IMMUNODEFICIENCY

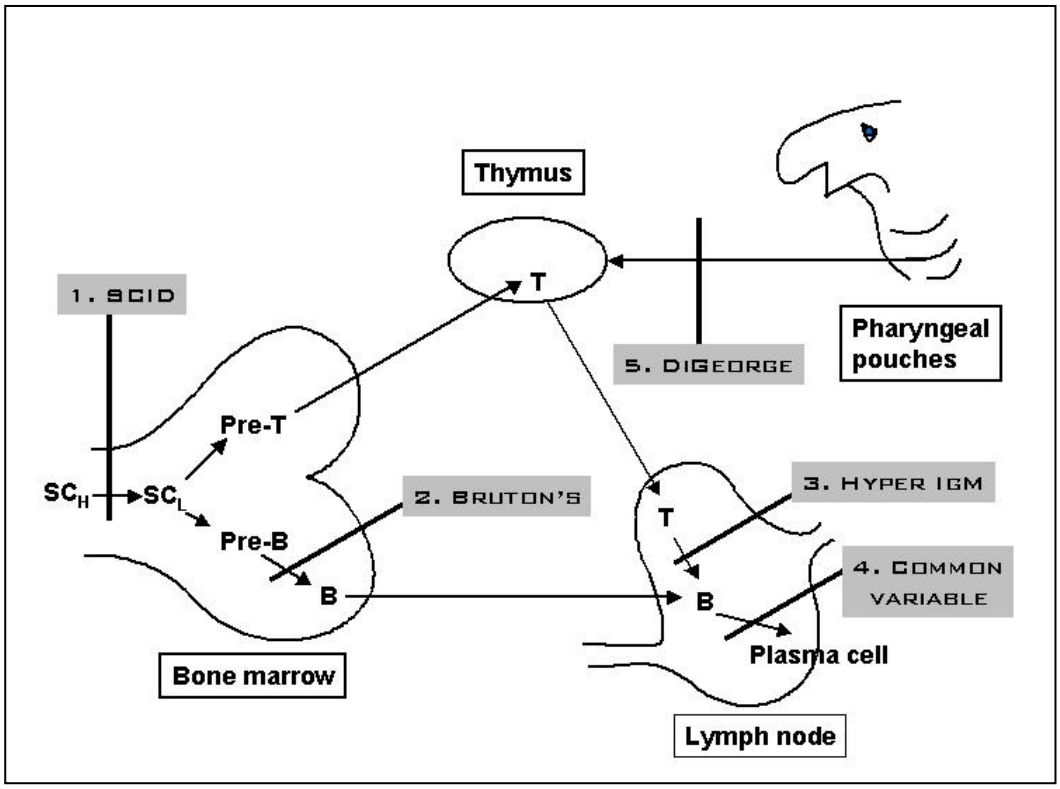
CATEGORIES OF IMMUNODEFICIENCY STATES. Immunodeficiency can be primary or secondary. Primary immunodeficiency means a disease with a genetic cause, while secondary implies that some known process outside the immune system has caused the immunodeficiency. If the thymus or bone marrow were congenitally dysfunctional that would result in primary immunodeficiency, while the immunodeficiency that follows treatment with immunosuppressive drugs, or that is seen in patients with advanced cancer, or AIDS, is secondary to those conditions.

Another way of putting it is that immunodeficiency can be congenital or acquired, depending upon whether the condition existed at birth or not. Acquired immunodeficiency will usually be secondary to some other condition.

Immunodeficiency can also be temporary and self-limited, as in the transient hypogammaglobulinemia of infancy, or during treatment with cancer chemotherapy drugs; or it can be permanent (at least until we can come up with a cure).

Remember also that deficiency of any component of the immune/inflammatory systems can lead to impaired immunity: in addition to the lymphocyte deficiencies we'll discuss here, there are deficiencies in complement components, in phagocytic cell functions, etc.

PRIMARY IMMUNODEFICIENCIES. These can affect T cells or B cells selectively, or both kinds of cells. It is largely by studying the clinical syndromes associated with immunodeficiency diseases that we know what T and B cells are really important for in humans. The following diagram shows probable sites of developmental blocks in conditions that are discussed on the next page.



