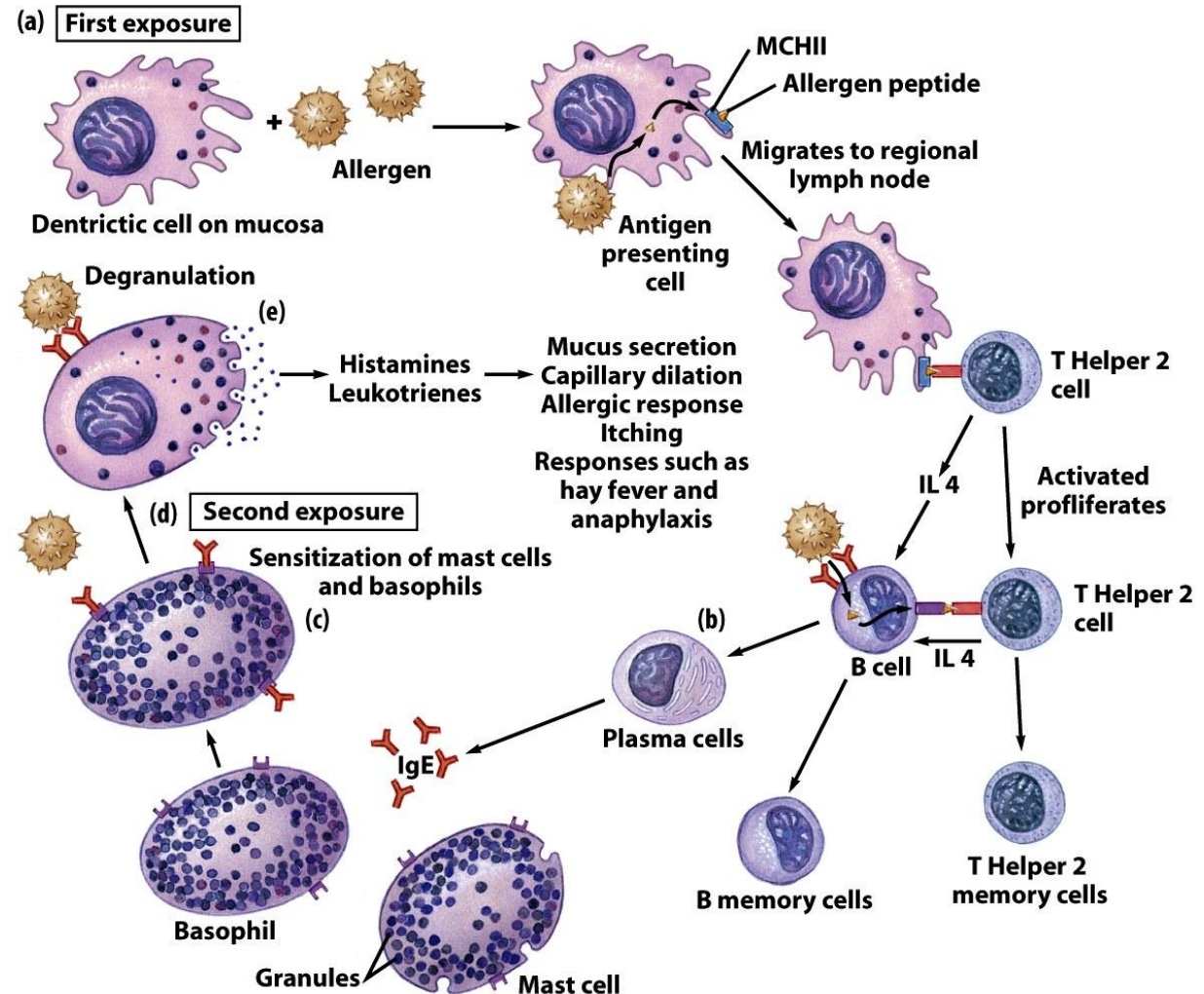


Preview: immunodeficiency

- What's allergy?
- What's acquired immunodeficiency?
- What's AIDS?

Type I Hypersensitivity (Anaphylactic)

Type I hypersensitivity is an immediate or anaphylactic reaction, often associated with allergy.
Immediate hypersensitivity



mediated by IgE released from mast cells and basophils

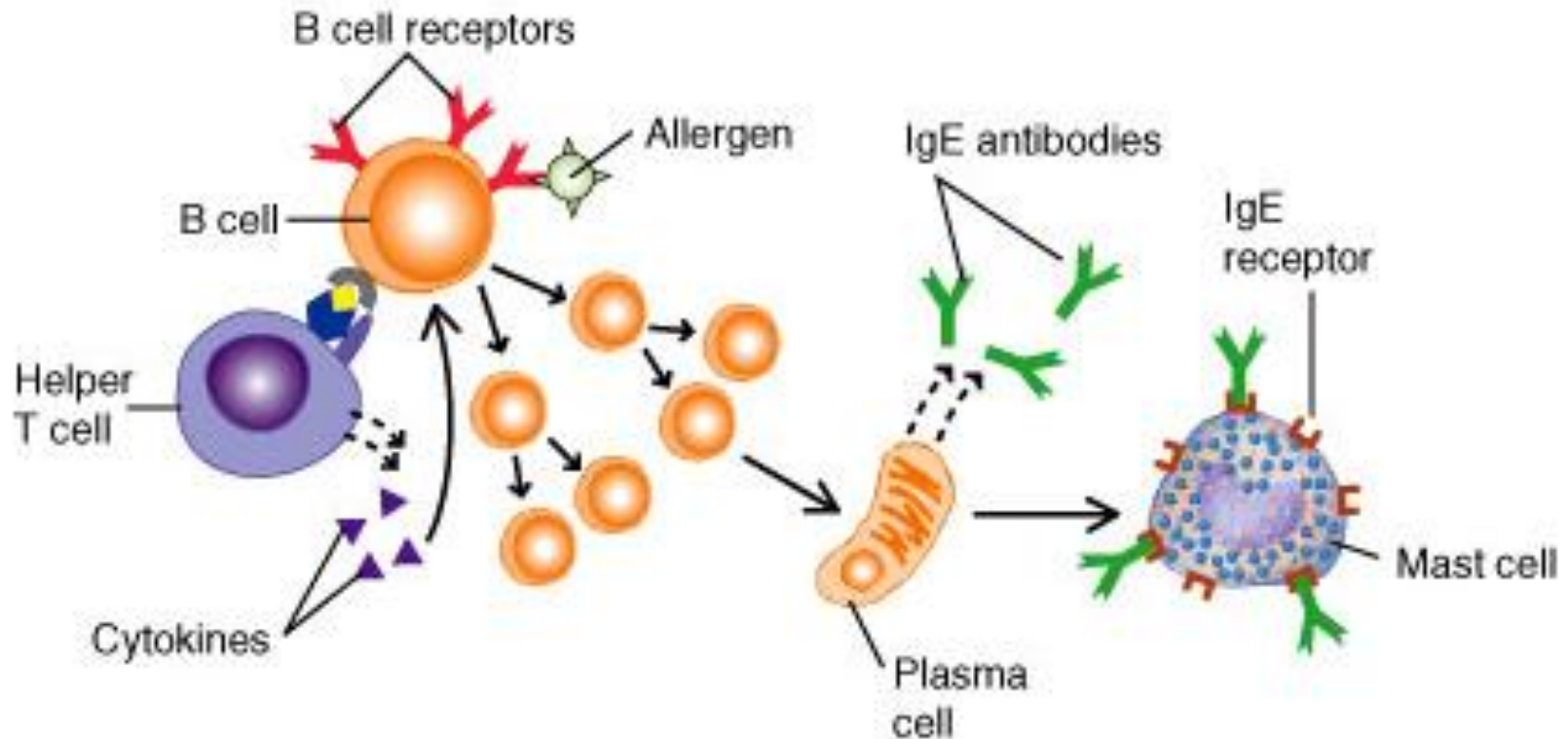
Allergy is called *type I* (or *immediate*) hypersensitivity. It is characterized by excessive activation of certain white blood cells called mast cells and basophils by a type of antibody known as IgE, resulting in an extreme inflammatory response.

Common allergic reactions include eczema, hives, hay fever, asthma attacks, food allergies, and reactions to the venom of stinging insects such as wasps and bees.^[1]

Allergy

Austrian pediatrician Clemens Pirquet (1874-1929) first used the term allergy, from Greek “allos” means “action”.

First Exposures to Allergen



Cytokines from an effector helper T cell cause class switching resulting in a clone of B cells destined to produce IgE.

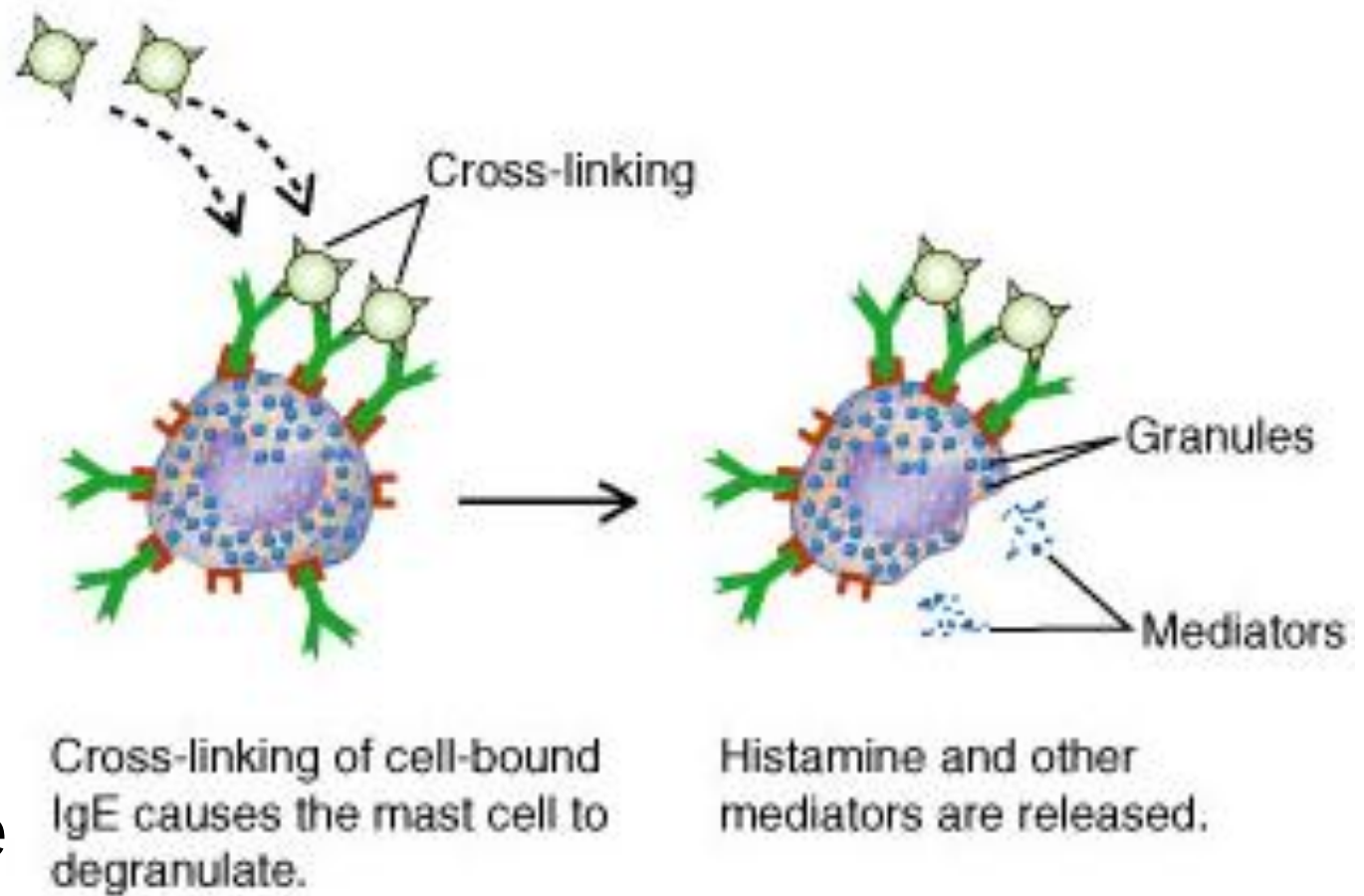
The B cells differentiate into IgE-producing plasma cells and memory cells.

