Foundations of Public Health Immunology

Primary Immunodeficiency

David Vetter was born in 1971 with X linked SCID and no functioning immune system. He lived his entire life inside a sterile isolator bubble.

Objectives

- Describe the difference between primary & secondary immunodeficiencies
- Identify signs/symptoms of primary immunodeficiency
- Identify SCID deficiencies, mutations in specific genes
- Describe the difference between X linked & autosomal recessive inheritance
- Identify specific defects that result in different primary immunodeficiency disorders
  - Adaptive & Innate/Other
- Identify treatment options for primary immunodeficiency
- Identify examples of secondary immunodeficiency

Two Types of Immunodeficiency

- Primary (Congenital) Immunodeficiency
  - Diseases caused by **genetic defects** in the immune system
  - Diseases are **not contagious**
- Secondary (Acquired) Immunodeficiency
  - Diseases caused by **other factors that compromise** the immune system
    - Infection (HIV/AIDS), malnutrition, chemotherapy for cancer, removal of spleen, etc.

Primary Immunodeficiency (PI)

- Group of single-gene disorders of the immune system
  - Single-gene defects may lead to a missing enzyme or structural component, developmental arrest at a specific stage of immune development, or nonfunctional proteins
- Nearly **100 separate primary diseases** have been described
  - Only ~20 diseases cause the vast majority of PI cases
- Estimates indicate **1 in 500 people** in US & Europe have a primary immunodeficiency
  - 80% of people affected are younger than 20 years old
- Diseases often inherited in **X-linked** recessive fashion
  - 70% of cases occur among males

Primary Immunodeficiency

- Immune disorders vary in severity & spectrum of symptoms
- All primary immunodeficiency cases have **increased susceptibility to infections & complications** from dysfunctional immune system

Type of immunodeficiency	Histopathology and laboratory abnormalities	Common infectious consequences
B cell deficiencies	Absent or reduced follicles and germinal centers in lymphoid organs Reduced serum Ig levels	Pyogenic bacterial infections
T cell deficiencies	May be reduced T cell zones in lymphoid organs Reduced DTH reactions to common antigens Defective T cell proliferative responses to mitogens *in vitro*	Viral and other intracellular microbial infections (e.g., *Pneumocystis carinii*, atypical mycobacteria, fungi) Virus-associated malignancies (e.g., EBV-associated lymphomas)
Innate immune deficiencies	Variable, depending on which component of innate immunity is defective	Variable: pyogenic bacterial infections

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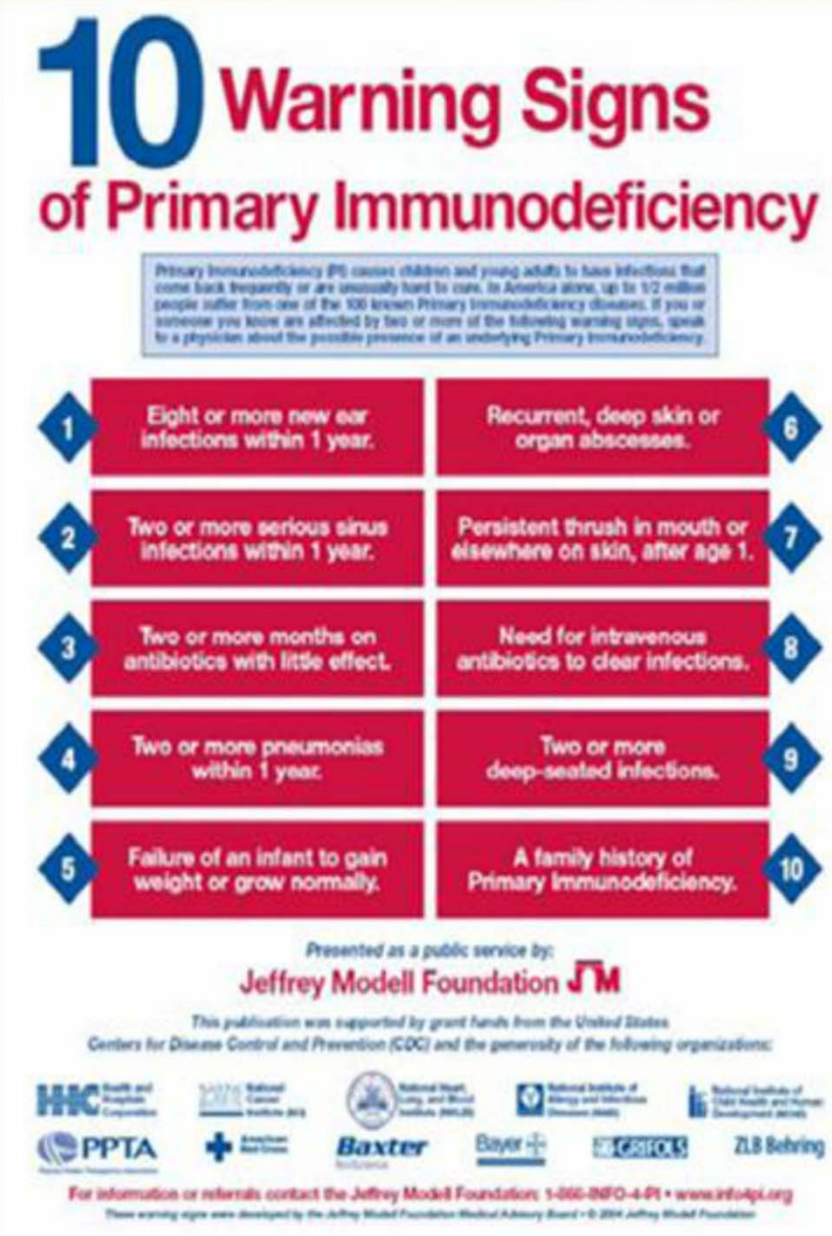
Signs & Symptoms

