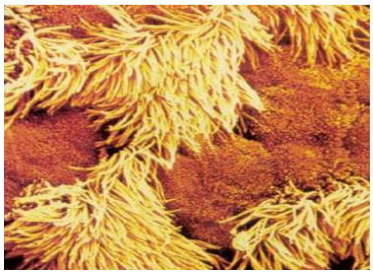
IMMUNOLOGY OVERVIEW

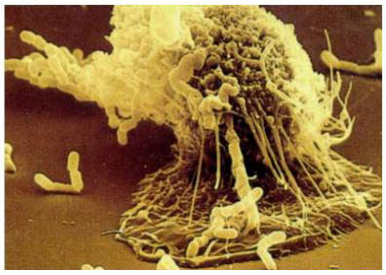
The immune system

The human body must defend itself against invasion by pathogenic organisms (viruses, bacteria, fungi, protozoa, helminths, arthropods) as well as the uncontrolled growth of abnormal cells (tumours). The immune system provides protection against both, but its various elements must be constantly regulated to maintain an appropriate level of protection. Heightened responses may cause auto-immune diseases, allergic reactions and hypersensitivity, while deficient responses leave us susceptible to infections and tumour (cancer) development. Cells of the immune system are produced in special organs and tissues and move around the body in the circulatory and lymphatic systems. They communicate and interact using numerous molecular signals (chemokines, cytokines, lymphokines). Collectively, there are three lines of immunological defense: barriers formed by membranes; innate immunity provided by phagocytes; and acquired (adaptive) immunity reliant on lymphocytes.

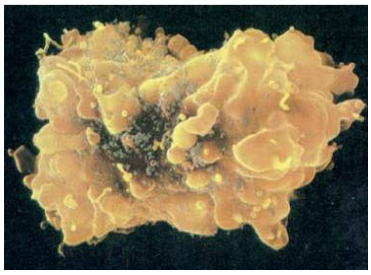
membrane barrier



phagocyte (macrophage)



lymphocyte (T cell)



Cells and organs

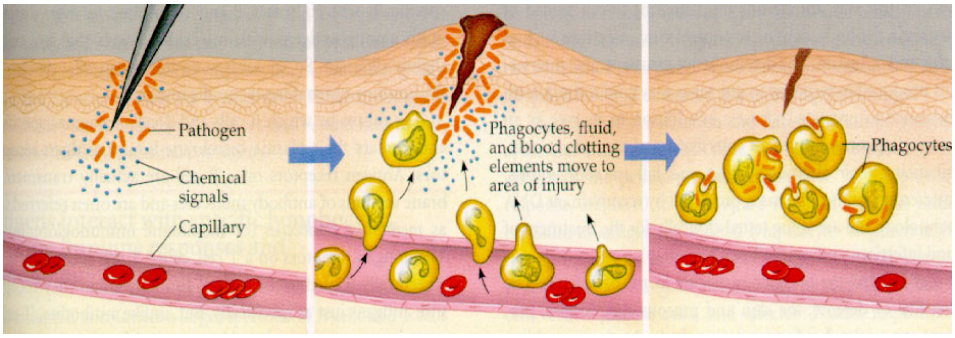
All cells of the immune system are formed by pluripotent stem cells in the bone marrow. Myeliod precursors give rise to phagocytic and dendritic cells, while lymphoid precursors give rise to lymphocytes. Cells of the immune system are evident in the blood as leucocytes (white blood cells) [both granulocytes (neutrophils, eosinophils and basophils) and agranulocytes (lymphocytes)]; in tissues as macrophages and antigen-presenting cells; and in lymphoid organs and tissues. Primary lymphoid organs (bone marrow and thymus) are said to be 'productive'; they 'produce' effector cells. In particular, they are the sites where lymphocytes proliferate, differentiate, acquire specific antigen receptors, learn to distinguish between self and non-self, and mature into functional cells (**B** cells in the **B**one marrow, and **T** cells in the **T**hymus). Secondary lymphoid organs are said to be 'reactive'; they are the sites where lymphocytes 'react' with foreign material (antigens) initiating specific immune responses. These organs include lymph nodes (which filter extracellular fluid, = lymph), the spleen (which filters the blood), and mucosal-associated lymphoid tissue (MALT)(which protects parts of the gastrointestinal, respiratory and genitourinary tracts).

Barrier defenses (nonspecific)

The first line of defense comprises physical and chemical barriers to infection; membranes and their secretions that foreign invaders first encounter. These barriers are nonspecific; that is, they are presented to all invaders, irrespective of type. The skin presents a formidable external barrier, while mucous membranes line all internal tubular organs producing mucus and various other chemical secretions (particularly the enzyme lysozyme). If invaders penetrate barrier defenses, they then meet hungry killer cells.

Innate defenses (nonspecific)

The second line of immunological defense involves phagocytic cells that seek out invaders in host tissues. The phagocytic cells may reside within specific tissues (fixed macrophages) or circulate throughout the body in the blood (neutrophils and monocytes). They engulf and digest foreign material irrespective of type: thus the immunity is said to be innate and nonspecific. It has long been known that infections elicit inflammation, innate responses characterized by four cardinal signs: redness (rubor), heat (calor), swelling (tumour) and pain (dolor).



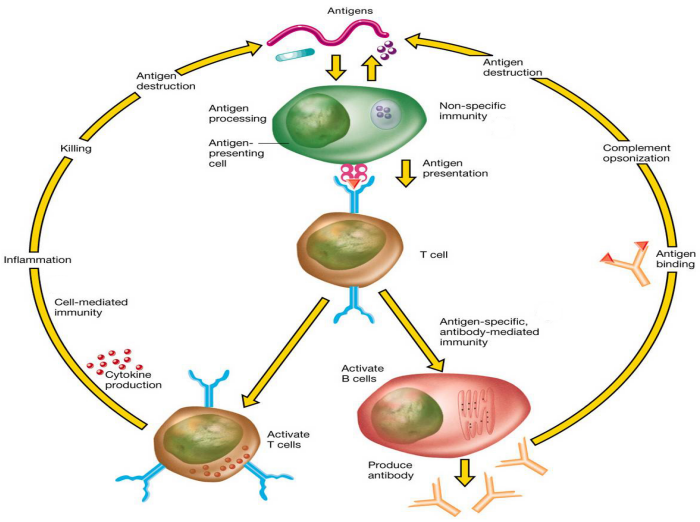
Localized inflammation occurs when injured cells release chemical signals (chemokines) causing dilation and increased permeability of blood vessels, allowing fluid and large numbers of phagocytes to enter the tissues to seek out and destroy invaders. Inflammation of organs is signified by adding the postfix '*–itis'* to the organ name (hepatitis indicating inflammation of the liver, encephalitis that of the brain, etc). Innate immune responses are particularly effective against bacterial invaders, whereas other larger organisms have become quite adept at avoiding death by phagocytosis. Survivors are not safe, however, as they then trigger a multitude of other defensive mechanisms.

Acquired defenses (specific)

The third line of defense (adaptive or acquired immunity) is highly specific and is reliant on lymphocytes (providing specificity, diversity, memory and self-tolerance). T cells invoke cell-mediated responses while B cells invoke humoral responses (involving antibodies). Both T and B cells recognize antigens via specific surface antigen receptors. Self tolerance develops as cells bearing receptors for native molecules are destroyed or rendered nonresponsive. Major histocompatibility complex (MHC) molecules are crucial to antigen presentation. Class I MHC molecules located on all nucleated cells present antigens to cytotoxic T cells, while class II MHC on macrophages and B cells present antigens to helper T cells. When an antigen binds to a particular lymphocyte, it is activated to produce numerous identical copies (clonal selection). The primary immune response (first exposure to an antigen) results in clones of short-lived infection-fighting effector cells as well as clones of long-lived memory cells. Subsequent exposure to the same antigen activates the memory cells and the resultant secondary immune responses are faster, stronger and often protective (providing the basis for vaccination).

