REVIEW OF THE IMMUNE SYSTEM AND GENETICS

AN AFTERNOON SALON COURSE AT OLLI

FRIDAY, MAY 26TH

1-3 PM AT VPC

RICHARD WENDEL MD,MBA MODERATOR

The Immune System: our intricate defenses that work behind the scenes.

- Most individuals have a frame of reference for the eye, ear, heart, skin and so on but limited knowledge about our body's defenses against infection, cancer, allergies, toxins, and how this immune system can go array in producing **autoimmune disease and inflammatory immune disease**.
- Today we will try to build a frame and familiarize you with some terminology realizing that the science of immunology remains in its infantcy.

<u>Antigens</u> are **foreign molecules (bad guys)** capable of stimulating an immune response. Each antigen has distinct surface features, or epitopes, triggers that result in specific responses. (**like the spike antigen in Covid-19)**

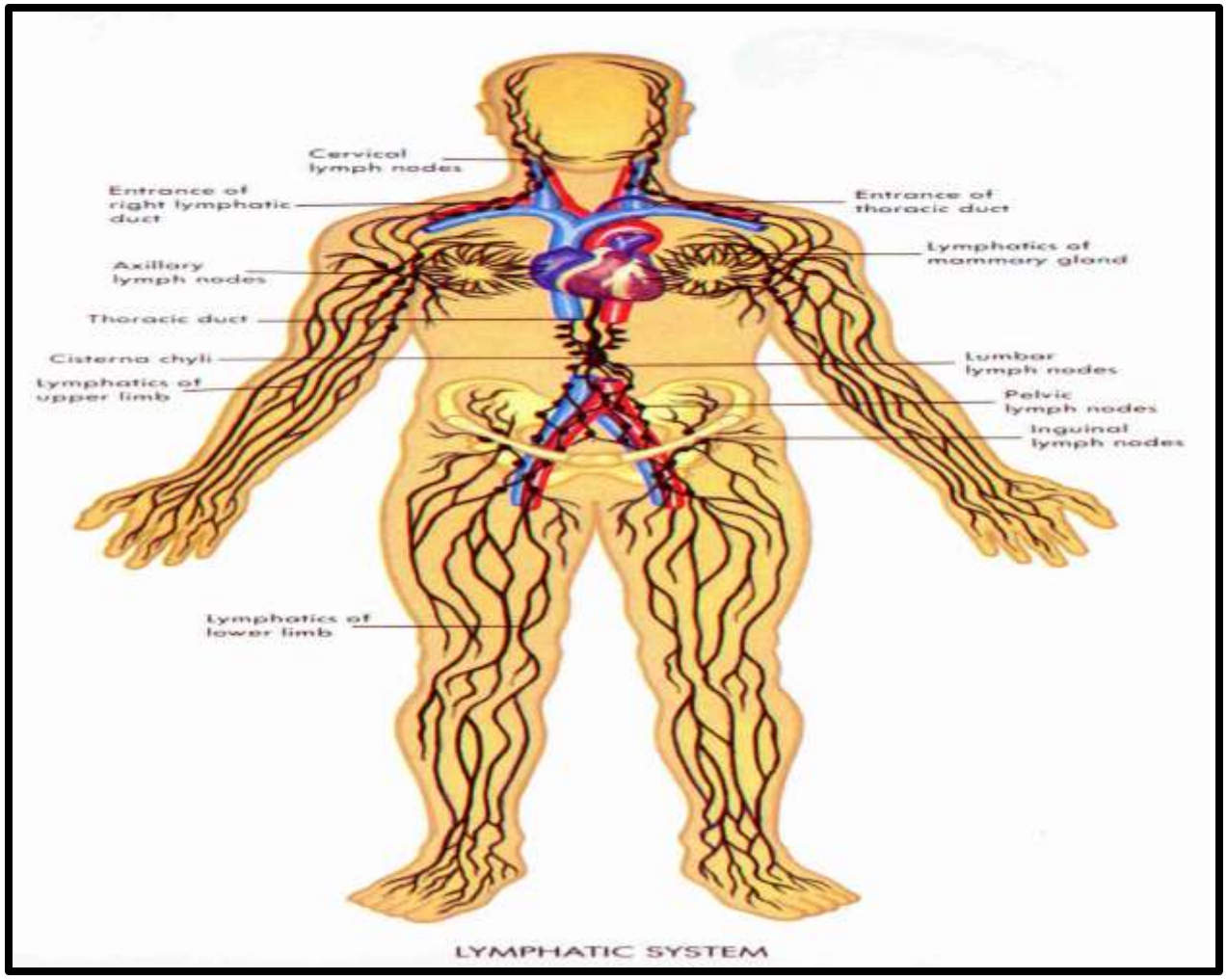
<u>Antibodies (immunoglobulins</u>) are proteins produced by **B cells** (Bone Marrow Cells) of the immune system in response to exposure to antigens. Each antibody contains a paratope which recognizes a specific epitope on an antigen, acting like a lock and key binding mechanism. This binding helps to eliminate antigens from the body, either by direct neutralization or by 'tagging' for other cells or agents of the immune system to eliminate.

What are lymphocytes and what do they do?

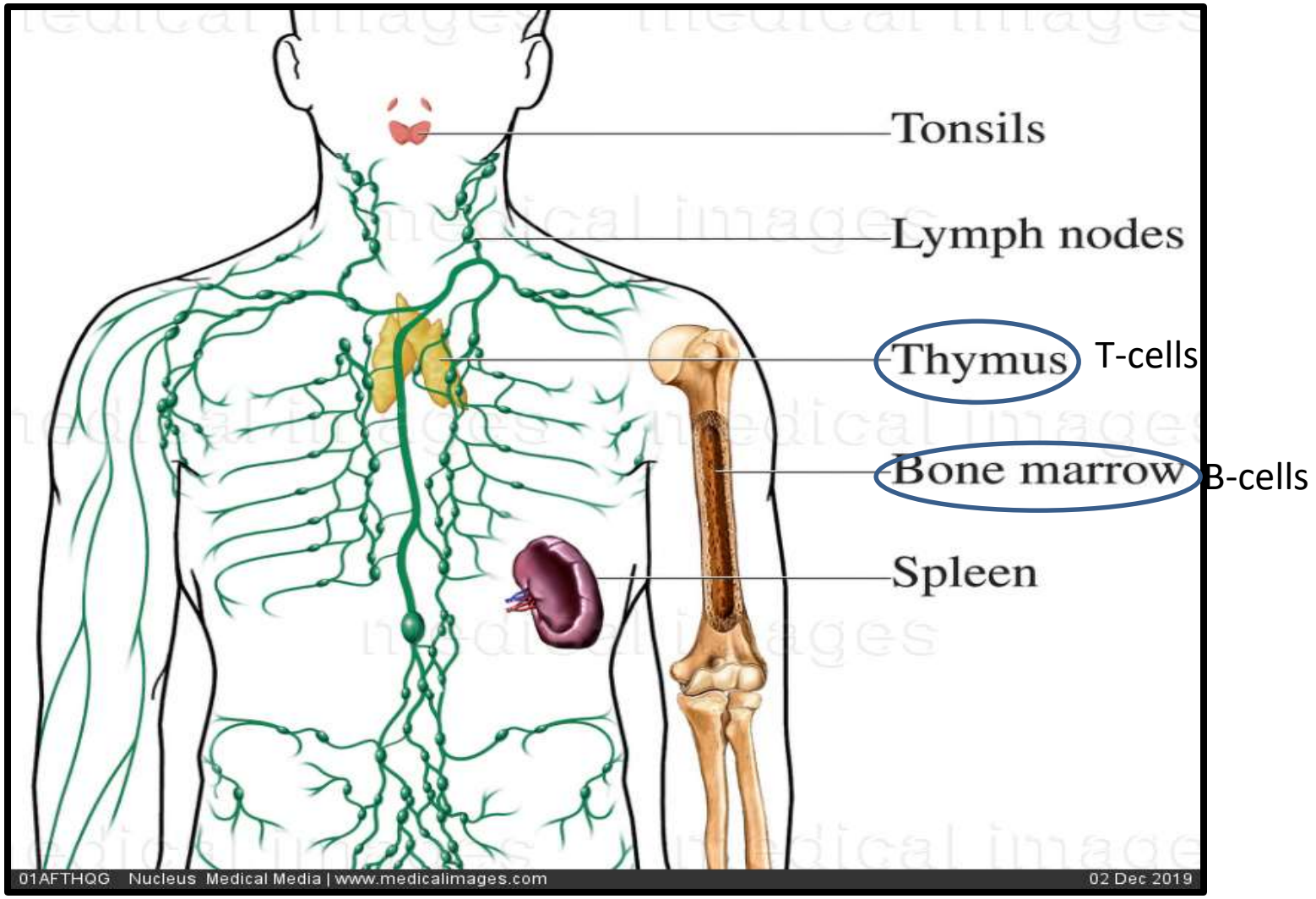
Lymphocytes are **cells that circulate in your blood and lymphatic system that are part of the immune system**. There are two main types of lymphocytes: **T cells (Thymus Cells) and B cells.**

- **B cells** produce antibody molecules that can latch on and destroy invading viruses or bacteria.
- There are two main types **T cells**. **Cytotoxic T-cells** destroy infected cells. **Helper T-cells** send signals that direct other immune cells to fight infection.

The Lymphatic System: a parallel system to the vascular system



Lymphatic System/lymphoid tissue/**lymphocytes**



The acute immune response (**first responders**) to antigens (like bacteria or viruses) and injury

- **Cytokines** are secreted by immune cells and act as signaling proteins reacting to injury, infections or insult. They include **Interleukins** (30 or more), **Interferons** (some20 or so), **Growth factors**, **Tumor Necrosis factor**.
- Cytokine storms as in overreaction of the immune system and sepsis (can cause immune cells to attack normal cells.
- Cytokines can be described as the **software** that runs the immune system and when that software malfunctions, dysregulation of the immune system can result in debilitating autoimmune diseases such as lupus, arthritis, and diabetes.