- Family history of PI
- Classic symptoms include:
  - Increased susceptibility to a variety of infections
  - Ear infections, pneumonia or bronchitis, oral thrush, and diarrhea
  - Multiple infections
  - Children fail to grow and gain weight (failure to thrive)
- Children with untreated SCID rarely live past age to two



Types of Primary Immunodeficiencies:
Adaptive Immune Diseases

- Severe combined immunodeficiency (SCID)
  - X-linked SCID
  - Autosomal SCID
- DiGeorge Syndrome
- Bare lymphocyte syndrome
- X-lined agammaglobulinemia
- X-linked hyper IgM syndrome
- Common variable immunodeficiency

Severe Combined Immunodeficiency

- **Combined B cell and T cell** immunodeficiencies constitute 20% of PI diseases
- **Most serious** forms of primary immunodeficiency
  - Survival beyond first year of life rare without early immune reconstitution through stem cell transplantation (or gene therapy)
- Early diagnosis critical to improve prognosis for infants who have not had severe opportunistic infections
- Caused by mutations in 8 different genes

Severe combined immunodeficiency (SCID)		
Disease	Functional deficiencies	Mechanism of defect
X-linked SCID	Markedly decreased T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common γ chain gene mutations, defective T cell maturation due to lack of IL-7 signals
Autosomal recessive SCID due to ADA, PNP deficiency	Progressive decrease in T and B cells (mostly T); reduced serum Ig in ADA deficiency, normal B cells and serum Ig in PNP deficiency	ADA or PNP deficiency leads to accumulation of toxic metabolites in lymphocytes
Autosomal recessive SCID due to other causes	Decreased T and B cells; reduced serum Ig	Defective maturation of T and B cells; genetic basis unknown in most cases; may be mutations in *RAG* genes

X-linked SCID

- 50% of SCID cases are linked to X chromosome
  - From **mutation in the interleukin 2 receptor gamma** (*IL2RG*)
  - Females may carry the mutation (carrier state), and 50% of her children may get the mutated genes (both male & female, see figure)
  - However, **only male children will develop the disease**
    - Male children have a 50/50 chance of inheriting the gene
- B cells normal in number, but defective in antibody production

Autosomal SCID

- Combined immunodeficiencies also may result from defective enzymes or other genes
- These diseases are rare, except when **consanguinity (incest) or descendants from limited ancestry** have children
- **Adenosine deaminase (ADA) deficiency**
  - Patients have decreased activity of this enzyme
  - Helps cells remove toxic byproducts of metabolism
  - Without the ADA enzyme, these toxins build up in lymphocytes & kills them
- **Recombination-activating gene (RAG) deficiency**
  - Defective recombinase enzyme
  - Impair V(D)J recombination in B & T cells
  - Unable to create new T and B cell receptors (especially impairs antibody production)

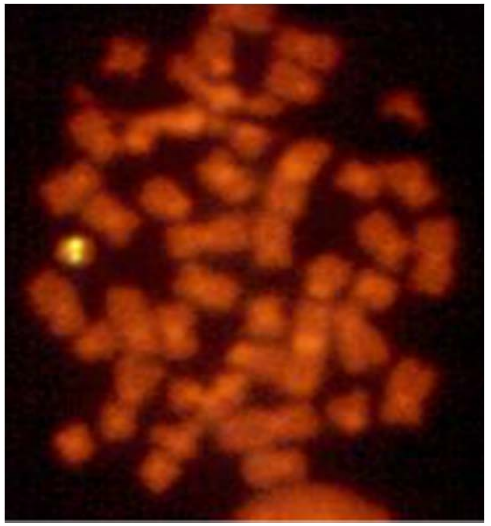
In 1990 Ashanti de Silva became the first patient to receive gene therapy for ADA deficiency. Shown here at age 13, she continues to lead a healthy, active life.

Photo: Courtesy of Van de Silva

Some of The Known Forms of SCID:	Gene	Lymphocyte Phenotype
X-linked SCID (gamma chain gene mutations)	IL2RG	T(-) B(+) NK(-)
Autosomal Recessive SCID		
Jak3 gene mutations	JAK3	T(-) B(+) NK(-)
ADA gene mutations	ADA	T(-) B(-) NK(-)
IL-7R alpha-chain mutations	IL7R alpha	T(-) B(+) NK(+)
CD3 delta or epsilon mutations	CD3 delta or epsilon	T(-) B(+) NK(+)
RAG1/RAG2 mutations	RAG1/RAG2	T(-) B(-) NK(+)
Artemis gene mutations	ARTEMIS	T(-) B(-) NK(+)
CD45 gene mutations	CD45	T(-) B(+) NK(+)

DiGeorge Syndrome

- Rare congenital disease
- Caused by **large deletion from chromosome 22**
  - DGS gene required for normal development of thymus and related glands
  - **Thymus is absent** in these patients
  - Difficult to medically counteract loss of this gene
- Symptoms vary greatly between individuals but usually include recurrent infections, heart defects, and characteristic facial features
  - Heart defects and some of speech impairments often treated either surgically or therapeutically
- **Loss of T-cells (produced by the thymus) is very difficult to treat**



Deletion of genes in DiGeorge syndrome can be visualized by a fluorescent signal on only one of the two couples of chromosome 22.

