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

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Functional deficiencies</th>
<th>Mechanism of defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked SCID</td>
<td>Markedly decreased T cells; normal or increased B cells; reduced serum Ig</td>
<td>Cytokine receptor common γ chain gene mutations, defective T cell maturation due to lack of IL-7 signals</td>
</tr>
<tr>
<td>Autosomal recessive SCID due to ADA, PNP deficiency</td>
<td>Progressive decrease in T and B cells (mostly T); reduced serum Ig in ADA deficiency, normal B cells and serum Ig in PNP deficiency</td>
<td>ADA or PNP deficiency leads to accumulation of toxic metabolites in lymphocytes</td>
</tr>
<tr>
<td>Autosomal recessive SCID due to other causes</td>
<td>Decreased T and B cells; reduced serum Ig</td>
<td>Defective maturation of T and B cells; genetic basis unknown in most cases; may be mutations in RAG genes</td>
</tr>
</tbody>
</table>
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)
### Some of The Known Forms of SCID:

<table>
<thead>
<tr>
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<th>Gene</th>
<th>Lymphocyte Phenotype</th>
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<tbody>
<tr>
<td><strong>X-linked SCID</strong> (gamma chain gene mutations)</td>
<td>IL2RG</td>
<td>T(-) B(+) NK(-)</td>
</tr>
<tr>
<td><strong>Autosomal Recessive SCID</strong></td>
<td></td>
<td></td>
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<tr>
<td>Jak3 gene mutations</td>
<td>JAK3</td>
<td>T(-) B(+) NK(-)</td>
</tr>
<tr>
<td>ADA gene mutations</td>
<td>ADA</td>
<td>T(-) B(-) NK(-)</td>
</tr>
<tr>
<td>IL-7R alpha-chain mutations</td>
<td>IL7R alpha</td>
<td>T(-) B(+) NK(+)</td>
</tr>
<tr>
<td>CD3 delta or epsilon mutations</td>
<td>CD3 delta or epsilon</td>
<td>T(-) B(+) NK(+)</td>
</tr>
<tr>
<td>RAG1/RAG2 mutations</td>
<td>RAG1/RAG2</td>
<td>T(-) B(-) NK(+)</td>
</tr>
<tr>
<td>Artemis gene mutations</td>
<td>ARTEMIS</td>
<td>T(-) B(-) NK(+)</td>
</tr>
<tr>
<td>CD45 gene mutations</td>
<td>CD45</td>
<td>T(-) B(+) NK(+)</td>
</tr>
</tbody>
</table>
**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**

<table>
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<tr>
<th>T cell immunodeficiencies</th>
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<tbody>
<tr>
<td>Disease</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
</tr>
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</table>

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

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

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
**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 to infections and **low levels of serum immunoglobulins**
  - IgG, IgA and IgE are low
  - IgM may be low, normal or elevated

Infant 1 year 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
**Bare lymphocyte syndrome**

- No production of MHC I or MHC II molecules
  - Most common type is failure to synthesize MHC II
- Compromises antigen presentation
- Few functional CD4+ T cells
- Inherited autosomal recessive genes
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 excessive 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 risk 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)
<table>
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<th>Disease</th>
<th>Functional Deficiencies</th>
<th>Mechanisms of Defect</th>
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<tr>
<td>Chronic granulomatous disease</td>
<td>Defective production of reactive oxygen intermediates by phagocytes</td>
<td>Mutations in genes encoding components of the phagocyte oxidase enzyme, most often cytochrome b558</td>
</tr>
<tr>
<td>Leukocyte adhesion deficiency-1</td>
<td>Absent or deficient expression of β2 integrins causing defective leukocyte adhesion-dependent functions</td>
<td>Mutations in gene encoding the β chain (CD18) of β2 integrins</td>
</tr>
<tr>
<td>Leukocyte adhesion deficiency-2</td>
<td>Absent or deficient expression of leukocyte ligands for endothelial E- and P-selectins, causing failure of leukocyte migration into tissues</td>
<td>Mutations in gene encoding a protein required for synthesis of the sialyl-Lewis X component of E- and P-selectin ligands</td>
</tr>
<tr>
<td>Complement C3 deficiency</td>
<td>Defect in complement cascade activation</td>
<td>Mutations in the C3 gene</td>
</tr>
<tr>
<td>Complement C2, C4 deficiency</td>
<td>Deficient activation of classical pathway of complement leading to failure to clear immune complexes and development of lupus-like disease</td>
<td>Mutations in C2 or C4 genes</td>
</tr>
<tr>
<td>Chédiak-Higashi syndrome</td>
<td>Defective lysosomal function in neutrophils, macrophages and dendritic cells, and defective granule function in natural killer cells</td>
<td>Mutation in a gene encoding a lysosomal trafficking regulatory protein</td>
</tr>
</tbody>
</table>
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 prophylactic 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**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Human immunodeficiency virus infection</td>
<td>Depletion of CD4+ helper T cells</td>
</tr>
<tr>
<td>Protein-calorie malnutrition</td>
<td>Metabolic derangements inhibit lymphocyte maturation and function</td>
</tr>
<tr>
<td>Irradiation and chemotherapy treatments for cancer</td>
<td>Decreased bone marrow precursors for all leukocytes</td>
</tr>
<tr>
<td>Cancer metastases to bone marrow</td>
<td>Reduced site of leukocyte development</td>
</tr>
<tr>
<td>Removal of spleen</td>
<td>Decreased phagocytosis of microbes</td>
</tr>
</tbody>
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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.