Interleukins: a large group of proteins that can elicit many reactions in cells

- Interleukins (IL) are a type of cytokine first thought to be expressed by leukocytes alone but have later been found to be produced by many other body cells.
- They play essential roles in the activation and differentiation of immune cells
- The primary function of interleukins is, therefore, to modulate growth, differentiation, and activation during inflammatory and immune responses.

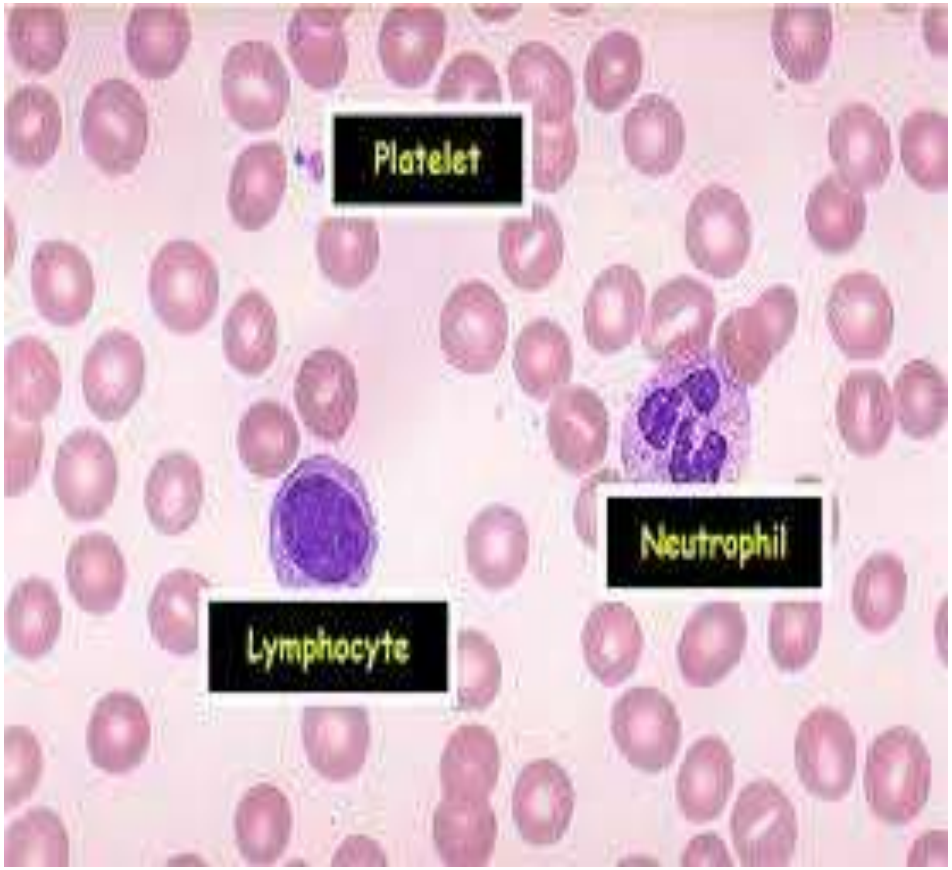
Interferons

- **Interferons**: Interferons signal cells to put up their defenses against viruses invading your body. In this way, interferons “interfere” in the process that allows viruses to replicate, or make more viruses once they’ve invaded a healthy cell.

Tumor Necrosis Factor

- **Tumor Necrosis Factor (TNF), is an inflammatory** cytokine produced by macrophages/monocytes during acute **inflammation** and is **responsible for a diverse range of signaling events within cells, leading to necrosis or apoptosis**. The protein is also important for resistance to infection and cancers.

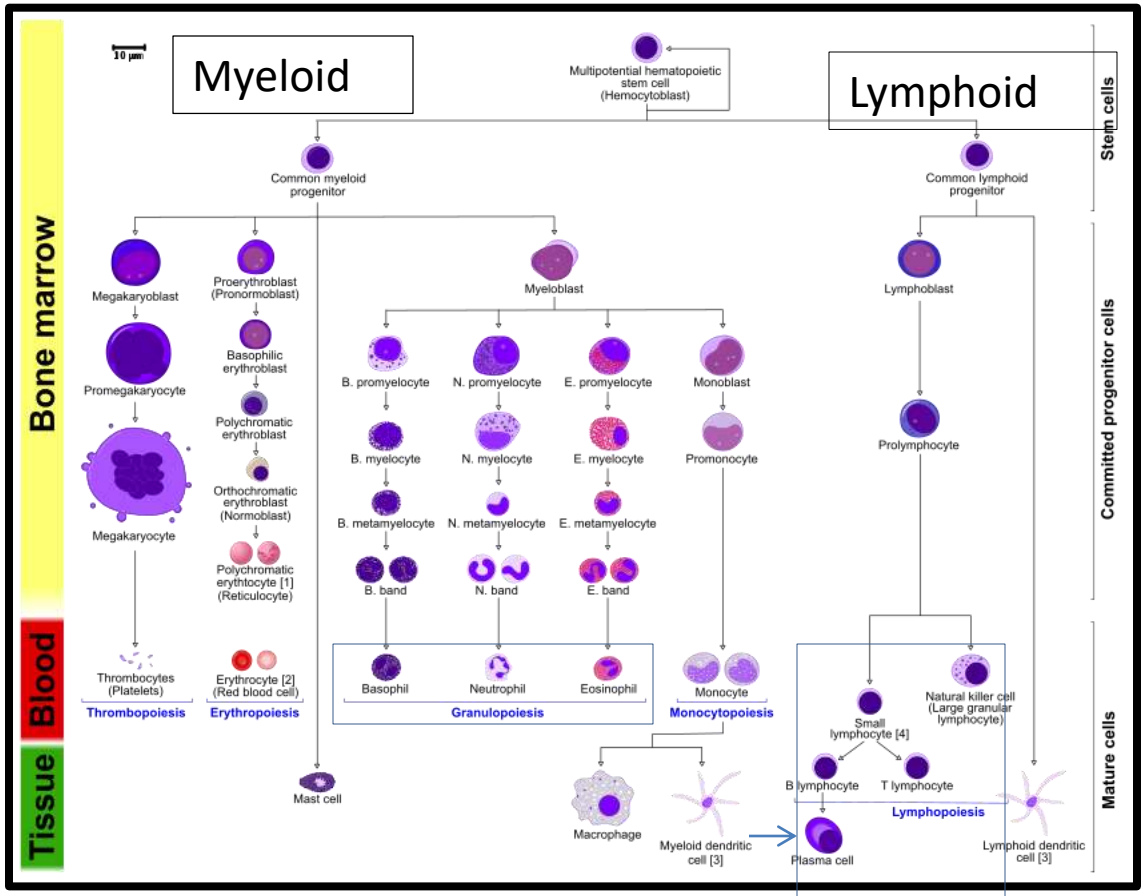
Peripheral Blood Smear: **Neutrophils or polys or polymorphic nuclear leukocytes** from the bone marrow circulate in the blood stream and are a major players in the body's defense against **bacterial infections**.



CBC and Differential Blood Cell Count (**WBC-5-10,000 normal**)

Neutrophils Relative	**37.0** %	*bacterial infections*
Lymphocytes Relative	**53.0** %	*immune system, leukemia*
Monocytes Relative	**7.0** %	*immune system, globulins, mature into macrophages*
Eosinophils Relative	**2.0** %	*Allergic reactions, parasitic diseases*
Basophils Relative	**1.0** %	*inflammation*
Neutrophils Absolute	**3.3** 10*3/uL	*1.5 - 7.8 10*3/uL*
Lymphocytes Absolute	**4.7** 10*3/uL	*0.8 - 3.9 10*3/uL*
Monocytes Absolute	**0.6** 10*3/uL	*0.2 - 0.9 10*3/uL*
Eosinophils Absolute	**0.2** 10*3/uL	*0.0 - 0.5 10*3/uL*
Basophils Absolute	**0.1** 10*3/uL	*0.0 - 0.2 10*3/uL*

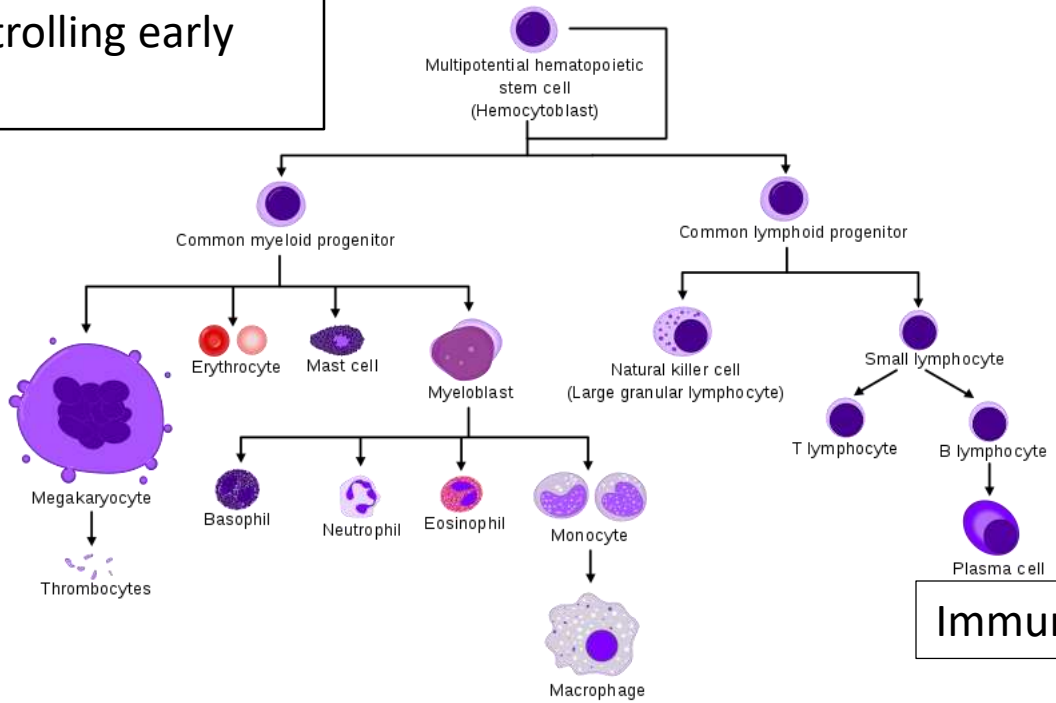
Blood Cell Formation (Myeloid and Lymphoid Cells)