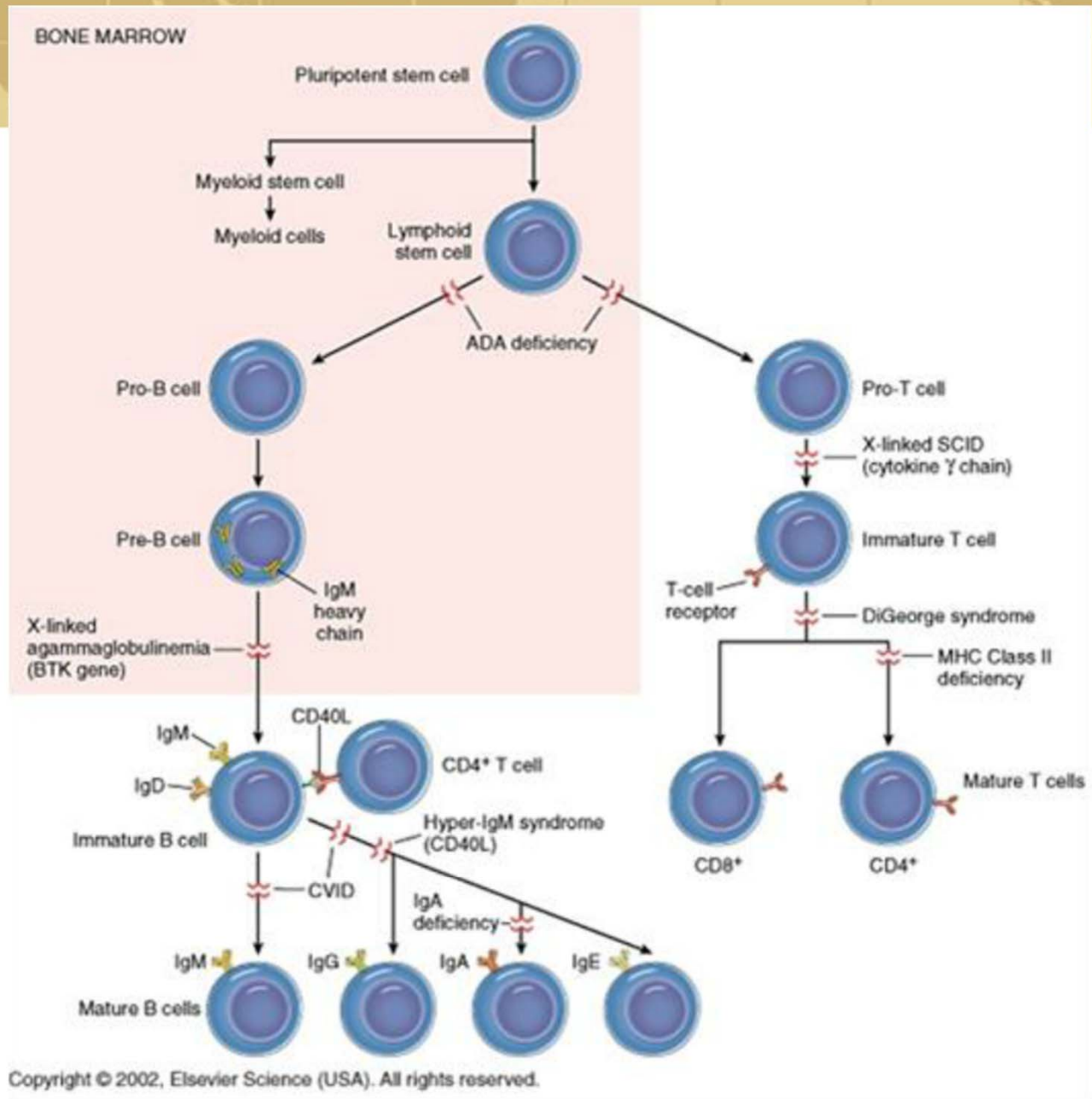
T cell immunodeficiencies		
Disease	Functional deficiencies	Mechanism of defect
DiGeorge syndrome	Decreased T cells; normal B cells; normal or decreased serum Ig	Anomalous development of 3rd and 4th branchial pouches, leading to thymic hypoplasia

X-linked agammaglobulinemia (XLA)

- **Failure of B cell precursors to mature into** B lymphocytes and ultimately **plasma cells**
  - **Mutations in BTK gene** located on X chromosome
- Need plasma cells to produce gamma globulins
- **Results in severe deficiencies of all serum Ig isotypes**, as well as reduced numbers of B cells
- 25% of patients also develop autoimmune diseases, commonly arthritis

Two brothers with Bruton's agammaglobulinemia (XLA). The younger brother was diagnosed first due to less-robust health. Source:http://www.emedicine.com/PED/topic294.htm

B cell immunodeficiencies		
Disease	Functional deficiencies	Mechanism of defect
X-linked agammaglobulinemia	Decrease in all serum Ig isotypes; reduced B cell numbers	Block in maturation beyond pre-B cells, because of mutation in B cell tyrosine kinase
Ig heavy chain deletions	IgG1, IgG2, or IgG4 absent; sometimes associated with absent IgA or IgE	Chromosomal deletion at 14q32 (Ig heavy chain locus)



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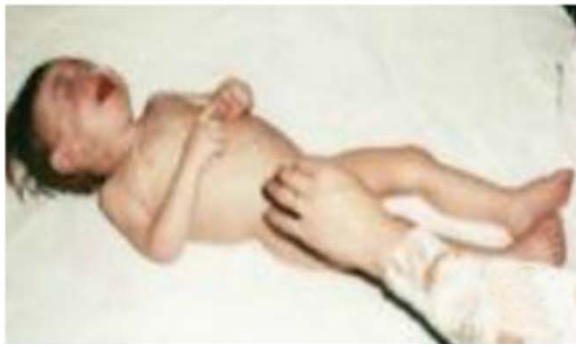
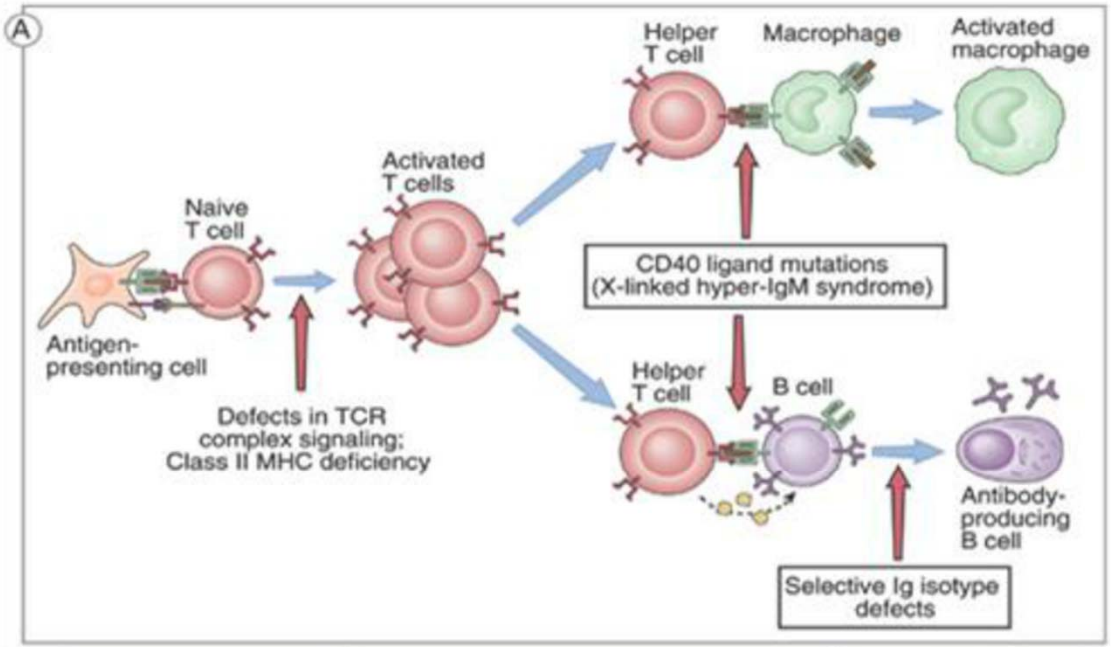
X-linked Hyper IgM Syndrome (XHIM)

