **memory response** (any time after sensitisation)

Sensitisation in Atopic Airway Disease:

1. APCs (Dendritic Cells) process allergens and **present it** to naïve (CD4+) T-Cells
2. **Naïve T-Cells** proliferate and differentiate into Th1, Th2 and T-Reg Subsets.
3. Th2 cells produce **IL-4 and IL-13** which **stimulate B-Cell Proliferation** into plasma cells.
4. Plasma cells **synthesize and release IgE**.

Subsequent Exposure:

- Antigen Presenting Cells (APCs) process allergens and present it to **memory T-Cells** (Th2)
- Memory T-Cells Produce **IL-4, IL-13 and IL-5**
- IL-4 and IL-13 (Similar to the sensitisation/initial reaction) stimulate plasma cells to synthesise and release IgE, which binds to Mast Cells.
- IL-5 stimulates eosinophils to enter vessels and release mediators
Eosinophils
- 2-5% of blood leukocytes
- Present in blood – most reside in tissues
- Recruited during allergic inflammation
- Generated from bone marrow
- Polymorphous nucleus – two lobes
- Contain large granules (toxic proteins)
- Lead to tissue damage

Mast Cells
- Tissue-resident cells
- IgE Receptors are present on their cell surface
- Crosslinking of IgEs lead to:
  - Preformed: Histamine, Cytokines, Toxic Proteins
  - Newly synthesised: Leukotrienes, Prostaglandins

Neutrophils
- Important in:
  - Virus-Induced asthma
  - Severe Asthma
  - Atopic Eczema
- 55070% of blood leukocytes
- Nucleus contains several lobes
- Granules contain digestive enzymes
- Neutrophils also synthesise:
  - Oxidant Radicals
  - Cytokines
  - Leukotrienes

Asthma: Immuno-Pathogenesis
Acute inflammation of the airways:
- Mast Cell Activation and Degranulation – leads to mediator release
- Preformed mediators – histamine
- Newly synthesised mediators – prostaglandins, leukotrienes
- Acute Airway narrowing occurs
Acute Airway narrowing occurs

Chronic inflammation of the airways:
- Cellular infiltration of **Th2 Lymphocytes, Eosinophils**
- Smooth muscle hypertrophy occurs
- A mucus plug forms
- The epithelium is shed
- Sub-epithelial fibrosis occurs

**Asthma – Clinical Features**
- Reversible generalised airway obstruction
  - *Chronic Episodic Wheeze*
- Bronchial hyperresponsiveness
  - *Bronchial Irritability*
- Cough
- Mucus Production
- Breathlessness
- Chest Tightness
- Response to treatment
- Spontaneous variation
- Reduced and variable peak flow (PEF)

**Treatment of Asthma:**
- **Step 1:** Use a β₂ Agonist drug *as required by inhalation* – e.g. *salbutamol*
- **Step 2:** Inhalation of a steroid
  - Low-moderate dose
  - Beclomethasone/budesonide (50-800μg per day)
  - Fluticasone (50-400mg per day)
- **Step 3:** Add further therapy
  - Add **long acting β2 Agonist, Leukotriene Antagonist**
  - **High Dose INHALED steroids** (up to 2mg per day via a spacer)
- **Step 4:** Add courses of **oral steroids**
  - Prednisolone (30mg daily for 7-14 days)

**Allergic Rhinitis – Clinical Features**
- Seasonal:
  - Hay Fever, Grass, Tree Pollens
- Perennial - Perennial Allergic Rhinitis
  - HDM, Animal
- Symptoms:
  - Sneezing
  - Rhinorrhoea
  - Itchy nose & eyes
  - Nasal blockage, Sinusitis
  - Loss of smell/taste

**Treatment of Allergic Rhinitis:**
- Anti-Histamines (sneezing, itching and rhinorrhoea)
- Nasal steroids (nasal blockage)
- Cromoglycate (Children, eyes)

**Allergic Eczema – Clinical Features**
- Chronic itchy skin rash
- Flexures of arm and legs
- HDM sensitisation and dry, cracked skin
HDM sensitisation and dry, cracked skin
- Complicated by bacterial and (rarely) viral infections (herpes simplex)
- 50% clears by the age of 7
- 90% by adulthood

Treatment of Eczema:
- Emollients
- Topical Steroid Cream

Food Allergy – Clinical Features
- Infancy – 3 Years
  - Eggs, Cow’s Milk
- Children/Adults
  - Peanut, Shellfish, Nuts, Fruits, Cereals, Soya

MILD ALLEGY
- Itchy lips
- Mouth
- Angioedema
- Urticaria

SEVERE
- Nausea, Abdominal Pain, Diarrhoea
- Anaphylaxis

Anaphylactic Shock
- Anaphylactic Shock is a severe generalised allergic reaction
- Uncommon
- Potentially fatal
- Generalised degranulation of IgE sensitised mast cells
  - Cardiovascular – Vasodilatation, Cardiovascular Collapse
  - Respiratory – Bronchospasm, Laryngeal Oedema
  - Skin – Vasodilatation, erythema, urticarial, angioedema
  - GI – Vomiting, diarrhoea

Symptoms:
- Itchiness around the mouth, pharynx and lips
- Swelling of the lips, throat and other parts of the body
- Wheeze, chest tightness and dyspnoea
- Faintness
- Feeling of apprehension
- Diarrhoea and vomiting
- Collapse
- Death if severe and untreated

Investigation & Diagnosis:
- Careful history essential
- Skin prick testing
- RAST (blood specific IgE)
- Total IgE
- Lung Function (asthma)

