other hand, discussion between basic scientists and clinicians concerning the therapeutic potential of at the moment purely experimental cytokines is very important for the development of cytokines for future clinical application.

All the participants agreed that there is an urgent need to establish formal research centres in order to understand the mechanisms involved in the regulation of cytokines and their effects. Such research projects, requiring basic scientists as well as clinicians, will be defined within the next months in order to determine the important aims of clinical development.

A circular will be sent out to all chairmen of Treatment and Research Groups of the EORTC as well as to other European groups involved in cytokine research. This circular will provide information on the activities of the Task Force Cytokines and request information on all running or planned clinical trials with cytokines in order to build up an accompanying scientific program. Research groups will be asked to give recommendations for these accompanying programs.

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Recent Advances in the Biology of Lymphomas

P.G. Isaacson

IN TERMS of lymphoma biology, the 1970s can only be described as the decade of classification. As more powerful chemotherapeutic agents became available, clinicians began to demand a more rational and reproducible histological classification of lymphoma which gave some indication of the biological behaviour of the disease and permitted comparison of the results of clinical trials. In this respect the Rye classification of Hodgkin's disease (HD), formulated in 1966 [1], was already a success but something of equal value was urgently needed for the non-Hodgkin lymphomas. Starting with the discovery by Lennert [2] that a significant number of lymphomas was derived from follicle centre cells, new classifications, each claiming both biological significance and reproducibility, flowered; this resulted in more rather than less confusion in both pathological and clinical circles and a louder than ever cry for a single meaningful classification. Pathologists responded with a complex and exhaustive multicentre study which resulted in the compromise, and to many wholly unsatisfactory, morphologically based classification of non-Hodgkin lymphoma known as the "working formulation for clinical use" [3]. By the time this classification appeared, however, exciting new techniques were already having a significant impact on lymphoma research. Immunocytochemistry, coupled with the availability of an ever increasing number of monoclonal antibodies, permitted identification of cell phenotype and other characteristics in histological sections providing opportunities for better and more scientifically based classifications. Even before the advances permitted by these techniques could be properly consolidated the principles of cell and molecular biology were finding ready application to lymphomas and this effectively ended the obsession with classification. The impact of these newer biological sciences on the study of lymphoma has been tumultuous, leading even to a blurring of the almost sacrosanct division between HD and the non-Hodgkin lymphomas. There is no doubt that at some time in the not too distant future the thorny problem of classification will have to be addressed again in the light of all these advances. Meanwhile, those engaged in lymphoma research continue to enjoy a rich harvest as the seemingly unending flow of new techniques continues to refine our knowledge of lymphoma biology and leads to the discovery of new entities.

Correspondence to P.G. Isaacson, Department of Histopathology, University College and Middlesex School of Medicine, University Street, London WC1E 6JJ, U.K.
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NEW TECHNIQUES IN LYMPHOMA BIOLOGY

Immunophenotyping

Before 1980 the methods for identifying the phenotype of lymphoma cells were confined to the study of cell suspensions. Because of the large reactive cell population present in lymphomas this technique was not entirely satisfactory. In 1980 Stein *et al.* [4] described successful immunophenotyping of lymphomas by applying monoclonal antibodies to cryostat sections using the immunoperoxidase technique and this, together with the development of newer techniques for the study of cell suspensions using the fluorescent activation cell sorter (FACS), has had a profound effect on lymphoma research and diagnosis. The vast number of monoclonal anti-leucocyte antibodies produced has led to the institution of special international workshops for their classification and standardisation and the introduction of the CD (cluster of differentiation) nomenclature. The antigens recognised by leucocyte differentiation antibodies not only assist in identifying the lineage and differentiation state of the cell or cells in question but also represent functionally important cell surface bound ligands and membrane associated enzymes together with both cytoplasmic and nuclear antigens. Thus, with improved optical resolution now afforded by antibodies that recognise formalin resistant epitopes in paraffin sections, the biology of cell to cell interactions can be studied. The addition of *in situ* molecular hybridisation techniques (see below) has served further to enhance the value of both current and archival histological material in lymphoma studies.

