B lymphocytes are cells with one major function, the formation of antibody. The mechanism by which this final secretion event occurs is under complex regulatory control, requiring in most cases, T cell and monocyte interactions. In mammals, B cells are derived from pleuropotent stem cells in the yolk sac which travel to the fetal liver. As best described in the murine system, in the liver these stem cells undergo rearrangement of the genes coding for constant region of the immunoglobulin heavy chain. This is the first recognizable event that commits cells to the B cell lineage, occurring at 13 to 15 weeks of gestation. These events appear to be random and control mechanisms are poorly understood. In the chicken, there is an organ called the bursa of Fabricius, located in the distal gut, wherein B cells arise and mature under presumably hormonal or factor influence. Removal of the bursa early in fetal life results in the total absence of B cells and antibody production. In man, bone marrow appears to be a bursal equivalent. Hence, the term B cell refers to bone marrow-derived/bursal cell. As will be discussed below, certain disease states are manifest by the lack of B cells due to maturational defects at this stage of B cell development.

Certain disease states are manifest by the lack of B cells due to maturational defects.

MATURATIONAL STAGES AND ACTIVATION

In the fetal liver and after travel to the bone marrow, pre-pre-B cells, by virtue of the genetic rearrangement of the heavy-chain gene, can now make immunoglobulin heavy chain (Figure 1). In keeping with the above described arrangement of the Ig gene, the first isotype transcribed is μ. Pre-B cells make heavy chain which remains intracytoplasmic due to the lack of light chain. This surface Ig−, cytoplasmic IgM+ state is the predominant characteristic of the pre-B cell. It is at this stage of maturation that the defect exists in X-linked Bruton’s agammaglobulinemia. The next step in maturation occurs when the gene coding for one of the two light chains, κ or λ, undergoes rearrangement. The existence of both light and heavy chain allows for assemblage of an intact Ig molecule which is then inserted into the membrane of the B cells. These surface IgM+ IgD+ cytoplasmic IgM− cells are termed virgin B cells having never seen antigen and having limited specificity. There is considerable controversy at this stage. It is thought that exposure to antigen in the presence (T dependent antigens) or absence (T independent antigens) of T cells causes the cell to lose slgD and develop memory for the specific antigen. Further exposure to antigen or T cells induces
Figure 1. B cell maturation pathway and cellular characteristics.

Legend
BCDF = B cell differentiation factor
BCGF = B cell growth factor
BCPF = B cell proliferation factor
these memory cells to undergo an isotype switch (see below) from IgM to IgG, IgA, or IgE. This switch allows for higher affinity, more specialized antibody (eg, complement binding, tissue localization, etc) to be produced. Once switching has occurred, the cell can remain a memory B cell, primed for re-exposure to antigen, or undergo terminal maturation to a plasma cell under influences described below. Defects in switching occur in some immunodeficiency states, most specifically in patients with immunodeficiency and hyper-IgM, where the defect can reside within the T cell or B cell population.

Most cells within lymph nodes and in the circulation are memory B cells having been primed earlier by the interaction of T cells, antigen-presenting cells, and antigen. The question then is, how are these primed cells finally triggered to secrete antibody? During the past few years there has been tremendous progress in understanding this process. There are three mechanisms by which B cells can be induced to undergo terminal maturation: 1) by antigen alone (T independent antigens); 2) by direct T cell to B cell linking in the context of antigen ( cognate interaction); and 3) by factor-mediated, noncognate interactions. There are several antigens (T independent) that can activate and induce terminal maturation of B cells in the absence of T cells. These antigens are commonly bacterial antigens/polysaccharide antigens with repeating antigenic units. These antigens can "crosslink" the surface Ig molecules, a process which induces membrane changes (depolarization), activation of the B cell, and proliferation. These antigens, such as lipopolysaccharide, pneumococcal polysaccharides, and Staphylococcus aureus organisms (SAC) are potent B cell mitogens.

Other antigens (T dependent), usually protein or glycoprotein antigens, require antigen-presenting cells and T cells to induce the B cell to respond. The interactions occur in close proximity or linking of these cells (cognate interaction), although some of the demonstrable effects may still be due to locally secreted factors. The T cell recognizes antigen in the context of "self" on HLA-D molecules and in turn can make available sites on the antigen for B cell binding through surface Ig receptors. In some cases, the B cell itself appears to be able to function as an antigen-presenting cell by low-affinity binding of the antigen by surface Ig. This process may actually be the most efficient form of T to B collaboration.

Finally, there are several antigen nonspecific potent factors derived from T cells which can induce either B cell proliferation, expansion of memory clones, or B cell differentiation, induction of terminal maturation, and antibody formation. Several such factors have been described but, despite the heterogeneity, the basic concepts persist. B cells are activated in vivo by antigen or in vitro by molecules that can crosslink sIg (anti-IgM, SAC), inducing an activation state rendering the cells responsive to growth and differentiation stimuli.

