Immunodeficiency
Immunodeficiencies

- Congenital/Primary
  genetic or developmental defect

- Acquired/Secondary
  result of disease or therapy
Congenital/Efferent

Chronic Granulomatous Disease

- defect in the ability of МΦ and PMNs to kill phagocytosed organisms
- chronic bacterial infections
- several possible genetic defects in the NADPH oxidase system (including X-linked)
- antibiotics (& possibly HSC transplant...)
Complement Deficiencies

• absence of one or another complement component

• C1,4: autoimmune diseases, some infections
  C5-9: Neisseria infections
  Properdin: many pyogenic infections

• maintained with antibiotics

Question: Would a stem cell transplant help?
Most C components produced in liver, notably C3.
LYMPHOCYTE DIFFERENTIATION

Bruton’s Agammaglobulinemia

DiGeorge Syndrome, Thymic Aplasia

Severe Combined Immunodeficiency
Congenital/Central

Bruton’s Agammaglobulinemia

• *bacterial infections starting ~4-8 months*
• *absence of functional B-cells*
• *X-linked recessive, gene for BTK* (Bruton’s Tyrosine Kinase)
• *Intravenous Ig therapy (“IVIG”)*
DiGeorge’s Syndrome, Thymic Hypoplasia

- postnatal hypocalcemic tetany, viral and fungal infections within first few months
- absence of thymus or functional T-cells
- development defect of 3rd & 4th pharyngeal pouches, defective thymus & parathyroid (part of the heterogeneous family of Cardiovelofacial Syndrome)
- sporadic deletions on chromosome 22 (22q11.2)
- supportive therapy (or thymic epithelial transplant)
  “ectopic” transplant

...but how can intrathymic “education” work without self MHC??
Severe Combined Immunodeficiency

- overwhelming infections in first year of life
- absence of functional T- or B-cells
- any of several genetic defects, including
  - ADA (adenosine deaminase), PNP (purine nucleotide phosphorylase),
  - IL-2Rγ (IL-2 receptor gamma, X-linked)
- cured with successful HSC transplant
David the “Bubble Boy”, born with SCID

- Born in 1971; older brother had died of SCID (with a Pneumocystis infection) one year earlier.
- Potential problem was expected; 50% male, 50% diseased
- “Germ-free” birth, reverse isolation chamber. (Not truly germ-free, 35 species of microorganism identified at age 6).
Six-year-old David shows off his NASA space suit.

- Phagocytic function, ADA & complement close to normal.
- IgM low, no IgG, traces of IgA, some IgD (determined with RID)
• No response to KLH, either by Ab or skin test (CMI).
• No Ab response to typhoid antigen
- Lymphocytes ~400/cmm (~15% of normal), ~1/3 sIg+, ~2/3 ERFC
- Minimal lymphocyte response to PHA, PWM, MLC.
- “Transfer Factor” given at 10-16 months (low MW extract of leukocytes from immune donors); showed no effect, remaining poor or absent response to fungal skin tests.
• Received bone marrow transplant in 1983 at age 12 (treated with mAb to deplete T-cells) from his 15-year-old sister.
• Died 4 months later with an EBV-associated B-cell proliferation resembling Burkitt’s lymphoma, leaving his bubble only 15 days before his death.
X-Linked Severe Combined Immunodeficiency Disease
aka XSCID, “Bubble-Boy Disease

Genetic defect identified in 1993 in CD132, the γ-chain of the IL-2R also shared with receptors for IL-4, 7, 9 and 15…
Congenital/Central

New Form of Human T-Cell Deficiency

- Two sisters in southern Italy, each born with complete absence of scalp hair, eyelashes and eyebrows.
- No thymic shadow visible on X-ray, striking impairment of T-cell function.
- One sister died at 12 months, the other survived after receiving a B.M. transplant at 5 months

- Mutation in WHN gene on chromosome 17

\textit{whn} is the mutated gene responsible for \textit{nu/nu} mice, encodes a transcription factor in thymus & skin
### 2003 Case report

13-year old Spanish boy, suffered from recurrent infections since one year of age.

<table>
<thead>
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<th></th>
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<td>217</td>
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<td>IgA</td>
<td>&lt;7</td>
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<td>IgD</td>
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<td>1.0 - 4.6</td>
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<tr>
<td>IgE (UI/ml)</td>
<td>&lt;40</td>
<td>50 - 600</td>
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Congenital/Central

X-Linked Hyper-IgM Syndrome

• bacterial infections beginning in first 2 years, upper respiratory and others
• low serum IgG, high IgM
• X-linked recessive gene
• Maintained by intravenous Ig

What gene is this?
ANTIGEN PRESENTATION BY MACROPHAGE TO $T_{H(V)}$-CELL

Classical Three-Cell Interaction
**Modified to account for generation of B memory cells**

**XHIGM - Absence of CD40L**

**no isotype switching**
Leukocyte Adhesion and Migration

Important for all aspects of generation and execution of immune responses
Congenital/Efferent

**Leukocyte Adhesion Deficiency, Type I (1979)**

- Failure to express CD18 β-2 integrin on lymphocytes, monocytes and neutrophils, part of adhesion complexes (including LFA-1) and C3b receptor
- Massive bacterial infections by 2 years
- Defective migration of lymphoid cells to sites of infection and inflammation
- Rare; ~400 cases worldwide as of 2009
- Cured by successful HSC transplantation
Acquired ("secondary")

Immunodeficiencies Secondary to Disease

- **Infectious disease** (toxins, immunosuppression; HIV...)
- **Malignancy** (immunosuppression, depression of hematopoiesis)
- **Malnutrition** (T-selective deficiencies)
- **Splenectomy** (loss of filtration & phagocytic cells; increased bacterial infections)
- **Renal failure & enteropathies** (loss of Ig, etc.)

etc...
Acquired

**Iatrogenic immunodeficiencies caused by therapeutic intervention**

- **Cytotoxic drugs** [6MP, MTX, et al.] & **corticosteroids** (malignancies, autoimmune & inflammatory conditions…)
- **Ionizing radiation** (cancer therapy, immunosuppression, “conditioning” for HSC transplant)
- **ALG** [anti-lymphocyte globulin], αCD3 [OKT3], et al.
- **Cyclosporin, FK506** [tacrolimus] (immunosuppression: organ grafts, autoimmune conditions…)

etc…
WEDNESDAY

Allergy, Chapter 21

Vaccination, Chapter 22
Fin