Molecular genetic analysis

In most instances immunocytochemistry permits determination of the lineage (i.e. either B or T cell) in a case of lymphoproliferative disease and in B cell lymphoproliferation

immunocytochemistry, by demonstrating immunoglobulin light chain restriction, is a reliable indicator of monoclonality. However a large component of reactive T cells can lead to the misassignment of lineage in a B cell neoplasm and in T cell lymphoproliferation, immunocytochemistry is of no help in determining clonality. The molecular analysis of rearranged immunoglobulin and T cell receptor genes, using the Southern blotting technique [5–7], can determine both lineage and clonality in very small samples of fresh tissue or body fluids. This technique can identify a clone of malignant lymphocytes when it comprises as little as 1% of the total population and is unrecognisable microscopically. The molecular hybridisation probes used in this technique are derived from DNA loci corresponding to immunoglobulin and T cell receptor genes which undergo somatic rearrangement in the course of lymphocyte ontogeny. Similar probes can be prepared from sites of chromosomal rearrangements (i.e. translocations) which, in cytogenetic studies, have been shown to characterise certain lymphomas; these probes can be used both to diagnose neoplasia and specific histological subtypes of lymphoma. Finally, probes can be prepared from viral nucleic acids that can detect viral sequences in lymphoma tissues as a way of investigating their role in the pathogenesis of the disease.

In situ hybridisation. Molecular hybridisation techniques can also be used directly on histological sections to demonstrate the presence of integrated viral DNA or certain chromosomal translocations [8]. Messenger RNA can also be demonstrated in this way to show gene expression where demonstration of the gene protein product is unsatisfactory [9]. The combination of immunocytochemistry and *in situ* hybridisation is a powerful tool which has been used, for example, to show the presence of Epstein–Barr virus (EBV) in the nuclei of Reed–Sternberg cells (see below).

The polymerase chain reaction. The discovery of the polymerase chain reaction (PCR) [10] has been one of the most important advances in molecular genetics in the past decade. This procedure allows amplification of a predetermined stretch of either fragmented or intact impure DNA by a simple chemical method. Using PCR it is possible to amplify specific DNA sequences more than a million-fold in only a few hours. Only minute amounts of DNA (a single cell will suffice) are required to start the reaction and DNA from fixed archival histological specimens (i.e. paraffin blocks) is a suitable substrate. Thus PCR can be used to carry out the same molecular investigations as Southern blotting but no longer requires adequate amounts of fresh tissue and is much more sensitive; indeed, the exquisite sensitivity of PCR constitutes a drawback insofar as great care is needed to avoid artifactual results.

NON-HODGKIN LYMPHOMA

Application of the techniques outlined above has resulted in a number of important advances in our understanding of the biology of non-Hodgkin lymphoma. These can be broadly divided into concepts related to phenotype, clonality, genotype and the role of viruses, and will be discussed under these headings. Where these recent advances have combined to give rise to significant new biological entities these will be discussed separately.

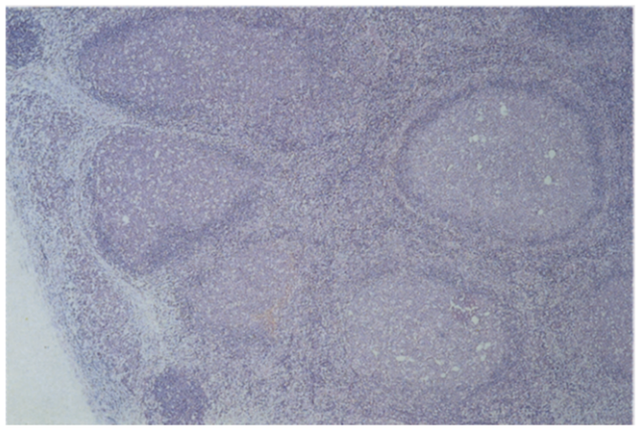
Phenotype

The Lukes and Collins and Kiel classifications of non-Hodgkin lymphoma formulated in the late 1970s [11, 12] already made gestures towards the possible biological significance of T or B cell lineage in these tumours. With the advent of histological immunophenotyping, which is now, thanks to the availability of antibodies reactive in paraffin sections, a routine procedure, it is clear that lymphomas of T lineage run a more aggressive course than those of B cell tumours [13, 14]. While more detailed lineage specific phenotyping may be of help in lymphoma classification it has been disappointing as a predictor of the biological behaviour of lymphomas. Other non-lineage specific phenotypic characteristics may, however, help to determine the biological behaviour and these include expression of the activation antigen CD30 [15] and proliferation markers such as those recognised by Ki67 in frozen material [16] and more latterly anticyclins which can be applied to paraffin sections [17]. Lymphomas showing CD30 expression coupled with certain morphological and cytogenetic features (see below) comprise a new biological entity, the so-called large cell anaplastic (CD30+) lymphoma, while CD30 expression alone may be indicative of biological aggressiveness. Proliferation rate has been shown to be predictive of the biological behaviour and to correspond closely to histological grade [16].