Plasma cell produce immunoglobulins

Another Diagram of Immune Cells

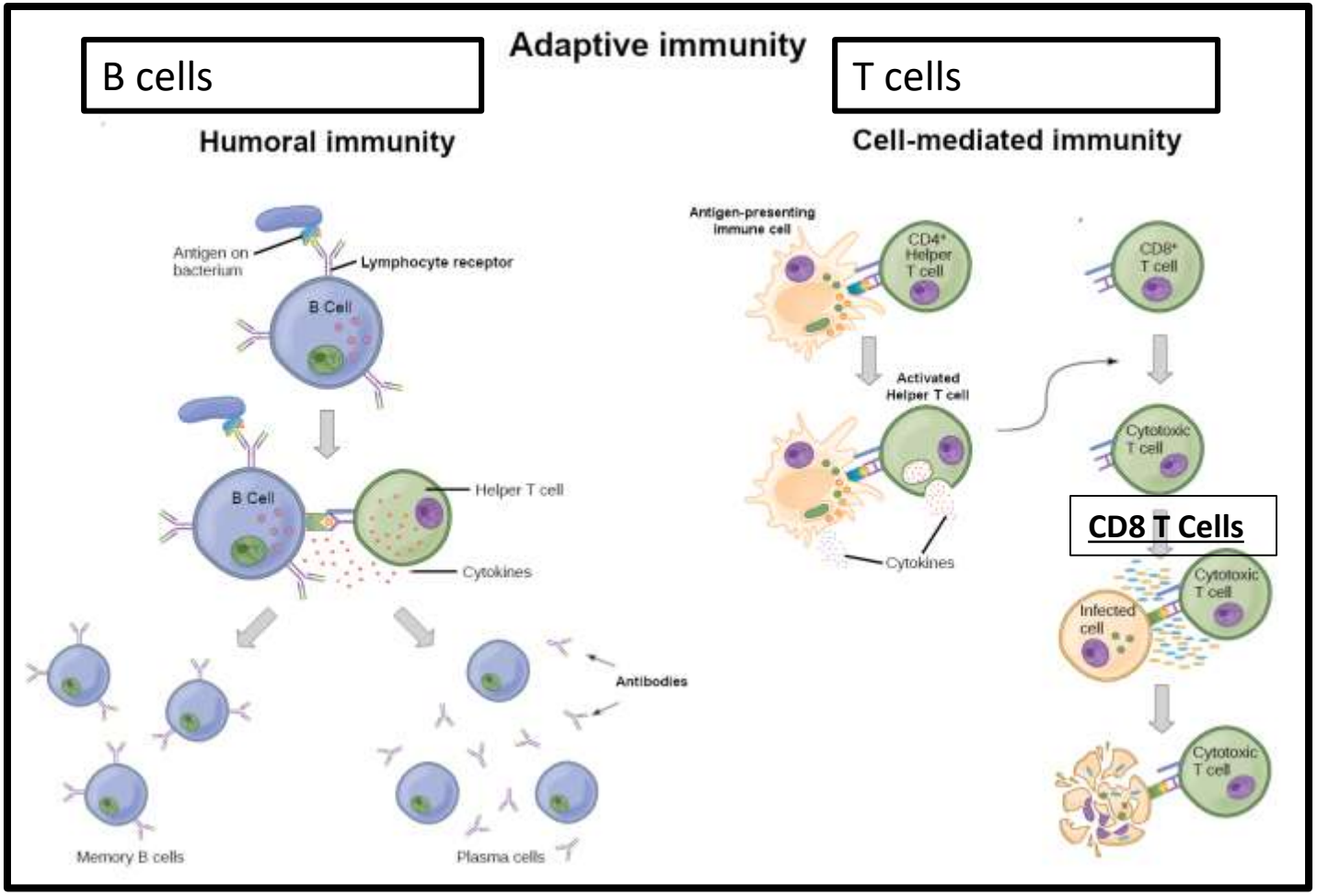
NK cells are best known for killing virally infected cells, and detecting and controlling early signs of cancer.



Immunoglobulins

Phagocytosis

The Lymphocyte or Lymphoid System and how it works



Cytotoxic T Cells (CD8 T Cells)

Cytotoxic T cells kill their target cells, primarily by releasing cytotoxic granules into the cell to be killed. These cells recognize their specific antigen (such as fragments of viruses) when presented by **MHC (Hyman leukocyte antigens (HLA) Class I)** molecules that **are present on the surface of all human nucleated cells.**

MHC Class I molecules interact with a protein called CD8 on the cytotoxic T cells, which helps to identify this cell type. **Cytotoxic** T cells require several signals from other cells to be activated, such as from dendritic cells and T helper cells.

Their main function is to kill virally infected cells, but they also kill cells with intracellular bacteria or tumorous cells.

T-Helper Cells (Th) (CD4 T Cells)

T helper cells have a wider range of effector functions than CD8 T cells and can differentiate into many different subtypes, such as **Th1, Th2, Th17** and regulatory T cells.

They become activated when they are presented with peptide antigens by MHC Class II molecules, which are expressed on the surface of APCs. **MHC Class II** molecules interact with a protein called CD4 on the T helper cells, which helps to identify this cell type.

The roles of a CD4 T cell may include activating other immune cells, releasing **cytokines,** and helping B cells to produce antibodies. They help to shape, activate and regulate the adaptive immune response.

Memory T Cells

Following an infection, antigen-specific, long-lived memory T cells are formed. **Memory T cells** are important because they can quickly expand to large numbers of effector T cells upon re-exposure to the antigen and have a low threshold for activation.

They provide the immune system with memory against previously encountered antigens. Memory T cells may either be CD4+ or CD8+.

Other T cells

- There are several types of T cells based on their specific function: helper/effector, cytotoxic, memory, regulatory and gamma delta (γδ) T cells

Immunoglobulins: Humoral Immunity; B lymphocytes that form plasma cells

- **Immunoglobulins**, also known as **antibodies,** are glycoprotein molecules produced mainly by plasma cells and initiate the immune response by specifically recognizing and binding to particular antigens, such as bacteria or viruses, and aiding in their destruction.
- These immunoglobulins are produced by B cells of the immune system in response to exposure to antigens. Each antibody contains a paratope which recognizes a specific epitope on an antigen, acting like a lock and key binding mechanism.

Classes of Immunoglobulins

The five major antibody classes are:

- **Immunoglobulin G (IgG)**, 80%, is found in all body fluids and protects against bacterial and viral infections.
- **Immunoglobulin M (IgM)**, is the first antibody to be released by B cells during primary response
- Immunoglobulin D (IgD), important in B cell activation
- **Immunoglobulin A (IgA)**, which is found in high concentrations in the mucous membranes, particularly those lining the respiratory passages and gastrointestinal tract, and prevent attachment of pathogens to epithelial surfaces. Allergies
- **Immunoglobulin E (IgE)**, found on mast cells and basophils and triggers release of histamine which is associated mainly with **allergic reactions** (when the immune system overreacts to environmental antigens such as pollen or pet dander). It is found in the lungs, skin, and mucous membranes.