Cell-mediated responses (defense against intracellular pathogens)

Helper T cells interact with antigen-class II MHC complexes on macrophages through T cell receptors and the cell surface protein CD4. Contact stimulates the helper T cells to grow and divide, as does interleukin-1 secreted by macrophages. The helper T cells secrete interluekin-2 which activates other cells in the immune system; including cytotoxic T cells (stimulated to become active killer cells), B cells (stimulated to become antibody-producing plasma cells) as well as additional helper T cells (stimulated to divide more rapidly and increase cytokine production). Viral, bacterial and tumour antigens are gathered in nucleated cells of the body and are presented on the surface by class I MHC proteins. They are recognized by cytotoxic T cell receptors and the cell surface protein CD8. Cytotoxic T cells are stimulated by contact and by interleukin-2 to release the protein perforin which punctures the target cell, allowing water and ions to rush in causing swelling and lysis.

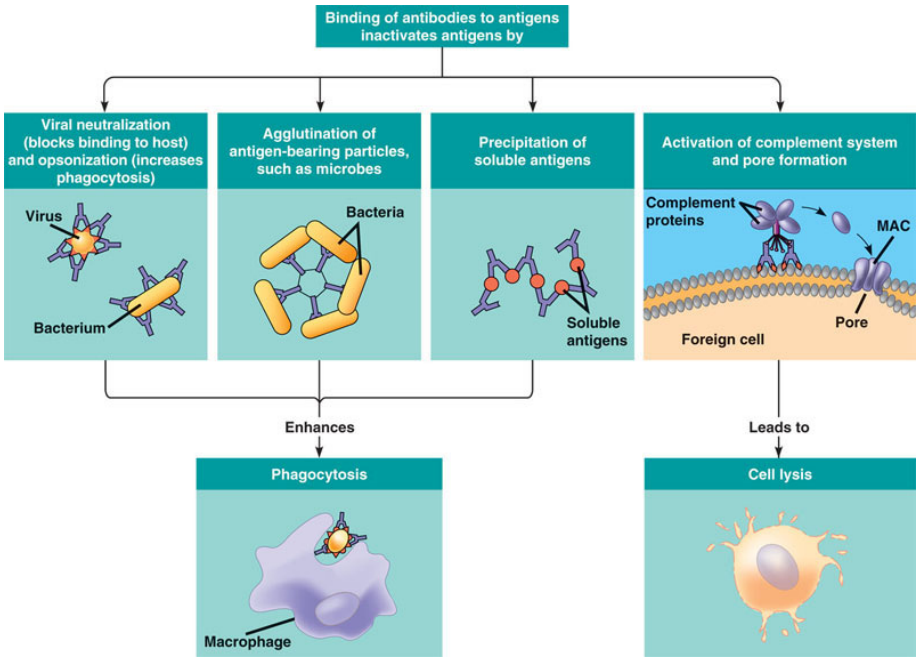


Humoral responses (defense against extracellular pathogens)

B cells have antibody receptors in their plasma membranes specific for particular antigens. Successful binding stimulates B cell proliferation producing clones of plasma cells and memory cells. Plasma cells secrete antibodies in increasing amounts peaking 10-17 days after activation. Antibodies flow through the body's fluids and tag foreign cells and molecules for destruction.

Helper T cells may also contribute to humoral responses involving T-dependent antigens. B cells may internalize antigens by endocytosis where they bind with class II MHC proteins and move to the cell surface. The B cell now presents the same antigen that fits in the receptor of the helper T cell. When contact occurs, the helper T cells secrete interleukin-2 and other cytokines that activate B cells to divide into plasma and memory cells.

The binding of antibodies to antigens tags foreign cells and molecules for destruction via neutralization, agglutination, precipitation and complement fixation. Neutralization of bacteria and viruses occurs when antibodies bind to and block the activity of the antigen. Neutralized viruses cannot invade cells and microbes and soluble antigens coated with antibodies are phagocytosed by macrophages (enhanced attachment called opsonization). Agglutination is the process whereby bacteria or viruses are effectively neutralized by clumping. Antibodies have at least two binding sites allowing them to crosslink microbes which are then phagocytosed by macrophages (opsonization). Precipitation is the cross-linking of soluble antigens to form immobile precipitates which are then phagocytosed by macrophages (opsonization). Complement fixation is the activation of a series of serum proteins leading to lysis of a microbe. First, complement proteins bind to IgM or IgG antibodies that have tagged a foreign cell. Some of the proteins are activated to form a membrane attack complex that creates a pore in the target cell, allowing water and ions to rush in causing the cell to swell and lyse.



Hypersensitivity

Hypersensitivity is an adaptive immune response that occurs in an inappropriate or exaggerated way, resulting in tissue damage or some other detrimental response. There are four major categories:

- Type I (immediate) hypersensitivity may occur within minutes and is generally provoked by environmental allergens and involves the production of IgE and degranulation of mast cells. Examples include anaphylactic shock, asthma, hives, and drug allergies.
- Type II (antibody-dependent cytotoxic) hypersensitivity occurs within hours when antibody binds to self or foreign antigens resulting in cell death from phagocytosis, killer cell activity or complement-mediated lysis. Examples include haemolytic anaemia and Rh blood group incompatibility.
- Type III (immune complex) hypersensitivity occurs within days and is caused by the deposition of antigen-antibody complexes in blood vessels and tissues. Examples include serum sickness and glomerulonephritis.
- Type IV (delayed type) hypersensitivity occurs over days and is mediated by T cells and macrophages producing skin reactions (erythema, itching, eczema, necrosis) on second exposure to simple antigens. Examples include contact dermatitis due to nickel, poison ivy, soaps, cosmetics, etc.

Immune pertubations

Autoimmune diseases (such as rheumatoid arthritis and insulin-dependent diabetes) occur when the immune system loses tolerance for self and turns against certain native molecules.

Immunodeficiencies may be congenital (such as agammaglobulinaemia and SCID), acquired through disease (cancers such as Hodgkin's disease) or infection (such as HIV-AIDS) and possibly influenced by physiological condition (reduced due to stress or depression). Individuals are rendered susceptible to a variety of opportunistic infections and pathological disorders.