Clonality

Until recently monoclonality could only be inferred in B cell proliferation by immunocytochemical demonstration of immunoglobulin light chain restriction in cryostat sections. Advances in immunocytochemical techniques now permit the demonstration of light chain restriction in paraffin sections of most low and high grade B cell lymphomas in the context of optimum optical resolution [18] (Fig. 1). Although no marker of monoclonality is available for T cell tumours, the aberrant expression of T cell phenotypic markers has been shown to be a fairly reliable indicator of malignancy in T cell proliferation [19]. The ability to study clonal genetic rearrangements by Southern blotting (Fig. 2) allows the demonstration of either B or T cell clones that constitute as little as 1–5% of the cells in any given population. Parenthetically, this is also a useful and sensitive technique for confirming the lineage of the proliferating clone. Applications of this technique have yielded a number of important biological findings, including the presence of widespread, albeit occult, dissemination in apparently localised low grade lymphomas such as mycosis fungoides [20], now known to involve many lymph-nodes as well as the skin, and the high incidence of peripheral blood involvement in follicular (centroblastic centrocytic) and other low grade B cell lymphomas [21]. Similarly, the effects of therapy can be much more closely monitored now that minimal residual disease can be detected. Some B cell lymphomas have been shown to be multiclonal with respect to different sites of disease and genetic mutations have been shown to occur [22]. The study of gene rearrangements has resulted in the assignment of the correct lineage to conditions such as "null" acute lymphocytic leukaemia (a B cell tumour) and helped to define conditions such as angioblastic lymphadenopathy, which has clearly been shown to be a T cell lymphoma rather than a reactive condition [23].

As new discoveries help to solve old problems, they invariably raise new problems of their own and molecular biology is no exception. Dissociation between phenotype and genotype is increasingly reported, with immunoglobulin gene rearrangements in lymphomas of T cell phenotype and vice versa [24, 25]. No sooner are firm rules for lineage assignment set than cases are reported that break the rules. It should be appreciated that these aberrant examples are relatively uncommon but,



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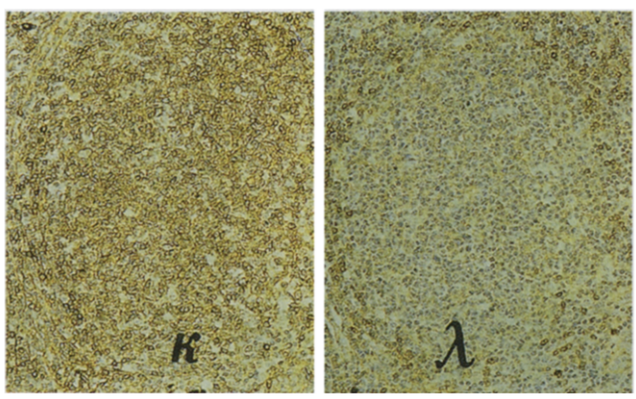


B

Fig. 1. (A) Section of enlarged lymph node from a 21-year-old female showing effacement of architecture by prominent B cell follicles. Despite the age and atypical histological features the possibility of malignant lymphoma (centroblastic/centrocytic, follicular) was raised. (B) Immunostaining of a paraffin section of the lymph-node for kappa and lambda immunoglobulin light chains shows clear kappa light chain restriction of the follicle centre in contrast to the polytypic mantle zone. This confirms the diagnosis of lymphoma. (A, haemotoxylin and eosin; B, immunoperoxidase.)

nevertheless, serve to stress that equal consideration must be given to the morphological features, immunophenotype and genotype of any given case.

The very sensitivity of Southern blotting in demonstrating monoclonality has raised the question whether monoclonality, heretofore considered to be synonymous with malignancy, does indeed imply malignancy in every case. Conditions formally designated as pseudolymphomas of the skin and mucosae and other conditions known occasionally to precede lymphoma, such as lymphomatoid papulosis, pityriasis lichenoides et varioloformis acuta and myoepithelial sialadenitis, have all been shown to be monoclonal [26–31]. Some of these, including most of the cutaneous and gastrointestinal "pseudolymphomas" have, when monoclonal, been shown to display the properties of malignant lymphoma [28, 31] albeit of an unusually indolent variety. Clinical experience, however, does not support the malignant nature of conditions such as lymphomatoid papulosis, although a proportion of cases (less than 10%) may be later complicated by lymphoma. The biological significance of the monoclonal population in these lesions remains unclear at present but is likely to provide clues relevant to the pathogenesis of lymphoma. The established criteria for a diagnosis of malignancy, which include clinical features and morphology as well as monoclonality, have all been thrown off balance by the finding that monoclonal lymphomas arising in patients immunosuppressed for the purposes of organ or tissue transplantation may disappear if immunosuppression is reversed (see below).