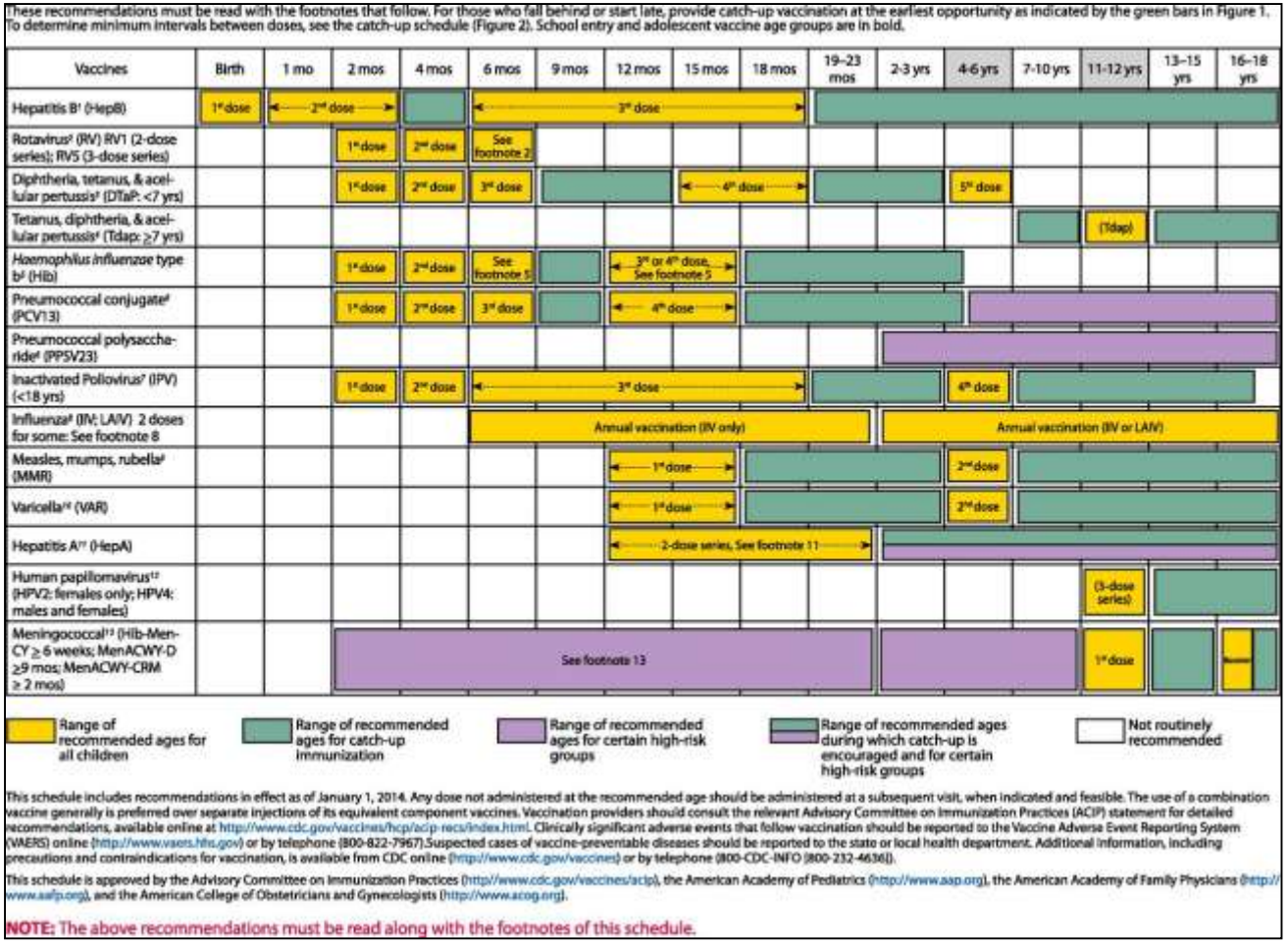
Complement (another element in the immune system) that is primarily made in the liver

- The complement system of which there are nine major components (**bind to antigen–antibody complexes) that facilitate the uptake and destruction of pathogens by phagocytic cells**. This occurs by the specific recognition of bound complement components by complement receptors (CRs) on phagocytes.
- The serum complement system is a series of dissolved proteins that protect against a variety of pathogens. Briefly, the classical pathway is activated by antibody that has bound to the surface of an invading cell. The membrane-bound antibody activates the first complement component, which activates eight additional complement proteins. The ultimate result is the formation of what is known as the membrane attack complex, a series of proteins that forms a pore in the membrane, resulting in the lysis of target cells.

What vaccines should kids receive?

- Chickenpox (varicella) vaccine
- Diphtheria, tetanus, and pertussis (DTaP) vaccine
- Hepatitis A and B (HepA+B) vaccine
- *Haemophilus influenzae* type b (Hib) vaccine
- Human papillomavirus (HPV) vaccine
- Influenza (flu) vaccine
- Measles, mumps, and rubella (MMR) vaccine
- Meningococcal (MenACWY, MenB) vaccines
- Pneumococcal (PCV13, PPSV23) vaccines
- Polio (IPV) vaccine
- Rotavirus (RV) vaccine
- COVID-19 vaccine
- Dengue vaccine

Immunization Records



These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are in bold.

Vaccines	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13–15 yrs	16–18 yrs
Hepatitis B[1] (HepB)	1st dose	2nd dose			3rd dose											
Rotavirus[2] (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See footnote 2											
Diphtheria, tetanus, & acellular pertussis[3] (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose			4th dose				5th dose				
Tetanus, diphtheria, & acellular pertussis[4] (Tdap: ≥7 yrs)														(Tdap)		
Haemophilus influenzae type b[5] (Hib)			1st dose	2nd dose	See footnote 5		3rd or 4th dose, See footnote 5									
Pneumococcal conjugate[6] (PCV13)			1st dose	2nd dose	3rd dose		4th dose									
Pneumococcal polysaccharide[6] (PPSV23)																
Inactivated Poliovirus[7] (IPV) (<18 yrs)			1st dose	2nd dose	3rd dose							4th dose				
Influenza[8] (IIV; LAIV) 2 doses for some: See footnote 8					Annual vaccination (IIV only)						Annual vaccination (IIV or LAIV)					
Measles, mumps, rubella[9] (MMR)							1st dose					2nd dose				
Varicella[10] (VAR)							1st dose					2nd dose				
Hepatitis A[11] (HepA)							2-dose series, See footnote 11									
Human papillomavirus[12] (HPV2: females only; HPV4: males and females)														(3-dose series)		
Meningococcal[13] (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥ 2 mos)			See footnote 13											1st dose		Booster

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

Range of recommended ages during which catch-up is encouraged and for certain high-risk groups

Not routinely recommended

This schedule includes recommendations in effect as of January 1, 2014. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines) or by telephone (800-CDC-INFO (800-232-4636)).

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/acip), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Adult Immunizations

Almost 1 out of every 3 people in the US will develop shingles in their lifetime (adult reactivation of chicken pox/varicella in nerves)

- Shingles vaccine, which protects against shingles and the complications from the disease (recommended for healthy adults 50 years and older) Two Shots/Expensive!
- Pneumococcal polysaccharide vaccine (PPSV23), which protects against serious **pneumococcal** disease, including meningitis and bloodstream infections (recommended for all adults 65 years or older, and for adults younger than 65 years who have certain health conditions)

Leukemias and Lymphomas

- Acute Lymphocytic Leukemia (ALL)
- Acute Myeloid Leukemia (AML)
- Chronic Lymphocytic Leukemia (**CLL--10 percent of all leukemia's**) Rx. Rituxan or rituximab.
- Chronic Myeloid Leukemia (CML) translocation of chromosome 9 &22 (Philadelphia chromosome) diagnosed with Karyotype, FISH, and PCR. New Rx. With tyrosine kinase inhibitors, good outcomes
- Chronic Myelomonocytic Leukemia (CMML)
- Polycythemia Vera-too many RBCS; JAK2 pathway, Dx. PCR and increase EPO. Thrombosis main issue. Phlebotomy, and Hydroxyurea.
- Essential thrombocytosis: JAK2, CALR and MPL mutations, too may platelets, usually asymptomatic
- Myelofibrosis; nasty disease, burned out bone marrow, allogenic stem cell transplant with 18 month survival or less.
- Multiple Myeloma **(10 percent second only to CLL)**

Multiple Myeloma: plasma cell dyscrasias

- More than 12,000 deaths per year
- Varying stages-early MGUS that you just observe that progresses.
- Plasma cells make abnormal proteins (M).
- Diagnosis based on increased CA+, renal insufficiency (CC<40), anemic <10 gms and lytic bone lesions. Bone marrow >60 percent plasma cells confirms the diagnosis.
- Improving therapies with >50% 5 year survival

Autoimmune and Inflammatory Immune Diseases

- Rheumatoid Arthritis
- Psoriasis
- Multiple Sclerosis
- Crohn's Disease
- Ulcerative Colitis
- Type I diabetes/juvenile
- Addison's Disease
- Graves Disease
- Scleroderma (system sclerosis-limited and diffuse-vascular injury) Raynaud's Phenomena-mycophenolate, cyclopsphanide, prednisone. ANA +
- Lupus Erythematosus
- Pernicious Anemia
- Polyarthritis Nodosa
- Myasthenia Gravis

Treatment of some Autoimmune Diseases that block Tumor Necrosis Factor

- Fortunately, there are drugs that block excess tumor necrosis factor.(TNF) They're part of a group called biologics that can be used to treat rheumatoid arthritis (RA), psoriatic arthritis, inflammatory bowel disease (Crohn's and ulcerative colitis), ankylosing spondylitis, and psoriasis.

- ❑ TNF inhibitors
- ❑ Anti-TNF drugs
- ❑ TNF blockers

Adalimumab (Humira)
Certolizumab (Cimzia)
Etanerce[t (Enbrel)
Golimumab (Simponi)
Omf;oxo,ab (Remicade)

SLE-SYSTEMIC LUPUS ERYTHEMATOSIS

- Rare (140/100,000) but more common in minorities and young women (9 females to 1 male)with a strong genetic predisposition. Related to deposition of C3 and C5 complement as an autoimmune disease.
- Treatment with Hydroxychloroquine, Steroids and Cyclophosphamide and now Rituximab.
- Symptoms; butterfly rash, Reynaud's phenomena, alopecia and depression
- Delay in diagnosis due to wide range of symptoms than mimic other disorders.

Common Tests for autoimmune diseases other than PCR.