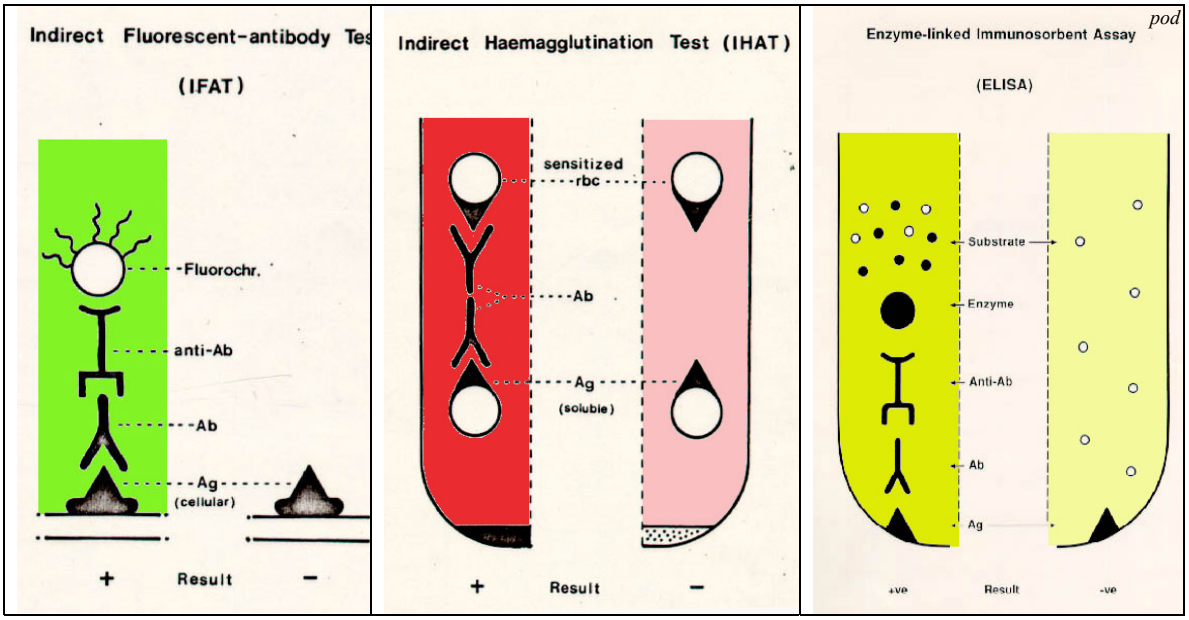
Immunological recognition determines the success of blood transfusions, tissue grafts and organ transplantations. Incompatibility between donor and recipient can have severe and even fatal consequences. Autografts (involving the same individual) and isografts (involving genetically identical individuals) do not induce immune responses, whereas allografts (involving non-identical individuals) and xenografts (involving different donor and recipient species) do provoke strong immune responses leading to graft rejection (unless strong immunosuppressive drugs are used).

Active protective immunity against disease can be generated by previous exposure (natural infection) or by immunization (vaccination) with inactivated, attenuated or subunit vaccines. Consider your own vaccination history.

Passive immunity involves the transfer of antibodies between individuals, either naturally (such as transplacentally or via maternal colostrum) or artificially (immunoprophylaxis/immunotherapy).

Antibody-antigen tests

Animals respond to most infectious diseases by forming antibodies against the infecting pathogen as part of their immunological defenses. Antibodies (also called gamma-globulins or immunoglobulins) are produced by plasma cells (transformed B lymphocytes) and are secreted into the blood stream to circulate through the body. When they come into contact with the relevant antigen, they bind to it and tag it for destruction. The presence of specific antibodies is frequently used as an indicator of infection, particularly for diseases which have nonspecific symptoms or clinical signs (fever, diarrhoea). A variety of immuno-serological tests have been developed to detect host antibodies against microbial antigens; including fluorescent-antibody labelling, haemagglutination and enzyme immunoassays.



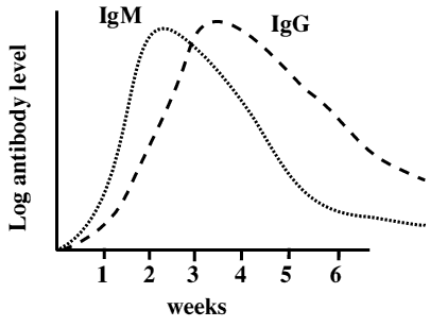
All tests operate on the same principle. Host serum is incubated in test vessels which have been coated with microbial antigens. If antibodies are present, they bind to the antigens and are subsequently revealed by chemical indicator systems (fluorescence, haemolysis, enzyme-substrate colour change). It is particularly important to quantitate the amount of antibody present as this provides an indication of the severity of infection and the immunocompetence of the host. The concentration of many other chemicals present in blood (hormones, electrolytes, drugs, etc) can be measured in absolute terms and expressed in specific units (μg/ml, etc). However, measuring the concentration of antibodies is much more difficult due to their variable specificity, cross-reactivity, highly reactive nature, and strong binding affinity to detection systems.

An accurate indication of the amount of antibody present can be obtained by serially diluting the blood to the point it no longer tests positive. The last positive dilution is then called the end-point titre and this indicates the quantity of antibody present. For example, an end-point titre of 1/100 indicates there was enough specific antibody present to still elicit a positive reaction when the blood was diluted 100 times. It is common for antibody titres during active acute infections to be in the vicinity of 1/500 to 1/1000. [Note that this reciprocal notation represents a fraction not a ratio; 1/10 means 1 in 10 (while 1:10 means 1 as to 10). A 1/10 dilution is therefore made by adding 1 part blood (usually serum) to 9 parts diluent (usually physiological saline) to give a 1 in 10 dilution]. The most commonly used series are doubling dilutions beginning with a 1/2 dilution (i.e. 1/2, 1/4, 1/8, 1/16, 1/32, 1/64, etc). Serial dilutions are usually made on 96-well plastic microtitre plates (wells arranged in 8 rows and 12 columns).

The results of serological tests are best read objectively and quantitatively; that is, without subjective interpretation by individual operators and with measurement of a related parameter, such as spectrophotometric absorbance (optical density), intensity of fluorescence, or degree of haemolysis. Various instruments have been developed to measure test results, compare and adjust them to standards and reference controls, and then calculate and present the results.

Regrettably, the test results can be influenced by many factors which affect the integrity of the relationships between parameters (such as edge effects, detectable levels, accuracy, interference, competition, cross-reactivity). Nonetheless, the end-point titre (= last positive dilution) of any particular sample can be given with a high degree of confidence.

Interpreting the significance of the test results requires thorough knowledge of the kinetics (onset and duration) and dynamics (intensity) of the host response to infection. Longitudinal samples are obtained to determine whether antibody titres in a particular individual remain stable or whether they are increasing or decreasing (plot titre over time). The results provide strong presumptive evidence on the status of infection within that individual, thus allowing appropriate therapy. Following most infections, there is an early transient IgM antibody response (usually coincident with the acute phase of infection) followed by a later but more persistent IgG antibody response (usually associated with the chronic stage of infection).



Test Sensitivity and Specificity

All serological tests provide indirect presumptive evidence of infection by demonstrating the presence and amount of antibody against a particular pathogen. These tests are not 100% perfect for a variety of reasons; such as:

- acute infection (host recently infected and antibodies not yet formed)
- chronic infections (host infected and cured years ago but antibodies persist)
- low dose infections (host immune response so low it cannot be measured)
- cross-reactivity (antibodies cross-react against other antigens)

It is therefore important that users of any particular test know how good it is (as determined by objective quantitative assessment). Measurement of test efficacy is done by comparing it against another more conventional test held to be very accurate (representing the 'gold standard'). Test sensitivity and specificity are then calculated as shown in the following table. Regrettably, gold standard tests are not always available so serological test efficacy may be poorer than reported as they were compared against semi-flawed tests. Nonetheless, these parameters (usually expressed as percentages) should be included in the product information accompanying all commercial test kits.

INFECTION STATUS

		INFECTED	NOT INFECTED	
TEST RESULT	POSITIVE	true positive (A)	false positive (B)	(A+B)
	NEGATIVE	false negative (C)	true negative (D)	(C+D)
		(A+C)	(B+D)	(A+B+C+D)(=N)

Prevalence: True prevalence of infection = (A+C)/N

Test prevalence (seroprevalence) = (A+B)/N

Accuracy: Accuracy = (A+D) / N

Sensitivity is the probability of a positive test in an infected individual = A/(A+C)

[clinical pneumonic = SnNout = with a sensitive test, a negative result rules the diagnosis out]

High sensitivity means there were few or no false negatives, while low sensitivity means they were frequent. The consequences of returning a false negative result (when the patient is actually infected) involves failure to treat, worsening of the disease and possible fatality.

