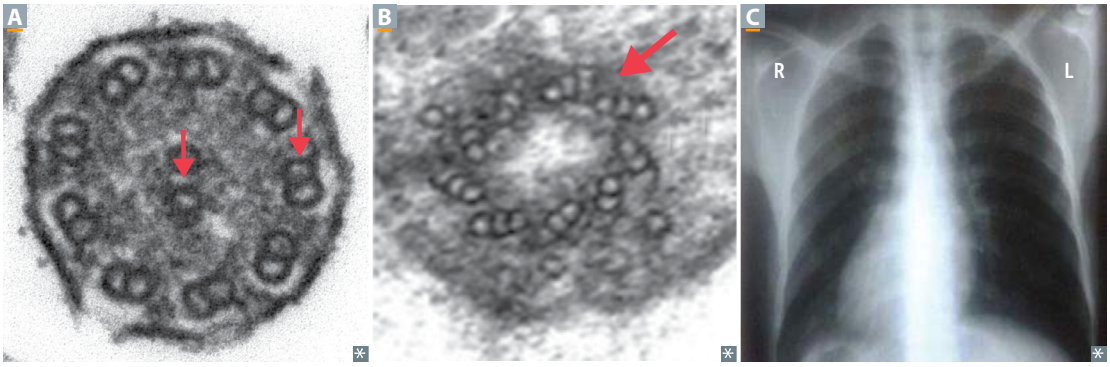
Cilia structure

9 doublet + 2 singlet arrangement of microtubules (arrows in A).
Basal body (base of cilium below cell membrane) consists of 9 microtubule triplets (arrow in B) with no central microtubules.
Axonemal dynein—ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.

Kartagener syndrome (1° ciliary dyskinesia)—immotile cilia due to a dynein arm defect. Results in ↓ male and female fertility due to immotile sperm and dysfunctional fallopian tube cilia, respectively; ↑ risk of ectopic pregnancy. Can cause bronchiectasis, recurrent sinusitis, chronic ear infections, conductive hearing loss, and situs inversus (eg, dextrocardia on CXR C).

C = New Image

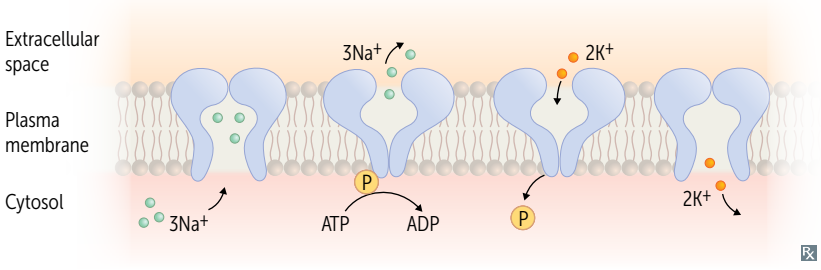


Sodium-potassium pump

Na^+-K^+ ATPase is located in the plasma membrane with ATP site on cytosolic side. For each ATP consumed, $3Na^+$ go out of the cell (pump phosphorylated) and $2K^+$ come into the cell (pump dephosphorylated).
Plasma membrane is an asymmetric lipid bilayer containing cholesterol, phospholipids, sphingolipids, glycolipids, and proteins.

Pumpkin = pump K^+ in.
Ouabain inhibits by binding to K^+ site.
Cardiac glycosides (digoxin and digitoxin) directly inhibit the Na^+-K^+ ATPase, which leads to indirect inhibition of Na^+/Ca^{2+} exchange → ↑ $[Ca^{2+}]_i$ → ↑ cardiac contractility.

Revised Figure



Helper T cells

Th1 cell	Th2 cell
Secretes IFN-γ and IL-2	Secretes IL-4, IL-5, IL-6, IL-10, IL-13
Activates macrophages and cytotoxic T cells	Recruits eosinophils for parasite defense and promotes IgE production by B cells
Differentiation induced by IFN-γ and IL-12	Differentiation induced by IL-2 and IL-4
Inhibited by IL-4 and IL-10 (from Th2 cell)	Inhibited by IFN-γ (from Th1 cell)

Macrophage-lymphocyte interaction—dendritic cells, macrophages, and other APCs release IL-12, which stimulates T cells to differentiate into Th1 cells. Th1 cells release IFN-γ to stimulate macrophages.