Block 1: If there are low numbers of T and B cells, it is as if there is a block in the development of the lymphoid stem cell, or its further maturation. This condition is the worst of the immunodeficiency states and is called **Severe Combined Immunodeficiency Disease,** or **SCID**. Children with the most profound deficiencies rarely survive beyond a year (they are to some extent protected in the neonatal period by maternal IgG). There is lymphopenia of both T and B cells, absent thymic shadow on X-ray, and tonsils are small; mitogen responses and serum immunoglobulins are low. This is a group of diseases with a similar phenotype. More than half the cases are X-linked recessive. In the commonest of these (SCID-X1), the defect is in the gene for the gamma chain that forms part of the receptors for IL-2 and other growth factors necessary for lymphoid development, or their signaling pathways. The rest of SCID cases are autosomal recessive. Most of these patients lack the enzyme adenosine deaminase (ADA); adenosine accumulates in all cells but apparently impairs lymphocyte development most severely. Among the rarest globally are defects in V(D)J recombination, although that is the most common form of SCID in Navajo children (incidence about 500/100000 births.)

Block 2: If there are normal T cells but low to absent B cells, it may be that there is a developmental block between the pre-B cell and the B cell. Most patients have pre-B cells in their bone marrow but are deficient in B cells and antibody (serum IgG less than 10% of normal, IgA and IgM virtually undetectable). The disease is called **X-linked (Bruton's) Agammaglobulinemia**, in which a protein tyrosine kinase gene, *btk*, normally expressed in pre-B and later B cells, is defective. Children with Bruton's have bacterial infections manifesting as pneumonia and chronic diarrhea. Enteroviruses, which gain entry through mucous membranes unprotected by IgA, may also be a problem; among these is poliovirus. These kids are the main reason we no longer use oral polio vaccine in America. Incidence about 0.4/100000 births.

ASK YOURSELF: Why? Wouldn't we particularly want to immunize such kids?

Block 3: A rare patient will have high IgM with low IgG and IgA; in such patients there is a defect in the IgM-to-IgG switch mechanism. The Tfh cell has an accessory molecule (CD154 or CD40-ligand) that interacts with CD40 on B cells, signaling them to switch classes (see diagram in T cell unit). If either molecule is defective, the B cell is driven hard but not instructed to switch past making IgM. This is called **X-linked hyperIgM syndrome**.

Block 4: It can happen that there are normal numbers of pre-B cells and B cells, but the B cells are difficult to trigger to make specific antibody. This condition is called **Common Variable Immunodeficiency (CVID)**, and is actually a group of about 20 conditions. This condition is relatively milder than the others, and may be diagnosed for the first time in people up to 50 years old. The main phenotype is recurrent bacterial infection. There is increased risk for lymphoma, enteropathy, or autoimmunity. The causes are unknown, but innate immunity as well as B and T cell defects have been described.

Block 5: The thymus is a two-component organ. The lymphoid part comes from precursors in the bone marrow, as we already know; the stroma is derived in the embryo from the endoderm and ectoderm of the 3rd and 4th pharyngeal pouches. If these develop abnormally the stroma will not support thymic lymphoid development, and the patient will have absent T cells with normal B cells. The condition is the **DiGeorge Syndrome,** and the cause is a large deletion on chromosome 22. The parathyroids also derive from the pharyngeal pouches, so this diagnosis is sometimes made in infancy when there are unexplained convulsions controllable by calcium. The heart develops abnormally, too. Cell-mediated immunity is depressed; viral and fungal infections are common. Incidence about 30/100000 births. **Nude mice** have quite a different mutation, but also fail to make a thymic stroma (and hair) and so they have no T cells, and are immunologically similar to DiGeorge kids.

T deficiencies are associated with severe infections with intracellular pathogens, including viruses, certain bacteria, and yeasts and fungi, especially *Candida albicans* and *Pneumocystis carinii* (whose new name is *P. jirovecii*). B cell deficiency is characterized by infections with "high-grade" (extracellular, pyogenic = pus-producing) bacterial pathogens such as *Staphylococcus aureus, Haemophilus influenzae* and *Streptococcus pneumoniae*. All of this makes good sense if you remember antibody and T cell-mediated mechanisms. Gut organisms may be abnormal in either type of disease, so diarrhea and malabsorption are frequent complaints, as is failure to grow normally.

TRANSIENT HYPOGAMMAGLOBULINEMIA OF INFANCY. This is a self-limiting condition, noticed about 3 to 6 months after birth and lasting up to 18 months (in a few cases, much longer). These children are slow to get their production of IgG going. They present mostly with recurrent and persistent Gram-positive bacterial infections, but may get just about anything. Perhaps 15% of all chronic diarrhea in infants is due to this condition.