Specificity is the probability of a negative test in a non-infected individual = D/(D+B)

[clinical pneumonic = SpPin = with a specific test, a positive result rules the diagnosis in]

High specificity means there were few or no false positives, while low specificity means they were frequent. The consequences of returning a false positive result (when the patient was actually not infected) include unwarranted treatment, waste of time and money, and potential harm to the patient through invasive treatment or toxic side-effects.

NOTES ON THE IMMUNE SYSTEM

Immunology is the study of how the body responds to infection. **Immunity** is the ability of the body to resist infection and disease. It may be nonspecific **innate** immunity; or specific **acquired** (adaptive) immunity involving **humoral** and **cell-mediated** responses.

Non-specific innate immunity

Mechanical barriers to infection
Drainage and irrigation
Chemical protection
Normal bacterial populations (commensals)
Cells (pattern recognition / phagocytosis / inflammation / NK cells)
Fever
Behavioural (good public health and hygiene)

Specific acquired/adaptive immunity

Two components: humoral immunity and cell mediated immunity
Diverse: can respond to a vast number of different antigens in a unique way
Memory: body can respond to second challenge with same agent
Activation of B lymphocytes to produce antibody: humoral immunity
Activation of T lymphocytes: cell mediated immunity
Most cell mediated reponses also have humoral response to same antigen to enhance defence

	Innate immunity	Adaptive immunity
Characteristic	non-specific response to molecules that are not self	specific recognition of unique target molecule
	rapid	lag phase first time; quicker subsequent encounters
	no memory: same response each time	memory: response improved by repeated encounter with same target
Soluble factors	complement, lysozyme, acute phase proteins eg interferon, C-reactive protein	antibody (immunoglobulins)
Cells	phagocytes (monocytes, neutrophils, macrophages) NK cells	B lymphocytes (humoral) T lymphocytes (cell mediated)

Active immunity

- develops when a person responds to an antigen
- provides life-long protection (usually)
- occurs naturally following infection
- can be induced by vaccination

Passive immunity

- occurs when a person receives antibodies or cells produced by another person or animal
- provides only temporary protection
- can be transferred person to person
- can be injected as ready-made "immune serum"

Harmful Effects of Immune Response

septic shock
allergy and hypersensitivity
organ-specific autoimmunity
neoplasms (tumours)
blood transfusion reaction
chronic infection: granulomas, abscesses
chronic inflammatory diseases
immune complex diseases
graft / transplant rejection
pregnancy

CELLS OF THE IMMUNE SYSTEM

Granulocytes or granular leucocytes (neutrophils, eosinophils, basophils) formed in the bone marrow from common precursor, the pluripotential stem cell.

Neutrophils

- most abundant circulating cells (apart from red cells)
- primary granules, secondary granules
- chemotactic stimulus leads to **diapedesis** (involving **margination** and **extravasation)**
- unable to recharge after killing mechanism activated

Eosinophils

- bilobed nucleus
- coarse red/orange staining granules
- special role in allergic responses and defence against parasites

Basophils

- rare! similar to mast cells in tissue
- attachment sites for IgE
- degranulation releases histamine

Neutrophil ingest (phagocytose) organisms and then kill them.

- pseudopodia of phagocytic cell wrap around particle to form **phagosome**
- phagosome fuses with intracellular granules (lysosomes) to form **phagolysosome**
- metabolic reactions generate hydrogen for reduction reactions: **respiratory burst**
- two killing mechanisms: enzymes damage bacteria directly, and/or reduction reactions alter pH within lysosome and generate toxic products
- process greatly enhanced by **opsonisation** (involving complement, antibody and CRP)
- *phagocyte* death by **apoptosis.** Failure leads to abscess forming.

Macrophages/Monocytes

- large cells, lots of cytoplasm with many fine vacuoles
- cells free or fixed in tissues

Location	Macrophage name/type
lung	alveolar macrophages*
liver	Kupffer cells
blood	monocytes
lymph nodes	resident and recirculating macrophages
kidney	intraglomerular mesangial phagocytes
brain	microglial cells
joints	synovial A cells
spleen	splenic macrophages
peritoneal cavity	serosal macrophages*

* 'wandering' macrophages

- Professional **phagocytes** remove antigen particles and apoptotic granulocytes
- Act as **antigen presenting cells** (APCs) to take up, process and present antigen to T cells

Major Histocompatibility Molecules (originally discovered as the basis for transplant rejection or acceptance) Unique identifiers for individuals:

Class I molecules are found on the surface of nearly all nucleated cells. Their function is to present endogenous foreign antigen (such as that made by a virus infecting the cell) at the surface of the cell so that the infected cell becomes a target for cytotoxic T lymphocytes (T_C CD8 cells). The target cell can then be destroyed. This is cell-mediated immunity.

Class II molecules are confined to cells which function by taking up antigen derived from exogenous (extracellular) foreign proteins. These include macrophages, B lymphocytes and other APCs which eliminate pathogens with the assistance of helper T lymphocytes (T_H CD4 cells) either by: B lymphocytes producing antibody to the foreign antigen; or activated macrophages destroying the pathogen by phagocytosis**.** This is humoral (antibody mediated) immunity.

Lymphocytes (B cells / plasma cells, T cells)

- each lymphocyte has unique receptors on its cell surface that recognise a particular antigen
- receptor diversity occurs by gene rearrangement
- clonal proliferation when activated; some become memory cells

B lymphocytes

- surface immunoglobulin acts as unique receptor for antigen
- when stimulated, develop into **plasma cells** producing antibodies or into **memory cells**
- most B cells carry MHC Class II molecules

T lymphocytes

- T cell antigen receptor (TCR) defines the T cell lineage
- two distinct populations develop in the thymus and function in one of two ways when activated:
  - Helper T cells (T_H cells; CD4+) help/amplify immune response by producing cytokines
  - Cytotoxic T cells (T_C cells; CD8+) kill cells bearing their antigen
- CD4 and CD8 molecules guide T cells to target by interacting with MHC Class II and Class I molecules respectively

Antigen presenting cells (APCs)

- macrophages* (the only APCs that are also phagocytic)
- Langerhans cells
- interdigitating cells
- follicular dendritic cells
- germinal centre dendritic cells
- interdigitating medullary cells

Endothelial cells

- accessory cells lining blood vessels, express molecules that recognise circulating leucocytes, controlling leucocyte traffic and distribution

ORGANS/TISSUES OF IMMUNE SYSTEM

Primary lymphoid organs are **productive**, include **B**one marrow (**B** cells) and **T**hymus (**T** cells)
Main sites where lymphocytes proliferate, differentiate, acquire specific antigen receptors, learn to distinguish between self and non-self, and mature into functional cells

Bone Marrow

- origin of blood cells / in central cavity of bones
- site of **B cell** development / T cells start in the bone marrow but migrate to thymus
- compact bone / network of connective tissue and cells / islands of haemopoietic cells & fat cells
- pluripotential stem cells / many macrophages / numerous vascular sinusoids

Functions of **active** bone marrow:

- **haemopoiesis** and release of blood cells
- steady state renewal
- storage and recycling
- phagocytosis
- mobilisation of cell reserves

Thymus

- T cells develop in the thymus which is essential for T cells to mature, but most die there
- specialised environment of thymus selects T cells with useful receptors
- macrophages delete by apoptosis all T cells that recognise self antigens, to leave a 'useful' set

