Master Answers for the B, T and B & T cell deficiency Small Group

Master Answer for Case 1

X-linked agammaglobulinemia

This male patient has a defect in early B-cell development that prevents differentiation and proliferation of antibody forming cells. The defect has been localized to the X chromosome and leads to defective tyrosine kinase signaling and subsequent defective or absence of appropriate display of B cell growth and survival receptors in many cases. Inability to produce specific antibodies to the capsular antigens of pathogenic bacteria leads to suboptimal binding to C3b and Fcγ receptors on neutrophils, which, in turn, subsequently causes inefficient phagocytosis and bacterial killing. Persistent bacterial survival leads to clinical infection. The clinical diagnosis can be made simply by doing a serum protein electrophoresis and absolute quantitation of the deficiency can be done by various light scattering and diffusion techniques for each Ig isotype. Direct analysis of the cellular defect can be done by phenotyping the patients B-cell population by flow cytometry. In this particular instance, the patient's B-cell population would be greatly reduced by all analyses; i.e., the patient has little or no lymphocytes with surface Ig markers-kappa and lambda light chain detection is an easy way to set it up. Availability of modified but intact Ig isolated from a large pool of normal volunteers (sometimes greater than 30,000) provides a means of therapy that can be given every 3 to 4 weeks and one that will maintain sufficient IgG levels and specific antibodies to most encapsulated organisms. The sister (x/x) will, by the Lyon hypothesis, inactivate the defective X and not be at risk.

Master Answer for Case 2

Severe Combined Immunodeficiency

This child has severe combined immunodeficiency (SCID). The clues here are early appearance of 'T-Cell' type infectious diseases such as disseminated fungus and protoza and the marked decrease in lymphoid cells in her blood and tissues like tonsils and spleen. This type of presentation suggests an early lineage defect in stem cell lines that leads to impaired production not only of lymphocytes but also neutrophils, platelets and sometimes erthyrocytes. The defect is usually associated with a growth signal or activating signal-found commonly in SCID are fundamental interleukin receptor defects that cause very broad defects in immune responses. There is also a group of patients who cannot generate appropriate enzymes to support lymphocyte proliferation. In either case, the defect

presents as a broad based inability to respond to infection - thus the wide spectrum of T&B-cell type infections which appear early after birth. Maternal antibody will not be sufficient for protection because the defect is in both T and B cells. Serum electropheresis will reveal very reduced globulins and FACS analysis, using CD3 and B cell markers, will confirm the virtual absence of all lymphocytes. More complex FACS or immunochemical analyses can be use to determine the exact site of the defect and could include, but not be limited to, RAG, double positive T cells or fundamental growth cytokine analysis. NOT IMPORTANT TO MEMORIZE ALL THE POSSIBLE SITES, ONLY TO UNDERSTAND THE IMPORTANT CONCEPT THAT LOCALIZATION MAY DEFINE SPECIFIC TYPES OF THERAPY UNIQUE TO THE PRECISE SITE! The only treatment that is "routinely" available is bone marrow/stem cell transplantation in these immunologically bankrupt patients. For a transplant a suitable donor must be identified and this is done by first typing all the MHC (HLA) antigens of potential donor and then setting up the most promising matches. In this case, the large family was life saving. There is a 1 in 4 chance that a sib will match and that was determined by setting up transplants "in vivo" between the affected sib and responder cells of the sibs. The lack of proliferation of one of the sib's lymphocytes after exposure to MHC of the affected sib predicted a successful grafting of the transplant.

Master Answer for Case 3

Common Variable Immunodeficiency

This patient does not have HIV (yet) - the <u>increased</u> number of lymphocytes in her peripheral blood coupled with <u>decreased</u> serum IgG makes a B-cell deficiency much more likely. Although the electropheresis confirmed a severe deficiency of immunoglobulins, the FACS analysis in this patient revealed normal numbers of B cells in the blood. This finding is typical of common variable immunodeficiency (CVI), a disease that has a different immunopathogenesis than the X-linked deficiencies. These patients have defective terminal B-cell differentiation, absence of plasma cell formation and antibody production. Early B-cell development is quite normal and is reflected by normal (even increased numbers) of B-cells in peripheral blood (detected by phenotyping) but a marked reduction in terminal B-cells, plasma cell and reduced numbers of germinal centers in lymphoid tissue. The picture is one of "frustrated" B-cell responses and the defects usually reside in some sort of defective cytokine signaling or cross talk between B and Th2 cells, which prevents the B-cells from differentiating to later stage or the inappropriate inhibition of terminal B cell maturation by CD4,25 FoxP3 cells. The common association of a T-cell helper defect is reflected clinically in diseases that do not appear in "pure" B-cell deficiency states. CVI patients are susceptible to autoimmune diseases and lymphoma.

Master Answer for Case 4

Severe Combined Immunodeficiency

In contrast to the child with many sibs, this patient had little to no opportunity for finding a

donor with matching MHC. There is a national bone marrow donor registry but the odds are very low that an A,B,C and D MHC match will be found. Even if one is found, there are usually undetectable (by current lab tests) "minor" MHC differences that can lead to major problems after transplant. No unrelated donor could be found in this case, so the only opportunity for cure rested with being able to restore normal gene function by transferring a normal gene into his bone marrow. As the posted article shows, retroviral mediated transfer of the defective gene into the bone marrow stem cells of this type of patient can be curative. The downside was the (almost completely unpredictable) point of insertion of the vector that led to a very unusual $\gamma\delta$ cell leukemia in several SCID patients. Conversely, the other posted article detailing the outcomes of 10 children with another form of SCID documents the great promise of gene therapy and how researchers are devising safer ways to insert genes into humans. Bottom line: be careful when you fool around with Mother Nature. You will not be tested on any techniques of gene transfer- Case #4 is for discussion purposes only