Some B cells develop receptors for B cell growth factors (BCGF) and in their presence will proliferate and expand the clone. After several divisions some of these cells will develop receptors for terminal maturation signals or B cell differentiation factors (BCDF). These BCDFs induce memory cells to mature to plasma cells secreting their specific antibody. It should be stressed here that these factors are antigen nonspecific and can trigger any B cell clone. The existence of antigen specific helper factors is quite controversial and it appears more likely that the potent antigen nonspecific signals generated by BCGFs and BCDFs augment a relatively weak antigen specific signal. Additional nonspecific factors have been described which can bypass the requirements of activation described above. One such factor is B cell proliferation factor (BCPF) which induces resting B cells to proliferate. Proliferation independent BCDFs can also act on resting B cells inducing maturation to plasma cells without undergoing division. The presence of these factors helps to explain the inherent nonspecificity of the immune response. For example, if an individual is revaccinated or boosted with tetanus toxoid, one always sees a rise in antibody titer to other antigens (eg, measles antibody, diphtheria antibody, etc). Other T cell derived factors have been found to induce or enhance B cell growth or differentiation. Interleukin 2 (IL-2), formerly thought to act only on T cells, can augment B cell responses to BCGF and BCDF. γ-Interferon, in addition to its antiviral activity, can induce B cell differentiation as well, although this effect is only clearly seen in the murine system.

**ISOTYPE SWITCHING**

As briefly described above, the initial immunoglobulin produced to any antigen is IgM. The IgM molecule is an effective first line of defense in that it has a pentameric structure (five Ig molecules joined together) and therefore ten antigen binding sites. It serves as an excellent agglutinator of antigen but it is bulky and inefficient at traveling through the lymph node and tissues. For this reason, the production of smaller, more efficient antibodies is required. The process by which the B cell stops making IgM and starts making IgG, IgA, or IgE is called isotype switching. This process can occur either by DNA rearrangement or differential RNA splicing. As depicted in Figure 2, there are segments of DNA coding for "switch" regions (S region) in front of the exons coding for each specific isotype. After a signal to switch is received (either an endogenous recombinase or an exogenous signal from a T cell), the DNA segment undergoes S-S recombination deleting the intervening DNA. In this case, since DNA has been deleted there can be no "back switching" to other isotypes and the isotype is fixed. DNA rearrangement can also occur by a process termed sister chromatid exchange where there is exchange of DNA during mitosis resulting in a new reading frame.

An alternative mechanism involves differential... continued on page 476
RNA splicing. Here, a long RNA transcript is transcribed but only a short segment coding for a new isotype is translated. The coexistence of IgM and IgD on the surface of the B cell occurs via RNA splicing. Whether this mechanism accounts for other isotypes is not proven as yet. The regulation of the isotype switch is controversial. There is evidence that switching occurs as a random event controlled by endogenous recombinases. However, there is growing evidence for the role of T cells in this process. Several groups have reported the existence of "switch" T cells which initiate and accelerate the switch process. In fact, it appears that an immunodeficiency disorder, immunodeficiency with hyper-IgM, may actually represent a deficiency in switch T cells rather than an intrinsic B cell defect.

DISORDERS OF B CELL
REGULATION AND MATURATION

With the complex regulatory and maturational pathways described above, it is obvious that any defect in these pathways can result in specific disease states. Since B cells basically produce antibody, B cell defects result in antibody deficiency (immunodeficiency states), autoantibody production (autoimmune disorders), or uncontrolled antibody production (B cell malignancy). B cell immunodeficiencies are dictated by the stage at which B cell maturation is arrested. Severe combined immunodeficiency results from an arrest at the stem cell level (both B and T cell dysfunction). X-linked (Bruton's) agammaglobulinemia results from a defect in progressing past the pre-B cell stage. Varied defects in later maturational stages can be seen in patients with acquired (common variable) agammaglobulinemia. These patients are plagued by infections usually controlled by antibodies, ie, gram-positive bacterial infections, frequent pneumonias, bronchitis, otitis media, sinus infections, and skin and dental abscesses. This correlates with the lack of response to polysaccharide antigens (T independent).

The role of B cell regulation in the pathogenesis of autoimmune disordering is less clear. Certainly, highly regulated B cell clones producing antibodies against self-antigens appear to be free of normal control mechanisms. This may account, in part, for the hypergammaglobulinemia seen in these disorders. Finally, malignant transformation of B cells at any stage of maturation can result in distinct malignancies, ie, acute lymphoblastic leukemia (ALL). More commonly non-B non-T can express a pre-B phenotype. Malignancies of later maturational stages are characteristically seen in chronic lymphoblastic leukemia (CLL). Depending on the stage of arrest, B cells can function (monoclonal spike) or not (hypogammaglobulinemia). In either case, these patients are susceptible to the same B cell infections seen in patients with immunodeficiency. From each of these B cell disorders we have learned a great deal about normal B cell maturation and the importance of specific antibody production.

SUGGESTED READINGS