IgE antibodies bind to mast cell receptors; the individual is sensitized.

Allergy

Subsequent Exposures to Allergen

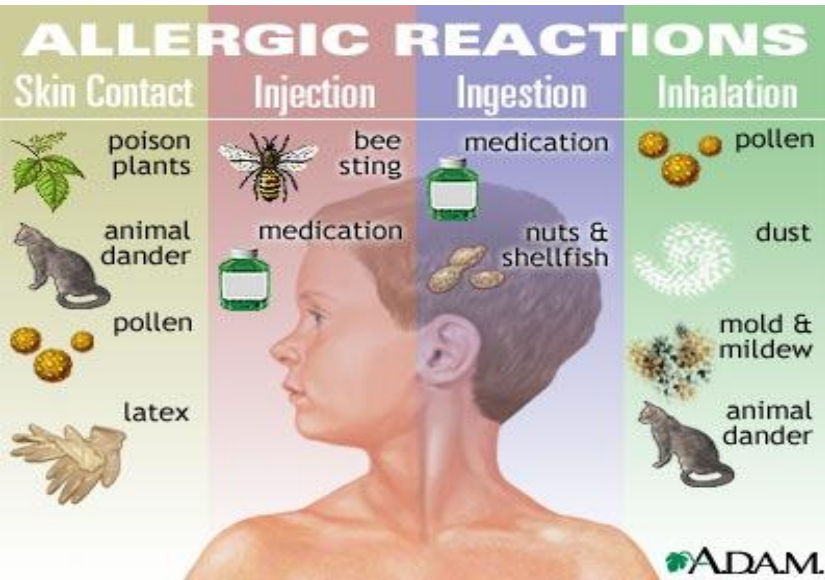
Inflammation:
protective
attempt by the
organism to
remove the
injurious
stimuli as well
as initiate the
healing
process for the
tissue.



Allergy

- It is estimated that **50 million** North Americans are affected by allergic conditions.
- The cost of allergies in the United States is more than **\$10 billion** dollars **yearly**.
- Allergic rhinitis (nasal allergies) affects about **35 million** Americans, **6 million** of whom are children.
- Asthma affects **15 million** Americans, **5 million** of whom are children.
- The number of cases of asthma has doubled over the last 20 years.

Why do some people have allergies in a family but not everyone? What actually makes someone prone to allergies?



Genetic bias: the likelihood of developing allergies is inherited and due to some irregularity in the way the immune system works, but the specific allergen, which causes the development of an allergy, is not.

Age: young >>old

gender: boys>girls

**industrialized >
agricultural**

Urban> rural

hygiene hypothesis: lack of early childhood exposure to infectious agents, symbiotic microorganisms (e.g. gut flora), and parasites increases susceptibility to allergic diseases by modulating immune system development.

Preconditioning....co-evolution

Allergy



Allergic Rhinitis("hay fever")

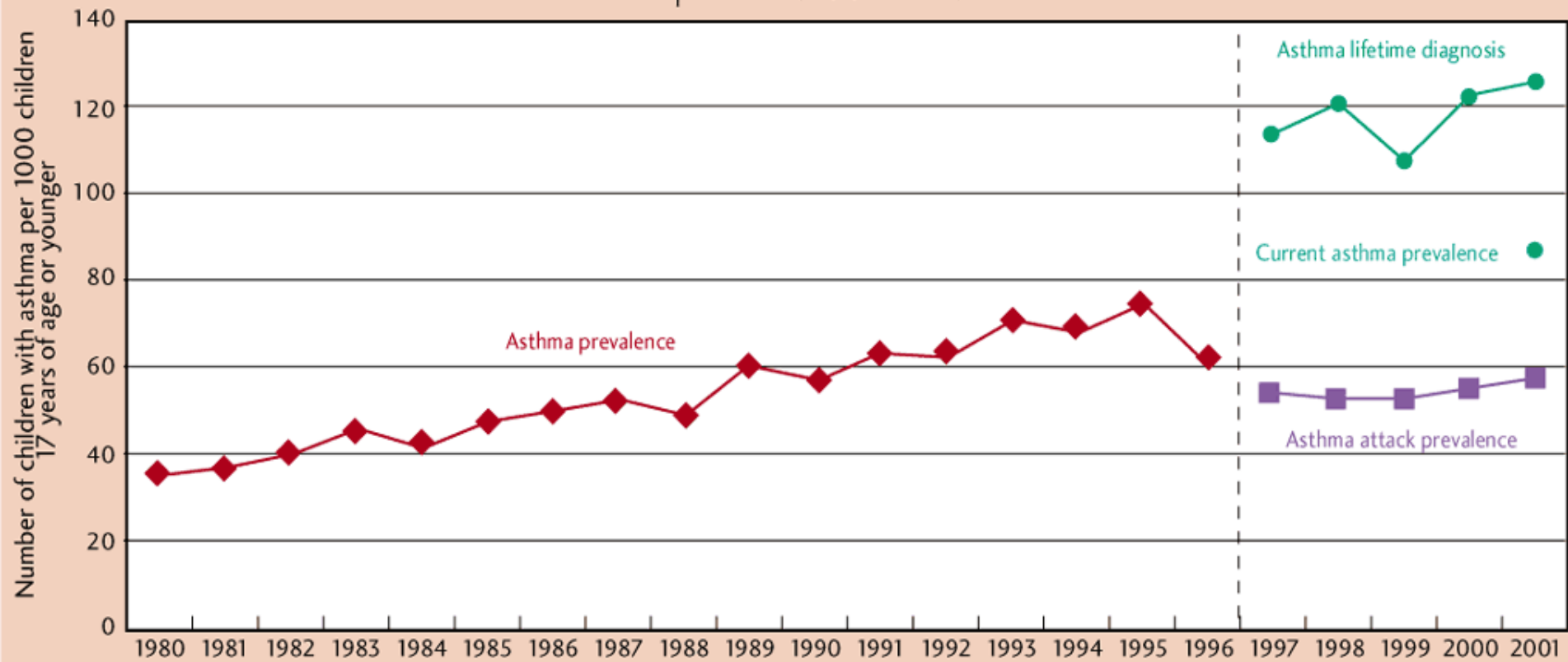
- Allergens: pollens, dust mites, or molds.
- Pathogenic: inflammation of the tissues that line the inside of the nose. Ears, sinuses, and throat can also be involved.
- Symptoms: runny or stuffy nose, sneezing, nasal itching (rubbing) itchy ears and throat, Post nasal drip (throat clearing) etc.
- Treatment/prevention: inhibit inflammation

Asthma

Asthma

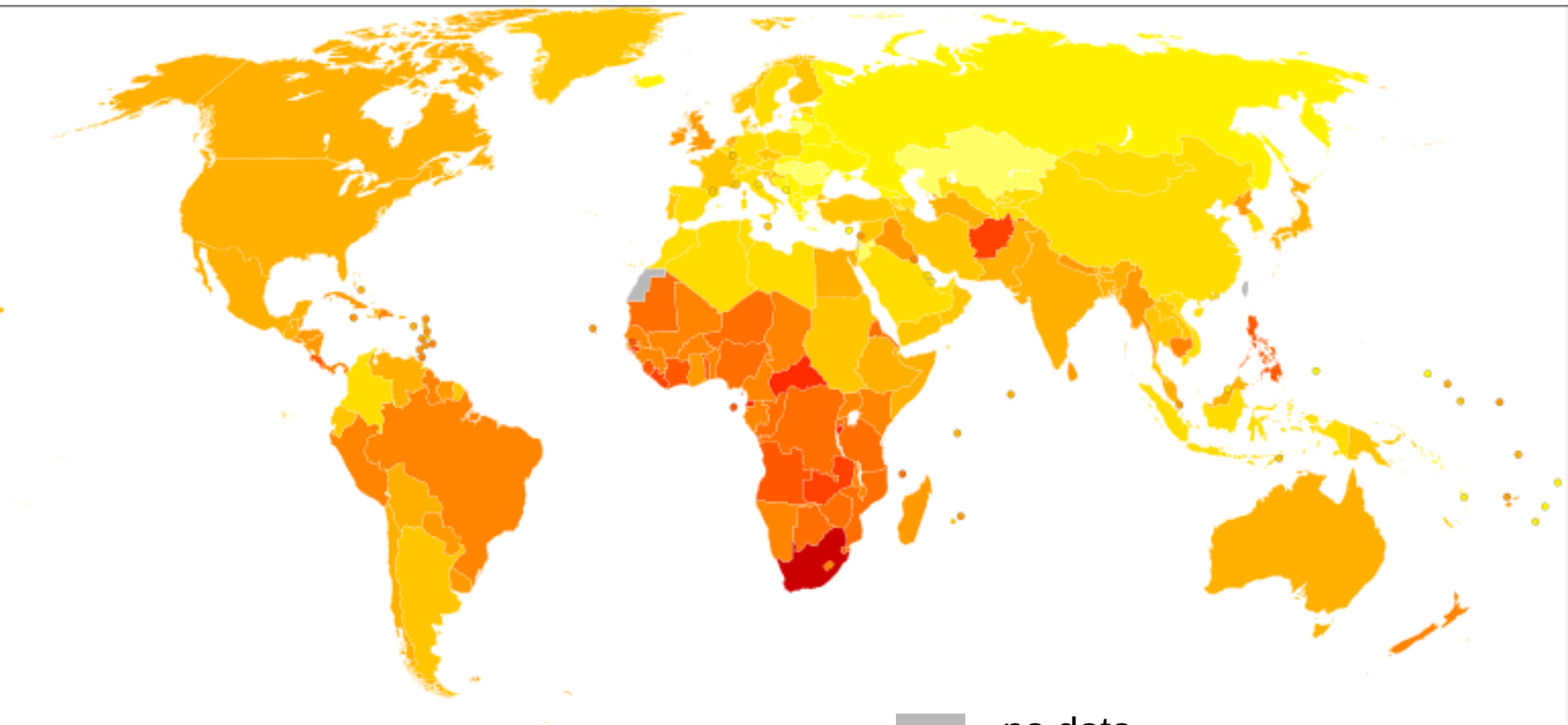
- Cause: genetic (>100 genes are associated) or environmental (allergens, polluted air, certain antibiotics, psychological stress etc.)
- Pathogenic: airflow obstruction, and bronchospasm--inflammation of the tissues that line the inside of the bronchi.
- Symptoms: wheezing, cough, chest tightness, and shortness of breath.
- Treatment/prevention: acute/chronic--to inhibit inflammation

