1. Normal production of lymphomyeloid cells and their neoplastic counterparts

Closely related lectures are:

Lecture 16 - Lymphoid system and lymphomas
Lecture 44 - Acute and chronic leukaemias
Lecture 48 - M-GUS and myeloma
Lecture 51 - Myeloproliferative disorders

Relevant parts of the second year Immunology/Haematology course are incorporated.

1. Haemopoiesis

Haemopoiesis is the process by which CD34+ve stem cells give rise to 1) the cellular components of blood 2) mast cells, macrophages and dendritic cells in tissues and 3) the cellular components of the lymphoid system. Haemopoiesis starts in blood islands in the extraembryonic yolk sac where a mesodermal cell (hemangioblast) gives rise to both the haemopoietic and vascular systems. The blood cell products of haemopoiesis are contained within the endothelial lining of the vascular system. There are important interactions between the haemopoietic cells and blood cells, particularly migration of leukocytes out into the tissues and mechanisms for the prevention or activation of clotting.

1. Sites of haemopoiesis

At six weeks of embryonic life haemopoiesis has switched from the yolk sac to the liver, by twelve weeks the spleen is also involved. From 20 weeks gestation onwards, haemopoiesis is predominantly in the marrow (medullary) cavity of bones. However, in disease states described in this and related lectures you will see that extramedullary sites, the liver and spleen, may again become sites for haemopoiesis or be infiltrated by neoplastic cells derived from the haemopoietic system. The bone marrow cavities are encased by compact bone and traversed by trabecular bone. The marrow has a rich blood supply and consists of adipocytes and other stromal cells interspersed with haemopoietic cells. In contrast to cells in solid organs, haemopoietic cells are not fixed to each other by intercellular junctions, rather they interact by reversible interaction of adhesion molecules and can be readily dispersed into a single cell suspension. A suspension of bone marrow cells can be aspirated for analysis by inserting a needle into the medullary cavity and applying suction by a syringe. Alternatively a bone biopsy can be taken, usually as a trephine biopsy, and analysed histologically.

At birth, all medullary cavities are involved in haemopoiesis and macroscopically the marrow is red. In children, marrow is usually aspirated from the tibia. As adulthood approaches, haemopoiesis is restricted to the axial skeleton (vertebrae, ribs, scapulae, pelvis, skull, proximal parts of humeri and femora) and the other medullary cavities are left with adipocytes only - yellow marrow. In adults, marrow is usually aspirated from the sternum or iliac crest.

2. Stem cells and haemopoiesis

Haemopoiesis produces platelets, red cells, mast cells, basophils, eosinophils, neutrophils, monocytes, dendritic cells, NK cells, B and T lymphocytes (see table 1). All of these different cell types are derived from a common pluripotent stem cell pool. The process of haemopoiesis involves cell proliferation, lineage commitment and maturation. Stem cells account for <0.1% of total cells in marrow but can be identified by the presence of a molecule on their surface called CD34. At any one time, most stem cells are in a state of deep quiescence - in G0. Only a small proportion of stem cells are in cell cycle, producing 1) new stem cells identical to the parent 2) progenitor cells for haemopoiesis. The stem cell population is effectively immortal; the progenitor cells are not immortal; they proliferate (and are therefore called blasts) and become committed to different cell lineages (megakaryoblasts / platelet production, erythroblasts / red cell production, myeloblasts / granulocyte production, lymphoblasts / lymphocyte production, etc.). Following commitment to a cell lineage, progenitor cells continue to proliferate but also mature, within a few days becoming non-dividing end-stage cells such as red cells or neutrophils. Lymphocytes are the exception to this since they can be activated at a later date by specific antigen to proliferate and undergo a further stage of differentiation and maturation. Neoplasias of the haemopoietic system can arise at the haemopoietic stage - leukaemias, or for lymphocytes, can also arise at the later stages of antigen activation - lymphomas, myeloma.