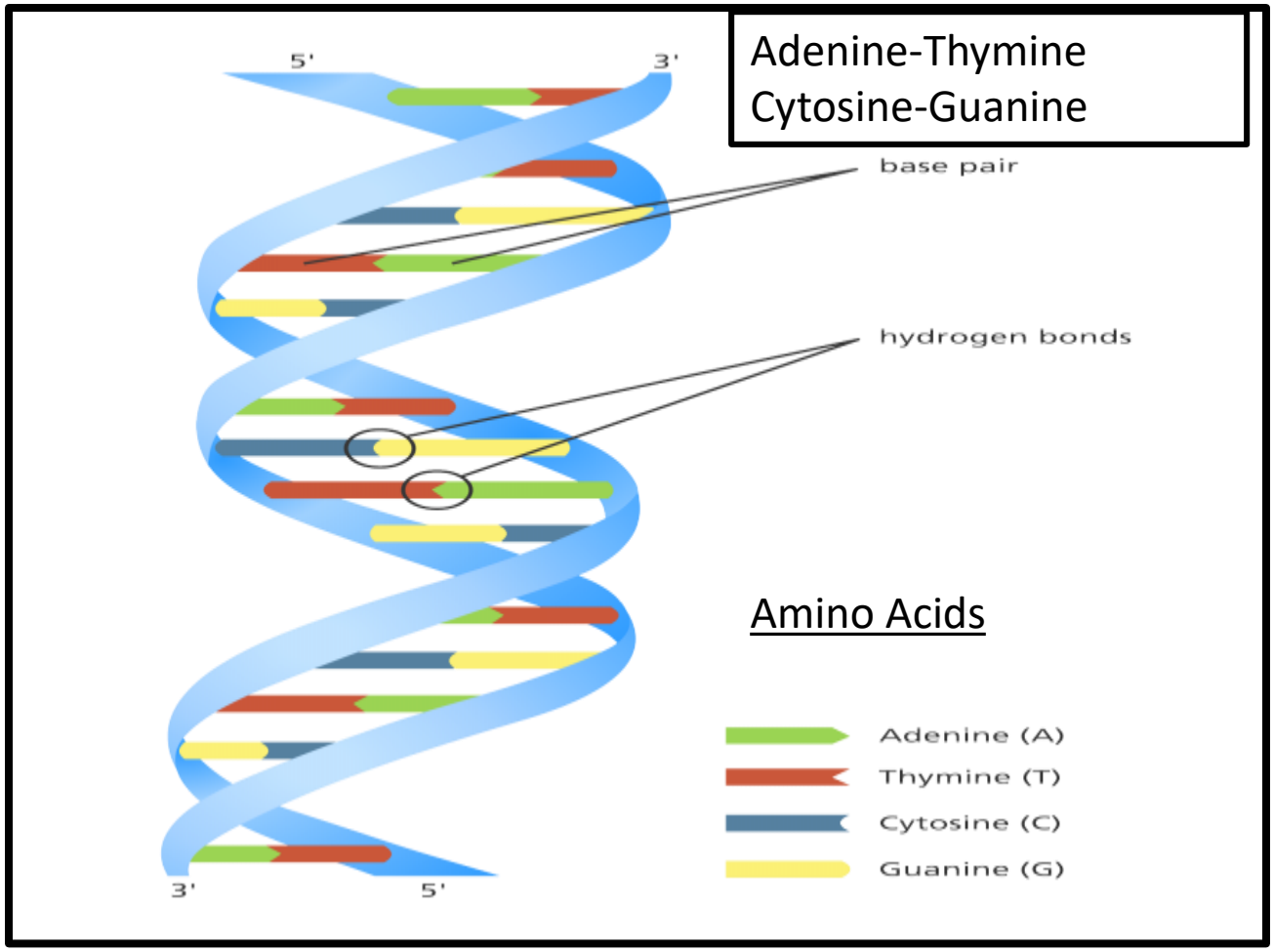
- Antinuclear antibody (ANA)
- Rheumatoid factor (RF)
- CBC (White Blood Cell Counts)
- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Urinalysis
- Complement Fixation test

10 MINUTE BREAK; HALF TIME

How recently did **Genetics/genome** Came into View?

- In **1956,** the double helix structure of genetic material DNA (deoxyribonucleic acid) was reported by James Watson and Francis Crick.
- In **1966,** the molecular make up of genes and chromosomes was found to consist of the sequencing of just four amino acids: namely **adenine, guanine, cytosine and thymine** (**A,G,C,T)** which were linked to a five carbon sugar **deoxyribose** (**$C_5H_{10}O_{5)}$.** with a **phosphate (PO_4**) backbone or linkage.
- The human genome consists of three billion of these nucleotides or "letters" and most all of the 60 trillion cells in the human body contain a complete copy of this genome.
- There are **23 pairs of chromosomes** that contain the genetic codes.

Genetics and Cellular Anatomy



What is a chromosome?

- **Chromosomes** are the things that make organisms what they are. They carry all of the information used to help a cell grow, thrive, and replicate. **Chromosomes** are made up of DNA. Segments of DNA in specific patterns are called **genes**. ... You will find the **chromosomes** in the nucleus of all cells.
- Mitochondria, the energy producing organelle in the cell, also contain DNA.
- A **chromosome** contains hundreds to thousands of **genes**.
- The shortest DNA molecule found in humans are about 17,000 nucleotides long and the longest consists of over 100 million.

Definition of an Allele: An allele is any one of two or more genes that may occur alternatively at a **given site (locus) on a** chromosome. **Alleles** may occur in pairs, or there may be multiple **alleles** affecting the expression (phenotype) of a particular trait.

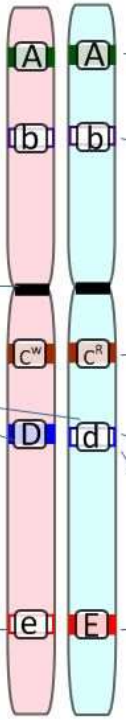
Genes and Chromosomes

Definitions

This image shows a pair of homologous chromosomes.
Name and annotate the labeled features.

Genotype
*The **combination of alleles** of a gene carried by an organism*

Phenotype
*The **expression of alleles** of a gene carried by an organism*



Homozygous dominant
Having two copies of the same dominant allele

Homozygous recessive
Having two copies of the same recessive allele. Recessive alleles are only expressed when homozygous.

Centromere
Joins chromatids in cell division

Codominant
Pairs of alleles which are both expressed when present.

Alleles
***Different versions** of a gene*
Dominant alleles = capital letter
Recessive alleles = lower-case letter

Heterozygous
Having two different alleles. The dominant allele is expressed.

Carrier
*Heterozygous carrier of a **recessive disease-causing** allele*

Gene loci
Specific positions of genes on a chromosome

Difference between DNA & RNA (DNA is the template for RNA)

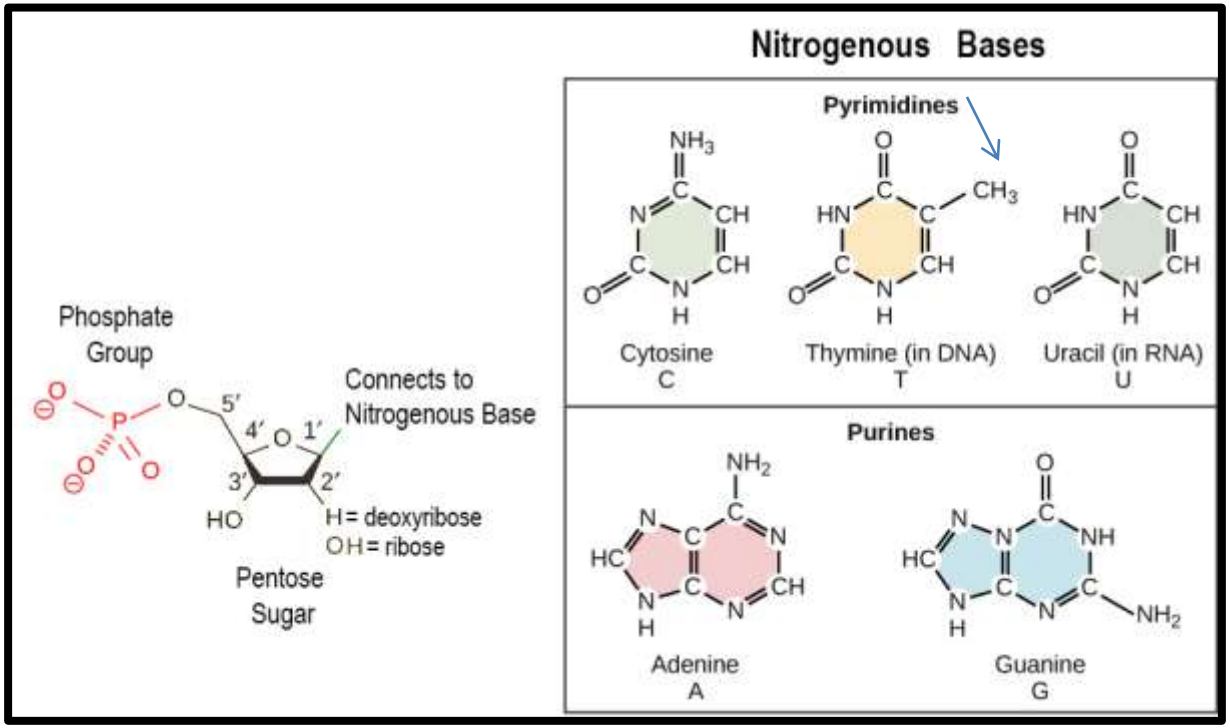
- **DNA** is a long polymer with **deoxyribose** (a sugar) and phosphate backbone. Having **four** different nitrogenous bases: adenine, guanine, cytosine and thymine.
- **RNA** is a polymer with a **ribose** (a sugar) and phosphate backbone. **Four** different nitrogenous bases: adenine, guanine, cytosine, and uracil.

Differences between DNA & RNA: **Thymine** is the pyrimidine base of the DNA, whereas **Uracil** is the pyrimidine base of the RNA. The occurrence of thymine and uracil is a crucial difference as thymine is only found in DNA and uracil is only found in RNA. **Methyl group** is absent in uracil whereas present in thymine at the C-5 position.