Helper T cells have CD4, which binds to MHC II on APCs.

Cytotoxic T cells

Kill virus-infected, neoplastic, and donor graft cells by inducing apoptosis.

Release cytotoxic granules containing preformed proteins (eg, perforin, granzyme B).

Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.

Regulatory T cells

Help maintain specific immune tolerance by suppressing CD4 and CD8 T-cell effector functions.

Identified by expression of CD3, CD4, CD25, and FOXP3.

Activated regulatory T cells (Tregs) produce anti-inflammatory cytokines (eg, IL-10, TGF-β).

IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome—genetic deficiency of FOXP3 → autoimmunity. Characterized by enteropathy, endocrinopathy, nail dystrophy, dermatitis, and/or other autoimmune dermatologic conditions. Associated with diabetes in male infants.

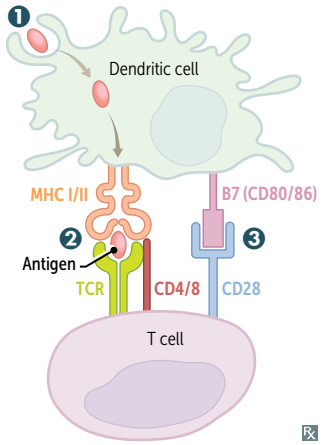
T- and B-cell activation

APCs: B cells, dendritic cells, Langerhans cells, macrophages

Two signals are required for T-cell activation, B-cell activation, and class switching.

T-cell activation

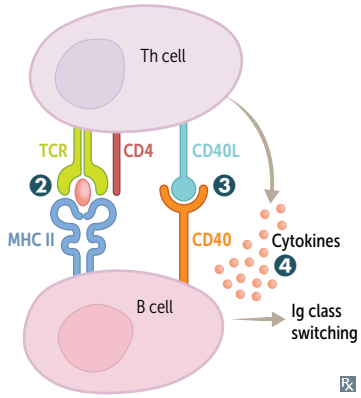
1. Dendritic cell (specialized APC) samples antigen, processes antigen, and migrates to the draining lymph node.
2. T-cell activation (signal 1): antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Endogenous or cross-presented antigen is presented on MHC I to Tc (CD8+) cell.
3. Proliferation and survival (signal 2): costimulatory signal via interaction of B7 protein on dendritic cell (CD80/86) and CD28 on naïve T cell.
4. Th cell activates and produces cytokines. Tc cell activates and is able to recognize and kill virus-infected cell.



Swapped Figure

B-cell activation and class switching

1. Th-cell activation as above.
2. B-cell receptor–mediated endocytosis; foreign antigen is presented on MHC II and recognized by TCR on Th cell.
3. CD40 receptor on B cell binds CD40 ligand (CD40L) on Th cell.
4. Th cell secretes cytokines that determine Ig class switching of B cell. B cell activates and undergoes class switching, affinity maturation, and antibody production.

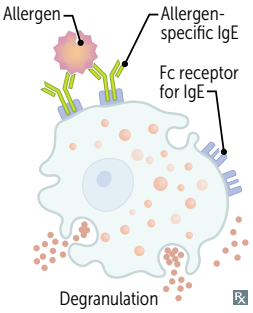


Swapped Figure

Hypersensitivity types Four types: **A**naphylactic and **A**topic (type I), **C**ytotoxic (antibody mediated, type II), **I**mmune complex (type III), **D**elayed (cell mediated, type IV) (**ACID**).

Type I

Swapped Figure

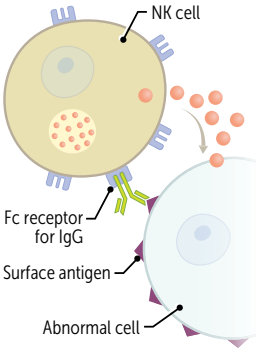


Anaphylactic and atopic—free antigen cross-links IgE on presensitized mast cells and basophils, triggering immediate release of vasoactive amines that act at postcapillary venules (ie, histamine). Reaction develops rapidly after antigen exposure because of preformed antibody. Delayed phase results from mast cells and basophils releasing cytokines that induce cellular inflammation.