3. The use of cytokines to increase haemopoiesis

Normal haemopoiesis is dependent on the presence of accessory stromal cells; these cells include fibroblasts, macrophages, adipocytes and endothelial cells. These cells together with some of the mature blood cells, are responsible for the production and presentation of a complex array of biologically active proteins which influence the development of blood cells. Many of these proteins or cytokines have been identified and their actions and target cell populations are becoming well understood. In response to hypoxia, there is increased erythropoietin production in the proximal renal tubular cells. In turn, erythropoietin increases erythropoiesis in the marrow and thus the number of red cells in the blood. Bacterial infection is associated with increased production of cytokines which increase myelopoiesis and thus the number of neutrophils in the blood - neutrophilia. The cytokines generated in the immune response to parasites or some allergic reactions, cause an increased production of eosinophils. Using molecular biology techniques, recombinant cytokines can be produced in sufficient quantities to be administered therapeutically. Erythropoietin is routinely used to boost erythropoiesis in patients with end-stage renal failure. G-CSF (granulocyte colony stimulating factor) greatly shortens the time for recovery of neutrophil numbers after whole body irradiation and bone marrow transplantation.

4. Haemopoiesis and cytotoxic therapy

Cytotoxic drugs and radiotherapy are used to eliminate malignant cells. Cytotoxic therapy will also kill haemopoietic progenitor cells and stem
cells that are in cell cycle but leave quiescent stem cells unharmed. Following a short course of chemotherapy or radiotherapy, there is a temporary absence of progenitor cells and therefore loss of blood cell production. This manifests about 5 days later as thrombocytopenia and neutropenia. Within 1-2 weeks, stem cells, which were quiescent and therefore unharmed at the time of chemotherapy, divide and replenish haemopoiesis. In the meantime the patient can be supported by platelet transfusion. Because neutrophil transfusion is not effective the patient is at risk of bacterial infection and so anti-bacterial prophylaxis and prompt i.v. antibiotics in the event of septicaemia are applied. Anaemia is not usually evident as red cells have a much longer half life than platelets and neutrophils (see table 1). Most mature lymphocytes are unharmed by chemotherapy because they are not in cell cycle. However, lymphocytes are uniquely sensitive to radiotherapy, even when they are not in cell cycle.

2. Stem cell transplantation

Cytotoxic therapy is administered to eradicate a malignant clone whether solid tumour or of haemopoietic origin. Just as a proportion of haemopoietic stem cells survive cytotoxic therapy, so can a proportion of the malignant clone. To eradicate the malignant clone, haematologists and oncologists are increasingly using intensive therapy schedules which result in the destruction of all haemopoietic stem cells. Immediately after therapy the patient is rescued by i.v. infusion of CD34+ve haemopoietic stem cells. Following infusion, these stem cells find their way to the denuded marrow cavities where they replenish haemopoiesis over a period of a few weeks.

Stem cell transplantation is also used in inherited disorders where some aspect of haemopoiesis is abnormal. These conditions include several types of primary immunodeficiency and some metabolic disorders.

1. Autologous bone marrow or stem cell rescue

Stem cells may be obtained from the patient prior to chemotherapy and stored in liquid nitrogen, to be thawed and administered at the end of the chemotherapy (autologous bone marrow rescue). The stem cells are obtained by aspirating a litre of bone marrow / blood from the iliac crests under general anaesthesia. The bulk of the red cells are removed by centrifugation leaving the less dense nucleated cells (buffy coat) for freezing. Usually, no attempt is made to purify the stem cells which represent only 0.1% of the total nucleated cells. However, there is a risk that the cell preparation is contaminated by tumour cells and sometimes attempts are made to purge these by monoclonal antibodies directed against molecules that are present on the tumour cells but not present on the stem cells.

An alternative source of stem cells is the blood. With the exception of cord blood at birth, the number of stem cells in blood is normally very low. However, the number of peripheral blood stem cells can be increased by prior administration of ‘low doses’ of cytotoxic agents - stem cell mobilisation. By a continuous process, blood is removed from one vein, nucleated cells separated by centrifugal force, and the remaining blood components reinfused into another vein - cell-phoresis. As for whole marrow, the nucleated blood cell preparation, containing stem cells, is frozen until required for peripheral blood stem cell (PBSC) rescue.