Cortex	Medulla
immature thymocytes proliferate and undergo selection	mature thymocytes undergoing selection
branched cortical epithelial cells	medullary epithelial cells
scattered macrophages	macrophages
	dendritic cells
	Hassall's corpuscles

Secondary lymphoid organs are **reactive**, include **lymph nodes, spleen,** and **m**ucosal-**a**ssociated **l**ymphoid **t**issue (**MALT**). Sites where a**ntigens** and **lymphocytes** will eventually meet each other

Lymph nodes

- the lymphatic system drains **extracellular fluid** through the lymph **nodes**
- strategically located meeting points of lymphatic vessels
- B cells need lymphoid follicles to survive

Nodes covered by **capsule** of loose connective tissue / **subcapsular sinus** underneath. Lymph arrives via the **afferent lymphatic** vessels / passes through the **capsule** into the **cortex. Outer cortex (primary follicles** / **secondary follicles** contain **germinal centres / paracortex** / **medulla**. E**fferent** lymphatic vessels return fluid to circulation via the **thoracic duct /** to bloodstream via **left subclavian vein / naive lymphocytes** can enter through high wall endothelial venules

Spleen

- collects and disposes of old red cells and platelets
- collects antigens from the blood and reacts promptly to them
- main site of IgM antibody production
- reservoir for platelets, granulocytes and red cells

capsule / **trabeculae** / **hilus** / **red pulp / white pulp.** Blood carrying lymphocytes and antigen enters the spleen via the **splenic artery** / flows from a **trabecular artery** into a **central arteriole** / cells and antigen pass into **marginal sinus** lined by PALS / drain into a **trabecular vein**, leaving the spleen via the **splenic vein**. B cells in white pulp arranged in primary 'unstimulated' follicles or secondary 'stimulated' follicles with **germinal centre**.

MALT – mucosal-associated lymphoid tissue

- lymphoid tissue **not** surrounded by a capsule / local response at mucosal surfaces
- protects submucosal areas of gastrointestinal tract / respiratory tract / genitourinary tract
- may be diffuse collections or organised follicles: tonsils / appendix / Peyer's patches

Soluble mediators of immunity include **Complement, Acute phase proteins (**C-Reactive protein (CRP) / ferritin / fibrinogen) and **Cytokines (**interferons/interleukins/colony stimulating factors/chemokines/others)

Complement

1. **classical pathway** — involves specific immune system
2. **alternative pathway** — occurs spontaneously
3. **lectin pathway** — similar to the classical pathway but activated independently of antibodies

Complement component	Biological effects
C3a, C5a	attracts neutrophils, causes mast cells to degranulate, leads to **inflammation**
C3b	attaches microorganism to phagocytic cells, enhances **phagocytosis**
C5 - C9	**attacks** cell membrane by punching a hole in it, kills cell by **lysis**

ANTIBODIES

An **immunogen** can elicit an immune response. An **antigen** leads to **anti**body **gen**eration and is usually a foreign protein, free or on a surface (complex carbohydrates are good antigens, nucleic acids and lipids are poor antigens). **Immunogenicity** is the capacity of a substance to stimulate an immune response

- **epitope** or **antigenic determinant** is the specific part of the antigen that reacts with the antibody
- every epitope is different (may be **linear** or **discontinuous)**
- **cross-reactivity** may occur if two epitopes are only a little bit different
- **haptens** are molecules too small to generate an immune response by themselves
- **carrier molecules** are immunogenic and can bind to a hapten to generate an immune response

Antibodies:

- highly specific globular proteins produced by mature B cells in response to antigen
- found in blood, tissue fluids, body secretions

Antibodies are symmetrical

- **two heavy chains** – five different types, only one type per antibody folded into domains
- **two light chains** – two different types, only one type per antibody
- chains linked by **disulphide bonds**
- diversity in antibodies is the result of gene rearrangement

ANTIBODY CLASS	PLASMA %	MOLEC WT	TYPE OF HEAVY CHAIN	HALF LIFE days
IgG	80%	150kD	γ	23
IgA	13%	160kD	α	5.5
IgM	6%	900kD	μ	5
IgD	1%	150kD	δ	2.8
IgE	0.002%	150kD	ε	2

Antibodies have two functions

- **Specificity**: neutralisation: binds soluble antigen in blood or extracellular (tissue) fluids
  blocks access to cells (viruses) or receptors (toxins)
  precipitation of antibody–antigen complexes

- **Biological effect** cell attachment: triggers phagocytosis
  complement activation: lyses some bacteria directly; assists opsonisation
  opsonisation: enhances phagocytosis

The end that has the biological effect does not vary within a class and is called
the **Fc** portion: **F**raction **c**onstant **CONSTANT DOMAIN**
The ends of the antibody that bind to antigen vary from antibody to antibody and are called
the **Fab** portion: **F**raction **a**ntibody **b**inding **VARIABLE DOMAIN**
The hinge region connects the Fc part to the Fab part and allows structural flexibility

Antibody-antigen interactions

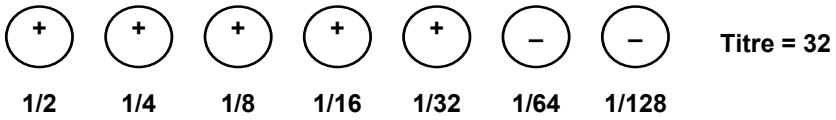
Serology is the technique of using **antibody-antigen reactions** to **detect, identify** and **measure** antibodies or antigens in serum. Antibodies form multiple reversible **non-covalent bonds** with antigen.

- **Affinity:** measure of strength of bond between antibody combining site and single epitope.
- **Avidity** is strength with which a multivalent antibody binds a multivalent antigen. It is greater than the sum of the individual affinities.
- **Specificity** is how exclusively an antibody recognises a particular antigen
- **Cross-reactivity** occurs when some of the epitopes of one antigen are shared by another antigen.

Serological screening: Is antibody or antigen present in the serum?

Quantitation: How much antibody or antigen is present in the serum?

Titration: serial (eg doubling or ten-fold) dilutions of serum are mixed with a known quantity of antigen.
The **titre** is the reciprocal (inverse) of the last dilution that is positive.
A **rising titre** of four-fold or more indicates an active response to an infectious or immunogenic agent.



Two essential aspects of all serological assays:
1. At least one of the reagents must be available in pure, detectable form in order to obtain quantitative information.
2. There must be a way of separating the **bound** fraction of the labelled reagent from the unbound, **free** fraction so that binding can be measured.

IMMUNOSEROLOGY

In vitro ways of making antigen–antibody reactions visible: Agglutination, Precipitation, Complement fixation, Radioimmunoassays, Immunofluorescence, Solid phase assays

Agglutination
- uses particles (tanned red blood cells, latex beads) attached to antigen or antibody

Precipitation (immune complexes precipitate out of solution)
- immunodiffusion – Ab, Ag diffuse out in gel, form visible line at Z of E
- radial immunodiffusion – quantitative form of above. Diameter of ring indicates amount
- immunoelectrophoresis – uses electric current. Separates antigen by mol wt & charge
- countercurrent electrophoresis – as above but Ab and Ag opposite charge so move towards each other
- rocket electrophoresis – quantitative form. Ab immobile in gel. Height of peak indicates quantity of Ag.

Technique	Advantages	Disadvantages
Capillary tube precipitation	easy to set up	insensitive reaction time long semiquantitative
Immunodiffusion (double diffusion)	can detect similarities among antigens	semiquantitative reaction time long
Radial Immunodiffusion	sensitive quantitative	reaction time long (18–48 hours)
Immunoelectrophoresis	sensitive less problem with antigen / antibody ratio	semiquantitative
Counterimmunoelectrophoresis (CIEP)	more rapid reaction than other tests	semiquantitative
Rocket immunodiffusion (Laurell)	rapid reaction time quantitative	can only detect one antigen per plate

Complement Fixation

Antibody–antigen complexes can activate complement and 'fix' it. Fixed complement can lyse cells.