- Inherited disorder of the immune system that affects **immunoglobulins & impacts only males**
  - Also can be autosomal recessive (much rarer) that can affect both males & females
- Caused by a **mutation** in the **CD40 ligand** gene
  - CD40L expressed on activated CD4+ T cells
- Characterized by susceptibility ot infections and **low levels of serum immunoglobulins**
  - IgG, IgA and IgE are low
  - IgM may be low, normal or elevated



Infant 1 years old with XHIM developed severe diarrhea & diaper rash that became septic from a bacterial infection. Source: http://www.emedicine.com/ped/topic2457.htm

- Focus on defects related to impaired helper TcR function
- These defects impair B cell, macrophage activation



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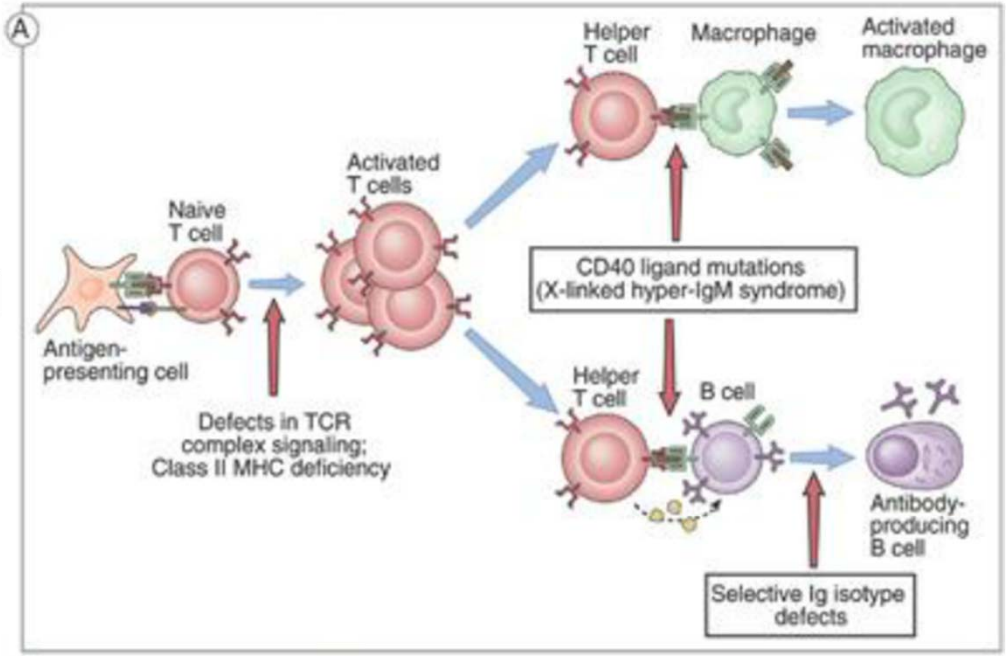
Disease	Functional Deficiencies	Mechanisms of Defect
X-linked hyper-IgM syndrome	Defects in helper T cell–dependent B cell and macrophage activation	Mutations in CD40 ligand
Selective immunoglobulin isotype deficiencies	Reduced or no production of selective isotypes or subtypes of immunoglobulins; susceptibility to bacterial infections or no clinical problems	Unknown; may be defect in B cell differentiation or T cell help

Bare lymphocyte syndrome

- **No production of MHC I or MHC II molecules**
  - Most common type is failure to synthesize MHC I
- **Compromises antigen presentation**
- Few functional CD4+ T cells
- Inherited autosomal recessive genes



B

Disease	Functional Deficiencies	Mechanisms of Defect
Defective class II MHC expression: The bare lymphocyte syndrome	Lack of class II MHC expression and impaired CD4+ T cell activation; defective cell-mediated immunity and T cell–dependent humoral immunity	Mutations in genes encoding transcription factors required for class II MHC gene expression
Defects in T cell receptor complex expression or signaling	Decreased T cells or abnormal ratios of CD4+ and CD8+ subsets; decreased cell-mediated immunity	Rare cases due to mutations or deletions in genes encoding CD3 proteins, ZAP-70

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Common Variable Immunodeficiency

