Master Answers for B Cell Mediated Pathology Small Group

Master Answer for Case 1
B-CELL-ANTIBODY MEDIATED PATHOLOGY

The patient had been immunized at least twice before with tetanus toxoid-this generated high levels of specific toxoid antibody which are present at the time of this injection of the toxoid vaccine. Thus, high levels of pre-existing antitoxoid antibody were available for rapid formation of toxoid-antitoxoid antibody complexes at the injection site. While this reaction generated pain at the site, it did not become systemic and lead to more generalized cytokine induced symptoms. The inflammatory reaction is generated by activation of the C3 direct pathway and, even more importantly, by binding to Fcγ receptors on neutrophils. In both circumstances, neutrophils are activated with the release of hydrolytic and other destructive enzymes, all of which lead to inflammation and tissue destruction. The inflammatory reaction could be characterized by the use of fluoresceinated or peroxidase labeled anti IgG and anti C3 reagents that will detect immune complexes in tissue. Routine histology would detect neutrophil infiltration, vasodilatation, and vascular endothethial damage. Treatment could range from simple analgesia as the limited dose of antigen is catabolized and the rate of immune complex formation decreases or, in severe cases, the immune inflammatory response could be suppressed by corticosteroids-a powerful anti-inflammatory drug.

Master Answer for Facilitators for Case 2
B-CELL ANTIBODY MEDIATED PATHOLOGY

In general, females have vigorous antibody responses to certain types of antigens. Post pubertal females are at higher risk of developing autoimmune diseases presumably based on, among other factors, the superimposed influence of estrogens. This propensity is further enhanced by the inheritance of certain MHC-II genes that are associated with loss of tolerance to self antigens and inadequate control of B-cell function. UV light, especially the B-wavelength, has strong influences on dendritic cell antigen presentation in the skin and, sunlight has been a common precipitant of systemic lupus erythematosus (SLE) in some patients [remember this factoid for third year clerkships, not the HD test]. Anyway, a working concept should be that once circulating autoimmune complexes of DNA and anti-DNA are formed, complement ***and Fc receptor*** *pathways are activated and serve as generators of inflammation by a final common pathway (neutrophil recruitment). The symptoms in this case are generalized and based on IL-1 & 6 induced muscle aches and severe fatigue. Treatment of SLE obviously cannot be directed at removal of DNA so either generalized suppression of the inflammatory response by corticosteroids, suppression of B-cell synthesis of antibodies so complexes cannot be formed or elimination of the B cell clones making the autoreactive antibody can be tried. The first 2 strategies have potentially severe side effects.*

Master Answer for Case 3
B-Cell Antibody Mediated Pathology

This patient may have had a congenital abnormality of his aortic valve as an underlining reason for his subsequent bacterial infection of it, which probably occurred during a routine bacteremic episode, (skin abrasion, brushing one's teeth, slide on Astroturf, etc.). The bacterial infection on the valve is resistant because the bacteria are encapsulated and thus relatively resistant to phagocytosis. The bacterial antigens are a potent and protracted stimulus to antibody formation, which leads to high levels of circulating immune complexes, which begin to deposit in extra hepatic sites after the latter organ is saturated in terms of its ability to dispose of them. Increased B-cell proliferation and plasma cell formation increase spleen size. Skin and kidney have extensive capillary networks with C3b receptors and Fcγ receptors that make deposition at these sites a frequent one for circulating immune complexes. Deposition at these sites will be manifest clinically by rash and glomerular damage-proteinuria and red cell casts. The intense stimulation of antibody formation by the persistent bacteria in the bloodstream leads to somatic hypermutation (think "frustrated response") during antibody formation and the end result seen clinically is a polyclonal increase in IgG in the blood and documented by doing the serum protein electropheresis. Conceptually, this should be viewed as an evolutionary adjustment that enabled B cells to continually improve the odds of synthesizing more efficient antibody by going after a new epitope or increasing their avidity for the antigens that are not being eradicated by the current antibody being produced. Blood cultures will document the source of antigen and biopsy studies of either of the kidney or the skin using the appropriate labeled immunopathologic reagents would provide circumstantial evidence for systemic immune complex disease. In some cases antibiotic therapy will reduce or eliminate the stimulus for circulating immune complex formation. Frequently however, in addition to poor penetration by antibiotics through thick fibrin deposition over the infection site, the valve must be replaced for hemodynamic reasons.

Master Answer for Case 4
B-CELL-ANTIBODY MEDIATED PATHOLOGY

Goodpasture's syndrome develops when a patient makes IgG antibodies directed against a specific epitope in Type IV collagen. This epitope is a vital structural component of the basement membrane in both the glomerulus and the alveolus. In contrast to the pathogenesis of circulating immune complex disease that is characterized by binding of circulating complexes of antigen (not specifically directed at the organ per se) to C3b and FcR in kidney, skin ,etc., this disease results from the binding of a specific IgG to its target epitope-in this case, collagen type IV. ***You don't need to know about the other specifics about Goodpasture's but be sure you know the difference in immunopathogenesis between Case #4 and the first three!*** *Goodpasture's syndrome is an example of Type II hypersensitivity, the first three are Type III hypersensitivity. As discussed in class, you need to know this classification for Boards even though it is obsolete. I included the deafness syndrome because, if for no other reason, it is a wonderful example of how the prepared mind of a physician can take a clinical observation made in a patient back to the bench and then back to*

patients. In this case, the failure of a control serum with known antiglomerular antibodies to stain the glomeruli of some patients allowed the conclusion that the latter had a defect in collagen . This, in turn, could only have been known because previous studies on Goodpasture's sera had shown that the antibody was binding to collagen. This conclusion led to the precise localization of the genetic defect, a broader understanding of collagen structure and finally getting close to better therapy of Goodpastures! This is why we have journal clubs!!!