Genotype

Karyotypic analysis of non-Hodgkin lymphomas has shown certain non-random reciprocal translocations which have proved to be associated preferentially with specific clinicopathological entities [32, 33]. Because of technical problems in performing routine cytogenetic studies, especially in low grade lymphomas, the assessment of the true prevalence of these chromosomal abnormalities is difficult. DNA probes that can detect these translocations using Southern blotting and, more recently, PCR, have now been developed which means that large series of lymphoma cases can now be investigated for the presence of these genetic abnormalities and their biological significance can be evaluated.

The first of these karyotypic abnormalities to be discovered was the t(8;14) translocation that characterises Burkitt's lymphoma [34]. Here the c-*myc* oncogene is brought into juxtaposition with rearranged immunoglobulin heavy chain gene sequences. In variants of this translocation the immunoglobulin light chain genes are translocated to juxtapose with the c-*myc* gene. The resulting deregulation of the c-*myc* gene, which normally plays a role in the regulation of cell proliferation, apparently leads to altered growth patterns that in turn lead to the expansion of the neoplastic B cell clone. Subtle molecular differences in the t(8;14) translocation and its variants have been identified which distinguish between endemic and sporadic Burkitt's lymphoma [35] and the translocation has also been found in other high grade B cell lymphomas [35]; in some cases the appearance of this translocation has heralded the transformation of low to high grade lymphoma. The precise role

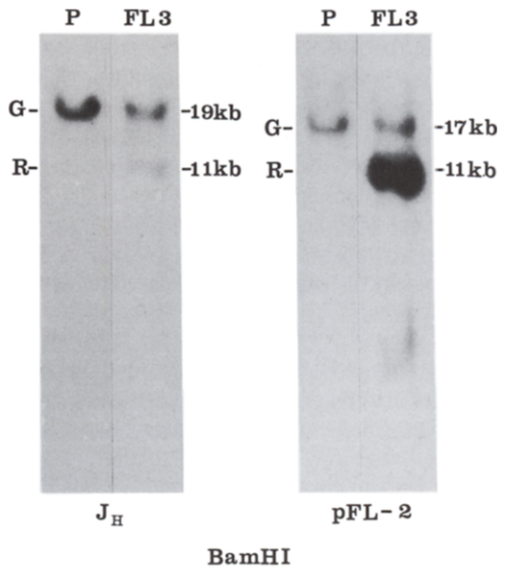


Fig. 2. Southern blot of DNA extracted from the case illustrated in Fig. 1 and digested with the restriction enzyme *Bam* HI. The results show monoclonal rearrangement of 11 kb of both the J_H immunoglobulin heavy chain gene and the *bcl-2* gene representative of the t(14;18) translocation. These results are further confirmation of a diagnosis of follicular lymphoma in this case. P = placental DNA control, FL3 = DNA from the lymphoma, G = germline band, R = rearrangement, J_H = immunoglobulin heavy chain gene probe, pFL-2 = probe for *bcl-2* minor breakpoint.

of the c-*myc* oncogene in these lymphomas awaits clarification but its importance in lymphoma biology is not in any doubt.

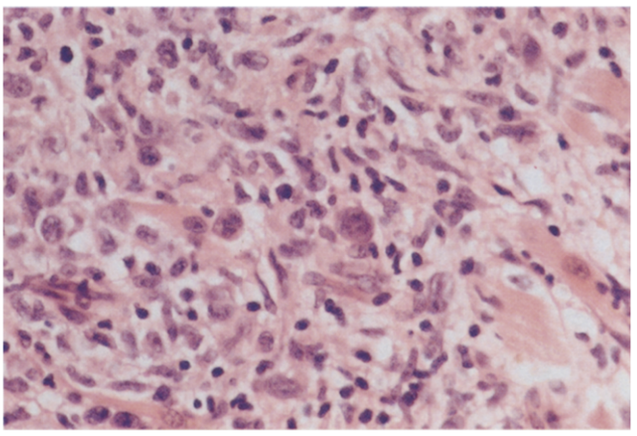
The close association between the t(14;18) translocation and low grade follicular (centroblastic/centrocytic) lymphoma is now well established [36, 37] (Fig. 2). Like the t(8;14) translocation this translocation brings an oncogene, *bcl-2*, into juxtaposition with the immunoglobulin heavy chain gene. The translocation appears to arise in the prefollicle centre stage of B cell maturation. The mechanism whereby the *bcl-2* gene product exerts its effect is still unclear but the suggestion that it prevents normal programmed cell death within the follicle centre is presently favoured [38]. Experiments using transgenic mice have shown that the juxtaposition of *bcl-2* with c-*myc* leads to the induction of primitive lymphoid tumours [39]. The precise breakpoints involved in the t(14–18) translocation vary and its detection, therefore, requires the use of several DNA probes. Nevertheless, even using the best techniques, the translocation is not found in every case of follicular lymphoma and its prevalence seems to be partly geographically dependent, being highest in the United States (90%), intermediate in Europe (70%) and lowest in Japan (30%) [40]. Another puzzling feature, which raises questions concerning the role of t(14;18), is that PCR techniques have identified the t(14;18) translocation in some examples of normal lymphoid tissue from normal individuals [41].