Exhibit 4-5: Asthma prevalence, 1980-1996, asthma lifetime diagnosis, current asthma, and asthma attack prevalence, 1997-2001, in children

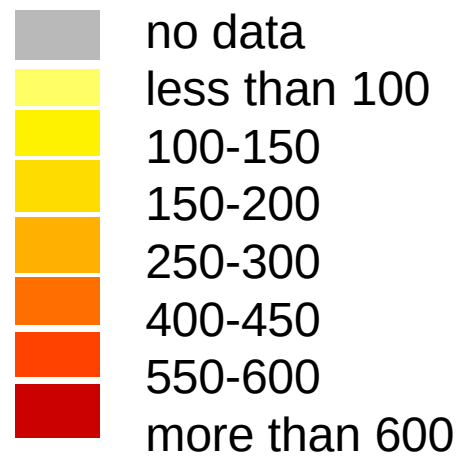


Note: The survey questions for asthma changed in 1997; data before 1997 cannot be directly compared to data in 1997 and later.

Source: Based on and updated from Akinbami, L.J. and K.C. Schoendorf. *Trends in Childhood Asthma: Prevalence, Health Care Utilization and Mortality*. 2002. Data from CDC, National Center for Health Statistics, National Health Interview Surveys, 1980-2001.

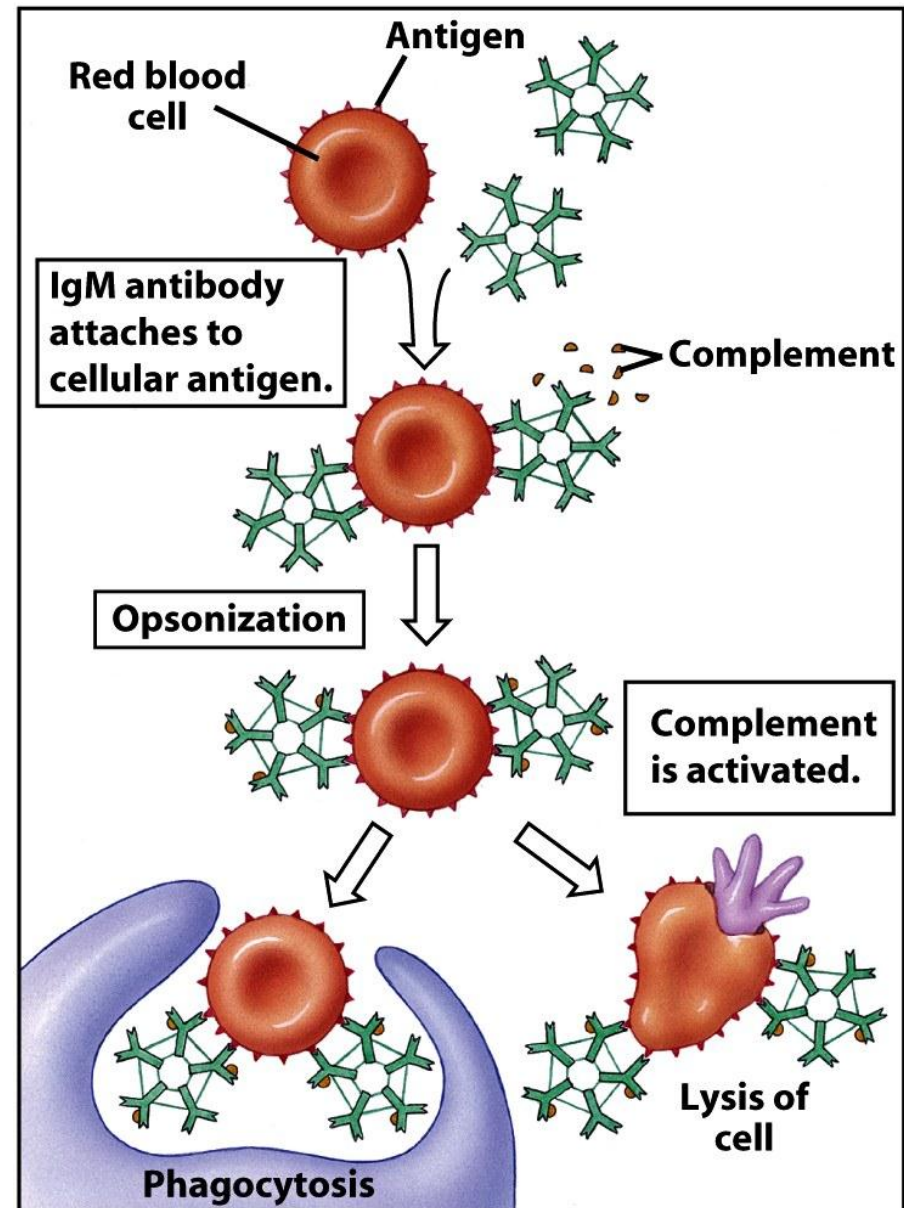


Asthma world map - WHO2004

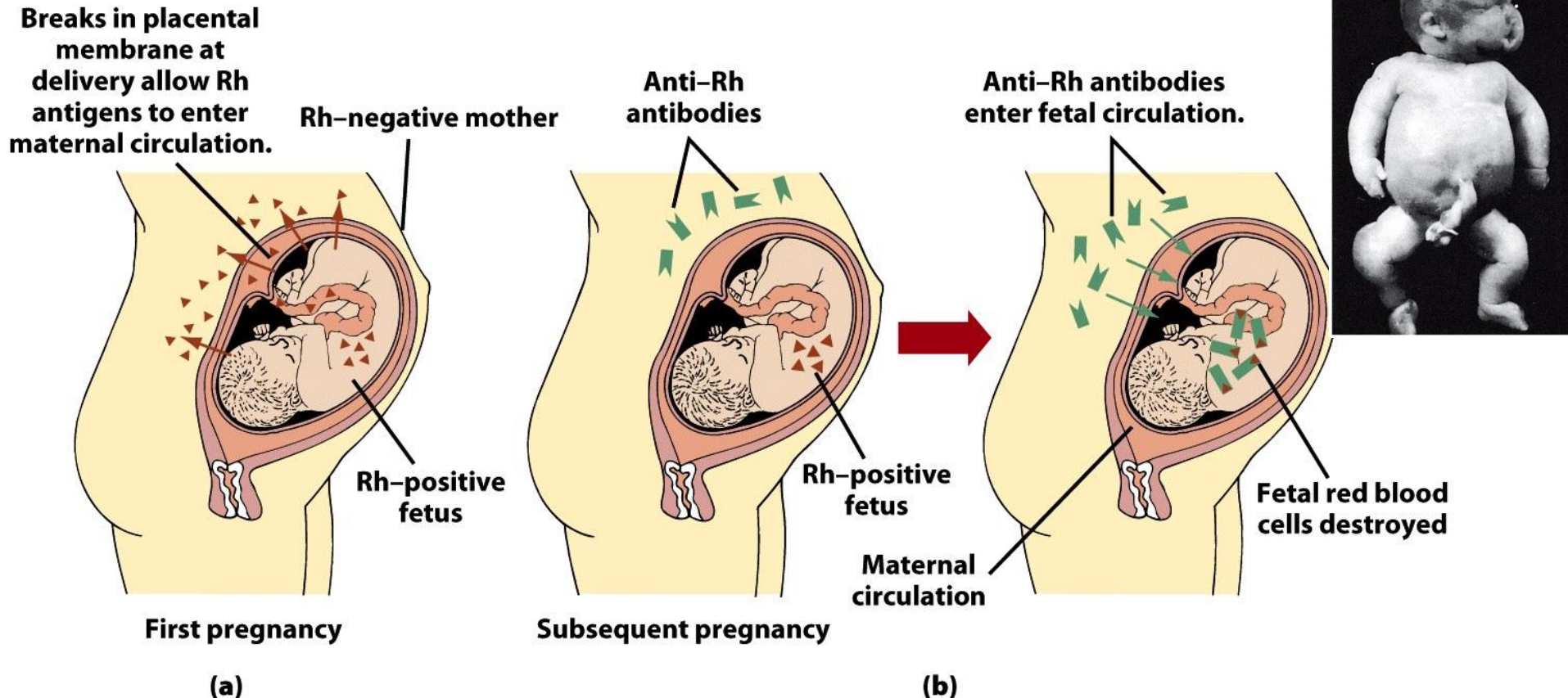


Type II Hypersensitivity (Cytotoxic)

Type II hypersensitivity occurs when antibodies bind to antigens on the patient's own cells, marking them for destruction. This is also called antibody-dependent (or cytotoxic) hypersensitivity, and is mediated by [IgG](#) and [IgM](#) antibodies.