SELECTIVE IGA DEFICIENCY is the most common immunodeficiency disease, with a prevalence of about 200 in 100000. Although it is usually asymptomatic, the patient may have diarrhea and sinopulmonary infections, or an increased frequency and severity of allergies. There is a familial tendency, and although several mechanisms have been proposed, none is yet clearly established. It is 10-15 times more frequent in people with celiac disease.

OTHER PRIMARY IMMUNODEFICIENCIES[1]. There are many other conditions which are more complex and harder to classify. Two examples:

> **Ataxia Telangiectasia** is an autosomal recessive disease characterized by recurrent pneumonia, ataxia (staggering) due to cerebellar atrophy, and telangiectasia (dilated abnormal blood vessels). There is both T and B cell deficiency, not absolute. It is caused by a defect in DNA repair which may explain the extraordinary incidence of tumors in these patients. The **Wiskott-Aldrich** syndrome is comprised of platelet and B cell deficiency, eczema, and many bacterial infections. It is X-linked.

SECONDARY IMMUNODEFICIENCY. Clinicians need to keep in mind that many of the treatments they administer will be toxic to the immune system and that some diseases will themselves be immunosuppressive. Drugs used in the therapy of autoimmune and inflammatory conditions, such as corticosteroids and some of the new monoclonal antibodies, can be profoundly suppressive, and patients treated with these drugs should be warned to keep away from people with infectious diseases (chicken pox, for example, can be devastating in an immunosuppressed person). Many viral illnesses, especially measles, mononucleosis, and cytomegalovirus (CMV) infection, are immunosuppressive, and secondary infection is common. **Acquired Immune Deficiency Syndrome** or **AIDS** is the most serious condition involving secondary immunodeficiency.

TREATMENT OF IMMUNODEFICIENCY.

1. Isolation = bubbles. (This is impractical for extended periods.)

2. Prophylactic antibiotics. These are used in combinations, which you change monthly.

> **ASK YOURSELF:** Why change them monthly?

[1] Excellent recent review by CU authors: Yoshikazu Morimoto & John M. Routes (2008). Immunodeficiency Overview. Prim Care Clin Office Pract 35:159–173.

3. Human immunoglobulin, where B cell function is deficient. This must be given approximately monthly. It is pooled from many donors, and is usually about 99% IgG, with a half-life of 3 weeks. The earliest form was injected intramuscularly; it was quite painful because aggregated molecules activate complement. It has been mostly replaced by a form for IV use (IVIg) from several manufacturers; effective but expensive, and often in short supply. Now there is a new form for subcutaneous self-administration.

Note: Caution must be used when giving immunoglobulins to people with selective IgA deficiency. The IgA in the preparation may be foreign to them, provoking an allergic or immune complex reaction.

4. Transplantation. In DiGeorge, fetal thymus or cultured thymic stromal cells have been used to try to minimize the risk of graft-versus-host disease. Some success is claimed; better diagnosis would aid in the selection of appropriate cases. This child shows some of the features of DiGeorge, including hypertelorism, down-slanting eyes, fishmouth deformity, micrognathia, and low-set ears. He was born with the heart defect Tetralogy of Fallot (which surgeons repaired soon after birth), hypocalcemia, and absent T cells. He received a fetal thymus graft. He developed GvH disease but responded to treatment and had a T cell count of at least 500. The thymic stroma was the donor's but the T cells were his.

For SCID, bone marrow transplantation has about a 50% success rate, but graft-versus-host disease (*see* Type IV Immunopathology) is always a problem. It is better to transplant stem cells than whole bone marrow. Sibling donors are the best, and a good Class II MHC match is imperative. For ADA-deficient patients, transfusions of *irradiated* red cells can be helpful (why do I stress the word irradiated?) Purified ADA, stabilized with polyethylene glycol (PEG) is also available for use as a drug. The first gene replacement therapy in humans has been done, successfully it seems, in ADA-deficient and SCID-X1 children. But problems have arisen…

Gene therapy link to cancer cases

Scientists confirm DNA treatment gave 2 boys leukemia

BIRMINGHAM, England, May 5 (AP) — A revolutionary gene therapy treatment that cured 10 French boys of a deadly inherited disorder known as "bubble boy disease" gave two of them leukemia, scientists said.

