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REVIEW

Lymphoma: an introduction into historical background, classification schemes, aetiology, geographical variation and epidemiological trend

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HISTORICAL BACKGROUND: EVOLUTION OF NOMENCLATURE

Lymphoma, a term first introduced by Rudolph Virchow in 1858[1], at present time is readily and generally conceded to mean primary malignant neoplasm of the lymphoid tissue, which include Hodgkin's lymphomas (HL) and non-Hodgkin lymphomas (NHL). However, the evolution of this concept and the nomenclature took more than a century, and was full of ambiguity and confusion. Even as late as in the second edition of "The Pathology of Tumours" by EH Kettle, published in 1925[2], the author attempted only a brief account on lymphoma, and defined it as blastoma composed of lymphoid tissue in his chapter on "General Pathology of Tumour." He addressed this topic with a concluding remark of:

> ***"It is obvious, then, that the subject is one of very great complexity, and, in the present state of our knowledge, to dwell on it would serve no useful purpose: all that is necessary is to indicate the questions that have to be answered in the future."***

Terminology like "reticuloendotheliosis" to represent hyperplasia of reticuloendothelial tissue was introduced by O Ewald in 1923[3], and "reticulosis" by E Letterer in 1924[4]. The latter, which was initially coined to mean reticulocytosis i.e. proliferation of reticulum cells without differentiation, was later also used synonymously as reticuloendotheliosis amongst others, as exemplified by the complex classification scheme made by Robb-Smith in later years in 1938 and 1947[5,6]. These complicated subdivisions of "reticuloses" were not popularly adopted. The concept and description of leukemia, after its first description independently in 1845 by Craigie and Bennett in Edinburgh[7,8], Lautner in Vienna and Virchow in Berlin[9] in the early days also became muddled some years later when other terms like pseudoleukemia were introduced. Hence, the term lymphadenosis was coined by C Stemberg in 1926[10], to describe primary proliferative disorders of the lymph node, to distinguish it from that of the blood-forming cells, also named myelosis.

On the other hand, the conceptual development of malignancies originating in the lymphoreticular system and their nomenclature were less controversial. Virchow used "lymphosarcoma" to describe the malignant tumour derived from the lymphoid cells in 1863[11], and T Billroth proposed "malignant lymphoma" in 1871[12], and this term is still widely used in the US and UK. In EH Kettle's second edition of "The Pathology of Tumours" (1925)[2], there was a text segment devoted to lymphosarcoma. In 1913, J Ewings suggested the occurrence of tumours derived from the reticulum cells[13], and in 1928, C Oberling introduced "reticulosarcoma"[14] as a generic name for a neoplasm from the lymphoreticular system. Reticulum-cell reticulosarcoma (also known as reticulum-cell sarcoma) emerged as the descriptive name for a neoplasm derived from the reticular cells in the lymphoid organs and bone marrow, as a distinction from a tumour derived from lymphoid cells. Other reticulosarcomas described included lymphocytic and lymphoblastic reticulosarcoma, pleomorphic or anaplastic reticulosarcoma. However, American authors preferred lymphoma or lymphoblastoma as the generic term for neoplastic diseases of the lymphoreticular system.

However, it was Thomas Hodgkin of Guy's Hospital, who in 1832 first gave a definitive vivid account on diseases originating in the lymphoreticular system, in his paper "On Some Morbid Appearance of the Absorbent Glands and Spleen"[15]. In his original text, Hodgkin wrote:

> ***"As far as could be ascertained from observation, or from what could be collected from the history of the cases, the enlargement of the glands appeared to be a primitive affection of the bodies, rather than the result of irritation propagated from some ulcerated surface or other inflamed texture through the medium of their afferent vessels."***

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The above account highlights the fact that earlier authors normally regarded changes that took place in the lymph glands as caused by diseases in the draining sites of the affected nodes. Two decades after Hodgkin's published observation, Sir Wilks, also from Guy's Hospital, in his reports of cases on enlargements of the lymph glands[16,17] honoured Thomas Hodgkin by proposing the name 'Hodgkin's disease'. In 1893, Dreshfeld and Kundrat made the first attempt at delineating subcategories of lymphoma[18,19]. They stated that Hodgkin's disease and lymphosarcoma were separate entities. However, the neoplastic nature of Hodgkin's disease was not ascertained, nor was generally accepted for a very long time. Over the years, the remarkable diverse clinical presentation, behaviour and pathology of the so-called Hodgkin's disease perplexed many, who tried to understand this disease. Until recently, Hodgkin's disease had been regarded as diverse a disease as, an atypical form of tuberculosis, a specific infective granuloma of unknown origin, a tumour or a transition form between a granuloma and a tumour. Even as recent as in 1953, W Boyd in his "A Text-book of Pathology"[20], wrote:

> ***"Hodgkin's disease – This is a disease of the hemopoietic organs, i.e.,bone marrow, lymph node, spleen and liver. It is invariably fatal. Whether it is inflammatory or neoplastic in character is a matter of dispute."***

In fact, a review of Hodgkin's original 7 cases revealed that they were unlikely to be comprised of one disease. Only two cases showed microscopical features that would definitely fit the present day's criteria for Hodgkin's disease. Conceivably, this was in part responsible for the difficulties in defining this disease satisfactorily for almost 150 years.