Clearly autologous stem cells are of no use in therapy for inherited disorders as they will carry the genetic defect. However current research is investigating the growth and genetic manipulation of stem cells in vitro. Stem cells can be harvested from the patient, the genetic defect corrected and those corrected cells used to replace the old haemopoietic system.

2. Allogeneic bone marrow transplantation

Allogeneic stem cells are usually obtained by harvesting bone marrow since it is deemed unethical to subject a healthy donor to the cytotoxic agents required for PBSC mobilisation. Allogeneic bone marrow transplants are used in therapy for inherited disorders (see above) or as a rescue procedure following cytotoxic therapy for malignancy (autologous stem cell preparations may be contaminated by tumour cells). The donor and recipient must be HLA matched to reduce the risk of graft versus host disease - the donor is usually a sibling (see section 9). Sometimes, the donor marrow is purged of mature T cells to reduce the risk of GVHD, however this also reduces the chances of an associated beneficial phenomenon - the graft versus leukaemia effect.

3. What is cancer / neoplasia?

Cancer or neoplasia (new growth) is believed to arise by the acquisition of somatic genetic changes in a single cell. These changes render the cell and its progeny (the neoplastic clone) a growth advantage over their normal counterparts. This advantage reflects changes in control of proliferation, differentiation and cell death. A neoplasm can be defined as an autonomous abnormal cell proliferation which continues after cessation of the stimulus which triggered it initially. It can be surmised from this that neoplasias arise from proliferating cell populations such as haemopoietic cells (leukaemias) or antigen stimulated mature lymphocytes (Non Hodgkins Lymphomas).

A single genetic change can produce a neoplasia. This is exemplified in acute promyeloctic leukaemia where a chromosomal translocation t(15,17) generates a new fusion protein called PML/RARα. PML is the promyeloctic leukaemia protein and RARα is a nuclear transcription factor called retinoic acid receptor alpha. A PML/RARα gene can be inserted into the genome of mice (transgenic mice) and its' expression induced in haemopoietic cells with the result that acute promyeloctic leukaemias develop. In this leukaemia the PML/RARα gene is frozen at the promyeloctye stage of myelopoesis. The neoplastic promyeloctyes proliferate but unlike normal promyeloctyes, the PML/RARα gene product prevents the neoplastic cells from maturing - maturation arrest. Instead, all of the neoplastic cell progeny also continue to proliferate and rapidly come to dominate the marrow and blood. This block in maturation can be overcome by the administration of pharmacological doses of retinoids with the result that the neoplastic cells all mature to non-dividing neutrophils and the patient enters remission - a state where leukaemia cells can no longer be detected. Retinoid therapy is routinely used to treat this type of leukaemia but on its' own is not curative.

In most types of neoplasia the neoplastic state is the result of an accumulation of genetic changes in a single progenitor cell. These genetic changes affect two large groups of genes: oncogenes and tumour suppressor genes which are described below.

1. Neoplasms are clonal

As a result of progress in immunological and molecular biological methods in the last two decades, neoplasms have become accessible to very detailed phenotypic and genotypic analysis. These studies initially focused on lymphoid and other haemopoietic
neoplasms and have served to disclose principles of the neoplastic process which have wider implications for neoplasia in general.

The presence of the same cytogenetic defect in all cells of a neoplastic population is evidence of clonality. As illustrated above, cytogenetic defects are important in diagnosis, predicting prognosis and revealing the biological mechanisms of neoplasia. Classically, such studies have depended on cytogenetic techniques which are time-consuming and require fresh tissue suitable for tissue culture. PCR methods have widened the scope of this methodology although do rely on knowing what cytogenetic defect to look for. In the absence of detectable cytogenetic defects clonality can be demonstrated by analysis of polymorphic X-linked markers, although this technique is applicable only to females and therefore not useful in a diagnostic setting.