Treatment of Anaphylaxis:
- Emergency treatment:
  - EpiPen and Anaphylaxis Kit:
    - Adrenaline, Antihistamine and Steroid
  - Seek immediate medical aid
- Prevention
  - Avoidance of the known allergy
  - Always carry a kit and Epi-Pen
  - Inform immediate family and caregivers
  - Wear a MedicAlert bracelet

Immunotherapy:
- Effective for venom allergies such as bee or wasp stings
  - Single Antigen
  - Antigen used is purified
- Effective with pollen induced allergies
  - Sublingual immunotherapy (SLIT)
Sublingual immunotherapy (SLIT)
Autoimmunity: Adaptive immune responses with specificity for self ‘antigens’ (autoantigens)

Mechanisms of Autoimmunity
- Adaptive immune reactions against self-tissue use the same mechanisms as immune reactions against pathogens and environmental antigens.
- Autoimmune diseases involve breaking T-Cell tolerance
- Because self-tissue is always present, autoimmune diseases are CHRONIC CONDITIONS
- Effector mechanisms resemble those of hypersensitivity reactions: Types II, III and IV.

The Impact of Autoimmune Diseases
- Over 70 chronic disorders have been identified, which relate to aberrant immune responses causing the body to attack its own tissues.
- About 5% of individuals in ‘developed’ countries are affected by autoimmune diseases.
- Nearly 80% of affected individuals are females.
- The incidence of autoimmune diseases (and hypersensitivity) is increasing.

Major Autoimmune Diseases
1 in 30 people in the USA has an autoimmune disease.
- Rheumatoid Arthritis
  1 in 100 – 2.1 million cases, 30-50,000 children
- Type I Diabetes
  1 in 800 – 300-500,000 cases (123,000 < 20yrs old)
- Multiple Sclerosis
  1 in 700 – 250-300,000 cases (25,000 hospitalisations per year)
- Systemic Lupus Erythematosus (SLE)
  240,000 cases
- Autoimmune Thyroid Disease (ATD)
  Includes Hashimoto’s and Grave’s Disease – 5 cases/1000 women, 0.8 cases/1000 men
- Inflammatory Bowel Disease
  (Including Crohn’s Disease and Ulcerative Colitis)

Gender Differences in Autoimmune Disease incidence
Autoimmune reactions in humans:
- Organs affected
- Involvement of auto-antigens
- Involvement of immune responses

Autoimmune diseases affect a wide range of organs and tissues

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organ-specific autoimmune diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td>Kidney</td>
</tr>
<tr>
<td>Pernicious anaemia</td>
<td>Stomach</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Liver, Bile</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Muscles</td>
</tr>
<tr>
<td>Dermatomyositis/Polymyositis</td>
<td>Skin/ Muscles</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Blood vessels</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Joints</td>
</tr>
<tr>
<td>SLE</td>
<td>Multiple targets</td>
</tr>
</tbody>
</table>

| **Multi-systemic autoimmune diseases**                          |                         |
| Autoantigens have been identified in various autoimmune diseases which play a direct role in the immunopathogenesis |
| Early experiments showed that auto-antibodies against red blood cells were responsible for autoimmune haemolytic anaemia in humans. |
| ○ Result in the clearance or complement-mediated lysis of autologous erythrocytes |
| ○ Direct link between auto-antibodies and disease (also antibody transfer experiments) |

**Immune reactions known to play a direct role in the pathology of human autoimmune disease**
- Antibody response to cellular or extracellular matrix antigen (Type II)
- Immune complex formed by antibody against soluble antigen (Type III)
- T-Cell mediated disease (Delayed type hypersensitivity reaction – Type IV)

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Autoantigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibody against cell-surface or matrix antigens (type II)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Rh blood group antigens, I antigen</td>
<td>Destruction of red blood cells by complement and phagocytes,</td>
</tr>
</tbody>
</table>
Goodpasture’s Syndrome
- Affects the renal corpuscle with neutrophil infiltration

Graves’ Disease

![Stimulation by TSH and release of thyroid hormones](image1)

**Type III – Immune Complex Disease (Systemic Lupus Erythematosus / SLE)**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DNA, histones, ribosomes, snRNP, scRNP</td>
<td>Glomerulonephritis, vasculitis, arthritis</td>
</tr>
</tbody>
</table>
Type IV – T-Cell Mediated Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantigen</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>Pancreatic β-cell antigen</td>
<td>β-cell destruction</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Unknown synovial joint antigen</td>
<td>Joint inflammation and destruction</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Myelin Basic Protein, Proteolipid protein</td>
<td>Brain degeneration (demyelination), weakness/paralysis</td>
</tr>
</tbody>
</table>

Cytotoxic (CD8+) and Helper (CD4+) T-Cell responses can be involved.