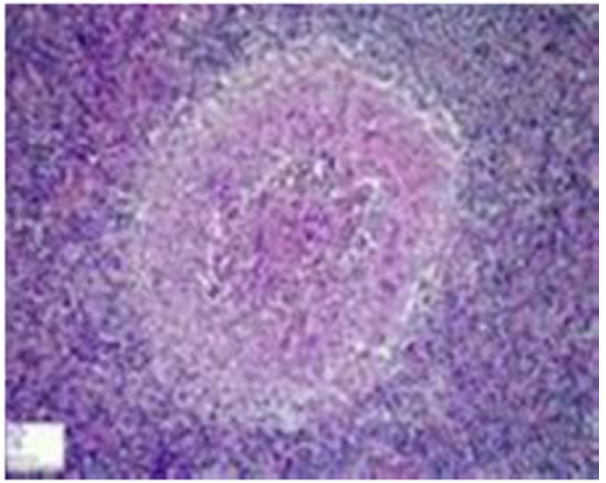
- Group of disorders that form most common primary immunodeficiency
- Exact cause is unknown, and clinical symptoms vary by patient
- **Characterized by low levels of serum immunoglobins**, increased susceptibility to infections
  - Most patients have normal numbers of B cells, but fail to undergo normal maturation into plasma cells
  - Results in poor antibody responses and reduced serum levels of IgG, IgA, and IgM
- Some patients have defects in helper T cell function
- Another group of patients have excesive numbers of cytotoxic T cells
- **Complication include lung damage, enlarged lymph nodes & spleen, arthritis and cancer**

Types of Primary Immunodeficiency: Innate Immune & Other Disorders

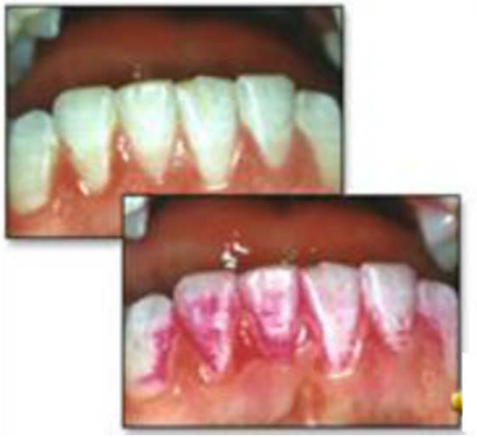
- Chronic granulomatous disease
- Leukocyte adhesion deficiency
- Complement deficiencies
- Chediak – Higashi syndrome
- Wiskott - Aldrich syndrome
- Ataxia - telangiectasia

Chronic Granulomatous Disorder (CGD)

- Rare, inherited disorders **caused by defects in phagocytes**
- Phagocytic cells cannot kill certain microorganisms
  - Phagocytes move normally and ingest microorganisms, but unable to kill specific types of bacteria and fungi
  - **Cannot process oxygen properly** to create oxygen-containing compounds needed for killing
- Children usually healthy at birth, but soon develop recurrent bacterial or unusual fungal infections
- CGD patients vulnerable to severe recurrent bacterial and fungal infections
  - Chronic inflammatory conditions including gingivitis, enlarged lymph glands, or granulomas are common



Granuloma formation in the kidney (above) & gingivitis (below).

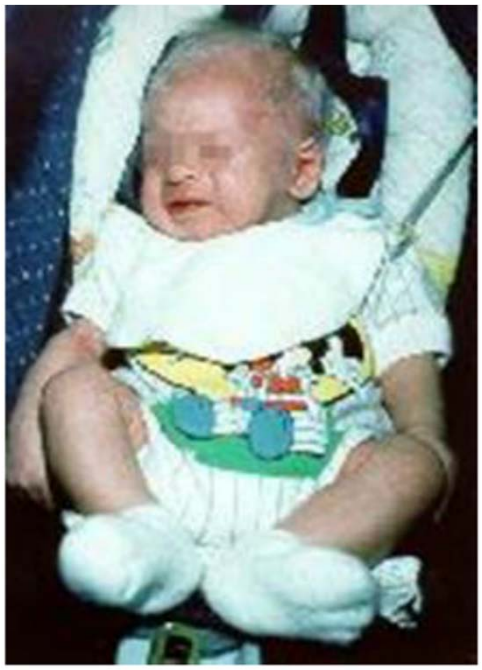


Leukocyte Adhesion Deficiency (LAD)

- Very rare disease with **fewer than 200 patients reported**
- Characterized by leukocytosis and localized bacterial infection
  - Difficult to detect until infections have progressed to life-threatening level
- Disorder results when patient **cannot produce CD18 protein**
  - CD18 is necessary for leukocytes to travel to the site of an infection
- **Leukocyte adhesion deficiency type I (LAD I)**
  - **Failure to express the CD18 integrin**, a receptor for C3b on myeloid, lymphoid cells
  - **No CD18 on lymphocytes, macrophages, and neutrophils**
  - **Patients succumb to infection** [mostly bacterial], commonly when younger than 2 years
- **Leukocyte adhesion deficiency type II (LAD II)**
  - More rare than type I
  - **Defect in expression of ligands for E and P selectins** (remember those?)
  - Patients have leukocytosis, recurrent infections, severe growth and mental retardation
  - **Usually do not die from infection**, but also may have neurologic impairment, and short stature

Chediak Higashi Syndrome (CHS)

- Rare childhood autosomal recessive disorder that **affects multiple systems of body**
  - Hypopigmentation of skin, eyes, and hair
  - Prolonged bleeding, bruise easily, and recurrent infections
- **Mutation in CHS** gene affects synthesis of storage/secretory granules in various types of cells
  - **Abnormal natural killer cell function**
  - **Defective lysosomal function in macs, dendritic cells & neutrophils**
- Often fatal in childhood as a result of infection or an accelerated lymphomalike phase
  - Few patients live to adulthood