Evidence is accruing that the t(11;14) translocation, in which the immunoglobulin heavy chain gene is once more juxtaposed with a putative oncogene, *bcl-1*, specifically characterises centrocytic lymphoma (also known as intermediate cell lymphoma), a variant of low grade B cell lymphoma [42, 43]. Information on the biological relevance of this translocation is awaited as it is with respect to the r(2;5) translocation found in the new entity large cell anaplastic (CD30+) lymphoma [44]. It is hoped that the identification of these non-random genetic alterations in lymphomas will lead both to clues relating to the aetiology and pathogenesis and to a more biologically relevant classification.

Viruses

The discovery of the association of a herpes virus (later characterised as EBV with Burkitt's lymphoma coupled with the observation that this virus could immortalise B cells in culture continues to fuel research into the role of EB virus in the pathogenesis of lymphoma. Direct implication of the retrovirus human T-lymphotropic virus type 1 (HLTV-1) as a cause of a variety of T cell lymphoma has served further to accentuate the possibility that viruses may play an important part in the aetiology of lymphoma and has led to the search for other pertinent viruses.

Epstein–Barr virus (EBV). Integration of EB viral DNA can be demonstrated in 95% of cases of endemic Burkitt's lymphoma but in only 15% of non-endemic cases which implies that it is not directly causative for this type of tumour [45, 46]. The relationship of EBV to non-Hodgkin lymphoma in general may not be highly significant since only 5% of unselected cases have been shown to contain integrated EBV DNA [47]. However, in lymphomas developing in immunosuppressed individuals, EBV seems to play an important role [48]. Here the virus, present either as the result of a newly acquired infection or reactivation of an established infection, becomes established in lymphoid cells in a latent form consisting of circular DNA episomes that drive cell proliferation. In the absence of effective T cell immunity this proliferation continues unchecked until, as the result of a mutation, such as the c-*myc* gene translocation, a



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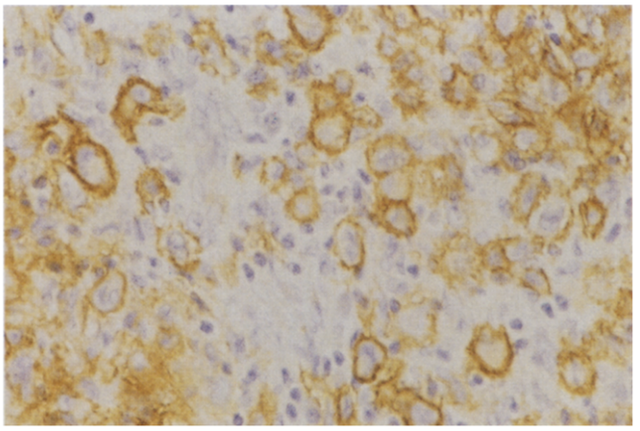

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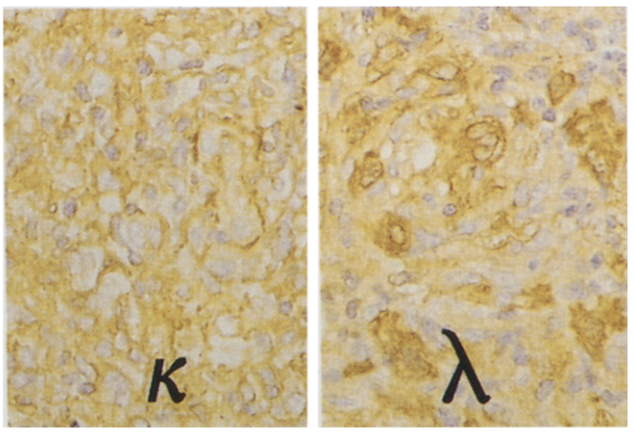

C

Fig. 3. (A) Biopsy of a large pharangeal mass which appeared 6 months after a renal transplant in a 59-year-old woman. Numerous large lymphoid cells together with smaller cells infiltrate between muscle fibres. (B) Immunostaining of this lesion with a pan B cell antibody (CD20) shows strong membrane staining of large tumour cells confirming their B cell phenotype. The small unstained cells are reactive T cells. (C) Immunostaining for kappa and lambda immunoglobulin light chains shows lambda light chain restriction of the large tumour cells indicating that the lesion is monoclonal. This lesion disappeared following reduction of the dose of cyclosporin used for immunosuppression. No further treatment has been necessary. This is an example of the post-transplant lymphoproliferative syndrome. (A) haemotoxylin and eosin, (B and C) immunoperoxidase on paraffin sections.

neoplastic clone emerges. With more sensitive means of viral detection EBV positive T cell lyphomas are now being described [49] and integration of the virus is now being reported with greater frequency in high grade lymphomas in immunocompetent individuals [50].