First (type) and **F**ast (anaphylaxis).
Types I, II, and III are all antibody mediated.
Test: skin test or blood test (ELISA) for allergen-specific IgE.
Example:
- Anaphylaxis (eg, food, drug, or bee sting allergies)

Type II

Revised Figure



Antibody-dependent cellular cytotoxicity

Antibodies bind to cell-surface antigens → cellular destruction, inflammation, and cellular dysfunction.

Cellular destruction: cell is opsonized (coated) by antibodies, leading to either:
- Phagocytosis and/or activation of complement system.
- NK cell killing (antibody-dependent cellular cytotoxicity).

Inflammation—binding of antibodies to cell surfaces → activation of complement system and Fc receptor-mediated inflammation.

Cellular dysfunction—antibodies bind to cell surface receptors → abnormal blockade or activation of downstream process.

Direct Coombs test—detects antibodies attached **direct**ly to the RBC surface.
Indirect Coombs test—detects presence of unbound antibodies in the serum

Examples:
- Autoimmune-hemolytic anemia
- Immune thrombocytopenic purpura
- Transfusion reactions
- Hemolytic disease of the newborn

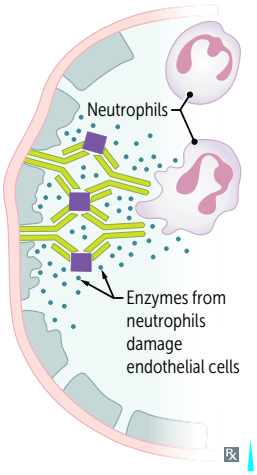
Examples:
- Goodpasture syndrome
- Rheumatic fever
- Hyperacute transplant rejection

Examples:
- Myasthenia gravis
- Graves disease

Hypersensitivity types *(continued)*

Type III

Revised Figure



Immune complex—antigen-antibody (IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes.
Can be associated with vasculitis and systemic manifestations.

In type III reaction, imagine an immune complex as 3 things stuck together: antigen-antibody-complement.
Examples:
- SLE
- Polyarteritis nodosa
- Poststreptococcal glomerulonephritis

Serum sickness—an immune complex disease in which antibodies to foreign proteins are produced (takes 5 days). Immune complexes form and are deposited in membranes, where they fix complement (leads to tissue damage). More common than Arthus reaction.

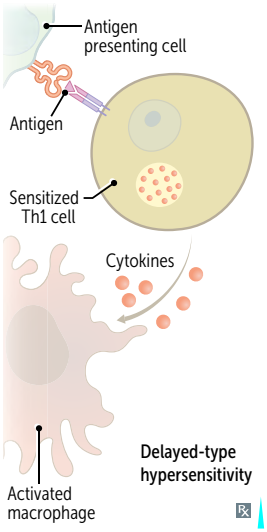
Most serum sickness is now caused by drugs (not serum) acting as haptens. Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 5–10 days after antigen exposure.

Arthus reaction—a local subacute antibody-mediated hypersensitivity reaction. Intradermal injection of antigen into a presensitized (has circulating IgG) individual leads to immune complex formation in the skin. Characterized by edema, necrosis, and activation of complement.

Antigen-antibody complexes cause the Arthus reaction.

Type IV

Swapped Figure



Two mechanisms, each involving T cells:

1. Direct cell cytotoxicity: CD8+ cytotoxic T cells kill targeted cells.
2. Delayed-type hypersensitivity: sensitized CD4+ helper T cells encounter antigen and release cytokines → inflammation and macrophage activation.

Response does not involve antibodies (vs types I, II, and III).
Example:
- Type 1 diabetes mellitus

Examples:
- Contact dermatitis (eg, poison ivy, nickel allergy)
- Graft-versus-host disease

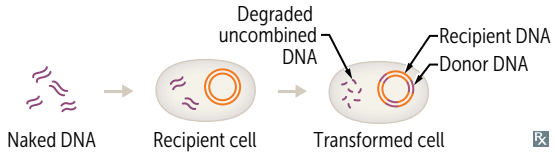
Tests: PPD, patch test.
4T's: T cells, Transplant rejections, TB skin tests, Touching (contact dermatitis).