What is the chemistry of cytosine, adenine, thymine and guanine made

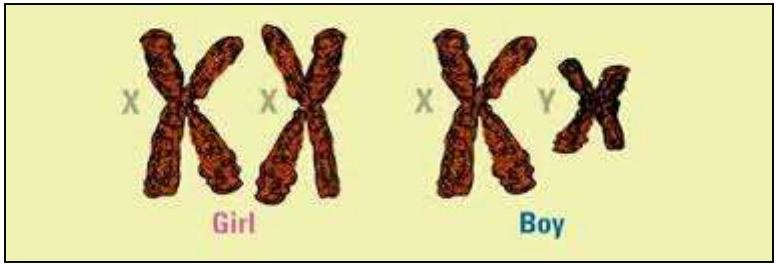
- As a nitrogenous base, cytosine is full of nitrogen atoms (it has three). It also has one ring of carbon, which makes it a **pyrimidine**. A **purine,** on the other hand, has two rings of carbon. There are two pyrimidines, cytosine and thymine, and two purines, adenine and guanine, in DNA.

Basic structure of DNA

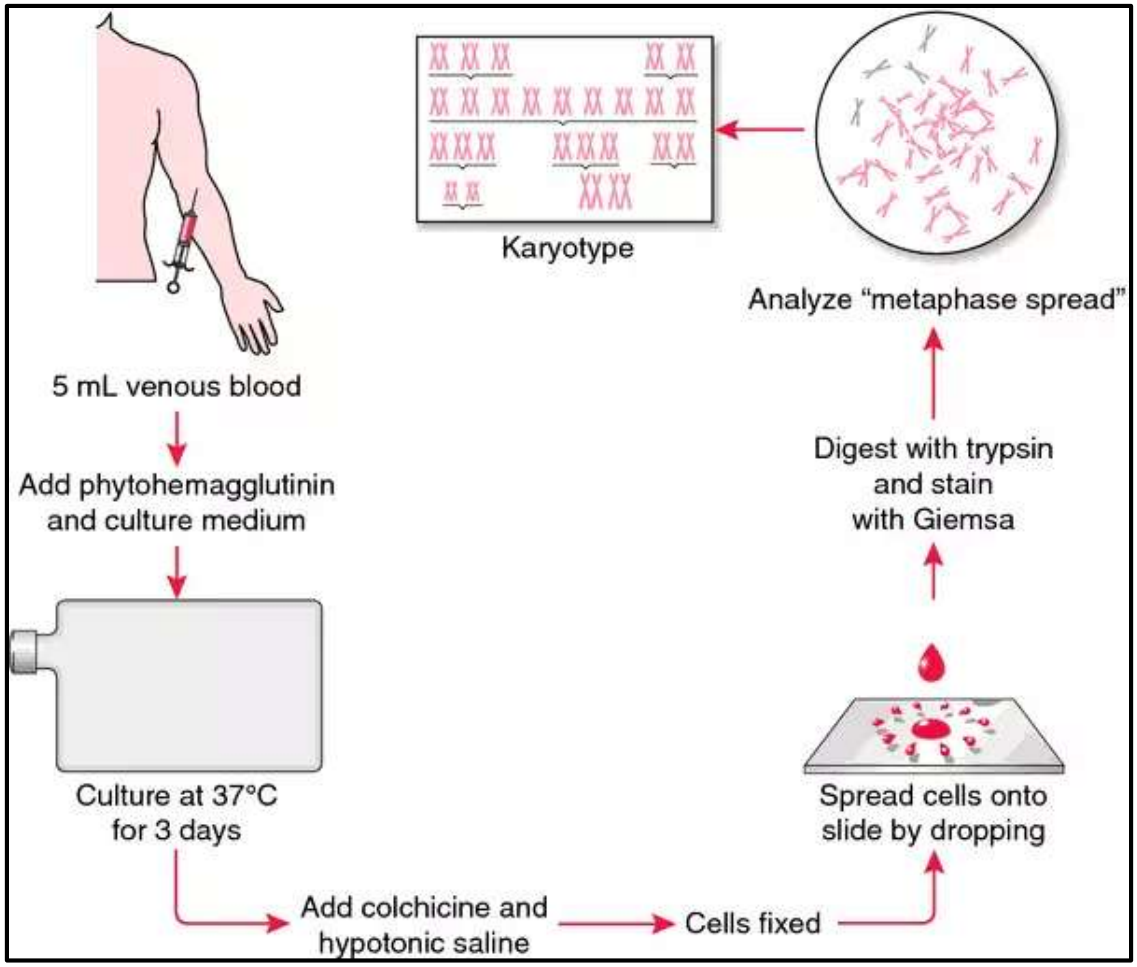


General Knowledge

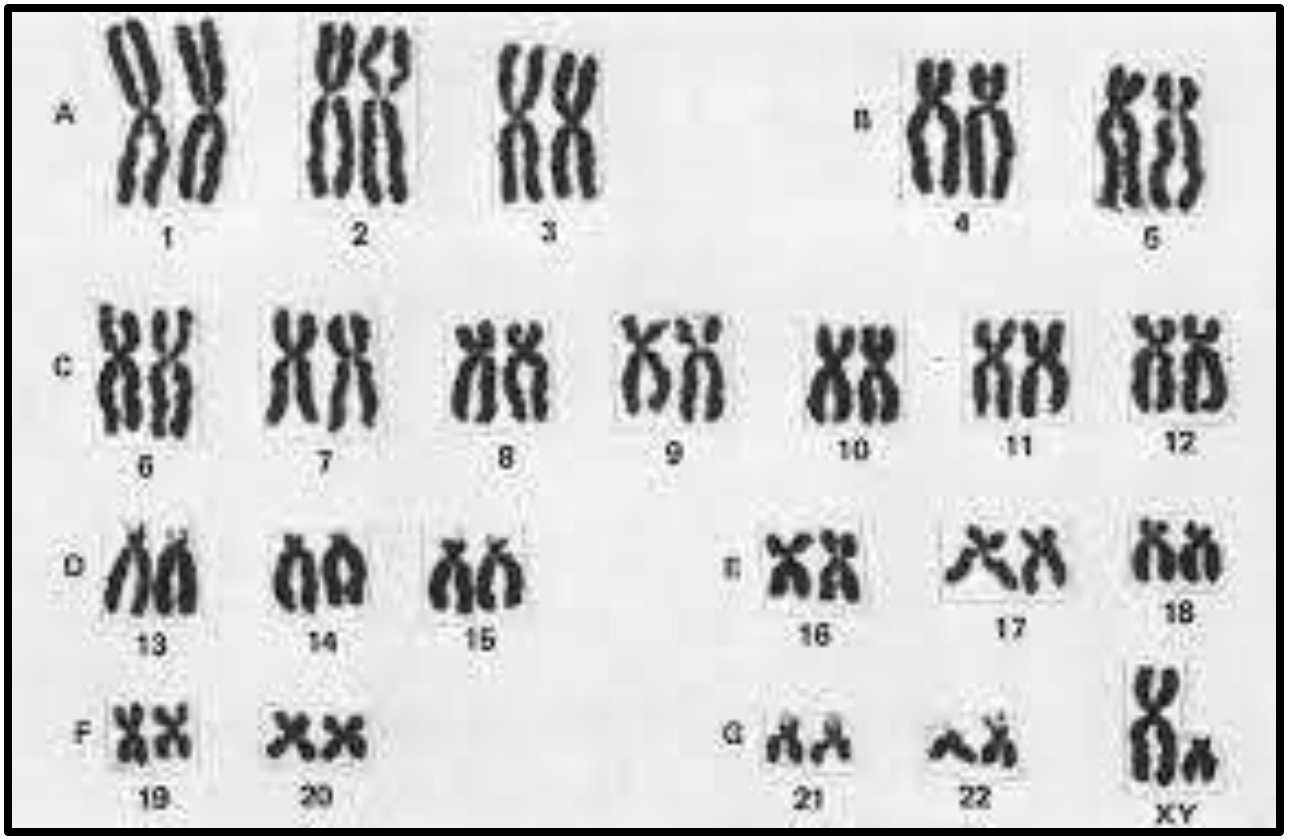
- In **humans**, each cell normally contains 23 pairs of **chromosomes**, for a total of 46. Twenty-two of these pairs, called autosomes, look the same in both males and females. The 23rd pair, the sex **chromosomes**, differ between males and females.