- If patient's serum **does** have antibodies to antigen, Ab–Ag complexes will form. Add complement. The Ab–Ag complexes will activate it. All the complement will be used up. Add 'indicator cells' (red cells coated with a different antibody). Nothing will happen. The red cells will sink to bottom of well. **Positive result: red cell button at bottom of well.**
- If a patient's serum **does not** have antibodies to a suspected antigen, no Ab–Ag complexes will form. Add complement. There is nothing to activate it. There will still be complement available. Add indicator cells. They are coated with antibody (stuck to antigen on their surface). These Ab–Ag complexes activate the complement. The cells lyse. Haemolysis visible. **Negative result: haemolysis gives red colour through well.**

Labelling Techniques

If antigen-antibody complexes do not agglutinate or precipitate, **labelling** techniques make them visible. A label may be **directly** attached to a specific antibody or antigen or **indirectly**, using labelled anti-immunoglobulin antibodies. This means that the one labelled compound can be used in many different assays even when they are detecting different antibodies. It is also useful for **amplifying** a reaction.

Radioimmunoassays

- Radioactive isotopes attached to molecules of antigen
- Antigen mixed with serum, separate bound Ab from unbound, measure radioactivity in a γ counter
- Advantages: sensitive; detects trace amounts of Ab; many tests in a short time
- Disadvantages: radioactive waste, short shelf life, hazard to workers
- Can also use labelled antibody in a **competitive binding assay**

Immunofluorescence

- label consists of fluorescent compound **(fluorochrome)** which emits light when exposed (excited) by ultraviolet illumination,eg **fluorescein isothiocyanate (FITC),** tetramethyl rhodamine isothiocyanate (TRITC), fluorescence is viewed under a specially constructed microscope.
- **Direct immunofluorescence** involves only ONE step. Labelled antibody is added to the test tissue to see where antibody will bind to antigen *in situ*. That is, we view *direct* evidence of Ab-Ag binding.
- **Indirect immunofluorescence** involves TWO steps. Patient antibody (in serum) is added to test tissue then a labelled 'anti-antibody' is added. We view evidence of Ab-Ag binding only *indirectly*.

Solid phase immunoassays (enzyme immunoassays)

- Wells coated with specific antigen
- Add standards, controls and patient samples in duplicate
- Incubate 15 - 30'. Wash wells
- Add enzyme-conjugated anti-serum (e.g. anti-human IgG). Incubate, wash.
- Add substrate. Enzyme cleaves it to form colour. DO NOT WASH!
- Add acid stop solution to fix colour
- Automatic plate-reader measures OD of wells at suitable wavelength
- Check standard curve, confirm controls within range, calculate patient samples

- Enzymes used to label second antibody include alkaline phosphatase and horse radish peroxidase.
- **Direct assay:** Ab-Ag complex can be detected immediately if second component already labelled.
- **Indirect assay** (more common) also called the **sandwich** technique.
- **Immunohistochemistry:** Enzyme-labelled antibodies can also be used on tissue sections to detect particular microscopic features. The tissue is incubated with the substrate and if the enzyme is present (attached to an Ab-Ag complex) there will be a visible colour change.
- **Immunoblotting** (also called Western Blotting): Analytical separation gel, transfer separated proteins to nitrocellulose membrane (blotting). Antibodies can bind to the immobilised antigen and be visualised by one of the labelling techniques above.

Flow Cytometry

- Lymphocytes can be distinguished by different proteins on their cell surfaces (CD markers)
- Monoclonal Ab to these CD markers labelled with fluorescent dyes absorb laser light energy, emit light of a different colour. *flow cytometry* because it involves the measurement (*metry*) of single cells (*cyto*)as they *flow* past detectors in a stream of liquid (isotonic saline) broken up into individual droplets by vibration. Beam of **laser light** projected through stream of cells. When it strikes the cells, it is scattered. Detectors called photomultiplier tubes (**PMT**s) capture the signals and convert them electronically for computer analysis.
- Many properties of a cell can be measured at once, at a rate of over 1000 cells a second. **Forward Scatter:** light from the laser beam is deflected by the **surface** of the cell. The detector converts this light into a voltage pulse proportional to **cell size**. **Side scatter:** light is deflected off **internal structures** or **granules** of the cell, proportional to **cell complexity**. Cells can also be **sorted**

VACCINATION

vaccination: giving vaccine or toxoid
immunisation: process of inducing or providing immunity
immunogenicity: the capacity to induce an immune response

Factors affecting immunogenicity

- foreignness
- size
- chemical composition and complexity
- three dimensional structure of the antigen
- genetics
- route, dose and timing of administration

Recognition of antigen

by B cells

- recognise / bind free antigen in solution
- antigens must be on 'outside' of molecule
- terminal side chains of polysaccharides / hydrophilic parts of protein molecules

by T cells

- antigens need to have been 'processed' / associated with MHC molecule on APC surface
- denatured linear hydrophobic areas of proteins
- polysaccharides not known to bind or activate T cells

Passive immunisation

- injecting ready-made antibodies formed in humans or unrelated animals
- immediate protection
- dose-related
- short-lived
- IgG most useful

Active immunisation

Inactivated (killed) vaccines

- protect by stimulating antibody production
- **primary response** –first injection of vaccine, produces mainly IgM
- **secondary response** – accelerated production of antibodies rising to a higher titre and mainly IgG
- immunity may last for months or years
- a 'booster' dose of vaccine will reinforce immunity

Live attenuated vaccines

- attenuated – thinned out or weakened
- induce protective antibodies and cell mediated immunity
- full, long-lasting immunity after one dose (Oral Polio Virus 3 doses)

Adjuvants [AD-ju-**VANT** = **AD-VANT**-age] are agents that are immunogenic but cannot evoke a response by themselves. They potentiate the immune response (make it stronger and more efficient)

Other uses for vaccines

- Veterinary vaccines
- Travel vaccination
- Special medical and occupational contexts
- Emergency passive immunisation

Monoclonal antibodies: are homogeneous populations of antibody molecules derived from a single antibody-producing cell in which all antibodies are identical and of the same specificity for a given epitope. The technique depends on the following characteristics of the cell types used in their production.

- Malignant plasma cells:
  - are immortal and can be cultured continuously for years
  - are unable to secrete immunoglobulin themselves
  - lack the enzyme hypoxanthine phosphoribosyl transferase (HPRT)
  - die in the presence of aminopterin
- Antibody-producing cells:
  - come from the spleen of an animal (usually mouse) immunised with the relevant antigen
  - die naturally after a couple of days in culture
  - contain HPRT
  - can survive in medium containing hypoxanthine, aminopterin and thymidine (HAT)

The malignant plasma cells are fused with antibody-producing spleen cells using PEG or inactivated Sendai virus. This produces a **hybridoma** that

- can be cultured indefinitely
- can produce antibody
- does contain HPRT
- can survive in HAT by using HPRT to switch to the purine salvage pathway

The hybridoma cells producing the desired antibody are selected and clones from a single cell then synthesise antibody of the desired specificity for as long as necessary (decades).

Monoclonal antibodies are used widely in diagnostic tests and research.
There are some disadvantages in using mice for human therapy though.
Genetic engineering is developing ways to produce monoclonal antibodies that do not rely entirely on mice cells. For example, chimeras are formed whose molecules consist of a human immunoglobulin constant (Fc) region and a mouse immunoglobulin variable region. This reduces the risk of humans developing anti-mouse immunoglobulins.

