

Historical Review

HISTORICAL REVIEW OF LYMPHOMAS

Introduction

While lymphoma history begins with the description of Hodgkin's disease in 1832, almost all the significant events in the field have occurred in the past 60 years. Lymphoma (together with acute leukaemia) played an essential role in the birth of medical oncology and contributed greatly to our understanding of the malignant transformation. The clinical discipline profited from the explosive growth of immunology after World War II and the clinic, in turn, provided the scientist with many insights. Curiously, Hodgkin's disease, a therapeutic triumph, only reluctantly yielded its pathogenetic secrets, while the much less therapeutically tractable non-Hodgkin's lymphomas readily disclosed a spectrum of detailed pathogenetic mechanisms of malignancy. Except for those with symptomatic advanced disease or the elderly, most patients with Hodgkin's disease are now cured by fastidious irradiation and/or combination chemotherapy, based on an accurate knowledge of disease distribution obtained from sophisticated diagnostic study; the major challenge today is reduction of late lethal second neoplasms and cardiac complications of therapy. A variety of different misadventures in immunoglobulin (Ig) gene assembly, involving oncogene regulators of mitosis, programmed cell death and differentiation, have been defined at the molecular level and probably determine the specific non-Hodgkin's lymphoma subtype.

Description of Hodgkin's disease

In 1832, Thomas Hodgkin (Fig 1) published a remarkable paper (Hodgkin, 1832), entitled 'On Some Morbid Appearances of the Absorbant Glands and the Spleen', describing the disease entity which was later to bear his name.

Distinguishing this uncommon disorder from the far more frequently encountered causes of lymphadenopathy and splenomegaly (tuberculosis, syphilis, amyloidosis, carcinoma, non-Hodgkin's lymphoma, and acute and chronic leukaemias) (Gunz, 1980) without the benefit of microscopic study was a *tour de force* in the early nineteenth century.

Hodgkin, trained in Edinburgh (and in Paris with Laënnec) represented a new breed of rational and modern physician who arrived at the basis of disease causation through close correlation of clinical findings with gross morbid anatomy (Hardwick, 1966; Kass & Kass, 1988). The young Hodgkin's first medical appointment at the newly established medical school of Guy's Hospital had been as Inspector of the Dead and Curator of the Museum. It was

surely meticulous observation at the post-mortem table that enabled him to recognize six cases, of which at least three (including Case 2 described below) were proven to be Hodgkin's disease by microscopic study a century later (Fox, 1926).

Case 2. 'September 24th 1828. Ellenborough King, aged 10 years, was admitted to Luke's ward on the 6th of August 1828, under the care of Dr Bright. He was the youngest of six children, of whom the first five were reported to be all healthy. This child had also been healthy till about 13 months ago, when his strength, flesh, and healthy appearance began to fail. He was living at that time in the West of England. A tumour was observed in the left hypochondrium in the situation of the spleen, the glandulae concatenatae on the right side were observed to be considerably enlarged.

It does not appear that he was ever subject to haemorrhage, nor till very lately to dropsical effusion; his appetite was generally good.

After admission into the hospital the tumour on the left side was observed to extend considerably below the left hypochondrium, but was reported not to be as large as it had formerly been. The glands on the left side of the neck were swollen, as well as those on the right (Fig 2); the abdomen was somewhat distended, and there was considerable oedema of the scrotum.

The head was not opened. The glands in the neck had assumed the form of large ovoid masses, connected together merely by loose cellular membrane and minute vessels: when cut into they exhibited a firm cartilaginous structure of a light colour and very feeble vascularity, but with no appearance of softening or suppuration. Glands similarly affected accompanied the vessels into the chest, where the bronchial and mediastinal glands were in the same state and greatly enlarged. There were some old pleuritis adhesions.

The substance of the lung was generally healthy. There was a good deal of clear serum in the pericardium, but this membrane, as well as the heart, was quite healthy.

In the peritoneal cavity there was a considerable quantity of clear straw-coloured serum mixed with extensive, recent thin diaphanous films.

The mucous membrane of the stomach and intestines was tolerably healthy.

The mesenteric glands were but slightly enlarged, and but little if at all indurated; but those accompanying the aorta, the splenic artery, and the iliacs were in the same state as the glands of the neck.

The liver contained no tubercles, and its structure was

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Fig 1. Thomas Hodgkin (1798–1866), ‘a man distinguished alike for scientific attainments, medical skill, and self-sacrificing philanthropy.’ Epitaph inscribed on his tomb in Jaffa.