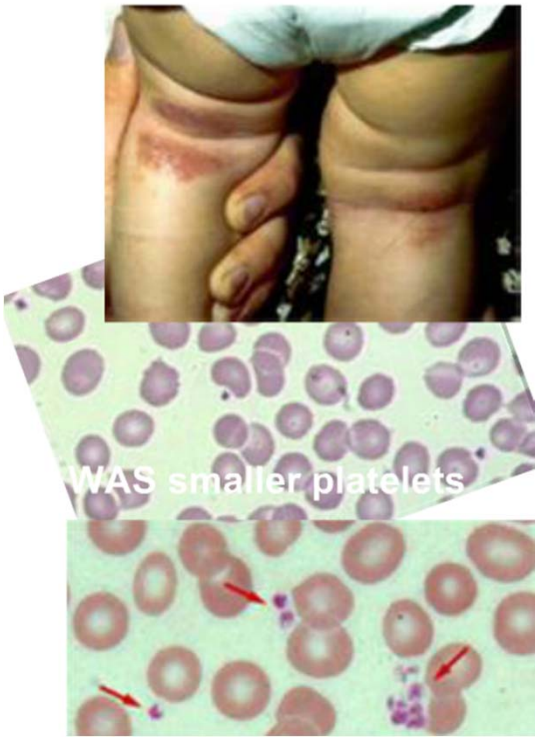


Infant with Chediak Higashi syndrome. Silvery hair and patchy pigmentation are common in patients with this disease.

Wiskott-Aldrich Syndrome (WAS)

- X-linked recessive genetic condition, found almost exclusively in males
  - Disorder causes persistent thrombocytopenia, IgM deficiency
  - **Reduced number of platelets, eczema**, combined immunodeficiency, and higher rist of developing autoimmune diseases
- Results from **defect in protein called Wiskott-Aldrich syndrome protein** (WASp)
- WAS protein important for migration and mortality of immune cells
  - **Platelets and leukocytes are smaller, do not develop properly, & fail to migrate**

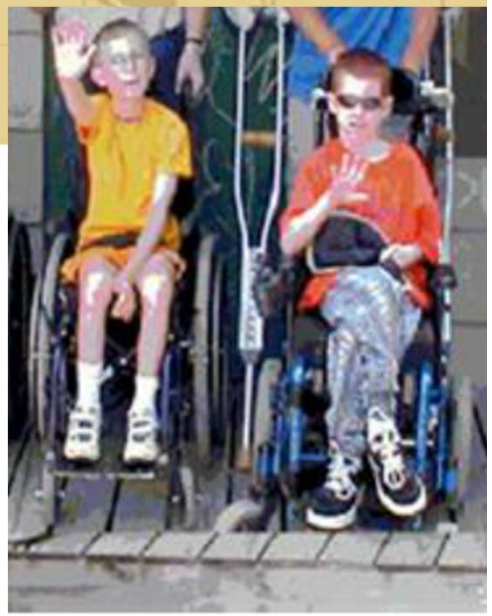
Infant with eczema & petechiae on back of legs



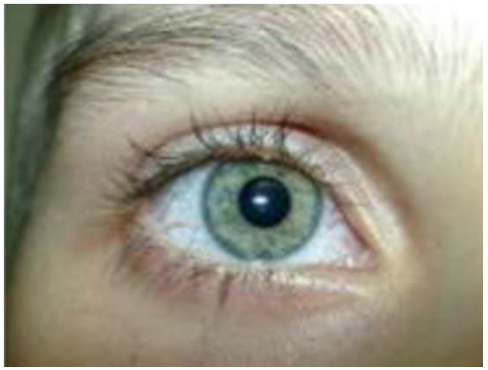
Blood smear with normal platelets (arrows). Note the size difference between the WAS smear & the normal.

Ataxia telangiectasia (AT)

- Autosomal recessive disorder is a **multi-system disease**
- Characterized by gait abnormalities (ataxia) & vascular malformations (telangiectasia)
  - Affects brain, skin & immune system
- Mutation in AT gene **impairs DNA repair during recombination** of antigen receptor genes
  - Compromises T cell maturation & function
- AT patients may have **defective isotype switching**, from dysregulation of immunoglobulin gene superfamily
- AT protein also **controls cell cycle** & mutation of this gene on chromosome 11 may **explain immunologic & neurologic symptoms**