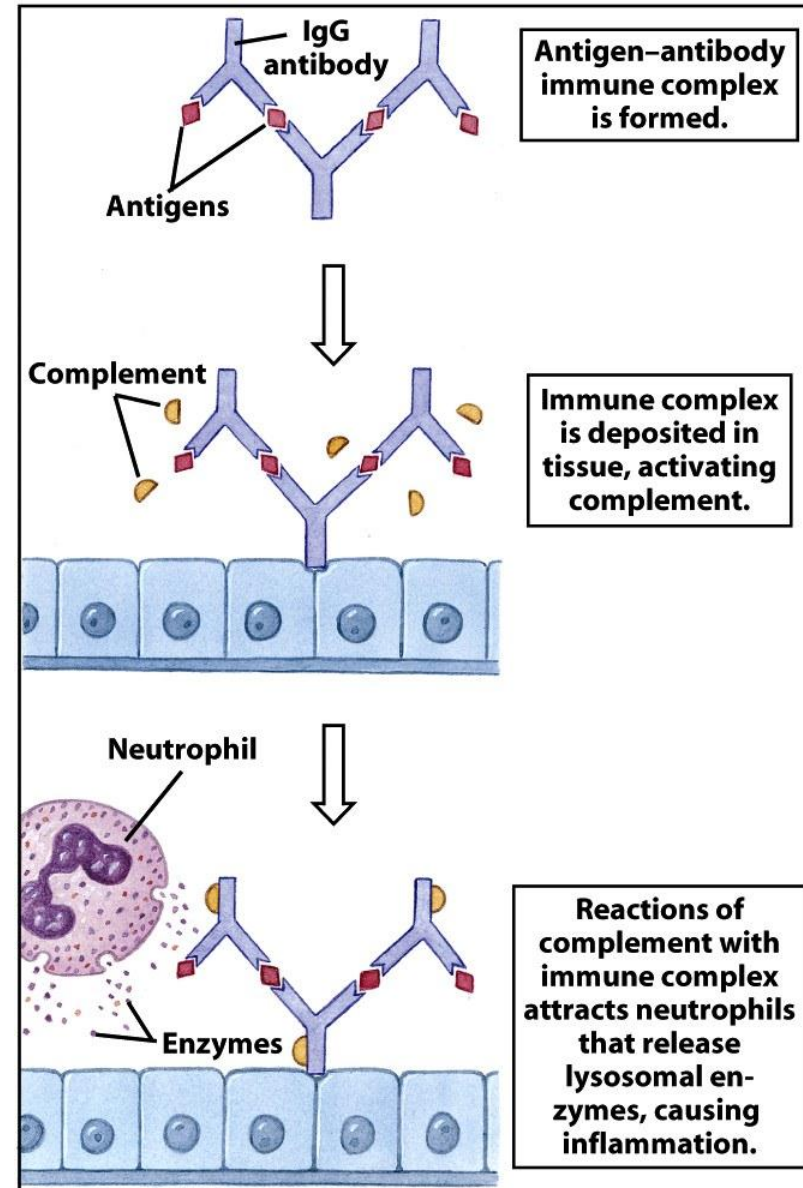
Hemolytic Disease of the Newborn



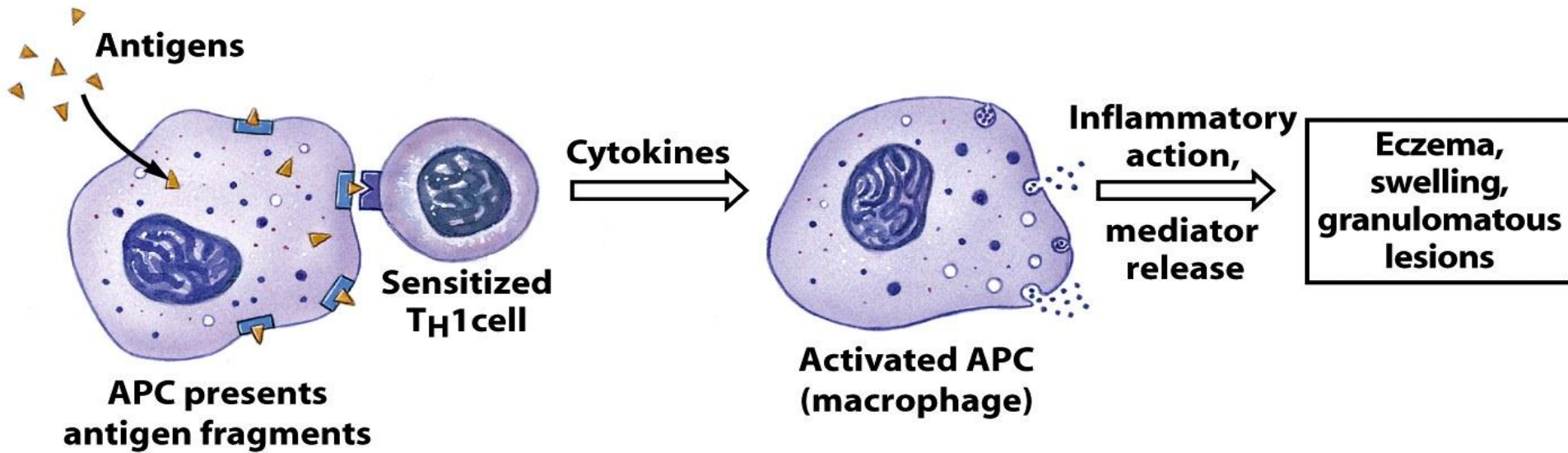
Type III Hypersensitivity (Immune Complex)

Immune complexes

(aggregations of antigens, complement proteins, and IgG and IgM antibodies) deposited in various tissues trigger Type III hypersensitivity reactions.

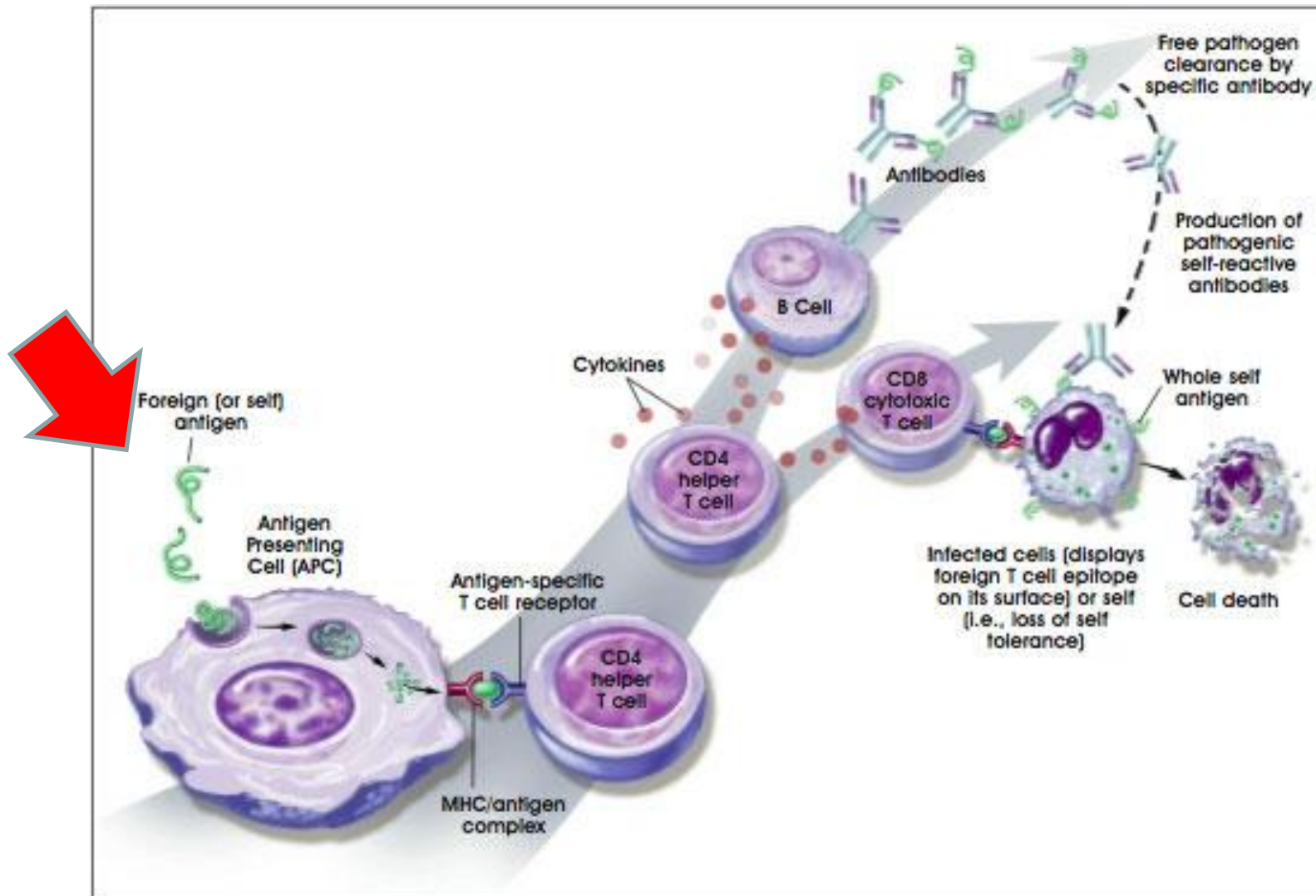


Type IV Hypersensitivity (Cell-mediated)



Type IV hypersensitivity (also known as cell-mediated or *delayed type hypersensitivity*) usually takes between two and three days to develop. Type IV reactions are involved in many autoimmune and infectious diseases, but may also involve [contact dermatitis](#) ([poison ivy](#)). These reactions are mediated by [T cells](#), [monocytes](#), and [macrophages](#).

Therapeutic vaccine: vaccine administered after infection occurs with the hope of activating immunity in time to prevent or ameliorate a disease. Compare--**Preventive vaccine**



Three immune disorder conditions:

The immune system is very complicated with many components. When these components do not function properly, the immune system fails to respond in the appropriate manner. This produces disease.

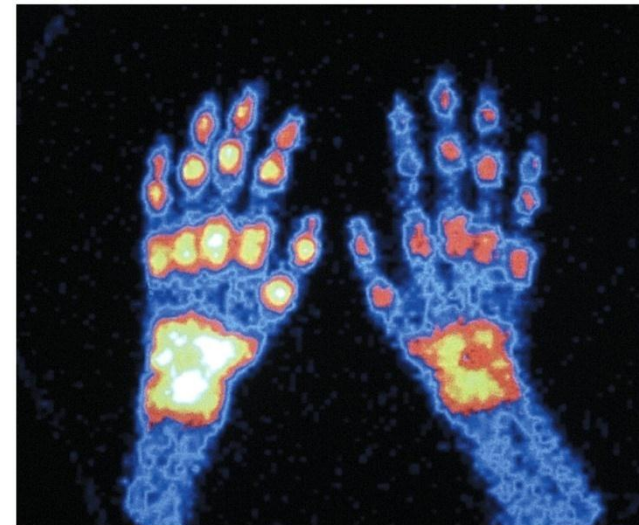
Hypersensitivities involve overreaction of the immune system.

