Introduction

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The mutual impact of genetically determined disorders and haematology on one another has long had a major influence on biological research. This influence derives from two main considerations: (1) genetic variants with both physiological and pathological function are extremely common in the cellular and non-cellular components of the blood, both in terms of the range of variants expressed (e.g. blood group antigens) and the frequency with which some variants occur in various populations (e.g., the thalas-saemia syndromes, variants of glucose-6-phosphate dehydrogenase), and (2) blood and, to a lesser extent, bone marrow are easy to obtain for study, relatively uncontaminated by the stromal or other elements present in more structured tissues.

The interplay of classical genetics and haematology has assisted the elucidation of important metabolic and biological processes by isolating individual steps in these processes for study in subjects with hereditary deficiency of single proteins. Thus, for example, in such a way were the individual steps in the classical coagulation cascade [1, 2] dissected out, identified, and the function of each genetically determined factor defined.

Haematology and genetics contributed to the original concept of ‘molecular pathology’ when the molecular basis of the sickling syndromes was established by Pauling et al. [3], correlating perfectly with the genetic evidence of Beet [4] and Neel [5], based on pedigree information. The thalassaemia syndromes [6] have proven to be one of the most powerful driving forces in human molecular pathology in the last 25 or 30 years. The profound social and economic effects on communities where these disorders are common (Cyprus, for example) have necessitated the development of practical and effective diagnostic and preventive measures, and much of this effort has been dependent on the evolution of our understanding of and capacity for genetic diagnosis using minute quantities of material, from umbilical cord red cells in the 1970s to DNA from early fetal chorionic villi at the present time.

The extensive interest in genetics and molecular diseases on the part of haematologists has greatly facilitated the development of our current knowledge of the somatic mutations involved in oncogenesis. It was but a small step from deletions and mutations of thalassaemia or the sickling syndromes to the disordered DNA of haematological malignancies, and again the ready availability of material for study and the relatively uncontaminated nature of blood and bone mar-

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row specimens has aided research in haematological oncogenesis. This symposium presents, in a series of essays, the current state of our knowledge in relation to genetic markers of leukaemia and lymphoma. Markers may appear as gross chromosomal distortions (e.g., the Philadelphia or Phil chromosome) or may appear only as point mutations (e.g., in the RAS series of proto-oncogenes in acute leukaemia). Detection of malignant cell populations, not readily distinguishable by conventional morphology, becomes possible by the detection of physiological gene rearrangements in expanded ‘clonal’ populations (as in non-Hodgkin’s lymphoma) or by more sensitive detection at the DNA level of the gene products of rearranged genes found in chromosomal translocations. These approaches may be useful in detection of residual disease after treatment (e.g. monitoring of the success of bone marrow transplantation in chronic myeloid leukaemia) as well as in diagnosis.

In the introductory paper, Dubé and his colleagues describe the evolution of our knowledge of chromosomal abnormalities in haematological malignancies using chronic myeloid leukaemia as a model, and elaborate on the concept of primary and highly specific abnormalities associated with specific clinicopathological syndromes and the addition of subsequent less specific or non-specific changes with progressive disease.

In the second paper, Gorska-Flipot and co-workers discuss in detail the molecular genetics of the Philadelphia chromosome in chronic myeloid leukaemia and the clinical relevance of the detection and definition of the gene rearrangement involved. Sheridan and Reis then give an account of the rapidly growing area of interest surrounding mutations in oncogenes in association with myelodysplastic disorders (‘preleukaemia’) and acute non-lymphoblastic leukaemia.

The two concluding essays deal with questions of molecular markers of lymphomatous disease. Reis et al. concentrate on the physiology and pathology of rearrangement of the T cell receptor and immunoglobulin genes in lymphoma and the value of detection of these rearrangements in the diagnosis and management of non-Hodgkin’s lymphoma, while Ngan and Berinstein give an extensive account of the translocations and gene rearrangements involving oncogenes (established or putative) in lymphoproliferative disease.

The editors have found the task of assembling the various parts of this symposium both informative and entertaining. It is hoped the readership will feel similarly.

References: