22.1 Introduction to haematology 5169 Chris Hatton

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ESSENTIALS Haematology is the study of the composition, function, and diseases of the blood. The approach to a patient suspected of having a haematological disorder begins with taking a history (particularly noting fatigue, weight loss, fever, and history of bleeding) and performing a clinical examination (looking for signs of anaemia, infection, bleeding, and signs of cellular infiltration causing splenomegaly and/or lymphadenopathy). Key inves- tigations include a full blood count, a blood film, and (in selected cases) examination of the bone marrow. Further diagnostic tests now routinely performed on blood and marrow samples include immunophenotyping and cytogenetic and molecular analysis. Mutational signatures may be diagnostically useful and potentially define treatment, keeping haema- tology in the vanguard of advances in modern medicine. Introduction Haematology has always been in the vanguard of advances towards truly modern medicine. The first disease defined at a molecular level was haematological (sickle cell disease); the first molecularly targeted treat- ment was designed for a haematological disorder (imatinib in chronic myeloid leukaemia); and the revolution of immunological treatments, whether in the form of allogeneic bone marrow transplantation, fo- cused therapies (such as rituximab) or cellular therapies (e.g. chimeric antigen receptor T-cells), was also begun from within haematology. This remains the case today, and the discipline is now advancing at an almost bewildering pace. However, despite the huge advances made in diagnostic techniques and imaging, the starting point for evaluating a patient relies on basic clinical skills. In this introduction, we outline the scope of haematology as a dis- cipline, give an overview of the nature and function of blood cells, and provide a system for the newcomer to haematology to consider the likelihood of haematological disease in his or her patient. The scope of haematology Haematology is the study of the

composition, function, and diseases of the blood. Its diversity as a specialism therefore immediately reflects the complexity of its subject. At its simplest, blood is div- ided into the plasma component (water, electrolytes, clotting factors, and fibrinogen—with serum being the same substance without the clotting factors) and the cellular component, comprising red cells, platelets, granulocytes, and lymphocytes. Each has its specific and irreplaceable role in the normal function of blood, which impacts in turn the function of every tissue in the body. Not only do diseases of the blood influence every downstream organ, systemic diseases will also manifest in the blood. An appreciation of normal blood counts and appearances is therefore central to many fields of medicine. Diseases and the blood Even a cell as apparently simple as the red blood cell, anucleate and devoid of intracellular organelles in its mature form, can manifest a variety of disorders. Inherited defects in the synthesis of globin genes, needed for the transport of oxygen to the peripheral tissues, constitute the commonest genetic diseases in the world. A host of additional genetic defects in glycolytic enzymes also impact on the survival of the red cell and the ability of the marrow to maintain a normal haemoglobin level. Meanwhile, the iron deficiency resulting from chronic occult blood loss may be the only clue to the presence of a malignant colonic tumour, and the failure to absorb vitamin B12 in pernicious anaemia may highlight the possibility of a range of additional autoimmune disorders. Erythropoietin, the key hor- mone controlling red cell production, is synthesized principally in peritubular interstitial fibroblasts in the juxtamedullary region of the renal cortex and renal disease may therefore result in either insufficient or excess marrow stimulation. Thus the finding of an- aemia, a low haemoglobin level, may point to either haematological disorders, or may reflect primary disease elsewhere. The careful in- vestigation of the cause of anaemia (see Chapter 22.6.2) is an im- portant part of general medical practice. Granulocytes (neutrophils, eosinophils, and basophils, so termed to reflect the staining characteristics of the granules that are crit- ical for their function) may also reflect both primary haematological disease and reactive conditions. The granules of neutrophils contain myeloperoxidase, needed in the cellular response to bacterial infec- tion, and a high neutrophil count (neutrophilia) is commonly seen 22.1 Introduction to haematology Chris Hatton

 in the context of infection or inflammation. The specific function of eosinophils in combating multicellular parasites means that a re- active eosinophilia may also be seen in infection with these organ- isms, as well as in allergic reactions. The uncontrolled proliferation of granulocytes of all kinds is seen in the myeloproliferative disorder chronic myeloid leukaemia, one of the first haematological malig- nancies to be defined at the molecular level. Neutropenia, by contrast, describes an inadequate number of circulating neutrophils, and may reflect primary marrow dysfunc- tion (e.g. aplastic anaemia), the result of myelotoxic chemotherapy administration, or immune attack. The key role of neutrophils in maintaining the integrity of mucosal surfaces is highlighted by the increased risk of Gram-negative infection in severe neutropenia, and the rapidly progressive sepsis that accompanies it is one of haematology’s most urgent medical emergencies. Along with red cells and granulocytes, platelets form the last of the ‘myeloid’ components of the blood. Their role in primary haemo- stasis (again effected in part by the presence of cell-specific granules) is highlighted in Chapter 22.7.3; they are the target of some of the most widely prescribed agents used in medical practice (aspirin and other antiplatelet agents are discussed in more detail in the Section 16 on cardiovascular disease). Lymphocytes divide into B cells, T cells, and NK cells. Each has its distinct role in the immune process, from the production of antibodies to cell-mediated immunity and the development of antitumour action (e.g. through perforins secreted in the gran- ules of cytotoxic T cells). As well as