During their normal development, lymphocytes rearrange the genes encoding for their antigen receptors (immunoglobulins or T-cell receptors) resulting in a unique configuration of these genes in individual lymphocytes and their progeny. Even if a lymphocyte acquires genetic changes which lead to transformation to a neoplasia the unique antigen receptor gene rearrangement is retained. This enables demonstration of monoclonality of the neoplasia by Southern Blotting or by PCR methods. Using this approach, it has been demonstrated that malignant lymphomas are monoclonal proliferations, and this is now accepted to be true for all neoplasms regardless of their cellular origin. Moreover, the detection of clonal antigen receptor gene rearrangements by Southern blot hybridisation or by PCR is an important diagnostic aide in the analysis of difficult lymph node specimens or for the detection of minimal residual disease in patients who are clinically in remission.

In generation of their antigen receptor, immunoglobulin, individual B cells use either kappa or lambda light chains. If all the cells in a population of B cells are either kappa or lambda then they are monoclonal in contrast to the normal circumstance of polyclonal populations which usually two thirds of cells express kappa and one third lambda. A blood sample might contain increased numbers of B lymphocytes. This increase may reflect a reactive process against infection (increased numbers of polyclonal B cells) or reflect a monoclonal expansion of B cells (e.g. chronic lymphocytic leukaemia). Staining the lymphocytes for kappa and lambda allows distinction between monoclonal and polyclonal cells.

Plasma cells secrete immunoglobulin. The immunoglobulin from individual plasma cells has a unique antigen binding structure which generates different behaviour on electrophoresis to that of immunoglobulin produced from other plasma cells. Also, immunoglobulin from an individual plasma cell or clone of plasma cells all utilises either kappa or lambda light chains. In plasma cell neoplasms, the blood often contains a paraprotein which is the immunoglobulin secreted from that clone of cells and which has a single electrophoretic mobility and light chain type.

2. Role of oncogenes and tumour suppressor genes in the transformation of lymphocytes

Oncogenes were first identified as the transforming genes in acutely transforming retrovirus (v-oncs) but subsequently it has been found that these genes are part of the genetic repertoire of every normal cell (c-oncs or proto-oncogenes). Oncogenes are now known to be cellular genes which positively influence cell growth. Several classes of oncogenes are known, including growth factors, growth factor receptors, nuclear transcription factors etc. In the oncogenic process oncogenes are activated by several mechanisms which include point mutation, translocation, and amplification.

Tumour suppressor genes have been identified as the genes involved in the development of some forms of hereditary cancer, e.g., retinoblastoma. For them to become involved in the development of malignant tumours, these genes have to be inactivated. This occurs through deletion and/or mutation. Alterations of another gene of this group, the p53 gene, are the most frequent genetic abnormality identified in any form of human tumours. P53 is a nuclear protein with crucial functions in the regulation of cell proliferation and cell death. It appears that p53 induces temporary cell cycle arrest in cells with damaged DNA. Following successful repair of this damage, cells are allowed back into the cell cycle. If, however, the repair attempts fail, p53 triggers elimination of the damaged cells by apoptosis.

In general, several genes have to be altered to effect neoplastic transformation, and usually a combination of oncogenes and tumour suppressor genes are affected.

Malignant lymphomas often carry translocations involving oncogenes. In some cases, these translocations are so characteristic as to become diagnostically relevant. In particular B-cell lymphomas often harbour translocations which bring an oncogene under the control of an immunoglobulin (Ig) gene. Because Ig genes are constitutively active in B-cells, this often leads to the overexpression of the oncogene. The best known examples are the t(8;14) (or less frequently t(2;8) or t(8;22)) in Burkitt’s lymphoma, the t(11;14) in mantle cell lymphomas, and the t(14;18) in follicle centre lymphomas. The fact that B-cell lymphomas often harbour translocations involving Ig genes suggests that these may occur as a result of errors during the physiological process of Ig gene rearrangement.

As a result of the t(8;14) translocation or either of the alternative translocations t(2;8) or t(8;22), the c-myc oncogene on chromosome 8 comes under the control of the Ig heavy chain or one of the Ig light chain genes and consequently is overexpressed. One of these translocations is found in all cases of Burkitt’s lymphoma, endemic or sporadic (see below).