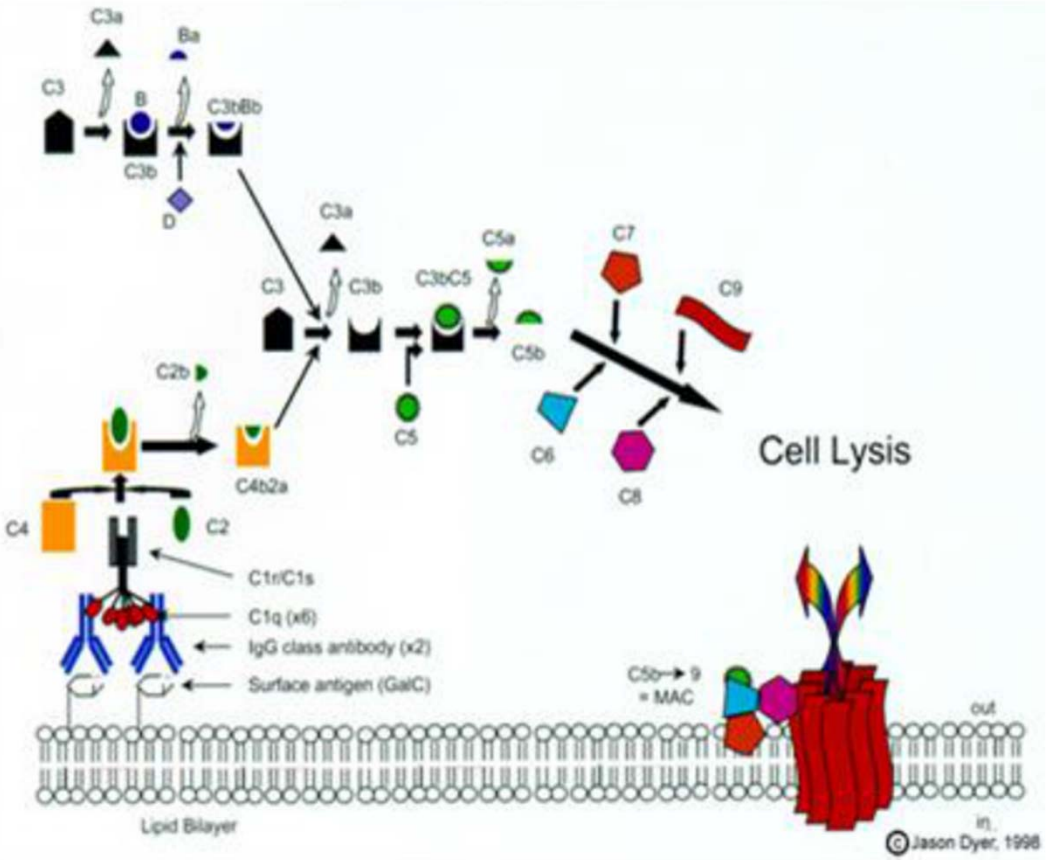
AT patients with neurologic symptoms



Advanced telangiectasia of the bulbar conjuntiva of the eye

Complement Deficiencies

- Patients with antibody or complement deficiencies can have near-normal life spans
- **Complement deficiencies are rare** (less than 2% of immunodeficiencies)
- We will concentrate on C2, C4, and C3 deficiencies



C2 & C4 Deficiencies

- Associated with recurrent infections by encapsulated bacteria (antibodies, complement and neutrophils required for proper clearance)
- **C2** is most widely reported deficiency of all the components in the complement pathways
- **Immune complex disorders are main problem with C2 deficiency**
  - Skin and joint manifestations are common
  - Frequently found in patients with SLE, Henoch-Schonlein vasculitis, polymyositis, and recurrent pyogenic infection
  - Most individuals with C2 deficiency are asymptomatic (until disease development)
- Almost all patients with complete **C4** deficiency have discoid or systemic lupus erythematosus (with or without associated glomerulonephritis)
- **Need classical pathway to eliminate immune complexes**
- Classical pathway is impaired in C2 & C4 deficiency
  - Not susceptible to infection (like C3 deficiencies) because **alternative pathway still available to protect host defenses**

C3 Deficiencies

- C3 deficiency may be due to a primary defect in the C3 gene or expression of the C3 protein
- Deficiencies predisposes person to frequent bouts of pyogenic bacterial infections (especially Gram-negative bacteria such as **meningococci and pneumococci**) and immune complex disease
  - Approximately, 78% of patients with C3 deficiency have repeated infections and 79% of patients experience autoimmune disorders (such as arthralgia and vasculitic rashes, lupuslike syndrome, and membranoproliferative glomerulonephritis)

Disease	Functional Deficiencies	Mechanisms of Defect
Chronic granulomatous disease	Defective production of reactive oxygen intermediates by phagocytes	Mutations in genes encoding components of the phagocyte oxidase enzyme, most often cytochrome b558
Leukocyte adhesion deficiency-1	Absent or deficient expression of β2 integrins causing defective leukocyte adhesion-dependent functions	Mutations in gene encoding the β chain (CD18) of β2 integrins
Leukocyte adhesion deficiency-2	Absent or deficient expression of leukocyte ligands for endothelial E- and P-selectins, causing failure of leukocyte migration into tissues	Mutations in gene encoding a protein required for synthesis of the sialyl-Lewis X component of E- and P-selectin ligands
Complement C3 deficiency	Defect in complement cascade activation	Mutations in the C3 gene
Complement C2, C4 deficiency	Deficient activation of classical pathway of complement leading to failure to clear immune complexes and development of lupus-like disease	Mutations in C2 or C4 genes
Chédiak-Higashi syndrome	Defective lysosomal function in neutrophils, macrophages and dendritic cells, and defective granule function in natural killer cells	Mutation in a gene encoding a lysosomal trafficking regulatory protein

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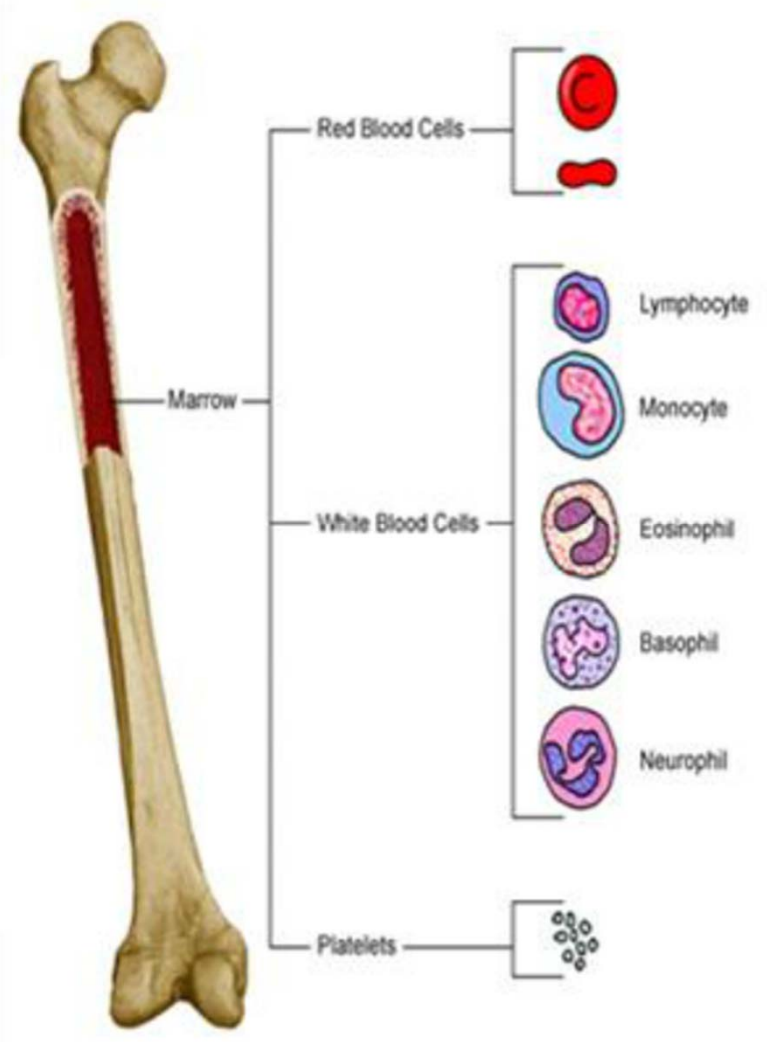
Primary Immunodeficiency Treatment