Human T cell lymphotropic virus type 1 (*HTLV*-1). This C type human retrovirus, which is endemic in southern Japan and the Caribbean, infects CD4+ T cells and can be shown to be monoclonally integrated in the adult T cell lymphoma that develops in 1 in 1000 infected individuals [51, 52]. The site of integration varies but the presence of viral genome appears to result in increased production of interleukin-2 receptors (and in some instances in increased interleukin-2 itself). Thus the role of this virus in the pathogenesis of lymphoma may be indirect, via uncontrolled cell proliferation, and similar to that of EBV in the immunosuppressed [52]. Transmission of HTLV-1 appears to be from mother to child via breast milk [53].

NEWLY DEFINED BIOLOGICAL CONDITIONS

B cell lymphomas arising in mucosa associated lymphoid tissue (MALT)

Lymphoproliferative lesions of the gastrointestinal tract, lung salivary gland and thyroid have been something of an enigma. The low grade lesions, although resembling lymphoma in many ways, seemed to behave in a benign fashion which gave rise to the term "pseudolymphoma". Likewise many of the clearly high grade lymphomas seemed to behave more favourably than comparable lymph-node lesions. The use of refined immunocytochemistry coupled with molecular biology has helped to define MALT lymphomas as a specific biological entity which includes those lesions previously called pseudolymphoma [54–56]. The low grade MALT lymphomas are of particular interest. MALT lymphomas do not share the cytogenetic alterations that characterise comparable low grade lymphomas of peripheral lymph-nodes [57] and tend to remain localised, only rarely involving the bone marrow. The reasons for this favourable biological behaviour await clarification.

Lymphomas associated with immunodeficiency

An increased incidence of lymphoma in patients with congenital (primary) immunodeficiency states has long been recognised [58] but two recent developments have focused attention on this association; these are, respectively, lymphomas complicating immunosuppression induced for the purposes of tissue or organ transplantation and lymphomas occurring as part of the acquired immunodeficiency syndrome (AIDS).

The post-transplant lymphoproliferative syndrome

The role of EBV in the pathogenesis of post-transplant lymphomas has already been discussed. The observation that a significant number of these lymphomas regressed, indeed disappeared, when immunosuppression was reduced has led to the term "lymphoproliferative syndrome", rather than lymphoma to describe this condition [48] (Fig. 3). The syndrome