Similarly, the t(11;14) in mantle cell lymphomas brings the gene encoding for the D1 cyclin next to the Ig heavy chain gene. Consequently, cyclin D1 is overexpressed in mantle cell lymphomas.

The t(14;18) translocation is found in most follicle centre lymphomas. Again this results in the juxtaposition of an oncogene, the bcl-2 gene on chromosome 18, and the immunoglobulin heavy chain gene on chromosome 14, leading to overexpression of the oncogene. The function of the bcl-2 oncogene product appears to be the protection of B-cells from apoptotic cell death. It is therefore assumed that constitutive overexpression of bcl-2 protein in germinal centre cells (which normally do not express the Bcl-2 protein) overrides mechanisms normally leading to apoptosis and thus contributes to the development of follicle centre lymphomas. This illustrates that in addition to the active promotion of cell proliferation, oncogenes may contribute to the neoplastic process by suppressing apoptotic cell death.

By comparison, less is known about the function of tumour suppressor genes in the development of malignant lymphomas. Several recent studies have indicated that alterations of tumour suppressor genes, rather than contributing to the initial development of lymphomas, may be important in the progression of the disease. Thus, mantle cell lymphomas with the t(11;14) translocation have been shown to carry a worse prognosis if they acquire mutations or other alterations of the p53 tumour suppressor gene. This
observation illustrates that even established malignancies can undergo further genetic changes which may lead to the development of new sub-clones with altered biological behaviour (clonal progression). Often, these emerging sub-clones show a more aggressive behaviour and will gradually replace the originally prevalent clone. This process is often accelerated by chemotherapy.

3. **Role of viruses**

Although retroviruses have been instrumental in the identification of oncogenes, as yet only one retrovirus is implicated in the pathogenesis of a human tumour. Human T-cell leukaemia virus-1 (HTLV-1) is associated with adult T-cell leukaemia/lymphoma which is endemic to Japan and the Caribbean basin.

The Epstein-Barr virus (EBV) is a human herpes virus which infects over 90% of the adult population world-wide. In vitro and in vivo, EBV displays a strong tropism for B lymphocytes. Primary EBV infection may cause infectious mononucleosis, a benign lymphoproliferative disease. During primary EBV infection, virus-carrying B lymphocytes proliferate and this triggers a reactive proliferation of virus-specific cytotoxic T-cells. Once an equilibrium has been established between EBV-positive B-cells and EBV-specific T-cells, this allows the establishment of a life-long asymptomatic infection.

B-cell transformation by EBV is effected through the concerted action of several virus-encoded proteins. One of these, the latent membrane protein 1 (LMP1) can be considered as a viral oncogene (see below).

EBV is associated with Burkitt's lymphoma, Hodgkin's disease and lymphoproliferative disorders in transplant patients as defined by the detection of the virus in the tumours' cells.

The role of the virus is clearest in post-transplant lymphoproliferative disease (PTLD) where iatrogenic suppression of the T-cell immunity allows the unchecked outgrowth of EBV-infected B-cells. This is further underlined by the observation that restoration of T-cell immunity in these patients may lead to the spontaneous regression of PTLD lesions. Furthermore, it has been shown recently that administration of cloned EBV-specific T-cells may be effective in the prevention and treatment of PTLDs.

Much less clear is the role of the virus in lymphomas which arise in patients without any obvious underlying immune defect.

Burkitt's lymphoma (BL) is endemic in certain regions in Africa whereas it occurs only sporadically in Western countries. As discussed above, all BL cases carry one of three translocations involving the c-myc oncogene. By contrast, the association with EBV is more heterogeneous. Thus, practically all African BLs are EBV-associated while the virus is detectable in only up to 30% of sporadic BLs.

Moreover, viral proteins commonly associated with B-cell transformation are not expressed in BL, and thus the role of EBV in the neoplastic process remains uncertain.

not all cases are EBV-associated further strengthens the notion that HD represents a More recently, EBV has been detected in up to 50% of HD cases in Western countries. That syndrome rather than a disease entity (see above). Interestingly, the LMP1 protein of EBV is consistently expressed in virus-associated HD, supporting the idea that the virus is involved in the pathogenesis of a proportion of HD cases. Recent research has shown that LMP1 expression can prevent apoptotic cell death by inducing bcl2 expression, suggesting a possible mechanism by which EBV infection can contribute to the neoplastic process.