Autoimmune diseases result when the body reacts against self antigens.

Immunodeficiency results in failure of the system to respond effectively against foreign antigens.

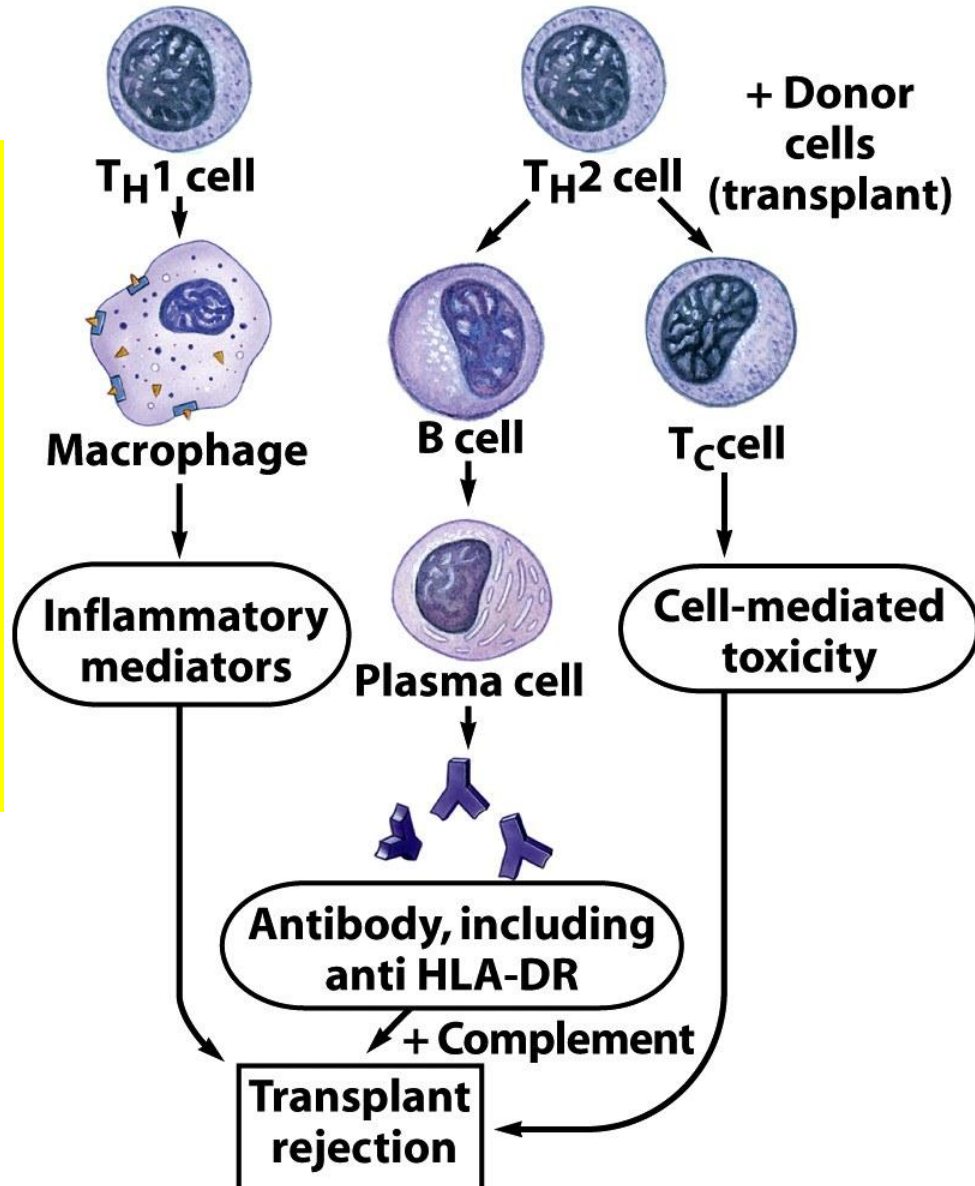
Autoimmune Disease

- Treatment of autoimmune diseases
 - Treatment aimed at:
 - Killing dividing cells
 - Immunosuppressant
 - Controlling T cell signaling
 - Cyclosporin
 - Anti-inflammatory medications
 - Cortico steroids
 - Replacement therapy
 - Insulin



Transplantation Issues

- Rejection
- Tolerance
- Immunosuppression

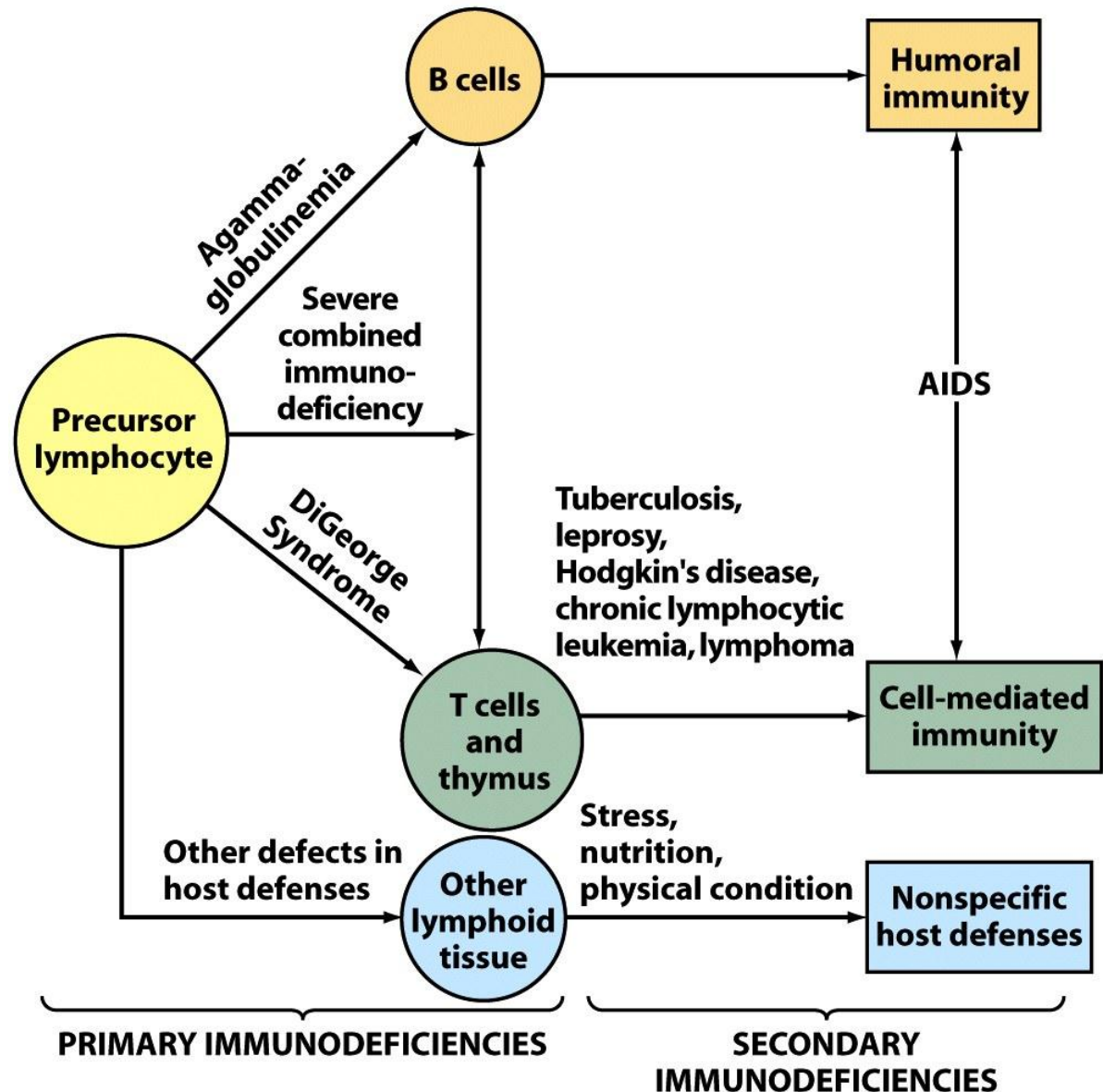


Quiz: What's the role of microbes playing in human immunity?



Immunodeficiency Disorders

- Primary
- Secondary



Immunodeficiency

What is it?

Immunodeficiency refers to a group of disorders in which the immune system does not function normally.

Primary immunodeficiency

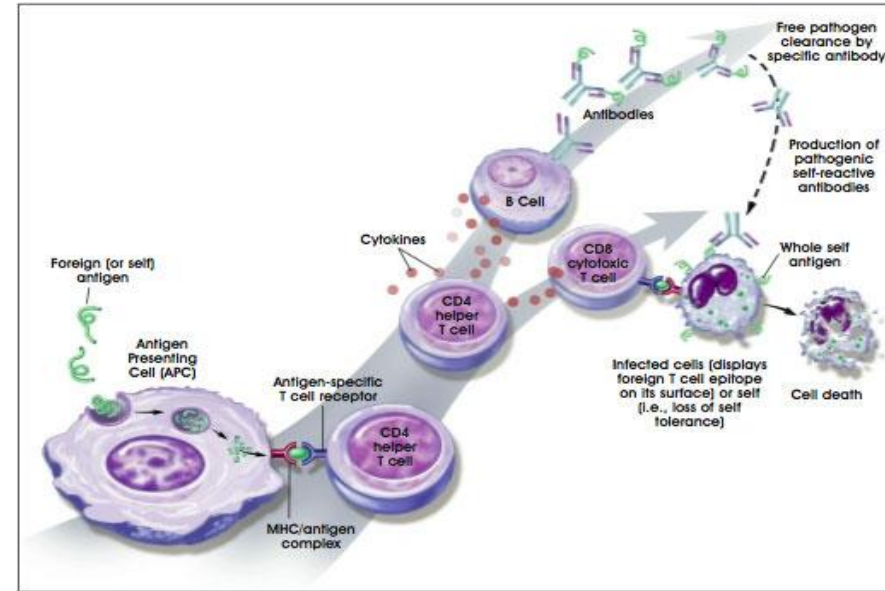
Genetic, obtained from parents

Acquired immunodeficiency

Malnutrition, aging, diseases like cancer, AIDS

Primary immunodeficiency

Mostly genetic,
1/500 born with



- (1) low levels of most or all of the immunoglobulin (IgG, E, D) classes,
- (2) a lack of B lymphocytes or plasma cells that are capable of producing antibodies
- (3) frequent bacterial infections.