a reactive lymphocytosis or lymphopenia seen in response to viral infection, malignant transformation of lymphoid cells may result in a circulating excess of clonal lymphocytes or lymphoid precursor cells, or in the develop- ment of lymphadenopathy. Perhaps the most protean of haemato- logical malignancies, lymphomas can affect any organ in the body. A discussion of the nature and treatment of these varied disorders is given in Chapters 22.4.3 and 22.4.4. Disorders of haemostasis, whether hereditary or acquired, may reflect a lack of key components of the clotting cascade, platelet lack, or platelet dysfunction. The modulation of the haemostatic machinery for therapeutic purposes also highlights the increasing awareness of overefficient haemostasis—for example, in the her- editary thrombophilias. These are discussed in more detail in Chapters 22.7.4 and 22.7.5. How does blood develop? Haematopoiesis is the term used to describe the cellular processes that produce blood cells. The sheer magnitude of the process is apparent in the observation that the bone marrow produces 2.5 × 1011 red cells, 1 × 1011 platelets, and 1 × 1010 white cells per day. Beginning in the yolk sac in utero, the process of haemato- poiesis switches to the spleen and the liver in the developing fetus before moving to the bone marrow. With increasing age, haemato- poiesis becomes confined to the axial skeleton, with very little red (haematopoietically active) marrow present in the long bones of the limbs in adults. The bone marrow contains an as yet undetermined number of pluripotent stem cells that are capable of both continuous self-renewal and differentiation. More mature cells lose the capacity for self-renewal as they differentiate into fully functional mature blood cells or form the structural cellular matrix of the bone marrow stroma. As they divide, progenitors have a progressively restrictive lineage potential manifested by their use of specific transcription factors. A number of cytokines such as erythropoietin, granulo- cyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF), and thrombopoietin induce proliferation of specific lineages; these, together with complex cel- lular interactions, lead to development of mature blood cells in the marrow and subsequent release into the blood. Although a detailed treatment of haematopoiesis is given in Chapter 22.2.1, it is clinic- ally useful to consider two different populations arising from this process: these differentiate into the two main lineages of myeloid and lymphoid cells. As described previously, myeloid maturation, or myelopoiesis, produces red cells (erythrocytes), granulocytes, and platelets; while lymphopoiesis describes the development of lymphoid cells into mature B cells, T cells, and NK cells. The identification of haematopoietic stem cells (HSCs) that traffic from the bone marrow to the blood and back provided a major step forward in haematological practice. The subsequent rec- ognition that it was possible to harvest these HSCs from humans, and that after reinfusion they could re-establish normal haemato- poiesis, has led to the development of the flourishing practice of HSC transplantation. Although very few HSCs are present in the peripheral blood, it is possible to increase their numbers in blood using the growth factors G-CSF or GM-CSF, or by blocking the molecule that anchors stem cells in the marrow matrix, CXCR4. In clinical practice, autologous or allogeneic stem cell infusion can be used to reconstitute haematopoiesis after appropriate chemo- therapy. The subject of HSC transplantation is covered in detail in Chapter 22.8.2. Bone marrow transplantation has had a huge impact, enabling long-term remissions to be achieved in patients suffering from aggressive haematological malignancies and bone marrow failure syndromes. Initial approach to the patient The approach to a patient suspected of having a haematological disorder begins with taking a history and performing a clinical examination. Potential features of the history may include fatigue (perhaps re- flecting anaemia or underlying malignancy), weight loss, and fever (again suggestive of the hypercatabolic picture of malignancy). A careful bleeding history, including responses to previous haemo- static challenges such as surgery and dental work, will be useful in delineating a possible bleeding

diathesis. A general impression of the patient's overall health status—perhaps via recording his/her Eastern Cooperative Oncology Group (ECOG) performance score—is important in assessing tolerance for treatment and in cat- egorizing patients entering clinical trials. Examination of the patient with a suspected blood disorder should concentrate on looking for signs of anaemia, infection, bleeding, and signs of cellular infiltration causing splenomegaly and lymphaden- opathy. Pallor is a frequent finding in patients with anaemia though normal pigment differences in the skin make this an unreliable sign. Pallor of the mucous membranes or palmar creases may be more useful. Jaundice, commonly seen in liver disease, is also a prominent