LYMPHOMA CLASSIFICATION: THE DEVELOPMENT OF HODGKIN'S AND NON-HODGKIN'S LYMPHOMA CLASSIFICATIONS

Classification schemes have traditionally been developed separately for Hodgkin's disease, and lymphomas other than Hodgkin's disease (non-Hodgkin's lymphoma). This was due to delineation of Hodgkin's disease as a separate entity from lymphosarcoma, a concept first initiated by Dreshfeld and Kundrat in the 19" century[18,19], which was favourably received and adhered to since then. Moreover, for a very long time, the uncertainty of its neoplastic character, and the true nature of the cell from which it is derived if neoplastic, perpetuated this division.

The classifications of Hodgkin's disease are essentially histological. The earliest histological description is attributed to WS Greenfield (1878)[21], who noted that the affected nodes were disrupted by chronic inflammation and fibrosis, with presence of multinucleated cells. Later, Carl Stemberg (1898)[22] stressed the large size of the cells and multilobed nuclei, and Dorothy Reed (1902) emphasized the prominent nucleoli[23]. The presence of these so called Sternberg-Reed cells, thus constitutes an essential pre-requisite for the diagnosis of this disease. Rosenthal's report in 1936 documented the prognostic importance of histology in Hodgkin's disease[24], in particular the density of lymphocytes, and he recognized the inverse relationship between lymphocyte numbers and frequency of Stemberg-Reed cells. He divided the histology into 3 groups, predominance, subordinance and absence of lymphocytes and nodules. Some 8 years later, Jackson and Parker (in 1944)[25] also divided Hodgkin's disease into 3 groups, paragranuloma, granuloma and sarcoma. This system was further modified by Smetana and Cohen (1956)[26], who subdivided the granuloma type into an additional subgroup, one with conspicuous thickening of the capsule and sclerosis within the node, the "sclerosing Hodgkin's granuloma", which had a significant better prognosis. Based on the study of biopsy material of 377 cases from the US Armed Forces in World War 2, Lukes was able to distinguish 6 histological types, which he published in 1963". Later, he and his co-workers showed a good correlation between histological type and prognosis (1966)[28]. However, during the Rye conference held in 1965, Luke's original classification was simplified to 4 groups, later known as the Rye classification[29]. The Rye classification gained general acceptance by both clinicians and pathologists, and was widely used all over the world until present time. Table 1 shows the comparison between Jackson and Parker, Lukes and Rye classifications.

TABLE 1: A comparison of the Jackson and Parker, Lukes and Rye classifications of Hodgkin's disease.

Rye Classification	Lukes Classification	Jackson & Parker Classification
Lymphocyte Predominance type	Lymphocytic and/or histiocytic types (nodular and diffuse)	Hodgkin's paragranuloma
Nodular sclerosis type	Nodular sclerosis type	Hodgkin's granuloma
Mixed cellularity type	Mixed cellularity type	Hodgkin's granuloma
Lymphocyte depletion type	Diffuse fibrosis type and reticular type	Hodgkin's sarcoma

Even until the 1990s, there was still much debate over the origin of Sternberg-Reed cells. The candidates included transformed B lymphocytes by Glick et al., 1976[30] and Taylor, 1974[31] by immunostaining methods, macrophage lineage by Kadin et al., 1978[32], Kaplan, 1980[33] and Carr, 1975[34] by immunostaining, tissue culture methods and electron microscopy respectively, and dendritic reticulum cell by Curran and Jones, 1978[35] by metalophil staining method. Hence, the lesions remained to be called Hodgkin's disease instead of lymphoma. In 1979 Poppema, Kaiserling and Lemert published that the nodular lymphocyte predominance subtype of HD was an entity different from the other subtypes[36], and in 1980 Poppema demonstrated that the L&H cells of this subtype contain J-chain and therefore are of B cell origin [37]. More recent studies employed phenotyping and molecular biological techniques and convincingly demonstrated the lymphoid origin of the Stemberg-Reed cells in the other subtypes. A large majority of cases were shown to be B cells, with aberrant hypermutation of immunoglobulin gene, suggesting B-cell derivation with biological properties of follicular-centre cell type. For the first time, Hodgkin's disease was put alongside the non-Hodgkin's lymphomas in one classification scheme, the R.E.A.L. proposed list of lymphoid neoplasms (1994)[38]. In this scheme, lymphocyte rich Hodgkin's disease was added as a provisional entity, and is now accepted to be a specific subtype of classical Hodgkin's disease. This was already recognized to be different from nodular paragranuloma in 1979 by Poppema, Kaiserling and Lemert as lymphocyte predominant, other.