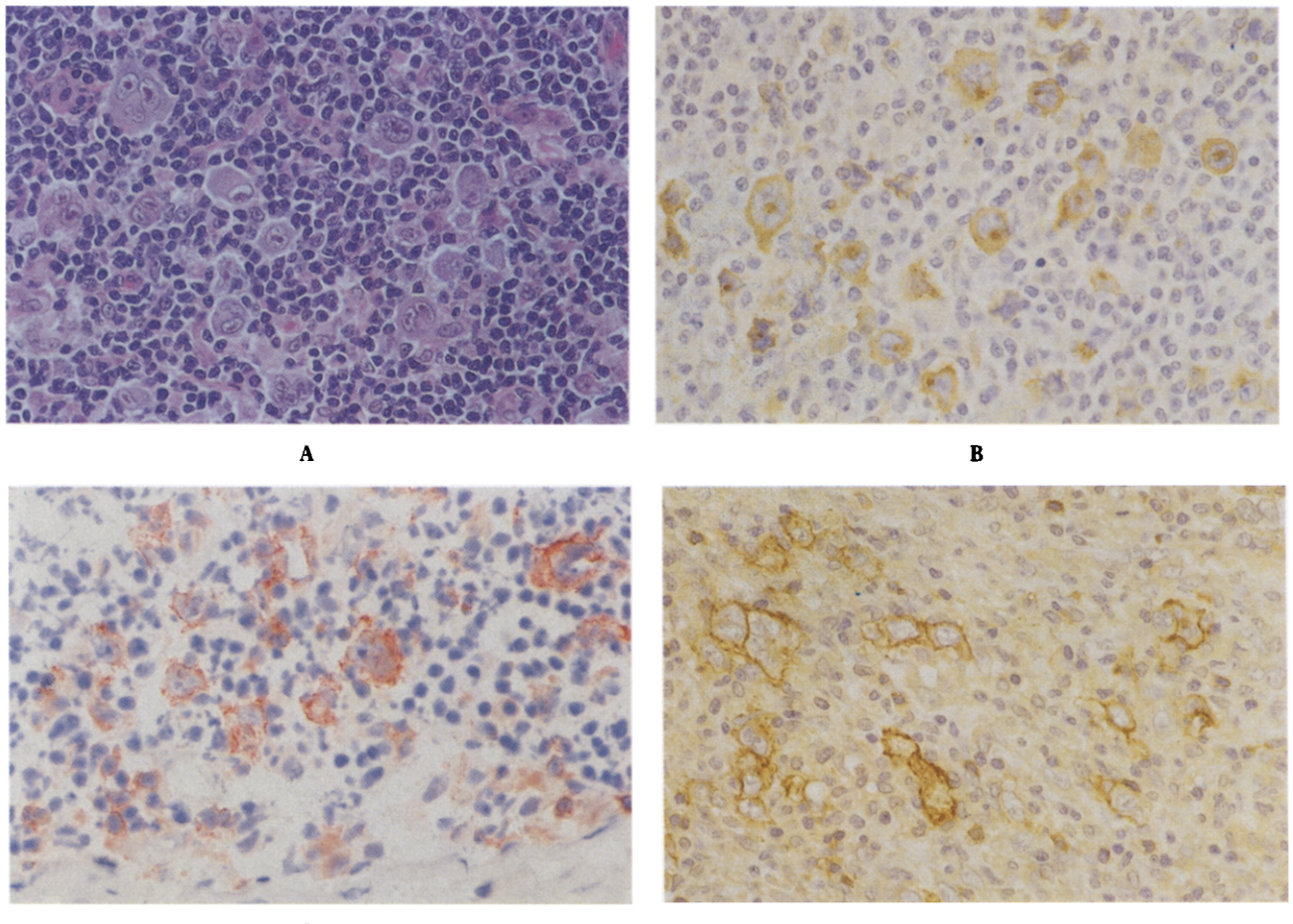

Fig. 4. (A) Mixed cellularity Hodgkin's disease showing (B) positive staining of the Reed–Sternberg cells with CD30 and (C and D) positive staining of the Reed–Sternberg cells with the pan B cell antibodies CD19 and CD20, respectively. (A) haemotoxylin and eosin (B and D) immunoperoxidase on paraffin sections, (C) immunoalkaline phosphatase on cryostat section.

encompasses five categories which, it is thought, correspond to stages in the evolution of lymphoma caused by the effects of EBV infection in immunosuppressed individuals. The first type comprises a polymorphic tumour which is non-clonal for both EBV and immunoglobulin gene rearrangement, the second a mixture of non-clonal and clonal lymphoproliferation, the third shows clonality for EBV but not immunoglobulin gene rearrangement, the fourth is clonal by both immunoglobulin gene and EBV DNA analysis and the fifth type is a monomorphic tumour which is again clonal by DNA analysis for these genes and also for c-*myc* gene rearrangement. The first four types usually (but not invariably) regress when the immunosuppression is reduced while the fifth type does not. For reasons that are not clear these tumours usually arise in extranodal sites such as the gut or the central nervous system.

Lymphomas occurring in AIDS

These lymphomas [59–61] closely resemble those in therapeutically immunosuppressed patients with respect to their site of occurrence, morphology, and relationship with EBV. It might be supposed, therefore, that a substantial proportion of AIDS associated lymphomas would regress should it be possible to reverse the immunodefficiency.

Anaplastic large cell (CD30+) lymphoma

The monoclonal antibody Ki-1, raised against an cell line and now clustered as CD30 [15, 62], recognises an activation antigen on lymphoid cells. Eexpression of this antigen has been found to characterise a morphologically distinct category of lymphoma often previously diagnosed as malignant histiocytosis [15]. The homogeneity of this newly defined entity is reinforced by the observation that a t(2;5) translocation is characteristically present [42]. Curiously, the primary cutaneous form of the disease usually runs a remarkably unfavourable clinical course in contrast to the highly malignant nature of the nodal disease [63]. The cells of anaplastic large cell lymphoma bear a strong resemblance to Reed–Sternberg cells, which also express CD30, and may be of either B, T or null phenotype. Thus, it has been proposed that this disease may form the interface between non-Hodgkin lymphoma and [64].

HODGKIN'S DISEASE

Investigative techniques used to study HD closely parallel those applied to the non-Hodgkin lymphomas. Much of the research on HD has, not surprisingly, centred on the nature of the Reed–Sternberg (RS) cell which is fundamental to understanding the biology of this disease.