TRANSPLANTATION AND THERAPY

Autograft (autologous):	same individual	– does *not* induce immune response
Isograft (syngeneic):	genetically identical	– does *not* induce immune response
Allograft (allogeneic):	*not* genetically identical	– *does* induce immune response; may be rejected
Xenograft (xenogeneic):	different species	– *does* induce immune response; usually rejected

Histocompatibility

MHC Class II antigens are the most important influence on transplant rejection or survival

- Major Histocompatibility gene complex (MHC) most important factor in transplant immune response
- Codes for MHC Class I and Class II molecules. These are the target antigens in a transplant.
- CD8+ T cells in *recipient* target MHC Class I molecules in the transplant; CD4+ T cells target Class II

In humans, the MHC is known as HLA, or Human Leucocyte Antigens.

- Human MHC Class I gene loci: HLA-A HLA-B HLA-C
- Human MHC Class II gene loci: HLA-DP HLA-DQ HLA-DR

Testing for Histocompatibility (Tissue Typing)

- Matching for all known HLA antigens is practically impossible
- Good graft survival occurs when donor and recipient share MHC Class II antigens (esp. HLA-DR)
- These are the antigens that directly activate recipient T_H cells

Assay types

- Serologic tissue typing
- PCR genotyping
- Mixed Lymphocyte Reaction (including one-way MLR)
- Microtitre antibody assay

Transplant Rejection

- **Hyperacute rejection**
- **Acute rejection**
  - First set rejection (a primary immune response)
  - Second set rejection (a secondary immune response) leads to **accelerated rejection** also called '**white graft rejection**'
- **Chronic rejection**

Type of rejection	Time taken	Cause / mechanism
Hyperacute	minutes to hours	pre-formed antibodies and complement (Type II hypersensitivity mechanism)
Acute	days to weeks	primary activation and clonal expansion of T_H cells and induction of macrophages (Type IV hypersensitivity mechanism)
Chronic	months to years	immune complexes (Type III hypersensitivity); slow Type IV; recurrence of original disease condition

Prolonging a transplant and improving survival

- Clinical immunosuppression: non-specific suppression of both cell-mediated and humoral immunity.
- Antiproliferative agents
- Lymphocyte depletion
- Most immunosuppressive therapy also leaves patient highly susceptible to infection and cancer

Graft versus Host Disease

- competent immune cells from donor attack the patient in response to HLA antigenic differences
- affects cells with high turnover
- serious effects include splenomegaly, liver damage, autoimmune haemolytic anaemia.
- prevented by careful tissue typing, removing T cells from graft pre transplant, immunosuppressive drugs

Intravenous gammaglobulin

- Replacement IgG therapy for patients with reduced or absent levels of immunoglobulins

IMMUNODEFICIENCY

Primary immunodeficiency: diseases present at birth. The defect may be in:

- the phagocytic system
- the B lymphocyte system
- the T lymphocyte system
- the complement system

Many primary immunodeficiency diseases are **genetic**. Some are inherited; some are single gene defects and do not appear to be inherited. Patients usually have increased susceptibility to infection. Some have non-infectious features (eg autoimmune disease, gastrointestinal disease or defective response to injury).

MAJOR PRIMARY IMMUNODEFICIENCY DISORDERS

Phagocytic system

- Chronic granulomatous disease
- Chediak-Higashi syndrome
- Myeloperoxidase (MPO) deficiency
- lazy leucocyte syndrome
- LAD (leucocyte adhesion deficiency)

B cell system

- (Bruton's) X-linked agammaglobulinaemia
- selective IgA deficiency
- common variable immunodeficiency

T cell system

- DiGeorge anomaly
- Wiskott-Aldrich syndrome
- ataxia-telangiectasia

Complement system

- defects in control proteins: C3b inactivator deficiency
  paroxysmal nocturnal haemoglobinuria
  C1 esterase inhibitor deficiency (hereditary angioedema)
- defects/deficiencies in proteins: C3
  C1, C4, C2
  C5-C9

Warning Signs of Primary Immunodeficiency include

- Multiple infections requiring antibiotics / hospitalisation
- Pneumonia more than twice
- Failure to thrive
- Abscesses, thrush, deep infections
- Family history of Primary Immune Deficiency

Secondary (acquired) immunodeficiency

- immune suppression
- viral causes of immunodeficiency

AIDS Acquired Immune Deficiency Syndrome
Primary infection with HIV, prolonged latent period,
Symptoms (minor), ineffective immunity -> opportunistic infections (chronic - fatal)
Diagnosis:Enzyme immunoassay (Ab to HIV virus), viral RNA serology,
Monitoring: Viral load, T cell counts (CD4: CD8 ratios)

HYPERSENSITIVITY

Hypersensitivity – excessive or inappropriate response to antigenic stimulus

- extreme forms of the **normal** immune processes
- classified by how they damage tissue.

Four categories:

- **Type I** Immediate
- **Type II** Antibody Mediated
- **Type III** Immune Complex Disease
- **Type IV** Delayed Type (Tcell Mediated)

Type I – Immediate (acute) systemic (anaphylactic) or localised (eg urticaria)

Atopy: the genetic predisposition to produce specific IgE to common environmental allergens
Allergy: detrimental immune-mediated IgE response to common environmental antigens that are otherwise harmless. **ALLERGENS = Allergy antigens** that stimulate this large production of IgE

INFLAMMATORY MEDIATORS of ACUTE HYPERSENSITIVITY REACTION

RESPONSE	SUBSTANCE	ACTIONS
pre-formed substances released from mast cell and basophil granules		
INSTANT	histamine	abundant fast acting smooth muscle contraction vasodilation increased vascular permeability
	eosinophil and neutrophil chemotactic factors	attract more eosinophils and neutrophils
	platelet activating factor	forms microthrombi (tiny clots)
	tryptase	proteolysis
products of arachidonic acid metabolic pathway		
SLOWER	leukotrienes	inflammatory response: vasoactive bronchoconstrictive chemotactic
LATE	prostaglandins thromboxanes	late inflammatory response: vasodilation bronchoconstrictive oedema, mucus secretion

Type II – Antibody mediated

- caused by IgG or IgM antibodies produced against cell surface or extracellular antigens
- antibodies damage cells and tissues by activating complement or binding and activating cells that carry Fc receptors
- pathology depends on which molecules or tissues are targeted by the antibodies
- when an antibody binds to an epitope on a cell, several mechanisms can destroy the cell:
  - engulfed by phagocytes
  - complement activation and cell lysis by membrane attack complex (MAC)
  - large cells or cells in tissue that can't be engulfed can be damaged exocytosis

Type III – Immune complex disease

- immune complexes normally removed by mononuclear phagocyte system after complement activation
- immune complexes can form in circulation or at localised site
- complement normally helps disrupt Ab-Ag bonds and keeps immune complexes soluble
- complement deficiency leads to large complexes forming
- Severity of reaction directly relates to ratio of antibody:antigen: worst at ZONE of EQUIVALENCE

Three categories of immune complex disease

CAUSE	ANTIGEN	Site of Complex Deposition
persistent infection	microbial antigen eg malaria, leprosy, viral hepatitis, *Staph*. endocarditis	infected organ, kidneys
autoimmunity	self antigen eg RA, SLE, polymyositis	kidneys, joints, arteries, skin
inhaled antigens	mould, plant or animal antigen eg Farmer's lung, pigeon fancier's lung	lung