The Normal T-Cell Response to Antigens

- Antigen is presented to T-Cells by MHC expressed on the surface of antigen-presenting cells.
- In response, T-Cells proliferate and function.
- MHC Class I molecules are found in every nucleated cell in the body.
- MHC Class II molecules are found in professional antigen presenting cells (APCs) including dendritic cells, Langerhans cells, B-Cells and macrophages.
- MHC Class II presents antigens to CD4+ T-Cells.
- MHC Class I presents peptide antigens to CD8+ T-Cells.
HLA (Human Leukocyte Antigen) is the dominant genetic factor affecting susceptibility to autoimmune disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA allotype</th>
<th>Frequency (%)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B27</td>
<td>&gt; 95</td>
<td>9</td>
</tr>
<tr>
<td>Birdshot chorioretinopathy</td>
<td>A29</td>
<td>&gt; 95</td>
<td>4</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>DQ6</td>
<td>&gt; 95</td>
<td>33</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>DQ2 and DQ8</td>
<td>95</td>
<td>28</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>DQ8 and DQ2</td>
<td>81</td>
<td>23</td>
</tr>
<tr>
<td>Subacute thyroiditis</td>
<td>B35</td>
<td>70</td>
<td>14</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>DQ6</td>
<td>86</td>
<td>33</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>DR4</td>
<td>81</td>
<td>33</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>DR8</td>
<td>38</td>
<td>7</td>
</tr>
<tr>
<td>Psoriasis vulgaris</td>
<td>CW6</td>
<td>87</td>
<td>33</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>DR3</td>
<td>69</td>
<td>27</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>DR3</td>
<td>65</td>
<td>27</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>DR3</td>
<td>50</td>
<td>27</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>DQ6</td>
<td>&lt; 0.1</td>
<td>33</td>
</tr>
</tbody>
</table>

Figure 13.24: The Immune System, 3rd ed. (© Garland Science 2009)

**Summary: Human Autoimmune Reactions**
- Mechanisms in autoimmunity are the same as in normal responses against foreign antigens.
- Immune responses to auto-antigens (self) have a direct role in the pathology of autoimmune diseases.
- Both B-Cells (antibody) and T-Cells can be involved.
- HLA associations strongly imply a role for T-Cells in initiating autoimmune diseases.

Why are autoimmune diseases not even more common, if most people have lymphocytes capable of recognising self?
- What are the mechanisms which normally prevent our immune system from attacking our own tissues?
- What are the original causes (triggers) of autoimmunity?

**Evidence for the concept of tolerance against self – 1:**
- Freemartin cattle have fused placetas and exchange cells and antigen in-utero.
- Non-identical twins have different sets of blood group antigens.
- As these twins are non-identical, as adult cattle they would normally be expected to react to each other’s cells and tissues.

However:
- Adult cattle tolerate blood transfusions from a non-identical twin.
- They also accept skin grafts from each other.

**Evidence 2: Timing is critical:**
- The adult accepts the skin graft if it receives spleen and bone marrow cells as a neonate.
- However, it rejects a normal skin graft (without neonatal infusion of spleen/bone marrow cells)

Medawar et al. 1953
Tolerance
- Defined as the acquired INABILITY to respond to an antigenic stimulus

The 3 A’s:
- Acquired – involves cells of the acquired immune system, and is ‘learned’
- Antigen Specific
- Active process in neonates, the effect of which are maintained throughout life

How does self-tolerance work and how does it fail?
Several mechanisms are involved in the generation and maintenance of the tolerant state:
- Central Tolerance
- Peripheral Tolerance
  - Anergy
  - Immune privilege (ignorance of antigen)
  - Regulation

Failure in one or more of these mechanisms may result in autoimmune disease.

The Normal Acquired Immune Response to foreign antigens – Basic Principles
1. T-Cells recognise peptide antigens presented by MHC on APCs
2. B-Cells recognise proteins via surface immunoglobulin receptors
3. T and B-Cells undergo clonal expansion

T-Cell recognise peptide antigen via T-Cell Receptors:
- CD4+ T-Cells recognise antigens presented by MHC Class II
- CD8+ T-Cells recognise antigens presented by MHC Class I

Evidence 3: Tolerance has Specificity:
- The recipient must receive the skin graft and the spleen and bone marrow cells from the same donor
T- and B-Cells Expand in a Clonal Manner

- T-Cell clones have unique T-Cell receptors which recognise specific antigenic peptides
- B-Cell clones have unique surface Ig receptors which recognise specific antigenic determinants on proteins.

Mechanisms of Tolerance: Central Tolerance

**Lymphocyte development**

Pre B-Cells → Lymphoid progenitors → Stem Cells → Pre T-Cells → Thymus → Export of T-cells to the periphery

T-Cells recognise peptides presented on MHC in the Thymus

*Thymic Epithelial Cells (TEC) or Dendritic Cells (DC)*

Immature T-Cells recognise antigens presented by MHC on thymic APCs
Clonal Selection in the Thymus ad Central Tolerance for T-Cells:
Selection by the thymus divides the thymocytes (immature T-Cells) into three categories:

- **Useless** – Cannot ‘see’ MHC
  These cells die by apoptosis
- **Useful** – See MHC weakly
  Receive signal to survive. ‘Positive selection’
- **Dangerous** – See Self-MHC Strongly
  Receive signal to die by apoptosis. ‘Negative Selection’

Only 5% of thymocytes survive selection

**B-Cell Tolerance**

- Central tolerance for B-Cells occurs in the bone marrow.
- Polyvalent antigens (expressed on bone marrow stromal cells) cause cross-linking of surface immunoglobulin: this facilitates deletion of immature B-Cells.
- Mature B-Cells survive

**Immature B Cells are deleted by polyvalent antigens:**

[IgM] 
[No crosslinking]
**Does Central Tolerance fail in Autoimmune Diseases?**

**APECED**
- Autoimmune
- PolyEndocrinopathy
- Candidiasis
- Ectodermal
- Dystrophy

(Autoimmune polyglandular disease / APD)

APECED is a rare autoimmune disease which affects the endocrine glands:
- Thyroid
- Kidneys
- Chronic mucocutaneous candidiasis
- Gonadal failure
- Diabetes mellitus
- Pernicious Anaemia