Lymphocyte predominance Hodgkin's disease differs from the classical types (mixed cellularity, nodular sclerosis, lymphocyte depletion and lymphocyte rich) in the phenotype expression of the atypical cells. The tumour cells in the classical types often express CD15, CD30 and EBV associated DNA, RNA and proteins, whereas the former does not express CD15 and EBV latent genes. Hodgkin's disease is now proposed to be named Hodgkin's lymphoma in the WHO classification, since the lymphoid nature of the Stemberg-Reed cells has been convincingly established (Jaffe, 1997)[39].

Various attempts at classification of non-Hodgkin's lymphomas have also been made over the years, from Robb-Smith (1938)[5] and Gall and Mallory (1942)[40] to the 1966 classification of Rappaport[41]. Then in the 1970s, several new classifications emerged, Dorfman 1974 (working Classification of non-Hodgkin's Lymphoma)[42], Bennett et al., 1974 (British National Lymphoma Investigation Classification)[43], Gerard-Marchant et al., 1974 (Kiel Classification)[44], Lukes and Collins 1974[45], 1975[46] (Lukes-Collins Classification), and Mathe et al., 1976 (WHO Classification of Malignant Lymphoma)[47]. This situation led to much confusion, to the exasperation of clinicians and pathologists. There were difficulties in translating one classification to the other, compounded by the use of similar terms in different sense e.g. well- and poorly differentiated lymphomas, and similar disease entities were given different names. Moreover, as non-Hodgkin's lymphomas are a diverse group of diseases, it is small wonder that each of these classification schemes could not completely encompass every entity. Hence, some entities were described in one and not in the others, which led to the proponents of these classifications advancing arguments on the superiority of their respective system over the others. In an attempt to resolve these issues objectively, an international study sponsored by the National Cancer Institute was conducted. A total of 1,175 previously

untreated patients' biopsy material from 4 centres with relatively standardised clinical and pathological staging, and treatment policies were examined and classified by the proponents of the 6 major Classification Schemes, using their respective scheme while visiting these 4 centres. It was followed by 6 experienced haematopathologists who were not proponents of any of these classifications to categorise the cases with all these schemes. Centres which took part in this study were Istituto Nazionale Tumori, Milan; Universtity of Minnesota Hospital, Minneapolis; Tufts-New England Medical Centre, Boston and Standford Medical Centre, Standford. These patients were seen in the hospital between July 1, 1971 and December 31, 1975. In brief, the analysis at the end of the study showed that no one classification was superior and each scheme allowed the categorization of patients into subgroups with spectrum of prognosis, from good to poor. Hence, the investigators involved in this study developed a "Working-Formulation of non-Hodgkin's Lymphoma for Clinical Usage", as a means to translate among all systems, and this so called Working Formulation was published in 1982[48]. In the subsequent 10 years, further information about these lymphomas became available, and new entities were recognized. It became evident that the existing histological categorizations of lymphoma were no longer adequate for further advancement of knowledge and understanding of lymphoid diseases. An international group of hematopathologists, comprising mainly of the United States and European members met to address this issue. It was deemed that the most practical approach was to list the well-defined entities based on current morphological, immunologic and genetic profiles. Even though it was recognized that classification according to their presumed normal counterpart would be ideal and in line with the system of classification for other tumours, the present limited understanding of the immune system and lymphomas render such conceptual framework not possible for the time being. Hence, the Revised European-American Classification of Lymphoid Neoplasms proposal emerged, which is better known as the REAL Classification. This classification encompasses the known lymphoid malignancies: the T-cell and B-cell lymphomas and Hodgkin's disease. The T- and B-cell neoplasms are divided into 2 main categories, the "precursors'" and "peripheral" types. The former corresponds to lymphoblastic lymphoma and leukaemia, and "peripheral" comprises the remainder types. The names given to these entities were based on the putative normal counterparts, the morphologic features, or established usage in the past. Additional categories of unclassifiable cases are permitted. This is a very practical approach to a classification scheme, making allowance for difficulties encountered, which can be due to the quality of processed tissue, level of experience of the pathologists, and entities yet to be better understood, described and categorised.