Type IV – Delayed Type (Tcell Mediated)

- specifically provoked
- evolves slowly (24-48 hr; maximum 48-72 hours in most cases)
- mixed cellular reaction mainly involving lymphocytes and macrophages
- caused by sensitised lymphoid cells

Delayed Type (Tcell Mediated) reactions

Example	reaction time	clinical appearance	cells	antigen
Contact	48 - 72 hr	eczema	lymphocytes, later macrophages	epidermal eg nickel
Tuberculin	48 - 72 hr	local hardening	lymphocytes, monocytes, macrophages	intradermal eg tuberculin
Granuloma	21 - 28 days	hardening of skin or lung	macrophages, epithelioid cells, giant cells, fibroblasts	persistent Ag / Ab complexes or inert material eg talc

The granulomatous reaction is a BALANCE between trying to contain the spread of the immunogenic / infectious agent, and the damage done by that protective inflammatory process

AUTOIMMUNITY

Autoimmunity: immune system reacts against own cells and tissues. Failure of self tolerance.
Immunological tolerance: unresponsiveness to a particular antigen. Induced by prior exposure.
Self reactivity: normally prevented during development. Lymphocytes deleted that recognise self.
Autoimmune diseases: spectrum from organ-specific to systemic disease. Can overlap.
Genetic factors including HLA type have an important role in autoimmune diseases
Immune complexes are often associated with systemic autoimmune disease (see Type III hypersensitivity)
Possible mechanisms for autoimmunity

- loss of suppression of inappropriate reaction (breakdown in self tolerance)
- cross-reactivity with foreign antigens
- exposure of hidden epitopes
- polyclonal activation
- aberrant antigen presentation

Diagnosis and disease monitoring uses assays for autoantibodies.

Treatment is either by metabolic control for organ-specific disease
or anti-inflammatory or immunosuppressive drugs for systemic conditions

Some examples of Auto Antibody Tests	
Test	**Disease Association**
Antinuclear antibody (ANA, ANF)	Connective Tissue Disease
Anti-ds DNA	Systemic Lupus Erythematosus
Anti-extractable nuclear antigen (ENA) comprising:-	
-Sm	-SLE
-RNP	-Mixed Connective Tissue Disease (MCTD)
-SS-A (Ro)	-Sjogren's Syndrome, SLE
-SS-B (La)	-Sjogren's Syndrome, SLE
-Jol	-Polymyositis
-Scl70 (Topol)	-Scleroderma, diffuse variant (systemic sclerosis)
-PCNA	-SLE
Anti-cardiolipin antibodies	Anti-phospholipid Syndrome, SLE
Anti-gliadin antibodies, Anti-endomysial antibody	Coeliac Disease
Anti-mitochondrial antibody	Primary Biliary Cirrhosis
Anti-smooth muscle antibody	Autoimmune Chronic Active Hepatitis
Anti-parietal cell antibody	Pernicious Anaemia
Anti-intrinsic factor antibody	Pernicious Anaemia
Anti-thyroglobulin antibodies	Hashimoto's thyroiditis
Anti-skin basement membrane antibodies	Bullous pemphigoid

IMMUNITY TO MICROBES

Immunity to Bacteria

The immune system responds to bacterial infection in different ways related to the structure of the organism (which is, of course, designed to *resist* the immune system and enhance infection). There are four main groups of bacteria based on **cell wall structure**. All types have an **inner cell membrane** and a wall of **peptidoglycan**. In addition, the following features are characteristic:

	Gram-positive	**Gram-negative**	**mycobacteria**	**spirochaetes**
capsule or microcapsule	√	√	√	—
fimbriae or flagella	√	√	—	—
lipid component	lipoteichoic acid	LPS in outer lipid bilayer, lipoprotein	glycolipids, lipoarabino-mannan	lipoprotein
other characteristics		mannose-binding lectin	mycolic acids, arabinogalactan	peptidoglycan (murein)
Examples	*Staphylococcus aureus*	*Escherichia coli, Salmonella sp.*	*Mycobacterium leprae*	*Treponema, Borrelia, Leptospira*

- The first line of immune defence is innate, non-specific and relies on barriers
- The second line of immune defence (also innate & non-specific) recognises common bacterial elements
- Specific immune responses to bacteria are antibody-mediated
- Phagocytosis is the main way that bacteria are killed. Phagocytes have several methods of killing
  1. Oxygen dependent mechanisms
  2. oxygen independent mechanisms
  3. cationic proteins
  4. acidification

Bacterial strategies to evade immune responses are multiple and varied

- Bacteria can avoid **complement** mediated damage
- Bacteria can avoid **phagocytosis**
- Bacteria can avoid **antibody damage**

Immunity to Fungi

There are four categories of (human) fungal infections

- superficial mycoses
- subcutaneous mycoses
- respiratory mycoses
- candidiasis

Immune response to fungal infection is similar to bacterial infections, with a cell-mediated component
A functional immune system appears to confine fungi to their normal commensal sites in the body
Not as much is known about fungal immunity as about immune responses to other types of organisms.

Immunity to Viruses

Viruses are obligate intracellular organisms and can cause acute or chronic infection
Immune response to virus infection

- The first line of immune defence is innate and involves interferons, and NK cells
- This influences early stages of infection and delays the spread of the virus
- The second line of immune defence against viruses involves T and B lymphocytes (including antibody).
- Antibody neutralises viral infectivity to prevent tissue spread and T-cytotoxic cells identify cells infected with virus and destroy them to arrest replication cycle

Antiviral effects of antibody

Target	Agent	Mechanism
free virus	antibody alone	blocks binding to cell blocks entry in to cell blocks uncoating of virus
	antibody + complement	damages virus envelope blockade of virus receptor
virus-infected cells	antibody + complement	lysis of infected cell opsonisation of coated virus or infected cells for phagocytosis
	antibody bound to infected cells	antibody-dependent cell-mediated cytotoxicity by NK cells, macrophages and neutrophils

Viral strategies to evade immune responses

- avoid recognition
- disrupt immune function

Consequences of viral infection and immune response to viruses

- immune complexes
- infected immune cells
- macrophage-enhanced viral infectivity
- hyperactivated complement system

Immunity to Parasites

The worldwide parasite burden has an enormous effect on health, education and economic development
Most parasitic infections are chronic Most parasites are host specific, though some can cross-infect

	example	location	vector
protozoa	*Entamoeba histolytica*	liver	
	Trypanosoma	blood stream	tsetse flies
	Plasmodium	blood stream	mosquitoes
	Leishmania	macrophages	sandflies
	Toxoplasma gondii	macrophages	
	Trypanosoma cruzi	muscle (esp heart)	bed bugs
worms (helminths)	cestodes (tapeworms)	gut	
	hookworms (*Ascaria*)	lung, gut	
	nematodes (roundworms)	lung	
	flukes *Schistosoma*	blood vessels, bladder	snails
	filaria *Wuchereria bancrofti*	lymphatics	
	Onchocerca volvulus	skin, eyes	

Eosinophilia and increased [IgE] are signs of immune response to parasitic worms

The first line of immune defence is innate and involves neutrophils, macrophages and eosinophils
The second line of immune defence involves specific cell-mediated responses.
The immune response to parasites can be more damaging than the parasites (involving organomegaly, granulomas, lymphocyte hyper-response, immune complex deposition, anaphylactic shock, autoimmune effects)

Parasite strategies to evade immune response

- Parasites withstand immune attack
- Parasites resist destruction by complement
- Parasites avoid destruction within macrophages
- Parasites disguise themselves
- Parasites hide
- Parasites interfere with immune function