HEMATOPOIETIC STEM CELLS originate in the yolk sac of the developing embryo, migrate early into the FETAL LIVER, and later into the BONE MARROW, which is the only normal site of hematopoiesis in the adult. The generation of immunocompetent cells from hematopoietic precursors in the bone marrow is a process which continues throughout the life of an individual. Human infants are born with a functioning immune system, and are additionally protected by transplacentally acquired maternal IgG for the first few months of life. Exchange of cells and immunoglobulins between mother and fetus takes place during gestation, which may result in MATERNAL IMMUNIZATION to HLA and blood group antigens, and the pathological consequences of Rh INCOMPATIBILITY (discussed in Chapter 10).

A discussion of the "development" of an organ system would normally consist simply of a description of its embryological origins. However, as we have already noted, the entire hematopoietic system (including the immune system) is in a continuous state of regeneration throughout life, and is therefore continuously being "developed." It is largely in this context that we will discuss the ontogeny of the immune system. We will also discuss some important aspects of the immunological relationships between mother and fetus; keep in mind, however, that this relationship is still only poorly understood, and is much more complex than is being discussed here.

ORIGIN OF HEMATOPOIETIC STEM CELLS

All cells of the hematopoietic system are continuously being generated from a single kind of precursor cell known as the Hematopoietic Stem Cell. This stem cell is capable of unlimited mitotic cell division, more specifically asymmetric division which results in two classes of products. One class includes cells in various stages of differentiation, eventually yielding each of the mature cells of the blood and immune system including lymphocytes (both B- and T-cells), granulocytes, monocytes, red blood cells and platelets. A second class of product is represented by new stem cells identical to the parent cells. The stem cell is therefore said to exhibit the property of self-renewal; in fact, self-renewal is a defining property of stem cells. This continuous regeneration of immunologically competent cells has many important consequences, not the least of which is the fact that whatever processes are required to maintain the normal state of TOLERANCE (see Chapter 18) must take place not only during embryological development, but continuously throughout life.
In normal human adults, the generation of all cells of the hematopoietic system, with one important exception, is restricted to the bone marrow. We’ve already discussed this exception in Chapter 13; while B-cells (and most other blood cells) are produced within the bone marrow, mature T-cells are produced exclusively within the thymus, from precursors ("pre-T-cells") which themselves are bone-marrow-derived and have entered the thymus from the blood.

The question of the origin of the immune system therefore can, in one sense, be reduced to the question of the origin of stem cells. As shown in Figure 17-1, the first stem cells (and the first blood cells) appear early in the course of human embryological development (at about two weeks of gestation) in the blood islands of the yolk sac. As the developing blood vessels begin making connections with the embryo itself, stem cells move into the developing fetal liver, the first hematopoietic organ of the embryo, and transiently into the spleen. By the time of birth, neither the liver nor the spleen remains a site of hematopoiesis in humans; the stem cells have migrated into the bone marrow, which remains the normal site of generation of all blood cells throughout life. This movement of stem cells from the yolk sac to the embryonic liver, and then to the bone marrow, adds two new paths to the patterns of cell migration we have already discussed in Chapter 16.

[NOTE: In certain pathological conditions, some anemias for example, development of blood cells may take place at sites other than the bone marrow, a condition referred to as "extramedullary hematopoiesis". In other species (mice, for example) the normal spleen may retain its hematopoietic role throughout life; it is for this reason that mouse spleen contains not only B- and T-cells characteristic of normal peripheral lymphoid tissue, but also hematopoietic stem cells capable of rescuing a lethally irradiated animal from hematopoietic death.]
IMMUNOLOGICAL STATUS OF THE NEWBORN

Fetal Development of Immunity

Mice are born at an immunologically very immature stage of development; few B-cells are found in the peripheral lymphoid tissue, and almost no T-cells. This explains the fact that removal of the thymus immediately after birth results in a profound and permanent T-cell deficiency in mice (as we discussed in Chapter 13), and accounts for the sensitivity of newborn mice to developing GvH.

Humans, on the other hand, are born with considerably more mature immune systems; the newborn human is capable of generating effective immune responses, both humoral and cellular, although not necessarily at adult levels. T-cell and B-cell areas of peripheral lymphoid tissue are already largely populated, and show the same basic architecture seen in adult tissues. (NOTE: One characteristic feature of newborn human peripheral lymphoid tissue is the presence of primary follicles. These are rare or absent later in life, due to the normal antigenic stimulation of these tissues, and the consequent development of germinal centers and secondary follicles).

Maternal IgG in the Newborn

If one examines the level and nature of immunoglobulins in the serum of a newborn human, an interesting situation becomes apparent. While the total Ig in newborn serum is at a level close to that of a normal adult, almost all of it is IgG of maternal origin. This results from the fact that IgG (but not other classes) can be transported across the placenta, passing from the maternal circulation to that of the fetus via a transport mechanism involving specific Fc-receptors in the placenta. This process begins around the 22nd week of gestation and continues to term.