Most progress has been made in the nodular lymphocyte predominant subtype of HD where the so-called L and H variant of the RS cell which characterises this form of HD has been shown unequivocally to be of B cell lineage [65–67]. Not only do these cells express a wide variety of B cell antigens but they have also been shown to synthesise J chain [68]. These findings, and the close association of high grade B cell lymphomas with this disorder, have led to the suggestion that this condition be no longer considered a part of the spectrum of HD but rather a B cell lymphoproliferative disorder. Surprisingly, however, immunoglobulin synthesis has not been demonstrated in L and H cells and there is as yet no evidence that lymphocyte predominant HD is a monoclonal proliferation.

Dispute as to the nature of the classic RS cell (as seen in nodular sclerosis and mixed cellularity HD) continues [69, 70] the principle protagonists favouring either a macrophage/interdigitating reticulum cell [71] or lymphoid origin [72]. Data favouring the relationship of RS cells to the monocyte/macrophage system are partly derived from phenotypic studies and partly from cell culture studies in which cells from HD derived cell lines have been shown to undergo differentiation towards macrophages [71]. The evidence for a lymphoid origin is much stronger and includes the expression of CD30 (rarely, if ever, expressed by macrophages) and of pan T or, more commonly, pan B cell antigens in many cases [72–74] (Fig. 4). These apparently contradictory findings have led to the suggestion that RS cells are derived from an uncommitted precursor lymphocyte. Molecular analysis of DNA from HD would seem to confirm this as there are reports of both monoclonal immunoglobulin and T cell receptor gene rearrangements in this disease [75, 76]. The recent finding, using PCR, of involvement of the *bcl-2* gene in over 40% of cases of HD is strong evidence in favour of a B cell phenotype but awaits wider confirmation [77, 78].

The detection of EBV genomes in HD [79] and more specifically the demonstration by *in situ* hybridisation that they are present in RS cells themselves [80] is also consistent with a B cell rather than a macrophage phenotype, since the virus does not infect macrophages. Of equal significance, perhaps, is the high frequency of EBV infected RS cells in HD and the finding that the viral DNA is monoclonally integrated. This raises the possibility that EBV is involved in the aetiology of HD which is currently a subject of intense speculation.

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News

European Conference on Pain Research

The first EEC conference on Pain Research will be held in Brussels on 12–13 December 1991. The meeting will focus on advances in the treatment of pain and methods for the evaluation of pain treatments in animals and man. The deadline for submitting abstracts is 15 October 1991. For further information, contact M. Staquet, Institut J. Bordet, Rue Heger-Bordet 1, B-1000 Brussels, Belgium. Tel. (32) 2 539 2805, fax (32) 2 539 3020.

Hormones and Cancer

The 4th International Congress on Hormones and Cancer will be held on 15–19 September 1991 in Amsterdam. For further information, contact RAI Organisatie Bureau Amsterdam, Europaplein 12, 1078 GZ Amsterdam, The Netherlands. Tel. (31) 20 65491212, fax (31) 20 6464469.

World Conference on Lung Cancer

The 6th World Conference on Lung Cancer will be held at the World Congress Centre, in Melbourne, Victoria, Australia, 10–14 November, 1991. The scientific programme will include sessions on the prevention of lung cancer, on recessive and dominant oncogenes in pathogenesis and on future directions in treatment. There will also be 16 "state of the art" sessions, including chemoprevention, endobronchial therapy, advances in pulmonary adenocarcinoma, controversies in the management of small cell lung cancer and mesothelioma. Abstracts should be submitted to the Scientific Secretariat, c/o Dr David Ball, Peter McCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne, Victoria 3000, Australia, before 30 May 1991. Further information can be obtained from Ms Jane Willis, MCS Convention Services, P.O. Box 335, Heidelberg, Vic. 3079, Australia. Tel. (613) 499 6722, fax (613) 499 7137.

AACR Special Conference in Cancer Research

The American Association for Cancer Research is holding a special conference on negative controls on cell growth and their breakdown during the pathogenesis of cancer. There will be special emphasis on growth factors, tumour suppressor genes and cell cycle regulation. The meeting will be on 20–24 October 1991 in Chatham (Cape Cod), Massachusetts. For further information, contact the AACR, Public Ledger Building, Suite 816, Sixth and Chestnut Streets, Philadelphia, PA 19106, USA. Tel (215) 440 9300, fax (215) 440 9313.

Sixth Sardinian International Meeting

The Sixth Sardininan International Meeting on genetic and epigenetic determinants of the premalignant and malignant phenotype will be held in Alghero, Italy, on 15–18 October 1991. For further information, contact Dr R.M. Pascale, Istituto di Patologia Generale, Università di Sassari, Via P. Manzella 4, 0710 Sassari, Italy. Tel (79) 228387, fax (79) 228305.