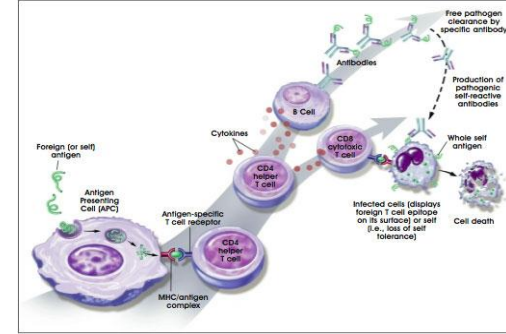
Primary immunodeficiency

Having infections more often and getting infections that are more severe, longer lasting, and harder to cure than for people with normal immune systems.

Getting infected with germs that a healthy immune system would be able to get rid of, known as **opportunistic infections**.

Having autoimmune problems, meaning that instead of the immune system attacking germs and disease-causing materials, it attacks the body's own organs and tissues by mistake.

Primary immunodeficiency



- (1) Clean up current infection
- (2) Prevent possible new infection
- (3) Correct gene error (bone marrow transfer, gene therapy, etc).

Common variable immunodeficiency (CVID)

Hypogammaglobulinemia: lower level of IgG, IgA and/or IgM

Acquired Immunodeficiency syndrome (AIDS)

- Symptoms
 - Appear after incubation period of 6 days to 6 weeks
 - Usually consist of fever, headache, sore throat, muscle aches, enlarged lymph nodes and generalized rash
 - Some develop CNS symptoms
 - Range from moodiness and to seizures and paralysis
 - Symptoms constitute acute retroviral syndrome (ARS)
 - Typically subside in 6 weeks
 - Acute illness followed by asymptomatic period
 - Period may end with persistent enlargement of lymph nodes
 - Lymphadenopathy syndrome (LAS)
 - Immunodeficiency symptoms include fever, weight loss, fatigue and diarrhea
 - Referred to as AIDS-related complex (ARC)

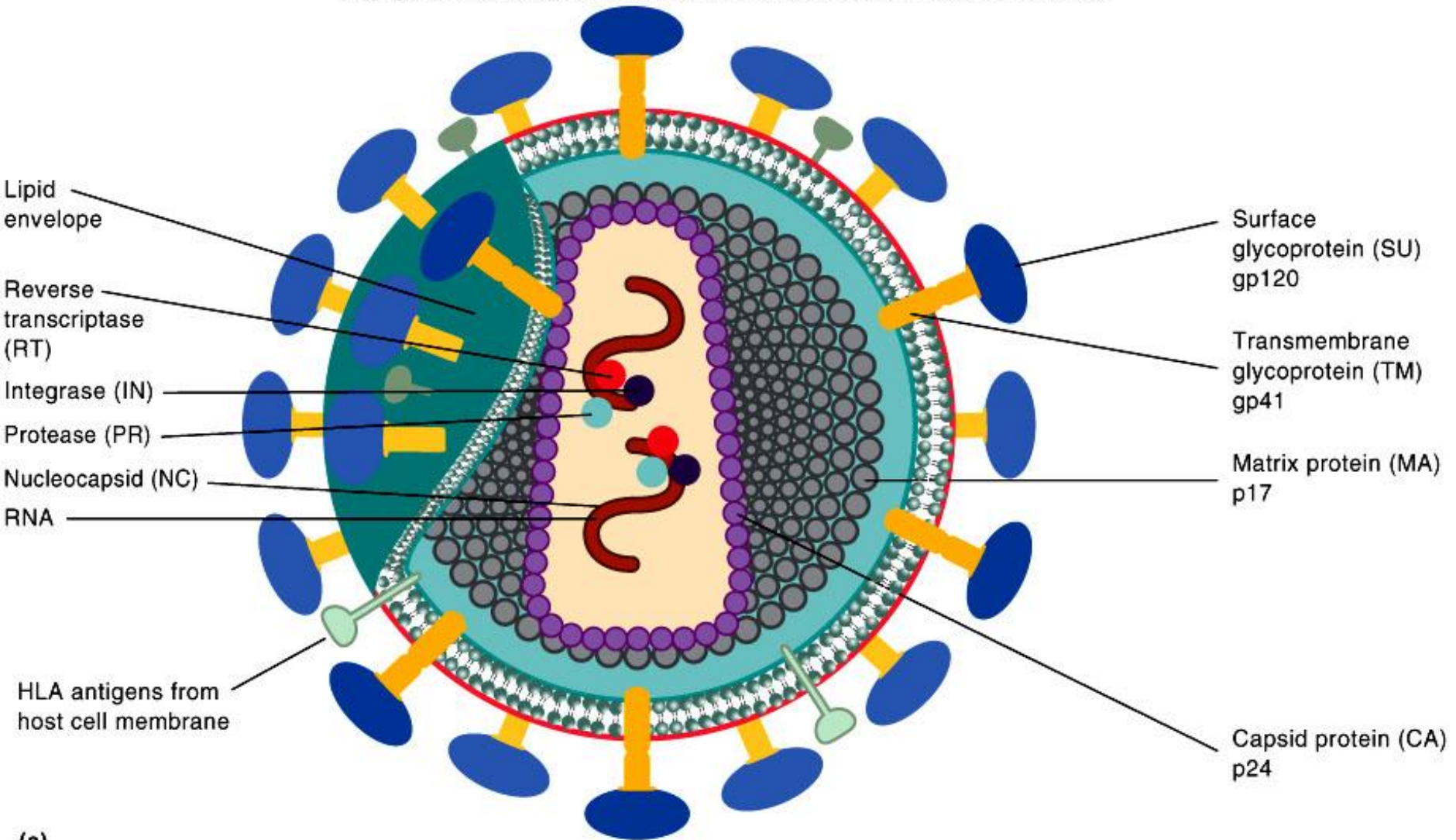
HIV Disease

- Causative agent
 - In U.S and most other parts of the world disease caused by human immunodeficiency virus type 1 (HIV-1)
 - Belongs to lentivirus subgroup of retrovirus family
 - Viruses characteristically infects mononuclear phagocytes
 - HIV-2 is similar in structure to HIV-1 but is antigenically distinct
 - Prominent cause of AIDS in parts of West Africa and India
 - Has appeared in the U.S.
 - Transmission of less efficient than HIV-1
 - Disease progresses slower

HIV

120 nm diameter

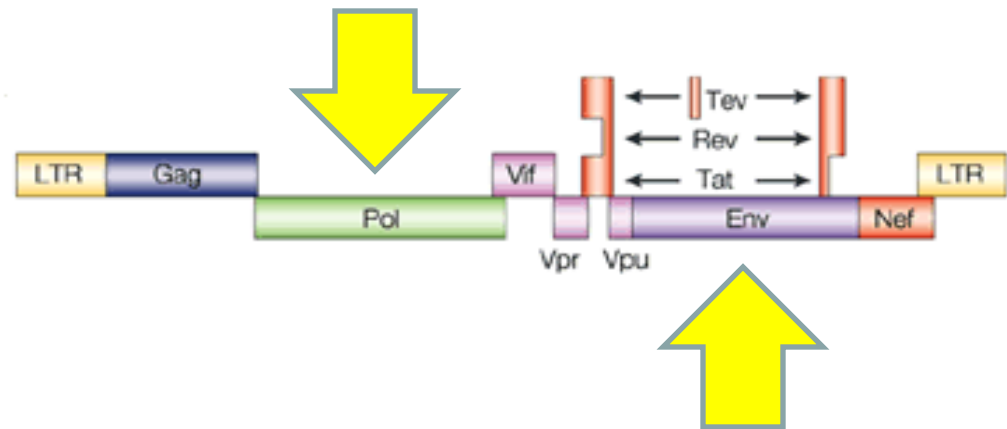
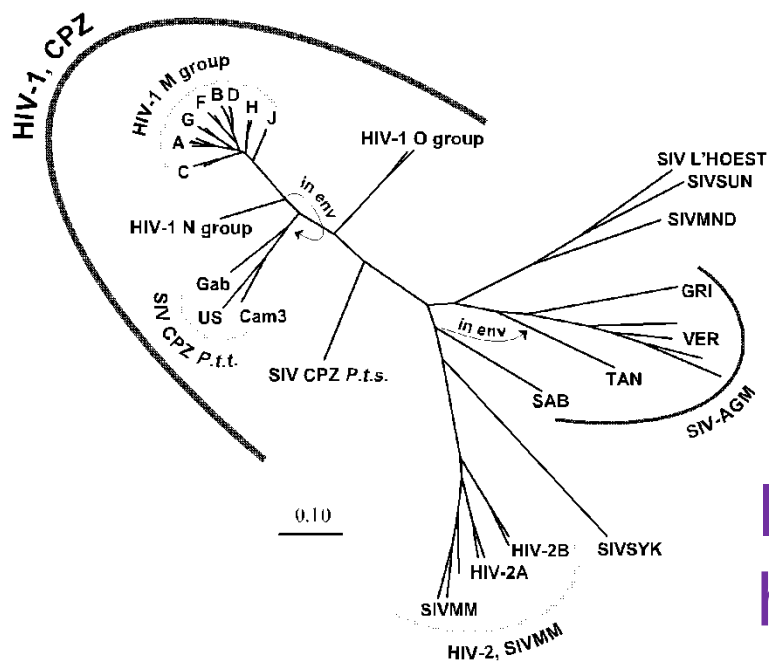
Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.



(a)

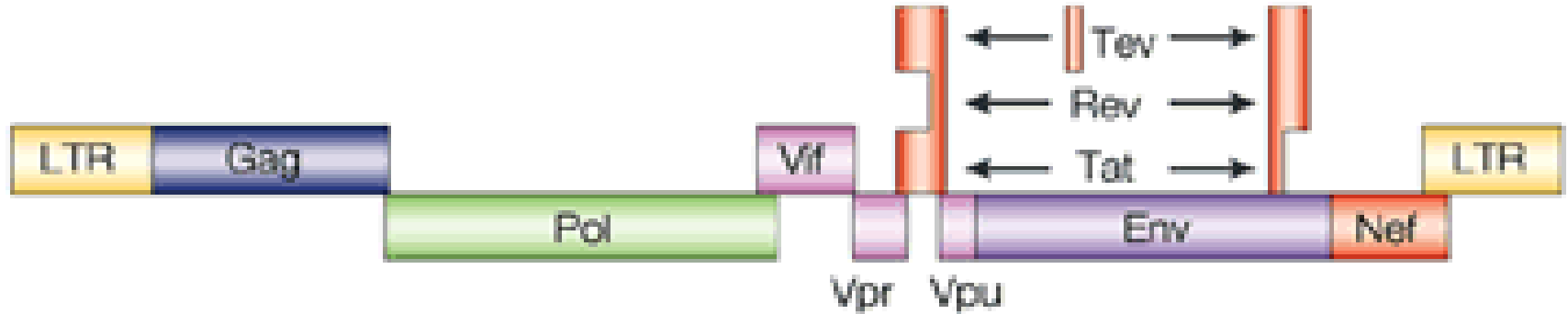
HIV genetic variation

HIV differs from many viruses in that it has very high genetic variability. This diversity is a result of its fast replication cycle, with the generation of 10^9 to 10^{10} virions every day, coupled with a high mutation rate of approximately 3×10^{-5} per nucleotide base per cycle of replication and recombinogenic properties of reverse transcriptase



In one single patient, in one day, hundreds subtypes can be generated.