AETIOLOGY OF LYMPHOMA: THE ROLE OF HUMAN HERPES VIRUS

There are 2 families of viruses known to be aetiologically associated with human malignant lymphomas, the retrovirus and the human herpesvirus. Human T-cell leukaemia virus-l (HTLV-l), a T-cell (CD4) trophic retrovirus, is closely related to the adult T-cell lymphoma-leukaemia (ATL), first described in the 1977 in Japan[49]. This variety of lymphoma is most common in South-Western Japan, the Caribbean basin and the sub-Saharan Africa. The specific geographical distribution prompted the suspicion of an infective cause for this disease. In the early 1980s, a retrovirus named HTLA-1 was isolated from ATL patients[50]. It is estimated that 1% of population in Japan is carrier of this virus, and 1% to 4% of these carriers develop ATL[51,52]. Outside these geographical locations, HTLV-1 infection and associated lymphomas are relatively infrequent. More than 10 years of research showed that there are no identifiable oncogene or tumour suppressor genes in this virus, or specific cytogenetic abnormalities found associated with ATL[53]. The site of viral DNA integration appears to be at random, and there is no activation, deregulation or loss of important cellular genes. However, there is increased expression of IL-2R-a, IL-2 and granulocyte-macrophage stimulating factor (GM-CSF), and the cells showed diminished dependence on IL-2 for growth in vitro[54]. Research has been focused on the regulatory factor, Tax and its interaction with the 21-bp repeat regions of the long terminal repeats (LRT) termed TRE1 (Tax responsive element-l) and the upstream region named TRE2, via DNA binding proteins CREB and CREM[51]. Tax protein is the first HTLV-1 virus protein to be produced, and is required for replication of the virus. It acts both as the antigen and mitogen, driving the cell division of infected CD4 positive and CD8 T-cells. In-vitro and transgenic mouse model studies on the pathways of Tax in transformation and tumorigenesis have so far not lead to conclusive results[55].

Human Herpes Virus

a. ***Epstein-Barr virus***

However, in the past 15 years, there has been massive accumulation of information and knowledge on human herpes virus and lymphomas with respect to the 2 important viruses, the Epstein-Barr virus (EBV) and human herpesvirus-8 (HHV-8). Following its discovery in the tumour cells of Burkitt's lymphoma in 1964[56], EBV has since been shown to be closely associated with nasopharyngeal carcinoma, T-cell and NW-cell lymphomas, immunodeficiency/AIDS-related lymphomas, post-transplant lymphoproliferative disorders and Hodgkin's disease. Numerous major reviews have been published in the recent past on the role of EBV in lymphomas[53,57-63]. There is convincing evidence that this virus is not just an innocent bystander. In most instances the virus is shown to be clonal, based on the study of terminal repeats sequence of the viral episomal form by Southern blot analysis. Although the exact pathogenetic role(s) of EBV in each lymphoma type has yet to be elucidated, some hypotheses can be made based on scientific evidence and observations.

At least 11 genes can be expressed during latency infections, EBNAs-1, -2, -3A, -3B, -3C, -LP, LMP1, LMP2A, LMP2B, EBER1 and EBER2. Each of these possesses their own function(s). There are 3 patterns of latent gene expression in EBV-associated lymphomas (Table 2).

TABLE 2: Patterns of latent gene expression in EBV-associated lymphomas

Pattern	Gene expression	Tumour types
Latency I	EBNA-1, EBERs	Burkitt's lymphoma
Latency II	EBNA-1, LMP-1 EBERs	HL NW-cell lymphoma
Latency III	EBNAs-1,2,3A,3B,3C,LP LMPs, EBERs	AIDS-related lymphomas and post-transplant lymphoproliferative diseases

Several of these latent gene proteins are involved in the transformation process e.g. EBNA-2, EBNA-3A and 3C, LMPl and LMP2[62]. LMPl has been shown to transform rodent fibroblast cell lines[a], and induces contact inhibition in Rat-l and BALB/3T3 cells[65], and LMPl expressing Rat-l cell are tumorigenic in nude mice whereas LMP1-negative Rat-l cells are not[a]. At least 4 signaling pathways are involved in the function of LMP1, namely, nuclear factor-κB (NF-KB), c-Jun N-terminal kinase (JNK)-AP-1, p38/MAPK (mitogen activated protein kinase), and Janus kinase (JAK)-STAT (signal transducers and activators of transcription).