Fourth (type) and last (delayed).

Bacterial genetics

Transformation

Competent bacteria are able to bind and import short pieces of environmental naked bacterial chromosomal DNA (from bacterial cell lysis). The transfer and expression of newly transferred genes is called transformation. A feature of many bacteria, especially *S pneumoniae*, *H influenzae* type B, and *Neisseria* (SHiN). Any DNA can be used. Adding deoxyribonuclease to environment will degrade naked DNA in medium → no transformation seen.

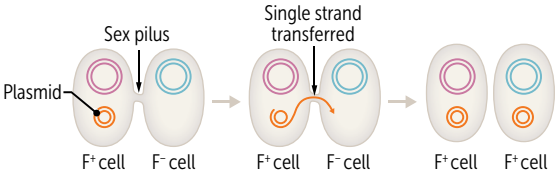


New Figure

Conjugation

$F^+ \times F^-$

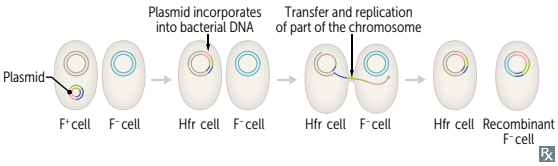
F^+ plasmid contains genes required for sex pilus and conjugation. Bacteria without this plasmid are termed F^-. Sex pilus on F^+ bacterium contacts F^- bacterium. A single strand of plasmid DNA is transferred across the conjugal bridge ("mating bridge"). No transfer of chromosomal DNA.



New Figure

Hfr × F^-

F^+ plasmid can become incorporated into bacterial chromosomal DNA, termed high-frequency recombination (Hfr) cell. Transfer of leading part of plasmid and a few flanking chromosomal genes. High-frequency recombination may integrate some of those bacterial genes. The recipient cell remains F^- but now may have new bacterial genes.

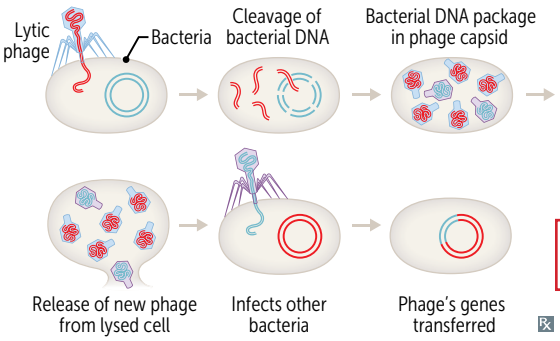


New Figure

Transduction

Generalized

A "packaging" event. Lytic phage infects bacterium, leading to cleavage of bacterial DNA. Parts of bacterial chromosomal DNA may become packaged in phage capsid. Phage infects another bacterium, transferring these genes.