22.1 Introduction to haematology 5171 sign in patients with premature red cell destruction (haemolysis), and is readily detected in the sclerae. Signs of a bleeding tendency should be sought in the skin, mucous membranes, and the retina. Haemorrhage into the skin characteristically produces petechiae and ecchymoses. Petechial haemorrhages are small (1–2 mm), often seen in areas with high venous pressure such as around the ankles, and are a common finding in patients with severe thrombocytopenia (platelet count <20 × 109/litre). Ecchymoses (commonly known as bruises) are larger subcutaneous haemorrhages, a frequent finding after trauma but also occurring spontaneously in patients with a low platelet count or a functional platelet defect. Lymphadenopathy is a common finding in patients with lympho proliferative disorders and is sometimes present in patients with mye- loid disease. Enlargement of a lymph node becomes significant when greater than 1 cm and nodes of this size should be biopsied when pre- sent for longer than 6 weeks without obvious cause. Splenomegaly may also be seen as a result of infiltration of the white pulp by a lymphoma or leukaemia, or more rarely in storage disorders such as Gaucher's disease; expansion of the red pulp in chronic haemolysis may also cause splenomegaly. Rarely, the spleen may enlarge as a result of extramedullary haematopoiesis in conditions where there is bone marrow failure, such as myelofibrosis. In this situation, the spleen takes over the function of the bone marrow in producing blood. Investigation of a suspected blood disorder Laboratory investigation for malignant haematological disorders is covered in detail in Chapter 22.2.2. In the investigation of a patient with a suspected haematological disorder, a careful inspection of the blood film is essential. Morphological abnormalities of red cells or white cells can be diagnostic. For example, the finding of immature 'blast' cells on a peripheral blood film is suggestive of acute leukaemia or marrow stress due to severe sepsis. The presence of immature red cell and white cell precursors (leucoerythroblastic anaemia) on the peripheral blood film is often indicative of bone marrow infiltra- tion by malignancy or marrow stress due to severe sepsis. There is a huge range of morphological changes affecting all blood cell lin- eages; the haematologist becomes accustomed to identifying those changes that are diagnostically significant. If necessary, inspection of the peripheral blood film is followed by bone marrow aspiration and biopsy, enabling the haematologist to assess the maturation of precursor cells and to look for infiltration by malignancy. The close link between immunology and haematology is em- phasized by the importance of immunological analyses for the diagnosis of lymphoid disease. The finding of a paraprotein may suggest a mature B-cell malignancy or plasma cell clone (myeloma). Further diagnostic tests are now routinely performed on blood and marrow samples obtained from the patient. Abnormal popu- lations of cells identified morphologically (e.g. blasts in acute leu- kaemia, or lymphoid populations in lymphoproliferative diseases) can be immunophenotyped using flow cytometry carried out on blood, bone marrow aspirates, and if indicated on cerebrospinal fluid, pleural fluid, or ascitic fluid. Histopathology of bone marrow, lymph nodes, and other affected organs which have been biopsied provide additional morphological and immunohistochemical diag- nostic information. Furthermore, cytogenetic and molecular ana- lysis may provide evidence of

clonality, define specific diagnostic translocations and chromosomal rearrangements, and identify the presence or absence of specific mutations. Increasingly multigene sequencing panels are being used to identify mutational signa- tures that may be diagnostically useful and potentially define treat- ment. Large haematology laboratories offer this complete range of diagnostic services, integrating the results into a single diagnostic report. These data add to those achieved through increasingly sophisti- cated imaging techniques such as positron emission tomography and magnetic resonance imaging, which give functional as well as anatomical data to define haematological diseases. Commentary In subsequent chapters, the detailed biology of normal and malig- nant HSCs and their progeny will be described. A single chapter is devoted to the laboratory analysis of malignant blood cells with a strong emphasis on determining the lineage of the malignant clone. The importance of the myeloid/lymphoid split is emphasized, and it will become obvious to the reader that the treatment of different leukaemias and lymphomas depends on the cell of origin of the malignant clone. It will be evident that much of haematology either relates to defi- ciency or dysfunction of blood cells or the noncellular components of blood. In addition, many treatments given for haematological dis- ease have the necessary side effect of depleting normal blood com- ponents. Therefore one of the major challenges facing haematology is the need to develop safe, readily available, and cost-effective blood component replacements, either from blood donors or via biotechnology. Blood transfusion services have developed to an extraordinary degree since their inception at the beginning of the last century, but still depend exclusively on community altruism. Stem cell technology particularly holds promise for the future of this aspect of our specialty. Few specialties occupy so wide a range as haematology, taking in both malignant and nonmalignant disease, chronic and acute care, clinical and laboratory practice, and aligning basic physicianly skills with the most up-to-date genetic and molecular advances. Keeping so disparate a specialty together, and maintaining skills in all areas, is increasingly difficult for clinical haematologists and will only be- come more so as our understanding of the pathological basis of dis- ease continues to expand. We hope this section of the textbook will inspire future haematologists to meet this challenge.

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