(i) ***Burkitt's lymphoma,***

Assay on tumorigenicity of EBV-positive and negative Akata cell clones in nude mice[s7] showed tumour growth from EBV-positive clones and not EBV-negative clones. This finding is very convincing of EBV conferring growth advantage to the Burkitt's lymphoma cells. One model based on the available data for endemic Burkitt's lymphoma is as follows. Early in the evolution, after primary EBV infection, malnutrition and chronic malaria infections results in polyclonal B lymphocyte stimulation and T lymphocyte immunosuppression. The setting favours the proliferation of EBV-infected B-cells, resulting in prolonged survival and higher steady state number. This may therefore favour the occurrence of the characteristic cytogenetic alterations involving the Ig and MYC loci. Up-regulation of MYC allows these altered cells growth advantage over other cells in the expanded pool[66]. Altered MYC expression may then replace the function of EBV, allowing cells to proliferate and survive. Hence, the EBNAs and LMPs expression are down-regulated. Because EBNAs and LMPs are targets for CTL response, decreased expression of these immune targets may lead to evasion of immunosurveillance, and hence increases the chance of survival.

(ii) ***Post-transplant lymphoproliferative disease***

It was documented that patients with active EBV infection are at risk of developing post-transplant lymphoproliferative disease (PTLD), and patients who acquire primary EBV infection in the post-transplant period are at special high risk. PTLD can present in 3 broad groups, based on the morphology and molecular pattern. First, plasmacytic hyperplasia as described by Nalesnik et al. in 1988[67], in which there is no oncogene or tumour suppressor gene alteration but shows multiple EBV infection events. Second, polymorphic B-cell hyperplasia or polyclonal B-cell lymphoma, with a single EBV infection event, but also lacking in oncogene and tumour suppressor gene alterations. Finally the third group of monoclonal disease with single EBV infection event, and frequent alteration in the N-ras or p53 genes. Cytogenetic analysis showed trisomy 9, 11 and BCL-6 alterations in large cell irnmunoblastic lesions, and MYC translocation in small cell, non-cleaved Burkitt-like tumours. In PTLD associated with EBV (>90%), the latent gene proteins, EBNA-2 and LMP1 were expressed in all cases. The patterns of viral antigen expression do not vary with the histology, clonality and cytogenetic group of the tumour. Hence, the suggested model for the pathogenesis of **PTLD** is that EBV drives the early proliferation and cytogenetic alterations evolve later. But unlike in endemic Burkitt's lymphoma, the viral proteins are probably required for maintaining the transformed state.

(iii) ***Immunodeficiency (AIDS)-related lymphoma***

Similar to ***PTLD,*** the pathology ranges from polyclonal lymphoproliferation to monoclonal lymphomas. However, AIDS-lymphomas are not uniformly EBV-associated[s3]. The average rate of virus association is 40%, with the exception of primary CNS lesions of immunoblastic type, which are about 100% associated[s3]. The data so far are most consistent with the hypothesis that multiple inciting events can lead to AIDS-related lymphoma, EBV infection being one.

(iv) ***Hodgkin's lymphoma***

An association of EBV and Hodgkin's lymphoma was proposed from early epidemiological and serological studies, indicating increased risk of developing Hodgkin's lymphoma from patients who had EBV-associated infectious mononucleosis, and presence of abnormally high titres of antibodies against EBV antigens prior to after the diagnosis of Hodgkin's lymphoma[68-74]. In 1985, Poppema et al. demonstrated the presence of EBNA-1 in the nuclei of RS cells in a case of mixed cellularity subtype of Hodgkin's lymphoma. However, it was the advancement in DNA molecular techniques on tissue biopsies in the late 1980s that enabled confirmation of the presence of the virus in the tumour. In 1987, Weiss et al. reported the presence of EBV in neoplastic tissue of Hodgkin's lymphoma, and subsequently demonstrated to be localised in the neoplastic Reed-Sternberg cells by in situ hybridisation method[75-77]. Interesting patterns of EBV association in Hodgkin's lymphoma had since been reported. A higher association rate is seen in the mixed cellularity subtype of Hodgkin's lymphoma than in nodular sclerosis, in children and old patients rather than in young adults, and also in certain geographical locations[78-81]. Within similar geographical locations, they are often related to poorer socioeconomic status[82]. The presence of monoclonal EBV viral genomes was demonstrated in Hodgkin's lymphoma by Anagnostopoulos et al. in 1989[83]. All the involved sites in EBV-positive cases show presence of the virus in the tumour cells, and it remains EBV associated during the course of the disease[84,85]. These data strongly suggest an aetiological role. Based on the available data, the favoured hypothesis is immune escape from the host CTL response, conferred by EBV, probably via the expression of cytokines. Interleukin (IL)-6 and IL-10 are significantly more frequently expressed in EBV-positive Reed-Sternberg cells than in EBV-negative cells[86,87]. It is postulated that up-regulation of the ILs expression is mediated by LMP1[88]. IL-10 is a pleiotrophic cytokine with inhibitory effects on cell-mediated immunity. It inhibits the synthesis of interferon-g and IL-2, which lead to inhibition of T-cell growth. It also mediates the immune response away from the Thl-type, which renders host T-cell protection ineffective. IL-10 is also capable of down-regulating expression of cytokines and MHC class II in macrophages, which further inhibits antigen-specific T-cell responses[g8].