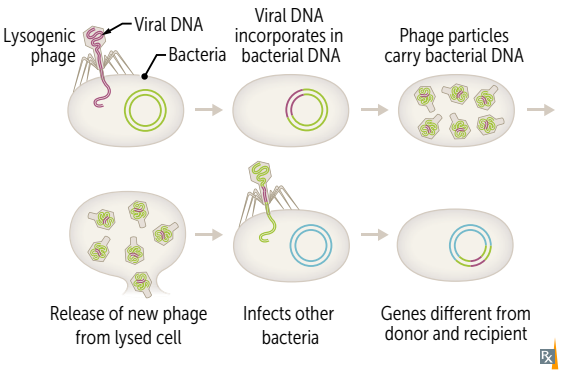


New Figure
Revised Figure

Specialized

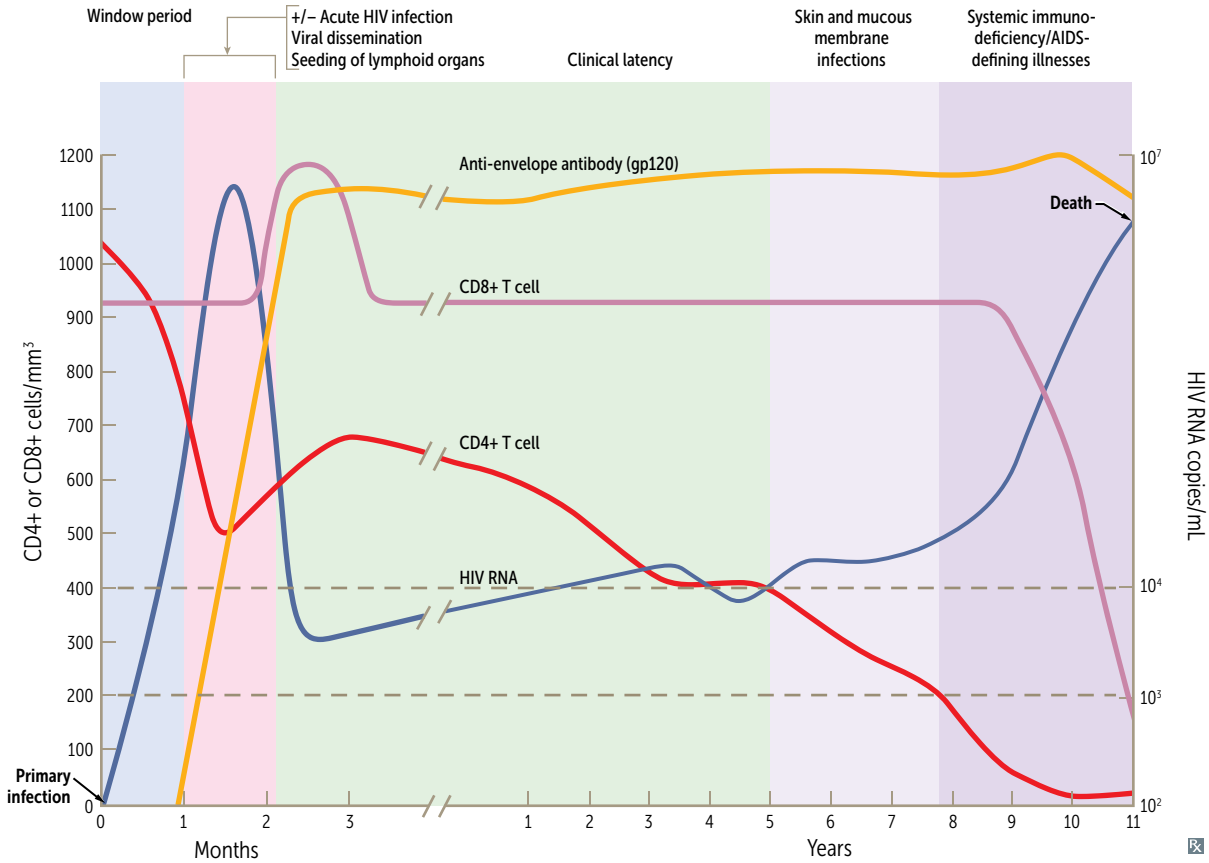
An "excision" event. Lysogenic phage infects bacterium; viral DNA incorporates into bacterial chromosome. When phage DNA is excised, flanking bacterial genes may be excised with it. DNA is packaged into phage capsid and can infect another bacterium.

Genes for the following 5 bacterial toxins are encoded in a lysogenic phage (ABCD'S): Group A strep erythrogenic toxin, Botulinum toxin, Cholera toxin, Diphtheria toxin, Shiga toxin.



Time course of untreated HIV infection

Revised Figure



Dashed lines on CD4+ count axis indicate moderate immunocompromise (< 400 CD4+ cells/mm^3) and when AIDS-defining illnesses emerge (< 200 CD4+ cells/mm^3).

Most patients who do not receive treatment eventually die of complications of HIV infection.

Four stages of untreated infection:

1. Flu-like (acute)
2. Feeling fine (latent)
3. Falling count
4. Final crisis

During clinical latency phase, virus replicates in lymph nodes

▸ ENDOCRINE—PHARMACOLOGY

Diabetes mellitus management

Treatment strategies:

- Type 1 DM—dietary modifications, insulin replacement
- Type 2 DM—dietary modifications and exercise for weight loss; oral agents, non-insulin injectables, insulin replacement
- Gestational DM (GDM)—dietary modifications, exercise, insulin replacement if lifestyle modification fails