DR. SALIMA HACIEN-BEY-ABINA said Sunday that genetic tests have confirmed that the treatment, the first time that gene therapy has cured a disease, triggered the cancer in the toddlers. The boys are responding well to anticancer therapies, she added. Experts said it is now clear that the virus used to carry the needed gene into the children's bodies landed in a bad place. Scientists had always feared that cancer might occur if the virus used in the therapy lodged near certain genes that control cell growth and affected those too.

Addressing a conference of the European Society of Human Genetics, Hacien-Bey-Abina of the Necker Hospital for Sick Children in Paris said tests have shown that in the first toddler stricken with leukemia, the correcting gene landed inside a cancer-promoting gene called LMO-2. In the second toddler, the gene landed near the LMO-2 gene.

RETROVIRUS VECTORS PROBLEMATIC

"Apart from the tragedy of those two kids, I think this has put an enormous skid under a great deal of gene therapy, on this whole business of using retrovirus vectors" to get the needed genes into the body, said Andrew Read, a professor of genetics at Manchester University and chair of the scientific committee for the conference.

"That is a perfectly general problem of retroviral vectors and not a problem of the particular virus they used or the particular disease they treated and I cannot see how in principle you can get rid of that risk," said Read, who was not involved in the research.

The boys were given the treatment starting in 1999 when they were babies, ranging in age from one month to 11 months. The first toddler who developed leukemia appeared healthy until August last year — 30 months after treatment — when scientists found leukemia-like overproduction of white blood cells. After that finding, the United States suspended its three gene therapy studies for the disorder. A second child then developed leukemia in December, 34 months after getting the therapy, Hacien-Bey-Abina said.

2 HAD 'BUBBLE BOY' DISEASE

The boys were born with severe combined immunodeficiency, or SCID, a rare inherited disease that occurs in about 1 in 75,000 births. The best known victim was David, Houston's famous "bubble boy" who lived in a germ-proof plastic enclosure until his death at age 12 in 1984.

The French boys had X-linked SCID, a severe form that strikes only boys. It is the most common form of SCID, accounting for about half of cases.

The disease involves a genetic mutation that leaves them without certain proteins crucial to developing disease-fighting immune cells. Without treatment, sufferers die very young. Many babies with the disorder are saved with bone marrow transplants, but they need monthly infusions of immune globulin, antibodies culled from donated blood, for the rest of their lives.

3-Month Wait Seen For Boy in Bubble

M&3

HOUSTON, Oct. 24 (AP) — A 12-year-old boy who was born without an immune system must wait about three months to learn whether a bone marrow transplant has given him the disease-fighting ability he needs to leave his sterile bubble, a hospital spokesman says.

The youngster, identified only as David, was in excellent condition after receiving the bone marrow from his sister on Friday, Gayle McNutt, a spokesman for Baylor College of Medicine, said.

"If everything is O.K., he should be able to move into the real world. He has long had the hope of one day being able to come out of his bubble and live a normal life," Mr. McNutt said.

David's condition was recognized before birth, and he was born into a sterile environment. The youngster lives in a three-room plastic bubble containing filtered air.

David received less than two ounces of specially treated bone marrow from his 15-year-old sister on Friday. Bone marrow develops T-cells and B-cells, which fight infection, Mr. McNutt said.

Because the bone marrow was not an exact match, doctors had to treat the transplant with monoclonal antibodies, to kill the adult cells, the spokesman said.

"Otherwise they would have attacked his body and that would have been serious," he said of the T-cells.

What was left, Mr. McNutt said, were embryonic bodies known as stem cells. Doctors hope the young cells will adapt themselves into cells compatible with David's body as they grow to maturity.

Doctors have said signs of rejection would be evident within a week.

Dr. Murdina Desmond, the pediatrician who has treated David since his birth, said he was "as happy as he's ever been" the day after the operation.

"When I saw him, he was tidying up the bubble and teasing the nurses, winking at them," she said.

David was kept in the bubble so long because no marrow donor with a good HLA match could be found. The advances in monoclonal antibody technology of the ’80s allowed his doctors to try treating his (mismatched) sister’s marrow with anti-CD3 and complement, to rid it of mature T cells which cause GvH, and then transfuse it into David. Infection still is a great problem in bone marrow transplantation, before the marrow has a chance to “take;” major culprits are latent viruses of the herpes family, like CMV (cytomegalovirus) and EBV (Epstein-Barr virus).