(v) T- *& NKIT-NHL*

Even though EBV is long known to be B-cell lymphotrophic, it is found to be present in the T-cells in rare, fulminant cases of infectious mononucleosis and T-cell lymphoproliferative diseases:

the virus-associated haemophagocytic syndrome-associated T-cell lymphocytosis, nasal NK/T-cell lymphoma, some varieties of peripheral T-NHL and rare cases of post-transplant T-NHL[89,90]. It is presently still unclear what host and viral factors contribute to the T-cell infection. It is postulated that EBV can infect T-cell as CD21, the C3d (EBV) receptor is expressed in low level in normal T-cells. Other proposed modes of entry of virus into the cells are by way of endocytosis, or via cytotoxic T-cell killing of EBV infected cells through close proximity of the CTLs with released viral particles. The tumour cells express LMP1 gene protein and CD30. Studies on cases of nasal NK/T-cell lymphoma reveal almost 100% EBV association rate, gene expression is detected in almost all the tumour cells and the virus is demonstrated to be monoclonal. The ligand for CD30 receptors has recently been cloned and studied. It was found to have pleotrophic biological activities. Hence, modulation of expression of CD30 by EBV, perhaps via LMP1, and CD30-CD30 ligand interactions may influence the growth of EBV-associated lymphomas[60]. On the other hand, the viral gene expression pattern is more variable in peripheral T-NHL of AILD-type. The majority of the EBV is present in the reactive B lymphocyte and immunoblasts, and smaller numbers of neoplastic and non-neoplastic T-cells[9']. It is deemed unlikely that EBV would play a central role the pathogenesis of these lesions. However, it may explain the occurrence of rare B-immunoblastic lymphomas arising in AILD[58].

b. ***Human Herpes virus-8 (HHV-8)***

In 1994, Chang et al. isolated a unique DNA sequences from Karposi's sarcoma (KS) tissue of AIDS patients[92]. This DNA sequence being characteristic of the herpes virus family was named HHV-8. This study showed that the virus sequence was present in 90% of the KS tissue and 15% of non-KS tissue in corresponding AIDS patients, and not found in DNA of non-AIDS patients. This virus was found in almost all epidemic (AIDS-related) as well as the classic and endemic KS in subsequent studies. Presence of virus sequence in the peripheral mononuclear cells and seroconversion in HIV-positive patients is predictive of subsequent appearance of KS lesions. In addition to KS, this virus is also found to be closely associated with the rare "primary effusion lymphoma", PEL[93,94], usually in HIV-positive patients, and multiple myeloma. Although the rare variety of body cavity lymphoma exhibits "null"-cell phenotype, it has been shown to have Ig gene rearrangement and to express CD45. The virus genome is known to encode homologues of bcl-2, chemokine receptor (the G-protein-coupled receptor, GPCR), interleukin-6 and cyclin D. However, the exact mechanism(s) of oncogenesis is yet to be elucidated. Cheng et al. in 1997 found that the KS bcl-2 blocks programmed cell-death[g5], which may be responsible for a step towards malignant transformation due to inappropriate prolongation of cell survival. On the other hand, Arvanitakis et al.[96] showed that HHV-8 GPCR is functional, and the signal cascade set in motion results in cellular proliferation. These investigators proposed that HHV-8 GPCR may therefore play a direct role in oncogenesis, by causing abnormal growth and/or transformation. On the other hand, the virus encoded cyclin is also functional, which can contribute to cellular growth and transformation through activation of the cell cycle[s3]. In a recent study on the role of HHV-8 in PEL, it was suggested that virus infection alone is insufficient for tumour development, and that lesions in the cellular genes may be required for tumorigenesis[97].