Fig 2. A 7-year-old boy (W.D.M., Case 7) in Dorothy Reed’s classic paper, showing similar presentation to Ellenborough King. (From Reed (1902), *Johns Hopkins Hospital Reports* 10, 133–196 with permission).

quite healthy. The pancreas was rather firm, and the glands situated along its upper edges were, as before stated, greatly enlarged. The spleen was enlarged to at least four times its natural size, its surface sprinkled with tubercles, presenting the same structure as the enlarged glands already described.’

Hodgkin’s perceptive observation was lost for a generation and might never have been appreciated but for Sir Samuel Wilks (1856, 1865), who, working independently at Guy’s a generation later with some of the same pathological material, provided a more detailed and critical clinical and pathological description of the disorder and acknowledged Hodgkin’s earlier contribution (Table I).

In the late nineteenth century, Greenfield (1878), among others, described characteristic giant cells in patients with Hodgkin’s disease. However, a full description of the diagnostic cells required Ehrlich’s staining methods, and awaited the publications of Sternberg (1898) and, in particular, Dorothy Reed (1902) (Fig 3). The latter clearly distinguished the process from tuberculosis, a condition complicating many of Sternberg’s cases.

The first histological classification of Hodgkin’s disease to enjoy wide recognition was the division into paragranuloma, granuloma, and sarcoma, introduced by Jackson & Parker (1947). In the early 1960s, Lukes & Butler (1966) added the nodular sclerosis category and further refined the earlier system. A conference held in Rye, New York in 1966 simplified the Lukes and Butler scheme into a four-part classification (lymphocyte predominance, nodular sclerosis, mixed cellularity, and lymphocyte depletion) (Lukes & Butler, 1966), which was further modified in the REAL (Revised European-American Lymphoma) classification (Harris *et al*, 1994).

The delineation of the Non-Hodgkin’s lymphomas

Subsequent to the report of Thomas Hodgkin, Virchow (1845) and Bennett (1845) independently described the first cases of leukaemia. In his textbook on tumours, published two decades later, Virchow (1864–1865) divided leukaemia into the leukaemic and ‘aleukaemic’ types, employing the designation ‘lymphosarcoma’ for a subdivision of the latter. Unfortunately, at about the same time a probable case of acute leukaemia was published by Cohnheim (1865) under the descriptive term ‘pseudoleukaemia.’ Pseudoleukaemia was to become a catch-all (a ‘misch masch’ according to Virchow) for a variety of conditions having in common lymphadenopathy and splenomegaly: that designation persisted into the twentieth century, and did much to obscure the delineation and subclassification of the non-Hodgkin’s lymphomas.

In the late nineteenth century, Kundrat (1893) and colleagues were again employing the term lymphosarcoma in the modern sense used by Virchow a generation earlier. However, it was well into the twentieth century before order began to emerge from the heterogeneous non-Hodgkin’s lymphomas. The follicular or nodular lymphomas were first clearly described by Brill *et al* (1925), initially without recognition of the malignant character of the proliferation. However, within a few years both these authors and

Table 1. Chronology of advances in lymphoma classification.