'Bubble boy' dies after brief freedom

HOUSTON (AP) — David, the 12-year-old "bubble boy" who emerged from his germ-free plastic world two weeks ago and kissed his mother for the first time, died Wednesday night of heart failure.

The boy, who suffered from a rare condition in which he had no immunity to disease, had until Feb. 7 spent his entire life in a sterile plastic bubble, breathing filtered air, eating germ-free food and playing with toys and books that had been chemically treated.

The illness that led to his death began with a bone-marrow transplant last October that doctors had hoped would enable him to live in the outside world. When he suffered nausea and diarrhea, doctors said they could not adequately care for him in the bubble.

MOMENTS AFTER he left the bubble, David kissed his mother for the first time. But he never got his often-expressed wish to walk barefoot in the grass in the outside world.

The boy's death was announced at Texas Children's Hospital by spokeswoman Susannah Moore Griffin.

David's family — mother, father and 15-year-old sister — were in the room at the time, she said. The boy's grandparents and cousins also were in the hospital. The boy's family name has never been disclosed.

"The cause of the heart failure is unknown," his doctor, William T. Shearer, said in a statement.

Shearer said the boy's doctors were not able to determine that he had an infection but that "some symptoms indicated a possible infection."

Late Tuesday night, David began receiving the antibiotic acyclovir, which is approved for herpes virus infections, Shearer said.

Shearer said an autopsy would be performed.

About 6 p.m., he developed irregular heartbeats. At 8 p.m., his heart failed, Griffin said.

Griffin said she did not know whether any measures were taken to restart the heart.

The death came just 33 hours after he went on the critical list and less than 12 hours after he was placed on a breathing device.

He was unconscious from the time he went on the breathing device, first because of sedation and later because he slipped into a coma, she said.

The Catholic priest who had blessed David on birthdays and holidays and who gave him his first communion in front of the bubble at the boy's home, performed rites for the sick boy Wednesday morning.

THE REV. Laurence Connelly of Sacred Heart Church in Conroe said he performed the rites "with the hope that health will be restored. It doesn't mean that the person was dying."

He said he administered the rites at 10:15 a.m. Wednesday.

David was the oldest living survivor of a condition called severe combined immune deficiency syndrome. He had no immunity to disease, and even ordinary bacteria could be dangerous. His plastic miniworld protected him from germs.

David was placed into a sterile incubator moments after his birth on Sept. 21, 1971.

As early as age 3, he talked of leaving the bubble. But prior to the last illness, his only venture into the outside world was while wearing a sterile spacesuit.

David had never been sick until the marrow transplant was attempted.

Common mono virus caused cancer that killed 'bubble boy'

By CHRISTY HOPPE
Dallas Morning News

HOUSTON — David, the 12-year-old "bubble boy" who died last February after a bone-marrow transplant, was overcome by a mononucleosis virus that spawned a rapidly spreading cancer, doctors concluded last week.

Detailed studies of his death have shown for the first time, in a step-by-step method, how a virus can cause cancer in immunologically deficient people, said William T. Shearer, David's doctor, and Ralph D. Feigin, chief physician at Texas Children's Hospital.

"The information gleaned from the autopsy definitively identified for the first time that a common virus carried by more than 90 per cent of the general population can, in a very limited circumstance, cause cancer," Feigin told a news conference at the Baylor School of Medicine.

Until his death last year, David had been the oldest victim of severe combined immune deficiency — an absence from birth of cells that defend the body against disease and infection.

For all but the last three weeks of his life, David was confined to a sterile isolation bubble.

Through the bone-marrow transplant, doctors hoped that David's body would develop missing B-cells, which fight bacteria, and T-cells, which fight viruses.

Instead, within four months of the transplant, David's brain, lungs and intestinal tract were lined with cancerous tumors, Shearer said.

David's body was overrun by Epstein-Barr virus, which causes infectious mononucleousis, Shearer said. The virus was transmitted through the bone marrow donated by his sister in October 1983.

While most of the general population is exposed to E-B virus, very few actually contract mononucleosis because of the body's immune system. But the latent virus remains in the blood system, as tests showed it had with David's sister, Shearer said.

Because David had hardly any immune system, the virus caused what few B-cells David had to go "berserk" and they "began to spread wildly," Shearer said.

The abnormal cells formed tumors and ulcers, which eventually caused internal bleeding and pressure on David's heart, resulting in his death.