Karyotyping



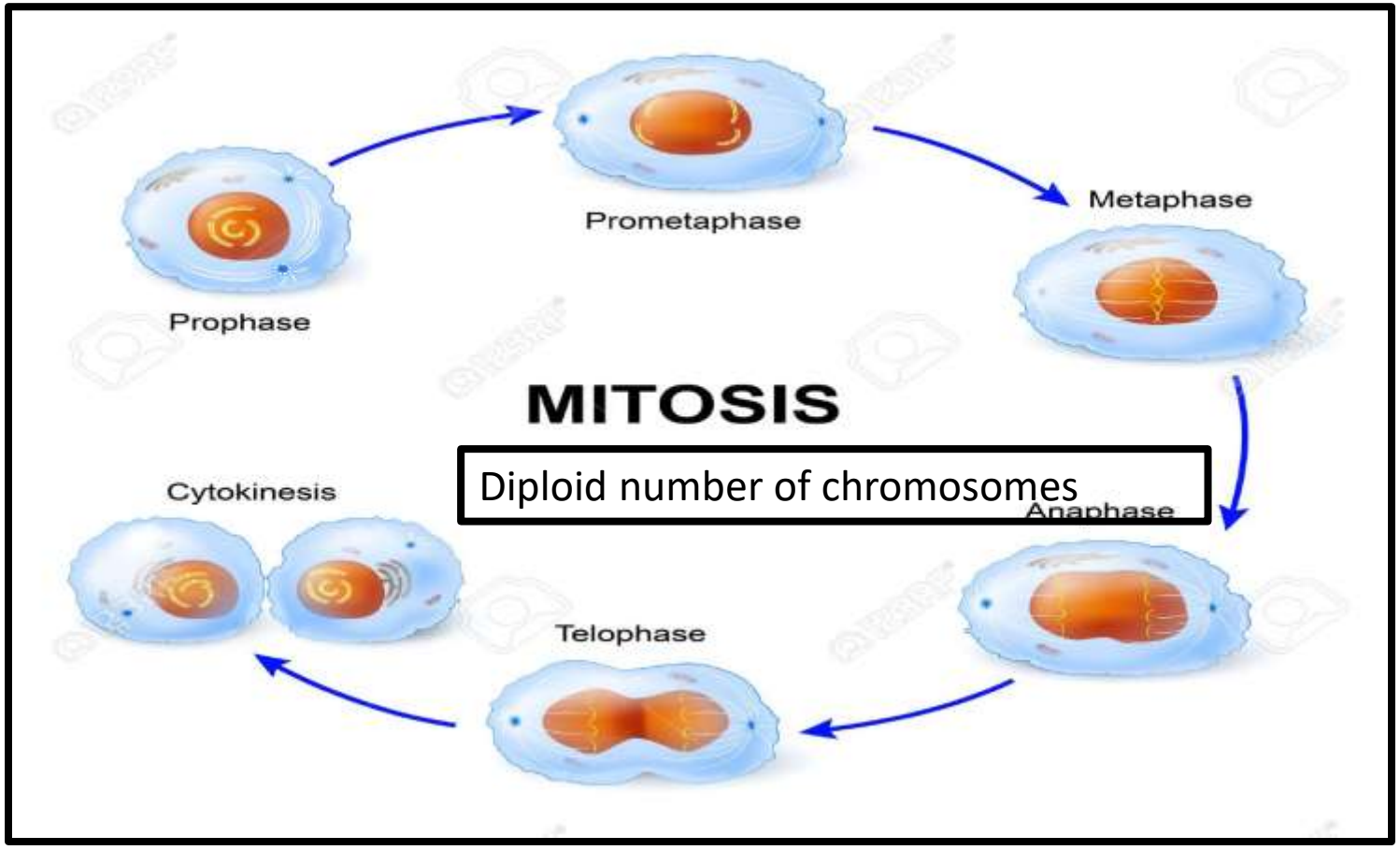
The Karyotype of the Human Species



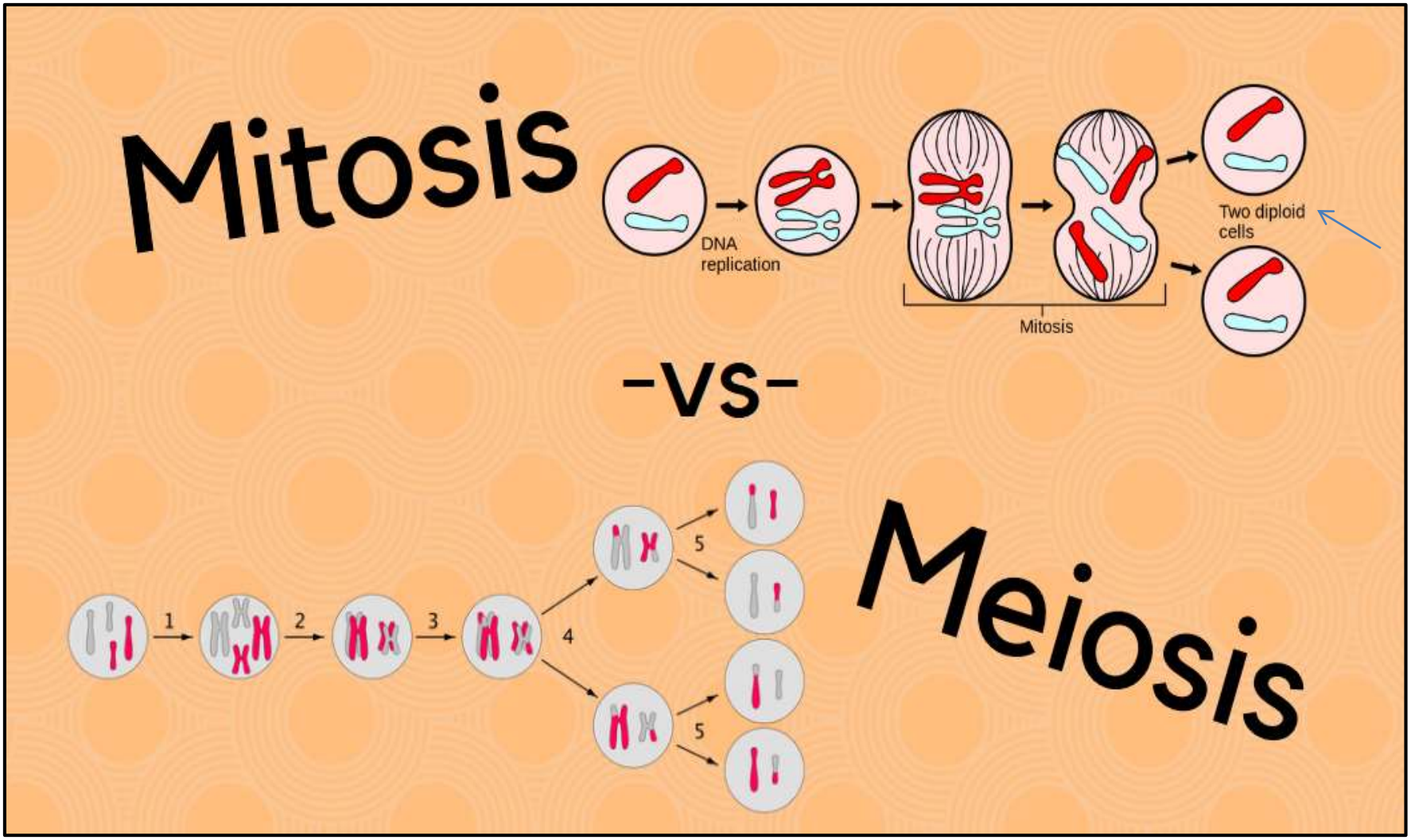
Gene Mutations

- Silent
- Deletions
- Insertions
- Translocations
- Errors in DNA replications
- Errors in DNA recombination
- Chemical or radiation effects
- DNA repair; mismatched, nucleotide excision and many more

Mitosis: Process of Cell Division



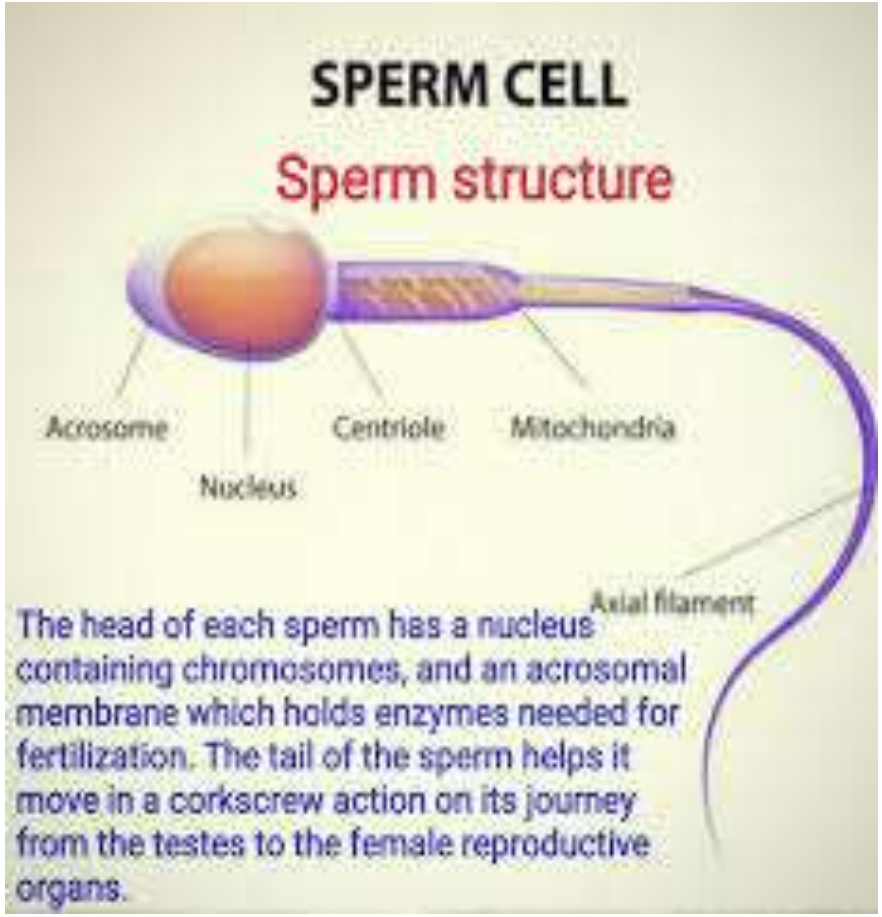
Meiosis split the DNA in two to produces the DNA of Sperm and Ova causing our offspring to be a combination of both parents