Year	Reference	Advance in classification
1832	Hodgkin	The primary malignant tumour of lymph nodes subsequently termed Hodgkin's disease described
1845	Virchow	The nature of leukaemia defined
1856, 1965	Wilks	Hodgkin's cases rediscovered; detailed clinical and pathological description of the disorder provided, and the eponym 'Hodgkin's disease' introduced
1864	Virchow	The concept of lymphoma is defined and placed under the rubric 'aleukaemic leukaemia'
1865	Cohnheim	The term 'pseudoleukaemia' proposed for Virchow's aleukaemic leukaemia
1892	Dreschfeld	Lymphosarcoma separated from pseudoleukaemia and Hodgkin's disease
1893	Kundrat	Lymphosarcoma separated from pseudoleukaemia and Hodgkin's disease
1898	Sternberg	The histological picture of Hodgkin's disease characterized including the diagnostic giant cells
1902	Reed	The histological picture of Hodgkin's disease characterized including the diagnostic giant cells
1925	Brill <i>et al</i>	Follicular (nodular) lymphoma described
1927	Symmers	Follicular (nodular) lymphoma described
1930	Roulet	Reticulum-cell sarcoma distinguished from lymphosarcoma
1947	Jackson & Parker	Hodgkin's disease divided into paragranuloma, granuloma and sarcoma
1956	Rappaport <i>et al</i>	The first modern classification of non-Hodgkin's lymphoma based on cytology and the presence or absence of follicular structure introduced
1958	Burkitt	Endemic (African) Burkitt's lymphoma described
1966	Lukes & Butler	Nodular sclerosis Hodgkin's disease described
1966	Lukes <i>et al</i>	The modern four-part classification of Hodgkin's disease developed
1972	Aisenberg & Bloch Preud'homme & Seligmann	Surface markers employed to establish B- and T-cell lineage of lymphoid neoplasms
1973	Barcos & Lukes	Lymphoblastic lymphoma defined
1973	Lennert <i>et al</i>	The concept of the follicle centre cell developed and employed in the Kiel classification of non-Hodgkin's lymphoma
1974	Lukes & Collins	An immunological classification of non-Hodgkin's lymphoma based on perceived B- and T-cell lineage proposed
1977	Uchiyama <i>et al</i>	Adult T-cell leukaemia/lymphoma described in Japan
1978	Isaacson & Wright	Delineation of MALT (mucosa-associated lymphoid tissue) lymphomas
1981	Korsmeyer <i>et al</i>	Lineage and clonality of B-cell lymphomas defined by immunoglobulin gene rearrangement
1982	Taub <i>et al</i> Dalla-Favera <i>et al</i>	Cloning of the <i>C-myc</i> oncogene from the t(8;14) of Burkitt's lymphoma
1984	Tsujimoto <i>et al</i>	Cloning of the <i>bcl-2</i> oncogene from the t(14;18) of follicular lymphomas
1985	Aisenberg <i>et al</i> Minder <i>et al</i> Waldman <i>et al</i>	Lineage and clonality of T-cell lymphomas defined by T-cell receptor gene rearrangement
1991	Rosenberg <i>et al</i>	Cloning of the <i>bcl-1</i> oncogene from the t(11;14) of mantle cell lymphoma
1993	Ye <i>et al</i>	Cloning of the <i>bcl-6</i> oncogene from diffuse large cell lymphomas
1994	Harris <i>et al</i>	Revised European-American Classification of Lymphoid Neoplasms (REAL classification)

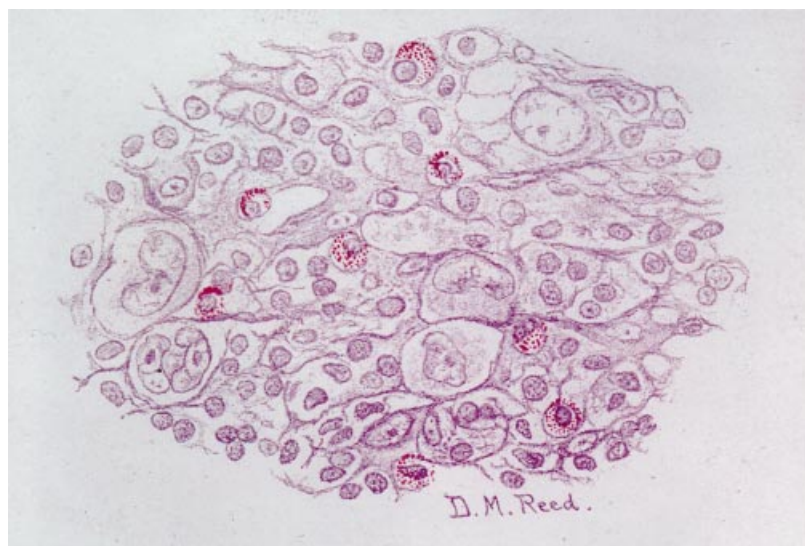


Fig 3. Reed–Sternberg cells drawn by Dorothy Reed's own hand. The mirror-image cell at the lower left is diagnostic. (From Reed (1902), Johns Hopkins Hospital Reports 10, 133–196 with permission).

Symmers (1927) were convinced that the condition was a malignant, albeit indolent, growth. The term reticulum cell sarcoma was applied to lymph node neoplasms by Roulet (1930), another designation which generated considerable confusion in lymphoma classification.

Gall and Mallory (1942) introduced a lymphoma classification based on clinicopathologic criteria, which, for all its shortcomings, was the first systematic attempt to make order out of the chaotic non-Hodgkin's lymphoma situation. Until then a number of influential pathologists still espoused the 'fluid' view of lymphoma, a view which held that the malignant lymphomas were not a group of separate and discrete diseases, but rather a single disorder capable of freely changing its microscopic appearance.