Currently, there is no medicine that can suppress E-B virus, and similar cancerous growths have been reported in about 10 per cent of all bone-marrow transplants, Shearer said.

For several years, doctors have suspected that E-B virus was what caused cancer in transplant patients but, through David's case, doctors have been able to fully document the process, he said.

The results should not deter bone-marrow transplants, however, he said. Many patients would be "handed a death sentence" if not for the procedure, Shearer said.

While tests exist to detect exposure to the E-B virus, it would prove futile to try to screen out the 90 per cent of all people who carry the latent virus. "It would virtually eliminate a compatible donor," Shearer said.

And while the E-B virus has shown the link between infections and cancer, "I believe any virus has the potential of doing this," Shearer said.

Shearer also theorized that David's transplant did not provide him with the necessary immune system because he may have been too old to adjust.

Other SCID victims who have successfully undergone the same operation have been very young children.

One of the ironies of David's transplant was that doctors initially believed the operation had been successful because immunoglobulins, which are potential antibodies, were detected in his blood shortly after the procedure.

In reality, the cancer itself was secreting the immunoglobulins. "It's a paradox," Shearer said.

AP Wirephoto

David lived in isolation for all but three weeks of life.

WORKUP FOR IMMUNODEFICIENCY.
When immunodeficiency is suspected, the family history and patient's history provide valuable clues. The physical examination is also important: How is the patient growing? Are tonsils visible, lymph nodes palpable? Are there, as in DiGeorge, associated abnormalities?

Don't overlook the obvious. © B. Grace

TESTS. You'll find it useful to keep three principles in mind.

First, if you have a good concept of the way in which the immune system fits together, you will be able to choose tests in a logical sequence. I guess this is true of any system.

Second, go from procedures which test a large integrated system to tests which are more limited. For example, if a skin test with an antigen that produces good Th1-mediated immunity is positive, it tells you that the patient can: process antigen in APCs, recognize antigen, expand a T cell clone, activate T cells, secrete lymphokines, and respond to lymphokines; which is a lot more information than can be had by measuring $CD4^+$ cells.

Third, go from cheap or easy tests to more expensive or painful ones. We will go into tests in more detail later (*see* Diagnosing the Immune System).

A LOGICAL APPROACH TO WORKING UP DEFECTIVE IMMUNITY.

	INITIAL TESTS	MORE ADVANCED TESTS
B cells	• Quantitative IgG, IgA, IgM levels • Specific Abs to prior immunizations • ABO isohemagglutinins	• Ab responses to novel Ags • Sequencing of suspect genes
T cells	• Skin test with recall Ag panel • Total lymphocyte count	• CD3, CD4, CD8 counts • Mitogen responses, MLR, cytokine measurements
Phagocytes	• WBC count, differential, morphology • NBT test, oxidative burst	• Assays for phagocytosis, chemotaxis • Genetics
Complement	• CH_{50} • Assay for C1inh (inhibitor)	• Individual complement component levels

Learning objectives for Immunodeficiency

1. Draw an outline diagram of lymphocyte development. On the diagram, indicate if possible locations of abnormalities of development in:
   - DiGeorge syndrome
   - Severe combined immunodeficiency (SCID)
   - X-linked (Bruton's) hypogammaglobulinemia
   - Common variable immunodeficiency

2. Characterize the infections you would expect in a pure B cell deficiency and in a pure T cell deficiency.

3. Describe the clinical features which, although not immunological, are associated with DiGeorge syndrome.

4. Discuss the incidence if selective IgA deficiency, and the associated syndromes.

5. Describe the immunological problem of the Nude Mouse, and name the human immunodeficiency condition it resembles.

6. Name the enzyme which is absent in some cases of SCID. Discuss possible approaches to replacing this enzyme.

7. Discuss transplantation therapy in immunodeficiency diseases. Include a consideration of side effects.

8. Given a child with recurrent infections, describe in principle tests which could be done to determine if there is a T, B or combined immunodeficiency, or a PMN, macrophage or complement problem.

9. On a diagram of a lymph node, label T and B cell areas.

10. Describe the contents of commercial gamma globulin and indicate the conditions in which it can be useful replacement therapy. Compare and contrast intramuscular and intravenous therapy.

11. Name two viruses which are immunosuppressive in humans. Discuss a possible mechanism for the immunosuppression caused by one of these viruses.