GEOGRAPHICAL VARIATION OF LYMPHOMA: THE EAST AND WEST PATTERNS

Published data show different malignant lymphoma patterns existing in Asian and Western populations[98-101]. Substantial differences in the frequencies of subtypes of non-Hodgkin's lymphoma are also evident across geographical regions[102]. T-cell non-Hodgkin's lymphoma is more common in the Far East[99,101,102], and NK/T-cell lymphomas of the nasal and nasal-type are more common in the East Asians[102-108] and Peru[109] than the United States and Europe[103,110]. In the case of ATL, it is clearly related to the aetiological factor, the HTLV-1 virus infection endemic in the South-Westem part of Japan even though the pathogenetic mechanism is yet to be elucidated[111]. However, the explanation for the other varieties of peripheral T-cell lymphomas is not as clear-cut. Although the sino-nasal NK/T-cell lymphoma disease is apparently related to EBV as the causative factor, EBV being ubiquitous, it is therefore not the most important factor for the geographical distribution pattern. In Asia, EBV is also known to be closely associated with nasopharyngeal carcinoma, which is particularly prevalent in the ethnic Chinese in Southern China, Taiwan, Hong Kong, Malaysia and Singapore. In the same ethnic population, there is also a higher frequency of

upper aerodigestive tract T-cell/NK cell lymphomas with a similarly strong association with EBV[112,113]. Hence, host factors are probably more important in the distribution pattern of NK/T-cell lymphoma.

In addition, variation is noticed in the subtypes of non-Hodgkin's lymphoma: follicular and lymphocytic lymphomas are relatively infrequent in Asian populations and more prevalent in Western countries, while high-grade diffuse lymphomas are more common in Asia[98,114-117].

The reason for these differences may be related to either environmental or host genetic and cultural factors. A recent study on Asian immigrants and their descendants in the United States shows that only some of the differences in disease pattern change[118]. Hence, it appears that the incidence of some varieties of malignant lymphomas such as follicular lymphomas can be influenced by exposure to social-environmentalfactors, while others are strongly linked with the host characteristics.

Hodgkin's lymphoma is relatively uncommon in Orientals when compared to Western populations. Various reports from Asia, such as Japan, Hong Kong, Taiwan and China have shown that Hodgkin's lymphoma makes up only between 5% to 15% of all cases of lymphomas in their series[100,101,119,120], whereas it is about 20 to 25% in Caucasian populations. The incidence rate of HL is approximately 3 per 100,000 person-year in North America, and only 0.5 in parts of Asia[121]. A study from India, however, observed a higher frequency (30%) of Hodgkin's disease, differing from other major published data from Asia[122]. Hodgkin's lymphoma is also found to be common amongst children in Costa Rica, where its incidence is recorded to be similar to acute lymphoblastic leukaemia, and ranks among the highest recorded incidence rates in the world[123]. This accumulated information also suggests a geographical variation in the prevalence of Hodgkin's lymphoma. Extensive investigations were made in the past decade on the role of EBV in Hodgkin's lymphoma. The findings strongly implicate the virus playing an important role in the pathogenesis of EBV-associated cases. Hence, it remains unsolved why Hodgkin's lymphoma is not more commonly seen in Asian countries, where other EBV-associated neoplasms are encountered more frequently than in the West. The questions regarding how the immune status of the host at the time EBV infection may influence the final outcome remain to be answered. Certainly, there is sufficient indication that the immune status of the host at the time of EBV infection is relevant to the development of EBV-associated Hodgkin's lymphoma, as it is present in higher frequency in the elderly and young patients[78,124]. Moreover, there is strong association between EBV and childhood Hodgkin's lymphoma of 100%, even in widely different populations such as the Peruvian[SO], Honduran[125], Chinese[126,127] and the Kenyan[E1]. These observations, together with the previous finding of a clonal episomal virus pattern strongly suggest that EBV may play an important aetiological role in childhood Hodgkin's lymphoma in developing countries, regardless of the ethnicity of the populations. This notion is also supported by a recent study of 277 childhood Hodgkin's lymphoma from 10 countries, which reported that the prevalence of EBV association varies from country to country, ranging from 50% in a developed country such as the UK, to 100% in Kenya[E1].

EPIDEMIOLOGICAL TREND IN LYMPHOMA: WHAT IS THE MESSAGE?

Recent reports indicate changing trends in both Hodgkin's lymphoma and non-Hodgkin's lymphoma. The mortality rate from Hodgkin's lymphoma decreased worldwide, and it was partly attributed to effective therapeutic regimes and management plans[128,129]. The application of immunophenotyping and immunogenetic characterization of lymphomas has also led to a shift in the categorization of the worse prognostic type of Hodgkin's lymphoma to non-Hodgkin's lymphomas[121,128,130]. However, there are also time trend reports on the true incidence of Hodgkin's lymphoma, which either remains unchanged[131,132], or has declined in the last 4 decades[121,133]. The diminishing incidence was observed in both sexes at about equal rate[133,134]. The decline is more substantial in the older age group, whereas remains high in the young and developing countries, such as Puerto Rico and Bombay, India. Although the trend is a steady decline, the pattern is complex, in that, the incidence increases in young adults, especially in the developed countries, with higher rate in the females[121]. There are also variations in the incidence of disease subtypes, mixed cellularity declined but nodular sclerosis increased over time. This interesting trend suggests a possible shift in the effect or influence of aetiological factors. Most all of the reports on time trend in Hodgkin's lymphoma are from Europe and North America, and a smaller number of relatively developed countries in Asia, such as Japan and Singapore, on their respective populations. How these changes can throw further light on the