Rappaport *et al* (1956), in their classic study, presented medicine with a lymphoma classification that could be applied easily and was prognostically useful. Two criteria were employed to differentiate lymphoma subtypes: the presence or absence of nodularity, and cell size (small, intermediate and large lymphoid cells). Subsequently, the Rappaport scheme was so extensively modified to incorporate new knowledge as to become almost unrecognizable. The follicle centre cell was recognized by Lennert *et al* (1978) as the progenitor of a major fraction of adult non-Hodgkin's lymphomas, was elaborated upon by Lukes & Collins (1974), and became the basis of alternate classifications: Lennert's Kiel system (Lennert *et al*, 1978; Lennert & Feller, 1992) remains popular among European haematopathologists. The recent National Cancer Institute sponsored Working Formulation for Clinical Usage (Rosenberg *et al*, 1982) provided an unsatisfactory solution to the vexing search for a clinically-relevant system that could be reproducibly applied by working pathologists. The revised European-American lymphoma (REAL) classification (Harris *et al*, 1994) represents a radical, if tentative, consensus redo of lymphoma classification, based on prior classifications and, for the first time, defining lymphoma subtypes by immunophenotype and molecular genotype, as well as by morphology and clinical characteristics.

Lymphoblastic lymphoma was identified early by Barcos & Lukes (1975) and Lennert *et al* (1978) as a separate clinicopathologic entity, closely resembling the T-cell variant of acute lymphoblastic leukaemia, and attacking older children and adolescents predominantly. Still earlier, Burkitt (1958) had described a new type of lymphoma in African children restricted to regions of high temperature and high rainfall. Another distinct subtype of lymphoma, adult T-cell leukaemia/lymphoma, was reported in 1977 from Japan, where cases were concentrated in the South-western islands (Uchiyama *et al*, 1977). Recently recognized lymphoma subtypes include mantle cell lymphoma (Banks *et al*, 1992), derived from lymphocytes of the mantle cells of the lymphoid follicle, MALT (mucosa-associated lymphoid tissue) lymphomas (Isaacson & Wright, 1978), which are predominantly extranodal neoplasms derived from marginal zone B-cells (Harris *et al*, 1994), and large cell lymphomas of the mediastinum derived from B cells of the thymic medulla (Aisenberg, 1999a).

In 1972, it became possible to immunophenotype B and T

lymphocytes, initially by the presence of clonal immunoglobulin and/or sheep cell receptor on the cell surface (Aisenberg & Bloch, 1972; Preud'homme & Seligmann, 1972), and later with a host of B- and T-subset-specific monoclonal antibodies (Knowles 1992). First applied to fresh cell suspensions, techniques were soon available for frozen and formalin-fixed material. While not replacing morphology as the primary basis of lymphoma diagnosis and classification, the availability of increasingly specific monoclonal antibodies illuminated the nature of many lymphoid proliferations and made the diagnosis of some lymphoma subtypes insecure on the basis of morphology alone.

Clonality and lymphoid cell lineage can also be established through molecular genetic analysis employing Southern blot hybridization. Thus, in 1981 B-cell lineage could be confirmed by the presence of clonally rearranged immunoglobulin heavy and light chain genes (Korsmeyer *et al*, 1981). Similarly, it soon became possible to identify clonal T-cell proliferations by the presence of clonally rearranged T-cell receptor genes (Aisenberg *et al*, 1985; Minden *et al*, 1985; Waldmann *et al*, 1985). The genetic techniques are not yet widely utilized for routine diagnosis.

Evolution of effective treatment

Diagnostic procedures which permit accurate assessment of the extent of the disease (stage) figured prominently in the development of effective lymphoma management (Table II). Lymphangiography of the lower extremities (Kinmonth, 1952) proved of great value in defining the extent of abdominal lymphoma.

The introduction of laparotomy and splenectomy (Glatstein *et al*, 1969) for the staging of Hodgkin's disease was equally significant: this means of understanding the orderly progression of the disorder played a critical role in disease control, allowing the apposite application of supravoltage radiotherapy and combination chemotherapy. Staging laparotomy played little role in the management of the non-Hodgkin's lymphomas. Computerized tomography emerged as the preferred diagnostic technique for assessing lymphoma in the chest and abdomen, although it was not as sensitive or specific as lymphangiography in the latter region.