**APECED results from a failure to delete auto-reactive T-Cells in the thymus:**
- Caused by mutations in the transcription factor AIRE gene
- AIRE is important for the expression of ‘tissue-specific’ genes in the thymus
- Involved in the negative selection of self-reactive T-Cells in the thymus

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**Medullary Thymic Epithelial Cell (mTEC)**

**Autoreactive Thymocyte**

**MHC**

**TCR**

**Clonal deletion or Tolerance**

**Persistence of autoreactive cells**

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**Most autoimmune diseases are associated with MULTIPLE DEFECTS and GENETIC TRAITS**

- SLE: Genes affecting multiple biological pathways may lead to a failure of tolerance
- Induction of tolerance – (B Lymphocyte activation: CD22, SHP-1): autoantibody production
- Apoptosis – (Fas, Fas-ligand): Failure in cell death
- Clearance of Antigen – (Complement proteins C1q, C1r and C1s): abundance/persistence of autoantigen

**Systemic lupus erythematosus (SLE):**
- Affects 1 in 1000 individuals
Affects more than 1 in 1000 individuals
More prevalent in females

**SLE: pathology**
- Butterfly rash
- Pleural effusions
- Heart problems
- Lupus nephritis
- Arthritis
- Raynaud’s phenomenon

**SLE: genes affecting multiple biological pathways may lead to a failure of tolerance**
- Induction of tolerance (B lymphocyte activation: CD22, SHP-1): auto-antibody production
- Apoptosis (Fas, Fas-L): failure of cell death
- Clearance of antigen (complement proteins C1q, C1r and C1s, serum IgM): abundance of auto-antigen

**Immune effectors in SLE:**
- Auto-antibodies
- Immune complexes (i.e. antigen-antibody complexes)

**Auto-antibodies:** generated against a broad spectrum of intracellular antigens, including...
- Cell nucleus: histones; DNA; snRNP
- Cytoplasm: ribosomes; scRNP

**Immune complexes:** form deposits and cause tissue damage in a wide range of tissues

**Summary: Central Tolerance**

**T Cell Selection in the thymus:**
- Dependent on MHC-Peptide-T Cell Receptor interaction
- Most cells (90%) die by **neglect** – no or very weak recognition of self antigen-MHC complexes
- 5% of cells undergo negative selection: high affinity, high abundance
- Cells die by **apoptosis** (possibly by other mechanisms also)
- Surviving cells undergo **positive selection**: low affinity, low abundance

**B-Cells selection in the bone marrow:**
- Cross-linking of the surface immunoglobulin by polyvalent antigens expressed on bone marrow stromal cells facilitates deletion of immature B-Cells.
- Failure in central tolerance can lead to **autoimmunity**, in most diseases; however, this usually involves a complex interaction of multiple defects.

**Induction and Maintenance of Tolerance in the periphery:**
- Some antigens may not be expressed in the thymus or bone marrow, and may be expressed only after
the immune system has matured.

- Mechanisms are required to **prevent mature lymphocytes becoming auto-reactive and causing disease**:
  - **Anergy** – A refractory state resulting from antigenic stimulation under unusual conditions
  - **Ignorance of Antigen** – expression of self-antigen at immunologically privileged sites
  - **Suppression by regulatory T-Cells** – Negative regulation of potentially auto-reactive cells by specialised factors/cells

### Anergy:
- Naïve T-Cells require **co-stimulation for full activation** – CD80, CD86 and CD40 are examples of co-stimulatory molecules expressed on APC.
- These are absent on most cells of the body.

![Antigen Presenting Cell (APC)](image)

- Without co-stimulation, then cell proliferation and/or factor production does not proceed.
- Subsequent stimulation – even in the presence of co-stimulatory molecule – leads to a refractory state termed ‘Anergy’

### B-Cell Anergy:
- B-Cell anergy is induced by **high concentrations of soluble antigen**

![B-Cell Anergy](image)

### Immunological Ignorance:
- Occurs when **antigen concentration is TOO LOW in the periphery**
- Occurs when relevant antigen presenting molecules are absent – most cells in the periphery are MHC Class II negative
- Occurs at **immunologically privileged sites** where immune cells cannot normally penetrate: for example, in the eye, central and peripheral nervous system and testes.
- In this case, cells have **never been tolerised** against the auto-antigens

### Failure of Ignorance: e.g. sympathetic ophthalmia
- **Trauma to one eye results in the release of sequestered Effector T cells return via bloodstream and attack**

- **Surface IgM (slgM) is down regulated**

- **IgM**
- **IgD**
**Suppression / Regulation**
- Autoreactive T-Cells may be present, but do not respond to autoantigen.
- Controlled by other cell types:
  - Regulatory T-Cells CD4+ CD25+ CTLA-4+ FOXP3+
  - CD25 is the interleukin-2 Receptor
  - CTLA-4 binds to B7 and sends a negative signal
  - FOX P3 is required for regulatory T-Cell Development

**IPEX – A failure in the regulation of peripheral tolerance**
- Immune dysregulation, Polyendocrinopathy Enteropathy and X-linked inheritance syndrome
- Fatal recessive disorder presenting early in childhood
- Mutation in the FOXP3 gene which encodes a transcription factor critical for the development of regulatory T-Cells

Symptoms include:
- Early onset insulin-dependent diabetes mellitus
- Severe enteropathy
- Eczema
- Variable autoimmune phenomena
- Severe infections