HIV genome



gag ([group-specific antigen](#)): MA (matrix protein, p17); CA (capsid protein, [p24](#)); SP1 (spacer peptide 1, p2); NC (nucleocapsid protein, [p7](#)); SP2, spacer peptide 2, p1) and [p6](#).

pol: codes for viral [enzymes reverse transcriptase](#), [integrase](#), and [HIV protease](#).

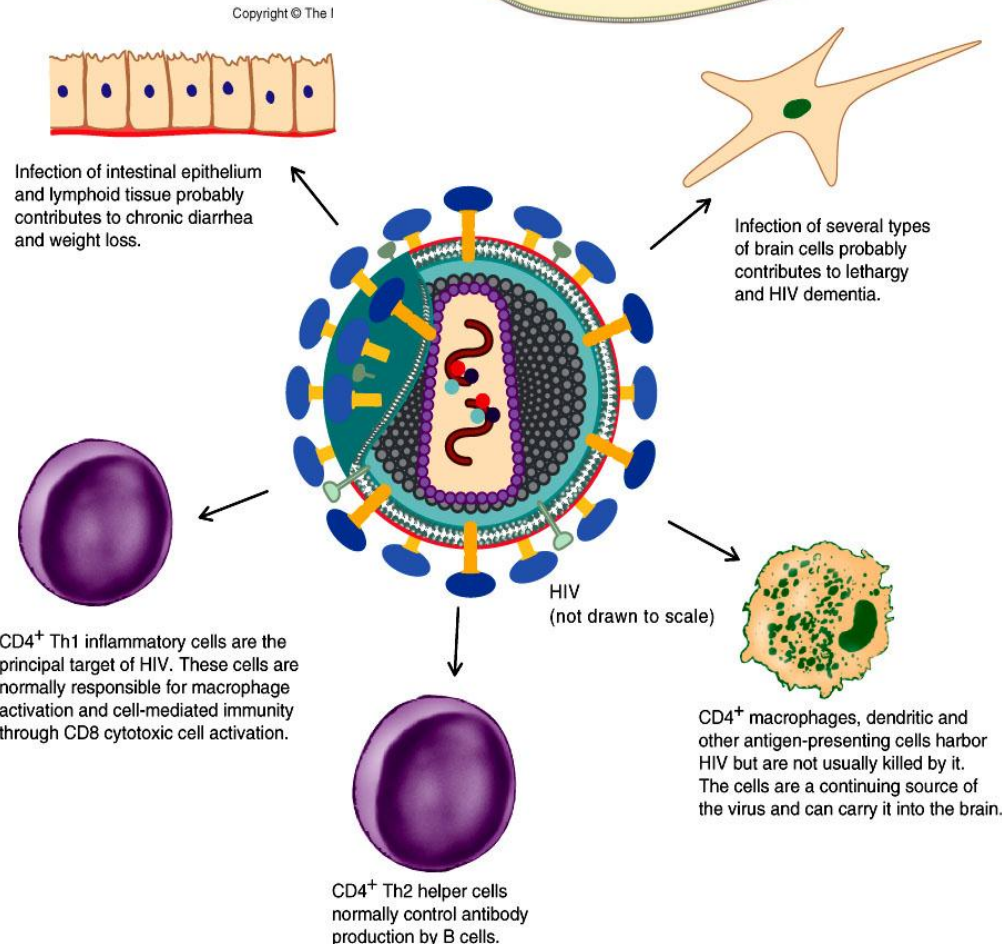
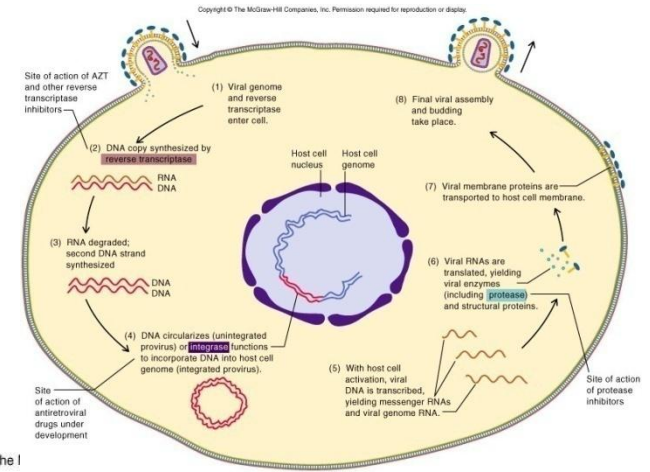
env (for "envelope"): codes for gp160, precursor of [gp120](#) , [gp41](#),
[Transactivators](#): [tat](#), [rev](#), [vpr](#) Other regulators: [vif](#), [nef](#), [vpu](#)

tev: This gene is only present in a few HIV-1 isolates. It is a fusion of parts of the *tat*, *env*, and *rev* genes, and codes for a protein with some of the properties of [tat](#), but little or none of the properties of [rev](#).

HIV Disease

Pathogenesis

- HIV attacks variety of cell types
 - Most critical are **Helper T-cells**
 - Attached to CD4 surface receptor
- After entry, DNA copies of RNA genome produced using reverse transcriptase viral enzyme
 - DNA copy integrates and hides on host chromosome
- In activated cells virus leaves cell genome and kills cell
 - Releases additional viruses to infect other cells
- Macrophages have **CD4** receptors
 - Virally infected macrophages are not generally killed but function is impaired
- Eventually immune system becomes too impaired to respond



HIV Disease

CD4 (cluster of differentiation 4) is a glycoprotein expressed on the surface of T helper cells, regulatory T cells, monocytes, macrophages, and dendritic cells.

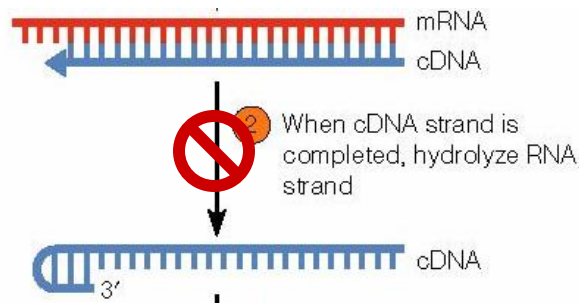
- Pathogenesis

- In nearly 80% of all cases immune system slowly loses ground to virus
- Peripheral **CD4+** count steadily falls to nearly 50 cells/ μ l/year
 - 500-1600/uI, alert line 350/uI
 - Symptoms usually appear when count falls below 200 cells/ μ l
- Atypical progression of disease occurs in roughly 10% of infected individuals
 - Disease progresses rapidly to AIDS within a few months
 - Another 5% - 10% do not experience a fall in CD4+ cells
 - Maintain high levels of antibodies and CD8+ cells
 - Disease progresses slowly
 - » May be AIDS free for 20 years

HIV Disease

Three routes:
sexual
blood
mother-baby

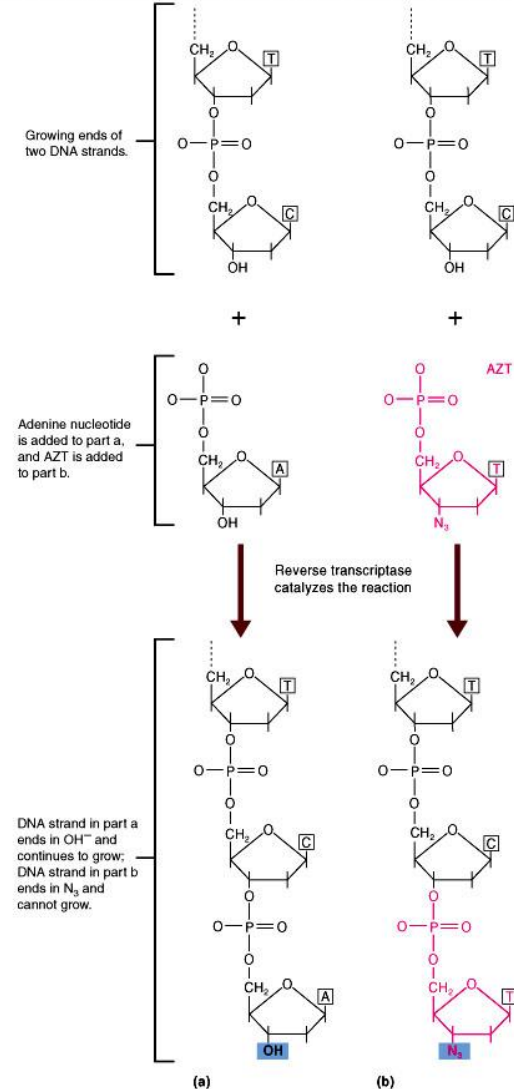
- Prevention and Treatment
 - No approved vaccine
 - Most people infected are unaware
 - Virus on surfaces can be inactivated with commercially available **disinfectants** and heat at **56°C** for more that **30 minutes**
 - Viruses in dried blood or pus may be more difficult to inactivate
 - Knowledge of transmission greatest tool for control
 - Use of condoms not 100% effective but have been shown to decrease transmission
 - Avoidance of practices that favor HIV transmission