knowledge of aetiological factors and Hodgkin's lymphoma is not immediately apparent. EBV being the agent most convincingly associated to the development of the disease, one wonders if this trend is related to the changing exposure pattern to this virus. Age at first exposure to EBV infection has certainly changed in the industrialized countries, shifting the primary infection to adolescence and young adults. How this could have changed the pattern is not immediately evident, though it may explain the rise in incidence in the young adults, but would not be able to explain the decline in the mixed cellularity subtype which is more closely associated with Hodglun's lymphoma. Occupational risk factors for Hodgkin's lymphoma may include exposures to solvents, wood dust and agricultural chemicals[135,136]. However, the trends in the prevalence of these exposures had not been linked to the trend of Hodgkin's lymphoma. In a more recent review on infant feeding and children cancer risk, the absence or short-term breast feeding is implicated to increase risk for Hodgkin's lymphoma but not non-Hodgkin's lymphomas[137].

On the other hand, non-Hodgkin's lymphoma is on the rise worldwide according to numerous reports[131,132,138-142]. This steady up-ward trend in the last 4 decades has resulted in non-Hodgkm's lymphoma being placed as the eighth most common cancer in the UK[143] and the sixth most common in the US[144]. Although diagnostic improvements and the emergence of acquired immunodeficiency syndrome-related NHL (AIDS-NHL) can contribute to the increment[121,145], these cannot account for the quantum and the pattern of the trend. A Danish study on non-Hodgkin's lymphoma during 2 periods, 1943-1977 and 1978-1989, the pre-AIDS and AIDS era respectively, the increasing trend was observed in both periods, in all age groups and both sexes[146]. Likewise, in a French study over a period of 10 years from 1980 to 1989, on 380 cases of non-Hodgkin's lymphoma, only one case proved to be associated with HIV infection[147]. In another French study[148], the authors concur with the previous observations and conclusion that the increased incidence is independent of AIDS. Some reports indicated increment is seen in some specific tumour subtypes, such as nodal peripheral T-cell lymphomas[141] and extra-nodal B-cell lymphoma, in particular, the primary CNS lymphomas[149]. Although AIDS contribute more to the overall increase in the incidence of CNS lymphomas[150], there is evidence that the increase in the incidence of non-Hodgkin's lymphoma and CNS lymphomas antedates the AIDS epidemic[147,149]. However, a number of reports indicated that the incidence of primary brain lymphoma does not show an upward trend, such as in Alberta, Canada[151], and non-AIDS-related cases in Denmark[152]. The reasons for these variations are not apparent. In addition, several reports also point towards the increasing incidence of high grade lymphomas[131,147,148].

Changing trends in disease pattern over time is a good indicator of a change in the' trend of exposures to the associated aetiological factors. The findings in the time trends of non-Hodgkin's lymphomas have resulted in a resurgence of interest in the investigations of aetiological factors in the last decade. Some of the preliminary investigations suggest that the increase in lymphopoietic neoplasms is related to agricultural practices, possibly the results of exposure to occupational chemicals such as pesticides and herbicides[153-155]. The compounds suspected include the dichlorophenoxyacetic acids in the herbicides[156,157] and the organochlorines and organophosphates in the pesticides[158]. Sunlight had also been implicated in a report from a study in Sweden[159]. Other chemicals include organic solvents, and hair dyes had also been identified as possible causes of NHL[139,160,161]. A recent review[162] implicates benzene, a substance which is present in many chemicals such as industrial organic solvents, petrol and diesel fuels, and as natural product from combustion in forest fire and volcanic eruption. Benzene is a class I carcinogen, proven to be highly effective in causing lymphoma and zymbal gland carcinoma in rats and mice experimentally[163,164]. There are also compelling evidence of benzene exposure and the risk of developing non-Hodgkin's lymphoma in human subjects. Increased incidences of lymphoma have been noted in children swimming in pools contaminated by petroleum products in The Netherlands[165], children living near railways, oil refineries, petrochemical plants in the UK[166], and in communities living in the vicinity of industrial plants in the US[167]. The rise in non-Hodgkin's lymphoma appears to take place after the second world war, as reflected in almost all the countries where a tumour registry is kept, and parallels the rise in environmental levels of benzene introduced into the atmosphere from motor vehicles since the 1950s[162].

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