- Need effective and **early** treatment
  - Untreated primary deficiencies characterized by frequent life-threatening infection, debilitating illnesses
  - Usually fatal if untreated
- Medical advances in treatment allow patients to survive childhood & live *almost* normal lives
  - **Requires life long therapy** including IV gamma globulin infusions, antibiotic therapy, or bone marrow transplanatation

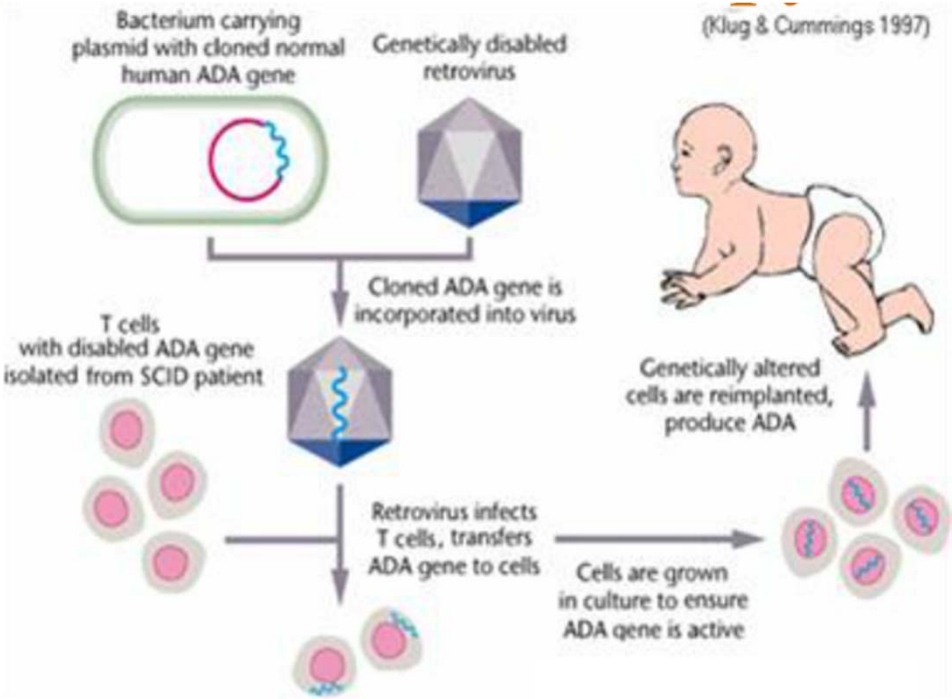
Treatment Options

- **Bone Marrow transplantation**
  - Undifferentiated stem cells taken from healthy bone marrow are injected into SCID patients
  - Stem cells can then differentiate into healthy immune cells
- **Antibiotics**
  - Patients often treated with IV antibiotics for bacterial infections
  - Also as a prohylactic method to prevent recurrent infections
- **Antibody replacement therapy**
  - Intravenous (IV) infusion of plasma with protective IgG antibodies in large doses
  - Helps reduce severity and frequency of infections



Treatment Options: Gene Therapy

- **New technology** that attempts to **replace or repair abnormal genes** in patients
  - Repair abnormal cells by introducing normal gene & then return "new" normal cells to person
  - Or target cells inside body & fix bad genes inside cell with viral vectors
- Proven successful in two forms of SCID
  - ADA SCID & X-linked SCID
- But, **serious adverse effects** reported in association with gene therapy, **not available in US**
- Virus vectors caused disease, by turning on oncogenes to cause cancer



Secondary Immunodeficiency

- Acquired immunodeficiency
- **More common than primary deficiencies**
- Causes include non-immune disorders (diabetes, malnutrition) and immunosuppressive treatment
- Prolonged serious illness may also lead to impaired immune response
- **Impairment is often reversible**

Cause	Mechanism
Human immunodeficiency virus infection	Depletion of $CD4^+$ helper T cells
Protein-calorie malnutrition	Metabolic derangements inhibit lymphocyte maturation and function
Irradiation and chemotherapy treatments for cancer	Decreased bone marrow precursors for all leukocytes
Cancer metastases to bone marrow	Reduced site of leukocyte development
Removal of spleen	Decreased phagocytosis of microbes

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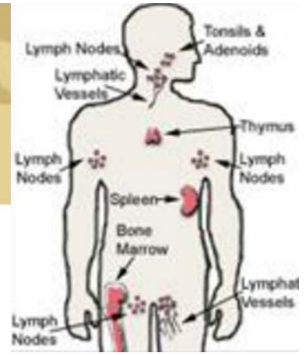

In Summary

- Understand the difference between primary & secondary immunodeficiencies
- Identify SCID deficiencies, mutations in specific genes
- Understand the difference between X linked & autosomal recessive inheritance
- Identify specific defects that result in different primary immunodeficiency disorders
- Adaptive & Innate/Other
- Identify treatment options for primary immunodeficiency
- Identify examples of immunodeficiency

Self-Test Questions

- Describe the difference between a primary & secondary immunodeficiency. Name 3 examples of each type.
- Describe how the patterns of inheritance (X linked & autosomal recessive) are different.
- What is SCID? How does this impact the immune response? What genetic defect causes X linked SCID?
- What is consanguinity? Which PI diseases are linked to this?
- What defect causes DiGeorge's Syndrome? CGD? Chediak Higashi Syndrome? WAS? AT? Describe the phenotype (problems) that occurs in each of these patients.
- Identify and describe the 4 different treatment options available for primary immunodeficiency.