Peters (1950) introduced a three-part classification describing the extent of Hodgkin's disease. The four-part staging system in current use was proposed in abbreviated form at the 1966 Rye conference (Rosenberg, 1966), and expanded into its present version at conferences held in Ann Arbor, Michigan (Carbone *et al*, 1971) and the Cotswolds (Lister *et al*, 1989). The system in modified form is also used for the non-Hodgkin's lymphomas, but with less success. A recently introduced international prognostic index for non-Hodgkin's lymphoma has proved useful, particularly for aggressive proliferations (International non-Hodgkin's Lymphoma Prognostic Factors Project, 1993).

Only six years after Roentgen's 1896 description of X-rays, dramatic but transient responses of Hodgkin's disease to irradiation were reported by Pusey (1902). During the period 1925 to 1939, Gilbert (1939) undertook an ambitious and systematic radiotherapeutic approach to

Table II. Chronology of advances in lymphoma management.

Year	Reference	Advance In management
1902	Pusey	First cases of Hodgkin's disease treated with X-rays
1939	Gilbert	Anatomic and clinical foundations, and principles for the radiation therapy of Hodgkin's disease
1946	Goodman <i>et al</i>	Nitrogen mustard treatment of Hodgkin's disease
1950, 1958	Peters	Improved survival (<i>cure</i>) of Hodgkin's disease by radiation of adjacent uninvolved lymphoid areas
1952	Kinmonth	Lower-extremity lymphangiography
1962	Kaplan	Improved technique, tumouricidal dosage, and megavoltage equipment for irradiation of multiple lymph node areas in continuity (mantle, paraortic, inverted 'Y' fields)
1966	Rosenberg	Rye system for clinical staging of Hodgkin's disease
1969	Glatstein <i>et al</i>	Anatomical distribution of Hodgkin's disease defined with staging laparotomy and splenectomy
1970	DeVita <i>et al</i>	Definitive report of cure of advanced Hodgkin's disease with MOPP (mechlorethamine, vincristine, prednisone, procarbazine)
1971	Carbone <i>et al</i>	Revised four-part Ann Arbor system for clinical and pathological staging of Hodgkin's disease
1975	Bonnadonna <i>et al</i>	Treatment of Hodgkin's disease with the non-cross resistant drugs, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), and also with alternating MOPP & ABVD
1975	DeVita <i>et al</i>	Cure of diffuse large cell lymphoma with C-MOPP (cyclophosphamide, vincristine, prednisone, procarbazine)
1976	McKelvey <i>et al</i>	Treatment of aggressive non-Hodgkin's lymphomas with the doxorubicin-containing combination CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
1977		Computerized tomography (CT scanning) of chest and abdomen
1982		Treatment of high grade non-Hodgkin's lymphomas with third generation drug combinations
1984		Autologous bone marrow transplantation in Hodgkin's disease and non-Hodgkin's lymphoma

the disease. He obtained consistent responses, both subjective and objective, but cure remained an elusive goal and extension of life arguable. Developing Gilbert's approach, Peters (1950 and Peters & Middlemiss (1958) were the first to assemble convincing evidence that adequate radiation dose delivered to appropriate treatment fields could extend survival and even cure a fraction of patients. Radiation therapy of Hodgkin's disease approached its present high state of development with Kaplan's (1962, 1980) introduction of improved equipment and technique (accurate simulation and dosimetry, and modern treatment fields such as the mantle and inverted 'Y').

Among the unexpected results of World War II was the development of the highly toxic, but therapeutically useful, mustard gas derivative, nitrogen mustard [methyl bis(beta-chloroethyl)amine]. This material was the first modern anti-tumour drug to regularly produce significant responses in malignant disease in man: Hodgkin's disease stood out among the disorders reported by Goodman *et al* (1946) to be responsive. Unfortunately, remissions proved to be short-lived, but over the next 30 years a variety of other drugs active in Hodgkin's disease emerged, including vinblastine (Nobel *et al*, 1958), vincristine (Whitelaw *et al*, 1963), procarbazine (Mathé *et al*, 1963), bleomycin (Blum *et al*, 1973), nitrosureas (Lessner, 1968), doxorubicin (Gottlieb *et al*, 1973), and etoposide (Issell *et al*, 1984). Following the promising report by Lacher & Durant (1965) employing chlorambucil and vinblastine in combination, DeVita *et al* (1970) assembled the landmark MOPP (mechlorethamine, vincristine, prednisone, procarbazine) regimen, which dramatically altered the outlook of patients with advanced Hodgkin's disease. The development of this curative drug regimen was the culmination of a decade of laboratory and clinical investigation involving experimental animals and

patients, particularly those with acute lymphoblastic leukaemia: Carbone, Frei, Freireich, Holland, Pinkel and Skipper were major contributors (Frei, 1982). Following the introduction of MOPP for the treatment of Hodgkin's disease, other effective drug combinations were reported, of which the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) programme introduced by Bonnadonna & Santoro (1982) was the most significant. This regimen is less leukaemogenic and, because the components do not overlap those of MOPP, an effective eight-drug programme alternating cycles of MOPP and ABVD is feasible. The latter is particularly effective for those with advanced and symptomatic Hodgkin's disease (stages IIIB and IVB) (Bonnadonna *et al*, 1986), though the superiority of eight-drug over four-drug programmes remains unproven (Canellos *et al*, 1992).