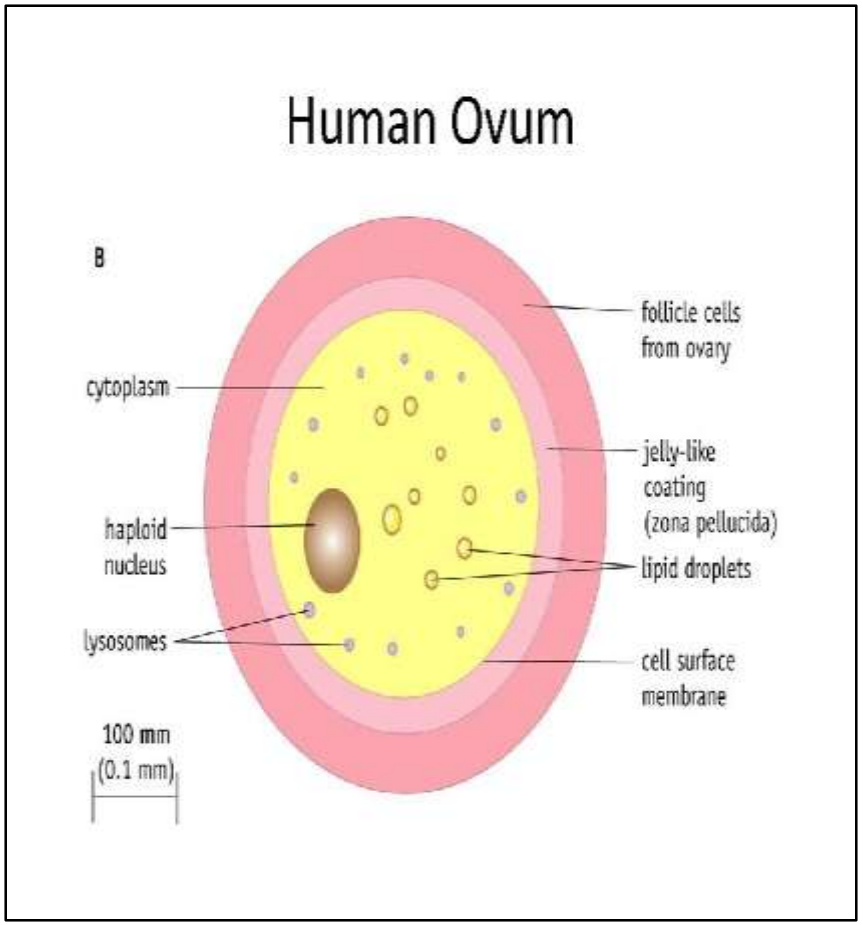


Replication of DNA and formation of MRNA

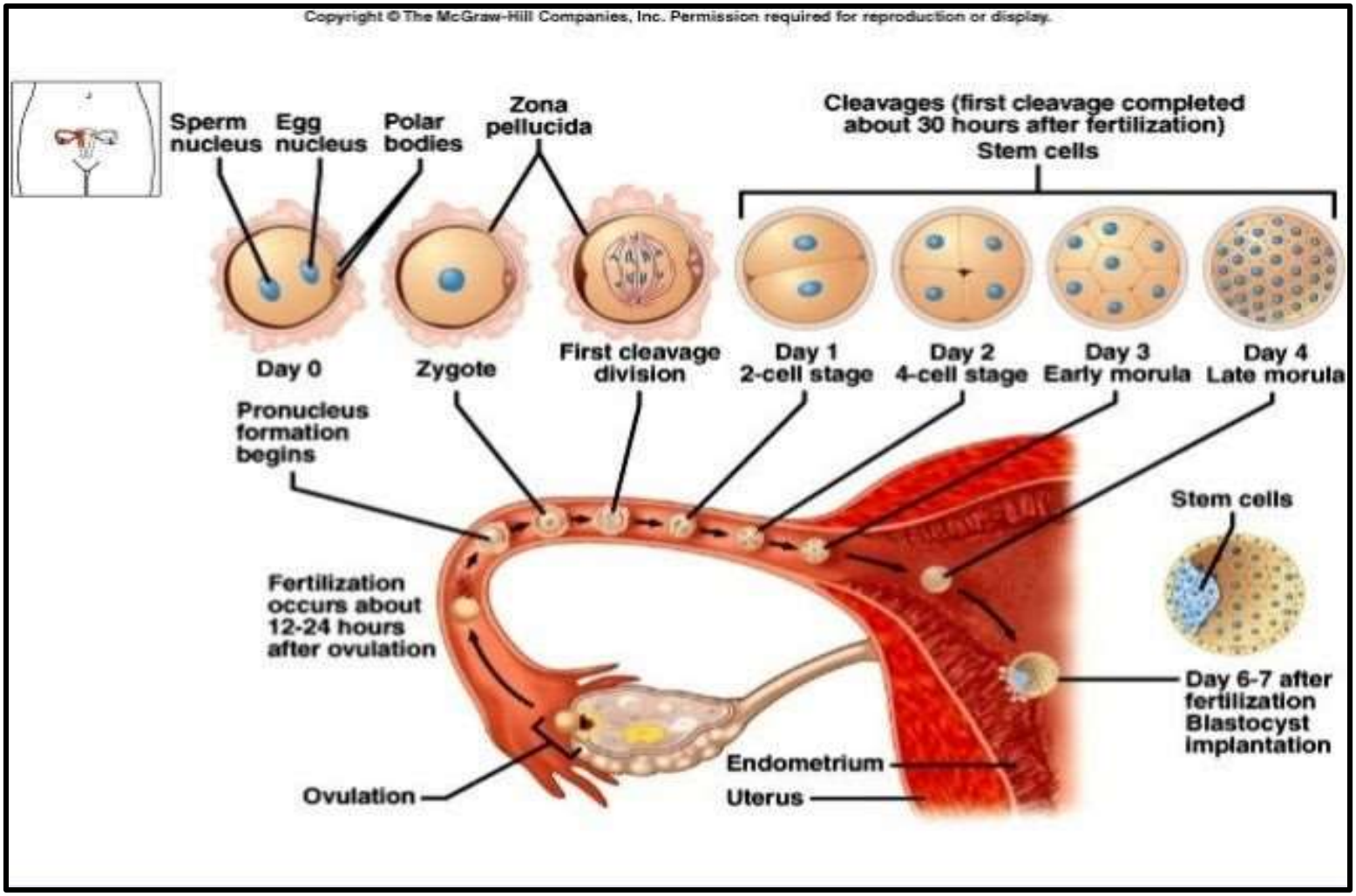
- DNA polymerase catalyzes the system of replication that works like a zipper that genetic DNA is the template with unzipping of the elements of the folded double helix.
- Helicase enzyme that causes unzipping.
- An RNA polymerase uses a DNA sequence (Exons and introns**)** as **a template** for a piece of RNA; every triplet of letters or **codons**
- **Exons and introns** are features of DNA, whereas **codons** are features of RNA.
- This message is read by the ribosome and every triplet of letters in the MRNA tells the translation mechanism what nucleotides to add to the triplet codons to form MRNA.
- The Ribosome adds additional proteins and folds it into shape.

Sperm (120,000,000 per CC) and Ova (300,000 remain at puberty and of these, only 300 to 400 will be ovulated during a woman's reproductive lifetime





The Travels of the fertilized ova



Early Spontaneous Abortions

In the first trimester, 1 in 3 pregnancies end spontaneously in the first trimester ("early pregnancy loss"), affecting 1 million patients in the US annually. The most common etiology of early pregnancy loss or miscarriage is fetal chromosomal abnormalities, accounting for more than two-thirds of pregnancy losses between 6 and 10 weeks' gestation.

Advancing maternal age, prior pregnancy loss, teratogenic exposures, and maternal endocrine or autoimmune conditions, such diabetes, hyperthyroidism, and systemic lupus erythematosus, are risk factors.

When Should Someone have a Genetic test? **Pharmacogenomics** is coming of age with 25 genes identified as being important in drug interactions, metabolism and efficacy.

- *At birth? Pregnancy?*
- *When you come down with a disease like cancer for* ***precision medical care?***
- *Reference and genetic guide for your decedents?*

<u>Arguments to get it in the newborn period</u>

1. Uncover repairable genetic defects (CRISPR-cas9 or gene replacement therapy on the horizon)
2. Predict predisposition for various illnesses
3. Guide drug treatment

Arguments against

- Undue Worry caused by a low degree of penetration of a genetic variant.
- Most of the common disorders have underlying genetic risk that is spread across multiple genes and alleles.
- Gene evaluation at this point in time as it relates to disease is imprecise and very early in its evolution and linkage to disease.

Common Genetic Disorders that relate to an identifiable gene (more than 100 disorders relate to just one gene)

- Cystic Fibrosis
- Hemophilia (sex linked autosomal dominant X—Type A (deficiency in Factor VIII and Type B Factor IX) Mild-Moderate-Severe
- Huntington's Chorea (single defective gene on chromosome 4-autosomal dominant)
- Neurofibromatosis (gene 17 and 22 (two types) dominant)
- Thalassemia
- Tourette syndrome (dominant gene)
- Von Willenbrands (autosomal dominant) 1% of the population (several types with abnormal bleeding: nose bleeds, dental extractions, heavy periods, bleeding after delivery and surgery)
- Sickle Cell (chromosome 11) Trait and Disease; one in 11 African Americans have the trait.
- Down's (a third copy of a gene trisomy 21)

Cancer Genes: Most cancers have some genetic basis and are related to gene mutations

- The **most commonly** mutated **gene** in people with **cancer** is p53 or TP53. More than 50% of **cancers** involve a missing or damaged p53 **gene**.
- BRCA1 and BRCA2: The **most common** cause of hereditary **breast cancer (**triple negative**)**
- **Prostate Cancer:** BRCA1, BRCA2, the mismatch repair **genes**, and HOXB13
- Lung Cancer: Somatic mutations in the TP53, EGFR, and KRAS **genes** are **common** in **lung cancers**

Designer Babies and Curative Technique for genetic disorders?

- Gene Splicing techniques/problems (Crispr-Cas9)
- Eugenics/ethical considerations
- Role inheritance plays; nature vs. nurture
- Crack babies, smoking, need for prenatal care

An Example of a rare genetic disease; Familial Mediterranean Fever

- Seen in patients with Middle East ancestry and hinges on 23 different gene mutations some of which are autosomal dominant and some recessive.
- Characterized by recurrent fever, arthritis and serosal inflammation (abdominal pain).
- Some succumb to amyloidosis with ESRD if not treated with colchicine which stabilizes the WBCs and overcomes inflammation.
- Four types have been identified TNT receptor, Hyperimmunoglbulinemia D, Cryopyrin and Mevalonate kinase deficiency.