DRUG CLASSES	CLINICAL USE	ACTION	RISKS/CONCERNS
Insulin preparations			
Insulin, rapid acting Lispro, aspart, glulisine	Type 1 DM, type 2 DM, GDM (postprandial glucose control).	Binds insulin receptor (tyrosine kinase activity). Liver: ↑ glucose stored as glycogen. Muscle: ↑ glycogen, protein synthesis; ↑ K^+ uptake. Fat: ↑ TG storage.	Hypoglycemia, lipodystrophy, rare hypersensitivity reactions.
Insulin, short acting Regular	Type 1 DM, type 2 DM, GDM, DKA (IV), hyperkalemia (+ glucose), stress hyperglycemia.		
Insulin, intermediate acting NPH	Type 1 DM, type 2 DM, GDM.		
Insulin, long acting Detemir, glargine	Type 1 DM, type 2 DM, GDM (basal glucose control).		
Oral drugs			
Biguanides Metformin	Oral. First-line therapy in type 2 DM, causes modest weight loss. Can be used in patients without islet function.	Inhibit hepatic gluconeogenesis and the action of glucagon. ↓ gluconeogenesis, ↑ glycolysis, ↑ peripheral glucose uptake (↑ insulin sensitivity).	GI upset; most serious adverse effect is lactic acidosis (thus contraindicated in renal insufficiency).
Sulfonylureas First generation: chlorpropamide, tolbutamide Second generation: glimepiride, glipizide, glyburide	Stimulate release of endogenous insulin in type 2 DM. Require some islet function, so useless in type 1 DM.	Close K^+ channel in β cell membrane → cell depolarizes → insulin release via ↑ Ca^{2+} influx.	Risk of hypoglycemia ↑ in renal failure, weight gain. First generation: disulfiram-like effects. Second generation: hypoglycemia.
Glitazones/ thiazolidinediones Pioglitazone, rosiglitazone	Used as monotherapy in type 2 DM or combined with above agents. Safe to use in renal impairment.	↑ insulin sensitivity in peripheral tissue. Binds to PPAR-γ nuclear transcription regulator.[a]	Weight gain, edema, HF, ↑ risk of fractures.

Tamoxifen, raloxifene

MECHANISM	Selective estrogen receptor modulators (SERMs)—receptor antagonists in breast and agonists in bone. Block the binding of estrogen to ER ⊕ cells.
CLINICAL USE	Breast cancer treatment (tamoxifen only) and prevention. Raloxifene also useful to prevent osteoporosis.
ADVERSE EFFECTS	Tamoxifen—partial agonist in endometrium, which ↑ the risk of endometrial cancer; "hot flashes." **Raloxifene—no ↑ in endometrial carcinoma (so you can relax!), because it is an estrogen receptor antagonist in endometrial tissue.** Both ↑ risk of thromboembolic events (eg, DVT, PE).

Trastuzumab (Herceptin)

MECHANISM	Monoclonal antibody against HER-2 *(c-erbB2)*, a tyrosine kinase receptor. Helps kill cancer cells that overexpress HER-2, through inhibition of HER2-initiated cellular signaling and antibody-dependent cytotoxicity.
CLINICAL USE	HER-2 ⊕ breast cancer and gastric cancer (tras2zumab).
ADVERSE EFFECTS	Cardiotoxicity. "**Heart**ceptin" damages the **heart**.

Vemurafenib

MECHANISM	Small molecule inhibitor of *BRAF* oncogene ⊕ melanoma. **VEmuRAF-enib** is for **V**600**E**-**mu**tated ***BRAF* inhib**ition.
CLINICAL USE	Metastatic melanoma.

Tumor lysis syndrome

New Fact

Oncologic emergency triggered by massive tumor cell lysis, most often in lymphomas/leukemias. Release of K^+ → hyperkalemia, release of PO_4^{3-} → hyperphosphatemia, hypocalcemia due to Ca^{2+} sequestration by PO_4^{3-}. ↑ nucleic acid breakdown → hyperuricemia → acute kidney injury. Treatments include aggressive hydration, allopurinol, rasburicase.

Rasburicase

New Fact

MECHANISM	Recombinant uricase that catalyzes metabolism of uric acid to allantoin.
CLINICAL USE	Prevention and treatment of tumor lysis syndrome.