**Accumulation of autoreactive T-Cells**

**Does infection ‘break’ peripheral tolerance?**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>Epstein-Barr virus (EBV), measles virus</td>
</tr>
<tr>
<td>Lyme arthritis</td>
<td>Borrelia burgdorferi</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>Coxsackie virus B4, rubella virus, cytomegalovirus (CMV), mumps virus</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Escherichia coli, mycobacteria, EBV, hepatitis C virus (HCV)</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>EBV</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Coxsackie virus B3, CMV, chlamydia</td>
</tr>
<tr>
<td>Rheumatic fever/myocarditis</td>
<td>Streptococci</td>
</tr>
<tr>
<td>Chagas’ disease/myocarditis</td>
<td>Trypanosoma cruzi</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Herpes simplex virus, HCV</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>CMV, EBV, Campylobacter spp.</td>
</tr>
</tbody>
</table>

**How can infections affect the tolerant state?**
- Molecular mimicry of self-molecules.
- Induce changes in the expression and recognition of self-proteins.
- **Induce changes in the expression and recognition of self-proteins.**
- **Induction of co-stimulatory molecules or inappropriate MHC Class II expression – pro inflammatory environment.**
- **Failure in regulation – effects on regulatory T-Cells**
- **Immune deviation – shift in type of immune response e.g. Th1, Th2**
- **Tissue damage at immunologically privileged sites**

**Peripheral Tolerance Summary**

- Induction and maintenance of peripheral tolerance will depend on:
  - Site of antigen expression (MHC expression, immune privilege)
  - Timing of antigen expression
  - Amount of antigen expression
  - Co-Stimulation
  - T-Cell help for B-Cell responses
  - Regulation
- Infections may help break tolerance by a variety of mechanisms

**Conclusions**

- Autoimmune disease pathology is caused by immune reactions against a wide range of tissues
- The immune system is normally tolerised against responses to self-antigens by mechanisms of both central and peripheral tolerance
- Autoimmune diseases can result from a failure in the mechanisms of central or peripheral tolerance caused by genetic defects, or induced by tissue damage (e.g. smoking), or infection, or a combination of factors.
Transplantation Notes

3rd March 2011

- To understand the terms autograft, isograft, allografts and xenograft
- To be able to give examples of each
- To be aware of the advantages of renal transplantation
- To understand what cadaveric and live organ donation entail
- To understand how currently used immunosuppressive drugs affect T-lymphocytes
- To be able to define the various types of organ rejection and their basic mechanisms
- To be able to outline the most important issues in connection with each of renal, corneal, liver, heart and lung transplantation.

- Organs are transplanted when they are failing or have failed, or for reconstruction.
- They can be life-saving or life-changing

Why have a kidney transplant?

Quality of Life on Renal Replacement Therapy

- ‘Time trade-off’ method
  - 0 = death, 1 = perfect health
  - Dialysis patients average score: 0.41
  - Transplant patients average score: 0.74
  - 27% increase in employment rates (38% among males) in those with transplant

Definitions
- **Autografts:** Transplants within the same individual
- **Isografts:** Transplants between genetically identical individuals of the same species
- **Allografts:** Transplants between different individuals of the same species
- **Xenografts:** Transplants between individuals of different species

Prosthetic Grafts (Plastic, metal)

Autografts
- Examples include:
  - **Coronary Artery Surgery** – left internal thoracic artery, radial artery, saphenous vein grafted to coronary arteries
  - **Reconstructive Surgery** – skin grafts, jaw from fibula, hair

- **Stem cells from bone marrow:** - Aspirate marrow cells and purify stem cells, irradiate malignant or deficient bone marrow cells, re-colonise with purified stem cells.
- **Use of pluripotent stem cells to make other tissues** (?)

Xenografts
- Heart valves (pig)
- Skin

Allografts
- **Solid organs** (kidney, liver, heart, lung, pancreas)
- **Small bowel**
- **Free cells** (bone marrow, pancreas islets)
• **Temporary** (blood, skin in burns)
• **Privileged sites** (cornea)
• **Framework** (bone, cartilage, tendons, nerves)
• **Composite** (hands and face)

### Deceased Donors for Allografts

#### Deceased Donor

- **Solid Organs:** Kidney, heart, pancreas, lungs and liver
- **Others:** Cornea, heart valves, bone, skin and composite tissue

#### Living Donor

- Bone marrow, kidney and liver

### Deceased Donors:

- **Brain Dead, Heart-Beating (DBD – donor after brain death)**
- **Non-Heart Beating Donors (DCD – donor after cardiac death)**

#### Deceased Donors:

- **Brain Dead, Heart-Beating (DBD – donor after brain death)**
  - E.g. In a road traffic accident, massive cerebral haemorrhage
  - Confirmation of brain death is necessary
  - **CONSENT** is important
  - Harvest organs and cool to minimise ischaemic damage
  - Irremediable structural brain damage of **KNOWN CAUSE**
  - Apnoeic coma **not due to**:
    - Depressant drugs
    - Metabolic or endocrine disturbance
    - Hypothermia
    - Neuromuscular blockers
  - Demonstration of **lack of brainstem function**:
    - Pupils both fixed to light
    - Corneal reflex absent
    - No eye movements with cold caloric test
    - No cranial nerve motor responses
    - No gag reflex
    - No respiratory movements on disconnection (with PaCO₂ >50mmHg)
  - Exclude:
    - Viral infection (HIV, HBV, HCV)
    - Malignancy
    - Drug abuse, overdose or poison
    - Disease of the transplanted organ
    - Ultrasound Scan (USS) the potential donor
  - The removed organs are **rapidly cooled and perfused**
    - Absolute maximum cold ischaemic time for kidney is 60 hours (ideally <24 hours)
    - Much shorter for other organs
  - Except cornea (96h – longer with cryopreservation)