4. **Classification of neoplasias arising from the haemopoietic system**

In general, neoplasias are classified according to the tissue and presumed cell of origin. Neoplasias arising from the haemopoietic system are classified according to cell lineage, equivalent developmental stage within that lineage and presence or absence of maturation arrest. These neoplasias may be lymphoid or non-lymphoid.

The non-lymphoid neoplasias are often termed myeloid even though some of them are not of the myeloid lineage. For example acute monoblastic, acute erythroblastic and acute megakaryoblastic leukaemias are classified as acute myeloblastic leukaemias - AML M5, AML M6 and AML M7 respectively. This anomaly is not important clinically as all of these leukaemias respond to similar therapeutic protocols. Quite different therapeutic protocols are required for the successful treatment of lymphoid neoplasias.

1. **Acute versus chronic myeloid leukaemias**

Myeloid leukaemias are classified as being acute (myeloblastic) or chronic (myelocytic) depending on whether or not the neoplastic clone exhibits maturation arrest. In acute myeloblastic leukaemias the neoplastic clone exhibits total or near total maturation arrest and consequently the clone expands quickly with rapid progression of clinical disease and urgent requirement for intensive therapy. In chronic myelocytic leukaemia only a small proportion of the total clone is proliferating, most of the progeny from this proliferating portion of the clone undergo maturation and finally growth arrest as neutrophils. The result is increased numbers of neutrophils in the blood but there is otherwise an equilibrium between production of the neoplastic cells by proliferation and the death of neoplastic cells as end-stage neutrophils. The disease progresses slowly and initially may not even require therapy. When therapy is introduced it is not intensive as compared to the therapy required for the treatment of acute myeloblastic leukaemia. However, in time, the neoplastic clone acquires a further genetic defect which brings about maturation arrest and thereby transformation to an acute leukaemia. Interestingly this transformation may be to either acute myeloblastic or acute lymphoblastic leukaemia, indicating that the progenitor cells within the original neoplastic clone were not irrevocably committed to the myeloid lineage.

2. **Lymphoid leukaemias and lymphomas**

Neoplasia of the lymphoid system may be either of the T cell or the B cell lineage. B cell neoplasms are far more common than T cell neoplasms. Unlike most other cell types, lymphoid cells undergo two waves of proliferation and differentiation. In bone marrow and thymus, mature naïve lymphocytes develop from lymphocytic precursor cells in an antigen-independent fashion. Antigenic stimulation of these cells in secondary lymphoid tissues then results in a second wave of proliferation and differentiation into effector cells. Neoplasms arising from lymphoid precursor cells almost invariably exhibit maturation arrest and are therefore classified as and behave as, acute leukaemias. These leukaemias are called acute lymphoblastic leukaemias. If of T cell lineage, they usually arise from T cell progenitors in the thymus. If of B cell lineage, they are most commonly derived from B cell progenitors in the marrow at a stage of ontogeny shortly before expression of
immunoglobulin heavy chain genes - Common Acute Lymphoblastic Leukaemia.

Neoplasms arising from mature lymphocytes are usually classified as Non-Hodgkin’s Lymphomas although one of the commonest forms of NHL is called chronic lymphocytic leukaemia. For practical purposes it is best to consider NHL as frozen in a particular stage of lymphocyte development. Thus chronic lymphocytic leukaemia is a lymphoma derived from small naïve circulating lymphocytes; lymphomas with tumour cells resembling centrocytes and centroblasts are called follicle centre lymphomas and lymphomas derived from follicle mantle cells are termed mantle cell lymphomas. A further point to be considered is the grade of the lymphoma. Lymphomas with small neoplastic cells and a low proliferative activity are of low grade and equivalent to chronic leukaemias whereas high grade lymphomas consist of large cells with a high proliferative capacity (blastic, e.g. immunoblastic NHL). In general, low grade lymphomas run a more protracted and indolent course than high grade lymphomas which behave more like acute leukaemias. However, paradoxically, cure seems to be more achievable in high grade than in low grade lymphomas, due to the availability of modern chemotherapeutic agents which are more effective in proliferating cells.