As shown in the figure above, the only immunoglobulin normally present at substantial levels in the newborn is maternal IgG (this can be determined by examination of allotypes). Small amounts of IgM and trace amounts of IgA are also present; since these immunoglobulins do...
not cross the placental barrier, they must be of fetal origin; their presence in the newborn circulation at high levels (detected by its presence in umbilical cord blood) is considered a sign of *intrauterine infection* and a resulting fetal immune response.

Mature B-cells and T-cells are already present at the time of birth, but it is only after birth and exposure to environmental antigens that they normally begin to generate appreciable immune responses. As a result, the levels of *endogenous* (as opposed to maternal) serum immunoglobulin begin to rise during the first few months after birth, IgM rising earliest, followed by IgG and IgA.

While endogenous synthesis of immunoglobulins is already underway at birth, it takes several months to reach levels which can effectively replace the protection conferred by the passively acquired maternal IgG. This maternal IgG disappears with a normal half-life of 2-3 weeks, and (of course) is not replenished. A low point in total serum Ig is typically reached at about 4-5 months of age, which is also the time at which humoral immunodeficiencies may become clinically evident (see Bruton's Agammaglobulinemia in Chapter 20).

**NOTE:** The newborn infant is also protected by maternal IgA which it acquires from its mother's milk (particularly the early form known as *colostrum*). However, while this IgA plays an important role by protecting against infection by gut-localized pathogens, *this IgA does not enter the infant's circulation.*

**Maternal/Fetal Interactions:**

The developing fetus can be regarded as a graft of "foreign" tissue onto the mother; it is clearly a *histoincompatible graft*, since at least some HLA antigens (those of paternal origin) will be foreign to the mother. If this is so, why is the fetus not recognized as foreign and rejected? In fact, the fetus *is* generally recognized as foreign by the mother's immune system, but is nevertheless not rejected. There are several (and still poorly understood) reasons for this.

*First*, the placenta itself may act as a *filter* for anti-HLA antibodies; maternal antibodies directed against paternal HLA antigens present in the fetal component of the placenta may be bound by the placental tissue. The placenta is not harmed by these antibodies, but it prevents their passage into the fetal circulation where they might be harmful, thus effectively neutralizing the mother's *humoral immune response* to the fetus. *Second*, this "coating" of antibody on paternal antigens present in the placenta may "hide" the foreign HLA antigens and prevent recognition and damage by the mother's *cell-mediated immune response* (in the manner of *enhancing antibodies*; see Chapters 11 and 23). *Third*, cells of the outermost layer of the placenta, the trophoblast, do not express the HLA Class I proteins which are present on all other nucleated cells, thus reducing the generation of, and the target for, anti-HLA cell-mediated responses by the mother. And *fourth*, the state of pregnancy induces a state of moderate *immunosuppression* of the mother (by various mechanisms), which has the effect of further discouraging anti-fetal responses.
While the placenta does a relatively good job of keeping the maternal and fetal sides of the circulation separate, several materials of immunological importance can cross the placental barrier to various extents, as outlined in Figure 17-3, below.

**Figure 17-3**

One example, as we have already seen, is that of maternal IgG, which is efficiently transported into the fetal circulation before birth; this IgG is critically important for protection of the newborn during its first few months of life. Another example is that of small numbers of cells of fetal origin (red blood cells as well as nucleated cells) which enter the maternal circulation, presumably through microscopic defects in the placental barrier. These cells are of interest for at least two reasons. First, they may eventually stimulate substantial anti-HLA antibody responses in the mother (already mentioned above), particularly after multiple pregnancies; in fact, *multiparous women* are an important source of the anti-HLA antibodies which are used in histocompatibility typing. Second, these rare cells can be identified and isolated from the mother's circulation; their use for prenatal testing of genetic disease, which would eliminate the need for the more expensive and hazardous process of amniocentesis, is currently under development. (Red blood cells may also trigger maternal antibody responses directed against blood group antigens, although such a response is far stronger after the appearance of the larger number of red blood cells which enter the maternal circulation at the time of birth and the separation of the placenta. The development and significance of maternal anti-Rh responses have been discussed in Chapter 10).
CHAPTER 17, STUDY QUESTIONS:

1. Follow a MEMORY T- or B-CELL back in time through its development; what are the membrane markers and anatomical localizations associated with each of its identifiable precursors?

2. How would you use heavy and light chain Ig ALLOTYPES to distinguish the origins of serum Ig in a newborn? How would your results be different if you looked at a 6-month-old or 2-year-old child?

3. Why are multiparous women not a good source for ANTI-Gm ANTIBODIES