#### Non-Heart Beating Donors (DCD – donor after cardiac death)

- Heart stopped before organ harvested
- Longer period of warm ischaemia time
- Suitable for kidney
- **Related:** genetically (HLA Typing)
- **Unrelated:** often **emotionally related** e.g. spouse

### Why do Organs Fail?

- **Cornea** – degenerative disease, infections, trauma
- **Skin/Composite** – burns, trauma, infections
- **Kidney** – diabetes, hypertension, glomerulonephritis, hereditary conditions
- **Liver** – cirrhosis (viral hepatitis, alcohol, auto-immune, hereditary conditions), acute liver failure (e.g. due to paracetamol)
- **Heart** – coronary artery or valve disease, cardiomyopathy (viral, alcohol), congenital defects
- **Lungs** – COPD/emphysema (smoking, environmental), interstitial fibrosis/interstitial lung disease (idiopathic, autoimmune, environmental), cystic fibrosis (hereditary), pulmonary hypertension
- **Pancreas** – type I diabetes
Multiple Challenges to Successful Transplantation:

- Bone marrow – tumours, hereditary diseases
- Small bowel – mainly children, hereditary conditions or related to prematurity (in adults – Crohn’s, Vascular Disease)

Statistics of Transplanted Solid Organs

<table>
<thead>
<tr>
<th>Organ</th>
<th>Deceased donor</th>
<th>Live donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>1570</td>
<td>927</td>
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<tr>
<td>Liver</td>
<td>667</td>
<td>34</td>
</tr>
<tr>
<td>Heart</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>Heart and lung</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>2552</td>
<td>961</td>
</tr>
</tbody>
</table>

Figures for 2008-2009 (NHSBT)

Transplantation Activity:
- Corneas – 2,500
- Bone grafts – 10,000
- Heart valves – 800

Multidisciplinary Approach
- Organ donor and family
- Organ recipient and family
- Transplant coordinator
- Physicians
- Surgeons
- Nurses
- Radiologists, Pathologists

Multiple Challenges to Successful Transplantation:
- Clinical
- Surgical
- Scientific
- Ethical and Psychological
- Legal
- Organisational

Number of deceased donors and transplants in the UK, 1 April 2000 - 31 March 2010, and patients on the active transplant lists at 31 March

Source: Transplant activity in the UK, 2009-2010, NHS Blood and Transplant
Who needs a transplant?
There are two issues with organising transplants:

- Access to the waiting list – selection
- Access to the organ – allocation

Transplantations can be either:

- Life-Saving
  - Other life-supportive methods not fully developed (LVAD/Left Ventricular Assist Device vs. Heart Tx, Liver Tx) or have reached the end of their possible use (total parenteral nutrition with venous access problems vs. small bowel Tx) (Tx = Transplant)

- Life-Enhancing
  - Other life supportive methods are less good (dialysis vs. kidney transplant, insulin injections vs. pancreas transplant)

Access to the waiting list

- Patient too ill
- Patient does not want a transplant
- Surgical/technical problems (obesity, atherosclerosis etc.)
- Too early to be placed on a waiting list

Organ Allocation and Distribution

- Ethical Determinants – What is fair?
  - Super-urgent transplants for those who face imminent death (liver, heart)
  - Time on waiting list

- Biological Determinants
  - Cold ischaemia time (geography) – heart
  - Organ size (of donor organ in relation to size of patient requiring transplant) – lung
  - Histocompatibility – kidney

NHS Blood and Transplant (NHSBT)

- Provision of a reliable, efficient supply of blood, organs and associated services to the NHS
- Rules for organ allocation are established by the medical community/health professionals/advisory groups/DH
- NHSBT monitors allocation

Donor Transplant Co-Ordinator

- Role and responsibility under review
- Registered nurses with experience in critical care
- Employment to shift from transplant centres to NHS BT
- Potential donors A&E/ICU
- Carry out family interviews – part of bereavement services

Other strategies to increase transplantation

- Marginal donors – elderly, sick
- High risk transplantation – across tissue compatibility
- Paired-exchange (live donation) – donor swaps for better tissue matching
- Xenotransplantation
- Stem cell research

Number of deceased and living donors in the UK, 1 April 2000 - 31 March 2010
Clinical Practice of Transplantation

Pre-transplantation management
- Waiting list
- Immunological investigations
- Other investigations

Transplantation surgery

Post-transplantation management

Immunosuppression
- Induction agents
- Corticosteroids (current tendency for reduction of steroids)
  - PLUS
- Other immunosuppressive drugs

Complications of Transplantation

- Rejection
- Infection
  - Early Period
    - Typical post-operative bacterial infection
    - Oropharyngeal Candidiasis
    - Aspergillosis
  - Medium Term
    - CMV (after 1-2 months)
    - Serogative recipients should have prophylaxis
    - Pneumocystis
    - Tuberculosis
  - Drug Side Effects
  - Malignancy
    - UV-induced Skin Cancer
    - Post-transplant lymphoproliferative disease
      - B-Cell
      - EBV-driven

Why a Graft Fails
- Surgical Complications
- Bad quality organ
- Rejection
- Recurrence of original disease

Rejection
- Recognition and destruction by recipient immune system (immune-mediated damage)
  - Acute cellular rejection (T-Cell Mediated)
  - Acute antibody-mediated rejection (antibody-mediated, B-Cells)
- Gold standard for diagnosis of rejection is the biopsy of the transplanted organ (easy for kidneys, more problematic for other organs)