5. Clinical features of haemopoietic neoplasms

Leukaemias predominantly involve the blood and bone marrow whilst Non-Hodgkin’s Lymphomas predominantly involve the secondary lymphoid tissues but can spread to involve blood and bone marrow as the disease progresses.

In leukaemias there are large numbers of leukaemia cells in the blood and bone marrow and normal haemopoiesis becomes impaired. It is the reduction in normal haemopoiesis which causes the main clinical features of leukaemias. Reduced erythropoiesis results in anaemia with lassitude, dyspnoea and pallor. Reduced platelet production results in thrombocytopenia with purpura, bruising and bleeding. Reduced neutrophil production results in neutropenia and increased risk of bacterial infection and invasive fungal infection.

Lymphomas usually present as increased size of secondary lymphoid organs - splenomegaly and/or lymphadenopathy. Secretion of cytokines from the neoplastic cells may cause weight loss and pyrexia - B symptoms - and lymphoma is part of the differential diagnosis in patients with pyrexia of unknown origin. Normal lymphoid function often becomes impaired. Antibody deficiency manifests as increased respiratory tract infections with pneumococci and haemophilus bacteria whilst deficiency in cell mediated immunity results in opportunistic infection.

Table 1. Blood cells their distribution and rate of production

<table>
<thead>
<tr>
<th>cell type</th>
<th>number/litre in blood of adults</th>
<th>life-span after leaving bone marrow</th>
<th>distribution</th>
<th>approximate number produced in adults per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>150-400x10^9/l</td>
<td>8-12 days</td>
<td>the blood</td>
<td>10^{11}</td>
</tr>
<tr>
<td>red cells</td>
<td>4.5-5x10^{12}/l</td>
<td>120 days</td>
<td>the blood</td>
<td>2.5 x10^{11}</td>
</tr>
<tr>
<td>mast cells/ basophils</td>
<td>Trace numbers</td>
<td>a month or so</td>
<td>only briefly in blood, are mainly in tissues</td>
<td>?</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.04-0.4x10^9/l</td>
<td>14-18 hr in blood</td>
<td>blood and tissues</td>
<td>&lt;10^{10}</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>2-8x10^9/l</td>
<td>5-7 hr in blood</td>
<td>blood and tissues</td>
<td>1.5x10^{11}</td>
</tr>
<tr>
<td>Monocytes/ macrophages</td>
<td>0.2-0.8x10^9/l</td>
<td>days to weeks</td>
<td>most are in tissues, e.g. the spleen, liver and lungs</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Dendritic (Langerhans) cell precursors</td>
<td>~0.2-1.0x10^9/l</td>
<td>uncertain</td>
<td>blood spleen and sites of inflammation</td>
<td>Uncertain</td>
</tr>
<tr>
<td>NK cells</td>
<td>~0.2-1.0x10^9/l</td>
<td>uncertain</td>
<td>blood spleen and sites of inflammation</td>
<td>Uncertain</td>
</tr>
<tr>
<td>B lymphocytes</td>
<td>0.03-0.7x10^9/l</td>
<td>2 days to several weeks; memory clones up to years</td>
<td>most B cells are in secondary lymphoid tissues&lt;5% are in the blood</td>
<td>~ 1.5% of marrow mononuclear cells are B cell precursors; many produced by antigen-driven proliferation of mature B cells</td>
</tr>
<tr>
<td>T lymphocytes</td>
<td>0.4-2.5x10^9/l</td>
<td>a day or so to several years</td>
<td>most T cells are in secondary lymphoid tissues or epithelia, &lt;5% are in the blood</td>
<td>probably very few in thymus; most T cells generated during development; many produced by antigen-driven proliferation of mature T cells</td>
</tr>
</tbody>
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