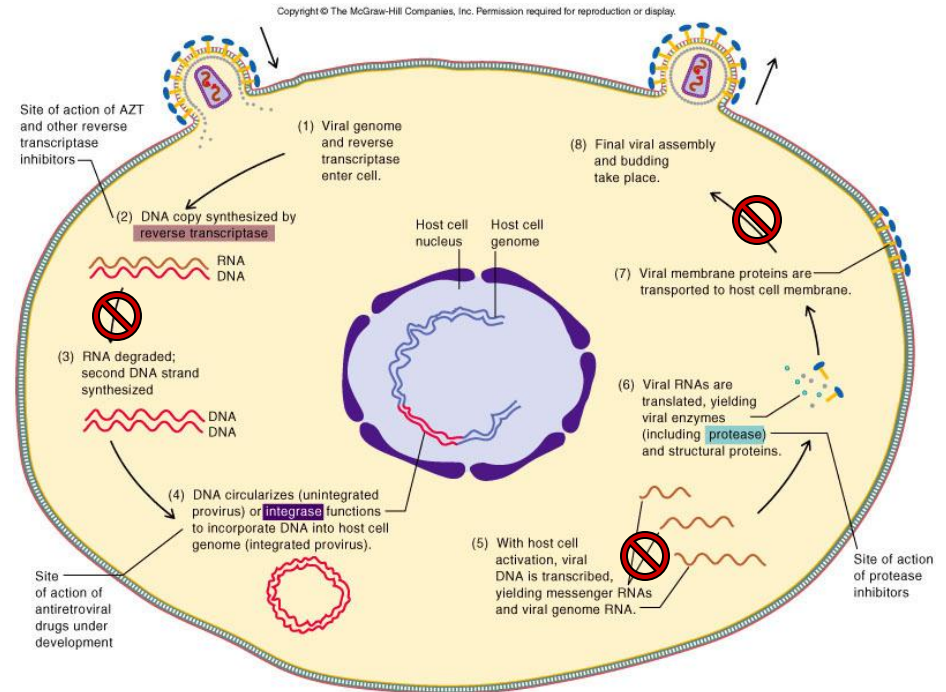
Prevention and Treatment

- Treatment directed at “cocktails” of drugs
 - Combination of reverse transcriptase inhibitors and protease inhibitors
 - HAART = highly active antiretroviral therapy
- Reverse transcriptase inhibitors fall into two categories
 - Nucleoside reverse transcriptase inhibitors
 - Zidovudine (AZT), stavudine (D4T) and lamivudine (3TC)
 - Non-nucleoside reverse transcriptase inhibitors
 - Nevirapine, efavirenz and delavirdine

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.



- Prevention and Treatment
 - Protease inhibitors
 - 6 in use
 - Act late in HIV replication to prevent packaging of viral proteins
 - HAART does not cure AIDS
 - **Viremia** becomes undetectable in approximately 50% of cases
 - Will reappear in absence of treatment
 - Many strains fail to respond to HAART due to resistance

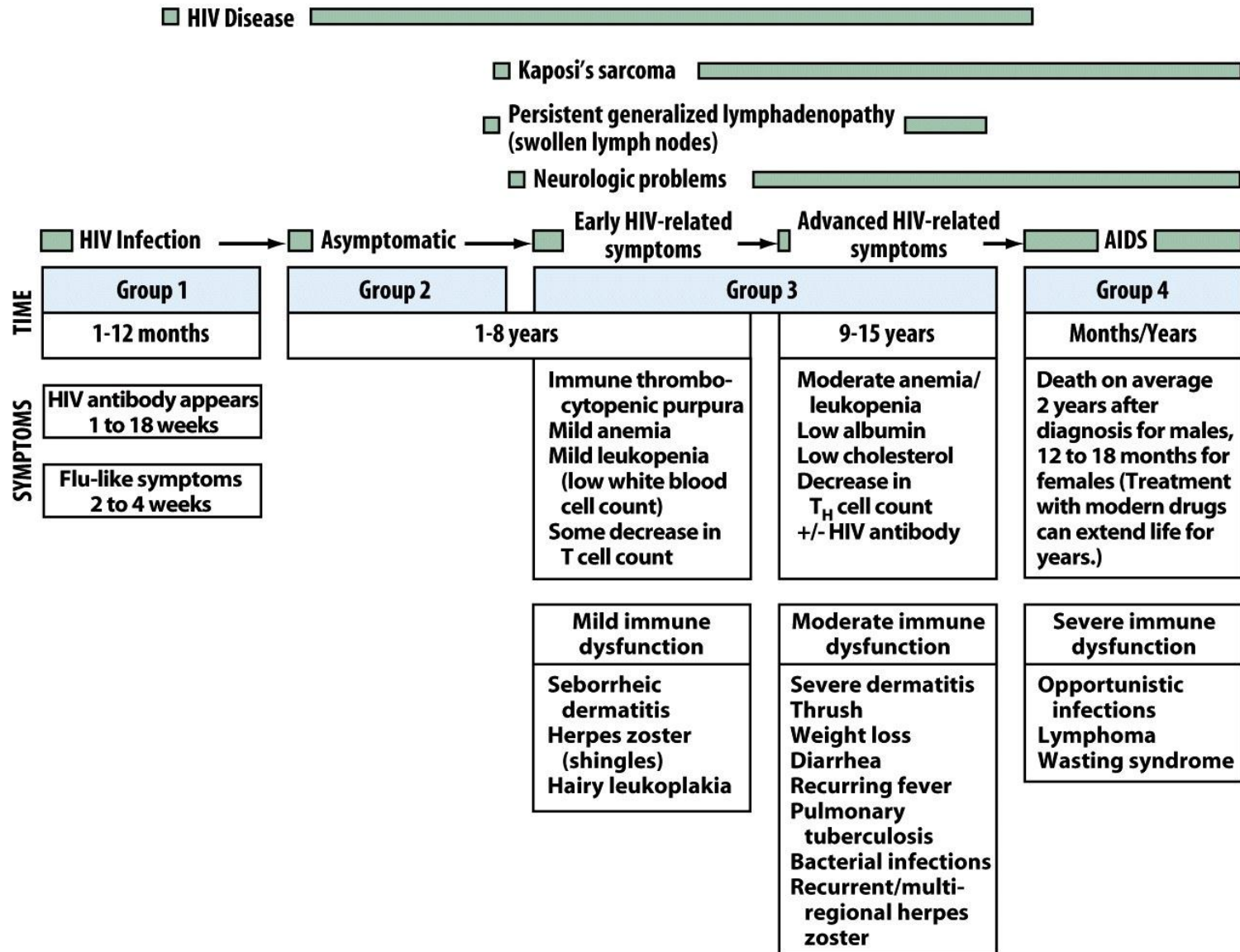


highly active antiretroviral therapy

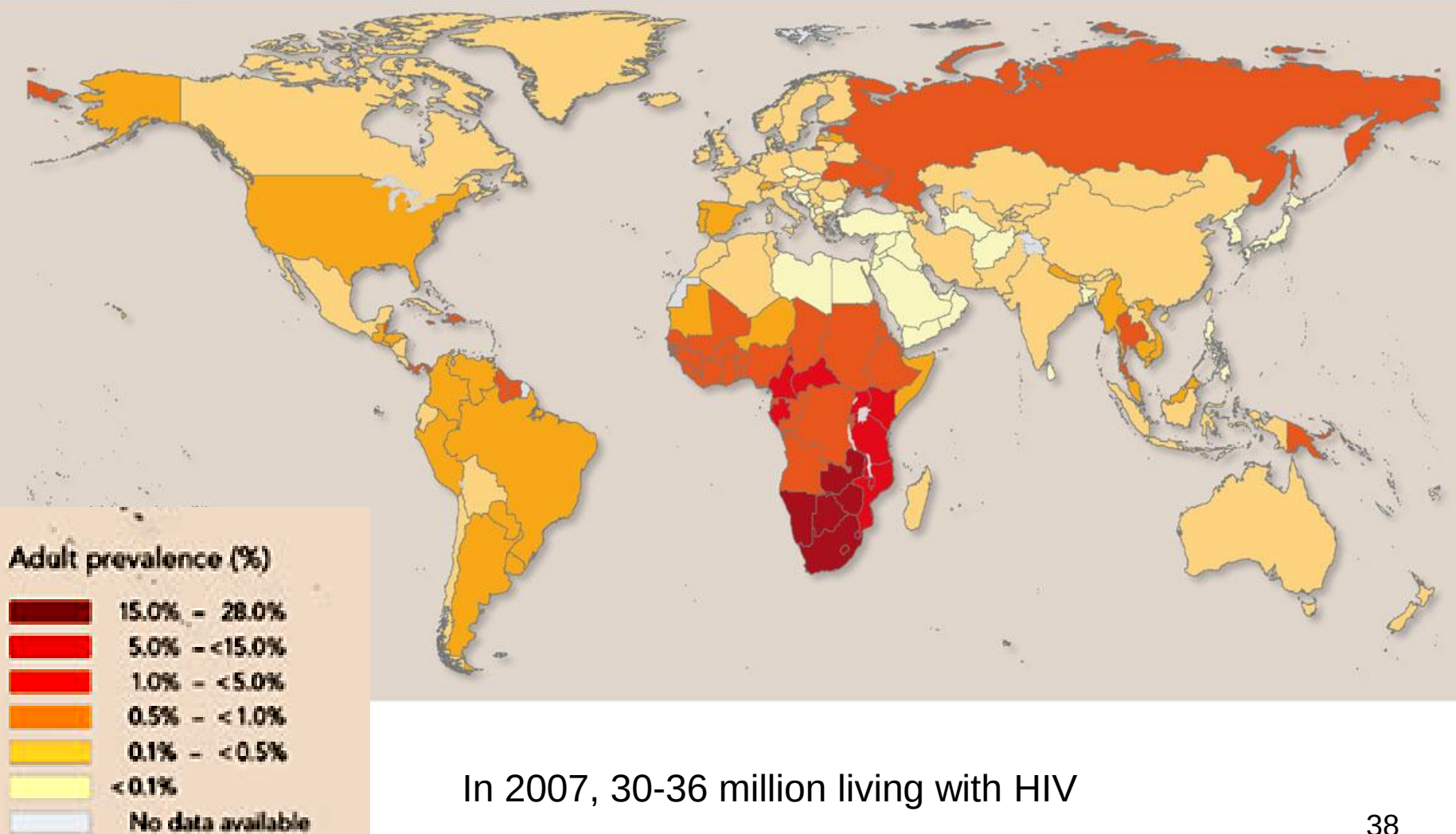
HIV Disease

- HIV vaccine prospects
 - Currently no approved vaccines
 - In theory vaccine could be used in two ways
 - Prevention vaccine
 - Immunize uninfected individuals against disease
 - Therapeutic vaccine
 - Boost immunity of those already infected
 - Successful vaccine must
 - produce both mucosal and blood stream immunity
 - get around HIV variability and stimulate cellular and humoral immunity

CDC AIDS Classification System



Global HIV



In 2007, 30-36 million living with HIV

Review: immunodeficiency

- What's allergy?

Type I hypersensitivity, it is characterized by excessive activation of certain white blood cells called mast cells and basophils by a type of antibody known as IgE, resulting in an extreme inflammatory response.

- What's acquired immunodeficiency?

The condition that a person's immune system can't function normally due to factors related with nutrition, aging and diseases.

- What's AIDS?

Acquired Immunodeficiency syndrome induced by HIV infection