Hyperacute Rejection
- Caused by pre-existing antibodies
- Historical sensitisation – the patient has ‘seen’ the antigen before:
  - Previous transplant
  - Previous transfusion
  - Pregnancy
  - Previous allergic reaction
  - Previous lymphoproliferative disease
  - Previous transfusion
  - Historical sensitisation – the patient has ‘seen’ the antigen before:
    - Previous transplant
    - Previous transfusion
    - Pregnancy
    - Previous allergic reaction
    - Previous lymphoproliferative disease
    - Previous transfusion
    - Historical sensitisation – the patient has ‘seen’ the antigen before:
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      - Previous transfusion
      - Pregnancy
      - Previous allergic reaction
      - Previous lymphoproliferative disease
      - Previous transfusion
    - EBV-driven
  - UV-induced Skin Cancer
  - Post-transplant lymphoproliferative disease
    - B-Cell
    - EBV-driven

Source: Transplant activity in the UK, 2000-2010, NHS Blood and Transplant
Pregnancy
- Bind to graft endothelium in minutes
- Destroys graft in hours
- Every patient screened by direct cross-match

**Acute Rejection**
- T- or B-Cell Mediated, or both

**Chronic Rejection**
- T- or B-Cell Mediated, or both

**Immunology of Transplantation**
- The immune system recognises someone else’s organ as **foreign**
- Most relevant protein variations in clinical transplantation
  - 1. ABO Blood Group
  - 2. HLA (Human Leukocyte Antigens) coded on chromosome 6 by Major Histocompatibility Complex (MHC)

1. **ABO Blood Group**
- A and B Proteins are found on red blood cells but also endothelial lining of blood vessels in transplanted organs.
- Naturally occurring anti-B antibodies in A patients, and anti-A antibodies in B patients.
- O patients have both anti-A and anti-B

**e.g. Patient Blood Group A**
*Red cells express A, Patient serum contains naturally occurring anti-B antibodies*

**Heart transplant from blood group B donor** – *i.e. cells express blood Group B*

The circulating, preformed recipient anti-B antibody binds to B-blood group antigens on the donor endothelium

- This causes an **activation of complement**
  - Complement-mediated lysis
  - Opsonisation
  - Increased **permeability**
- Other cells are rapidly recruited
  - Phagocytes
- Disruption of endothelium
  - Platelets activated
  - Inflammation
  - Thrombosis
- Leading to **HYPERACUTE REJECTION**

**ABO-Incompatible Transplantation** - In recent years, it has become possible to **remove the antibodies** in the organ recipient with good outcomes

2. **HLA (Human Leukocyte Antigens)**
- Discovered after **first failed attempts** at human transplantation
- Cell surface proteins
- Highly variable portion
- Variability of HLA molecules is important in the **defence against infections** and **neoplasia**
- Foreign proteins are presented to immune cells in the context of HLA molecules recognised by the immune cells as ‘self’
Human Leukocyte Antigens:
- Class I (A, B, C) – expressed on all cells
- Class II (DR, DQ, DP) – expressed on immune cells but can also be upregulated on other cells
- Highly Polymorphic – lots of alleles for each locus (for example: A1, A2, A3 etc.)

HLA Antigens
- In the case of a mismatch, the recipient’s immune system mounts a reaction against the donor’s HLA, as if it were an infection or cancer.
- This results in ‘rejection’ – destruction of the graft by cellular and antibody mediated immune processes, eventually resulting in graft failure

HLA matching in organ allocation

<table>
<thead>
<tr>
<th></th>
<th>HLA-A</th>
<th>HLA-B</th>
<th>HLA-DR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient</strong></td>
<td>HLA-A1</td>
<td>HLA-B4</td>
<td>HLA-DR3</td>
</tr>
<tr>
<td></td>
<td>HLA-A2</td>
<td>HLA-B27</td>
<td>HLA-DR7</td>
</tr>
<tr>
<td><strong>Donor</strong></td>
<td>HLA-A1</td>
<td>HLA-B8</td>
<td>HLA-DR3</td>
</tr>
<tr>
<td></td>
<td>HLA-A11</td>
<td>HLA-B51</td>
<td>HLA-DR7</td>
</tr>
<tr>
<td><strong>Number of mismatches</strong></td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Minimising HLA Differences between donor and recipient improves transplant outcome

**HLA Matching in Organ Transplantation**
- Important for certain organs (e.g. kidney, bone marrow)
- Controversial (e.g. liver)
- Not important (e.g. heart and lung)

**Rejection**
- This is the most common cause of graft failure
- Mediated by:
  - T-Cell (T-cell mediated rejection)
  - B-Cells (Antibody-mediated rejection)
- Gold standard for diagnosis – histological examination of a biopsy
- Treatments – suppressing the immune system

**Acute T-Cell Mediated Rejection**
- Recognition of donor HLA antigens by CD4+ T-Cells
- Activation of CD4+ cells
  - Production of cytokines
    - Help for CD8+ Cells
    - Help for B Cells
    - Recruitment and activation of macrophages and neutrophils
- Leads to **Type IV Hypersensitivity Response**

**Acute Antibody-Mediated Rejection (B-Cells)**
- Antibody against graft HLA and AB Antigen
- Antibodies can be present before transplantation (recipient has seen the antigen before) or arise after
Antibodies can be present before transplantation (recipient has seen the antigen before) or arise after transplantation. Antibody activates complement and macrophages.

Activation of complement
- Complement-mediated lysis
- Opsonisation
- Increased permeability

Other cells rapidly recruited
- Phagocytes

Disruption of endothelium
- Platelets activated
- Inflammation
- Thrombosis

Diagnosis of Rejection
- Kidney, liver, pancreas – graft dysfunction detected by regular blood tests (creatinine, liver function, amylase) – A graft biopsy and histological interpretation are ideal.
- Heart – no good tests for dysfunction, regular biopsies are necessary

Prevention of Rejection
- Maximise HLA Compatibility
- Suppress the immune reaction of the recipient – using immunosuppressive drugs

Treatment of Rejection
- Increased immunosuppression

Immunosuppressive Drugs:
- Target T-Cell Activation and Proliferation
- Target B-Cell Activation and Proliferation
- Life-long

T-Cells
In orange is the possible drugs that can be administered.
- Costimulation Blockade
- Others...
- Signal transduction / Calcineurin Inhibitors
- T-Cell Depleting Agents - Thymoglobulin (AntiCD3, AntiCD52)
- Corticosteroids: Block cytokine production
- Anti-II2 Receptor
- mTOR Inhibitors
- Anti-proliferative Agents

B-Cells
* Bortesomib has Anti-T Cell Actions but causes plasma cell apoptosis*

Modern Transplant Immunosuppression
- **Induction Agent** to deplete immune cells before transplantation (example: anti-CD52 = Campath)
- **Base-Line Immunosuppression: Variable**
  - Signal transduction blockade, usually CNI inhibitor (Tacrolimus or Cyclosporin), sometimes mTOR Inhibitor (Rapamycin)
  - +/- Antiproliferative agents: MMF or Azathioprine
  - +/- Corticosteroids
- **Treatment of Episodes of Acute Rejection**
  - Cellular – Steroids, anti-T Cell agents
Antibody-mediated: IVIG, plasma exchange, anti-C5

**Improvement in Kidney Transplant Survival**

[Graph showing transplant year vs. percent of grafts surviving]

**Immunosuppression:**
- Rejection Vs. Infection/Tumours/Drug Toxicity

**Post-Transplantation Infections**
- Increased risk for conventional infections (bacterial, viral, fungal)
- Opportunistic infections - Normally relatively harmless infectious agents give severe infections because of immunocompromise
  - Cytomegalovirus
  - BK Virus
  - Pneumocystis Carinii

**Post-Transplantation Malignancy**
- Skin Cancer
- Post-transplant lymphoproliferative disorder – EBV driven
- Others

[Diagram showing time post transplantation with categories such as infection, drug toxicity, technical complications, delayed graft function, and acute rejection]

Infection
- Viral: CMV, VZV, EBV
- Fungal: eg aspergillus
- Bacterial: TB, Nocardia, Listeria
- Parasitic: pneumocystis,
- Toxoplasma
- Other common infections

Drug toxicity - hypertension, hyperlipidaemia, cardiovascular
RENAL TRANSPLANTATION

- Matching
  - ABO blood group matching
  - HLA matching
- 60-80% kidneys produce urine “on the table”
  - others have “delayed graft function”
- 10-25% suffer acute rejection
  - usually reversible
- Monitoring for good blood and urine flow and rejection
  - serum creatinine
  - DTPA perfusion scan/ultrasound
  - serial renal biopsy
- Outcome
  - 5-year graft survival rate currently around 89% (living) – 83% (deceased)
  - 10-year survival around 60-70%
  - current “life-expectancy” of first kidney: 11yr
  - in ideal conditions, could be up to 40 yr

CORNEA TRANSPLANTATION

- Based on supply and demand
  - Most patients never get on waiting list, but corneas are “ordered”
- Cornea is “immunologically privileged site”
  - Immunosuppression not required
  - Rejection does occur
- Matching
  - Historically not considered important
- Outcome
  - First graft: c75% 5 year survival

LIVER TRANSPLANTATION

- Supply and demand
  - Relatively well matched
- Options for transplantation
Orthotopic transplantation - replacing the diseased liver
Heterotopic transplantation - placing a new liver in a different place (right subhepatic region)
Live lobe transplantation

Organ-specific issues
- Surgical technique is very difficult and complications are common
- Thrombosis of hepatic artery or portal vein may occur
- Haemorrhage is very common

Matching
- ABO blood group
- Size
- HLA matching controversial and not practical

Rejection
- Liver is less aggressively rejected than many other organs

Outcome
- 3 year survival:
  - cirrhosis: 69%
  - emergency: 56%
  - cancer: 39%

HEART TRANSPLANTATION

Supply and demand
- Predicted demand: 20-60/million population
- Current supply: 6/million in UK

Matching
- Appropriate blood group
- Size
- ?HLA matching

Rejection
- Only reliable way to detect is regular endomyocardial biopsy

Outcome
- 85-90% 1 year survival
- 75% 5 year survival
- 50% live 10-12 years
- Functional rehabilitation excellent

Lung transplantation

Supply and demand
- Approx. 200 suitable donors per year in UK
- 111 on heart/lung waiting list and 205 on lung waiting list at 31.12.2000

Options for transplantation
- Heart-lung transplant
- Single lung transplant
- Sequential double lung transplant

Matching
- ABO match
- Size

Outcome
- For heart-lung and single lung transplant
  - 80% 1 year survival
  - 50% 5 year survival
- Less good for double lung transplant

Conclusions:
- Transplantation is life-saving/life-enhancing
- Not without risks – surgery, immunosuppressive burden (infections, malignancy, drug toxicity)
- Issues related to supply/demand, ethics, biology limits its use
Transplantation is: highly successful, potentially life-saving and cost-effective