The cumulative impact of advances in radiation therapy and chemotherapy on Hodgkin's disease survival is dramatically illustrated in Fig 4.

Hodgkin's disease mortality in the United States fell from 1.8 per 100 000 patients in 1950 to 0.4 per 100 000 patients in 1994, while disease incidence remained constant at approximately 3.0 per 100 000 (Aisenberg, 1999b; Reis *et al*, 1997; National Cancer Institute Division of Cancer Control, 1987). However, the unforeseen consequence of this success is a cumulative treatment mortality which exceeds that of Hodgkin's disease itself by 15 years (Fig 5) (Hoppe, 1997; Aisenberg, 1999b). Acute non-lymphocytic leukaemia secondary to MOPP chemotherapy, second non-Hodgkin's lymphomas, solid tumours (particularly of lung, breast, and gastrointestinal tract origin), and cardiac disease secondary to irradiation, account for most of the treatment-related mortality.

Treatment of the non-Hodgkin's lymphomas has lagged

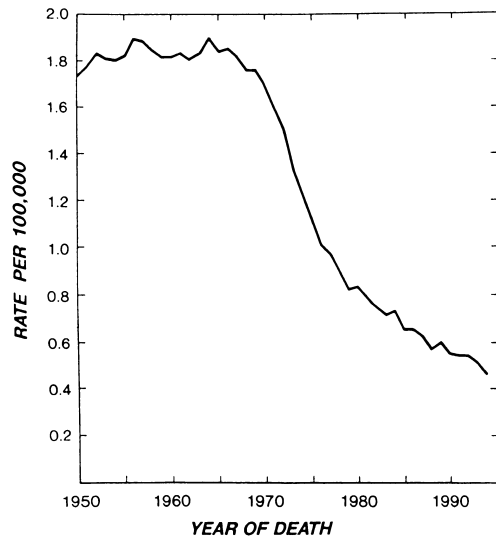


Fig 4. Hodgkin's disease mortality in white men and women in the United States from 1950 to 1984. [Adapted from the National Cancer Institute Division of Cancer Control (1987) with additional data from Reis *et al* (1997)].

behind that of Hodgkin's disease: few of the former are cured with radiation therapy.

However, in 1975 investigators at the National Cancer Institute (DeVita *et al*, 1975) reported the cure of a small number of patients with advanced stage diffuse large cell lymphoma with the C-MOPP (cyclophosphamide, vincristine, prednisone, procarbazine) drug combination. The next year, the first (McKelvey *et al*, 1976) of many reports appeared attesting to the efficacy of the doxorubicin-containing CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen in intermediate and high grade lymphomas (diffuse large cell, follicular mixed and large cell, and immunoblastic).

Alternatives to the CHOP programme have been explored with the twin goals of simultaneous tumour exposure to the maximum number of drugs (the Goldie-Coldman hypothesis) (Goldie *et al*, 1982) and the maximum drug intensity (Hryniuk & Bush, 1984; DeVita *et al*, 1987). While

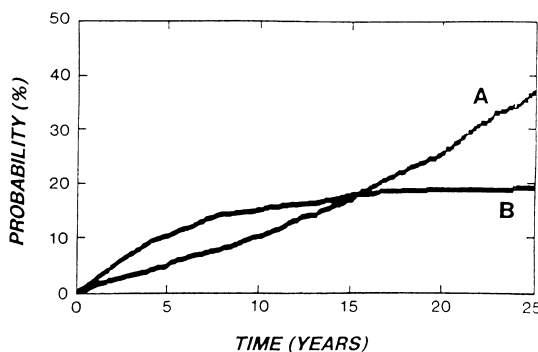


Fig 5. Actuarial risk of death from Hodgkin's disease (curve B) or other causes (curve A) in 2498 patients treated at Stanford University from 1960 to 1995 [adapted from Hoppe (1997)].

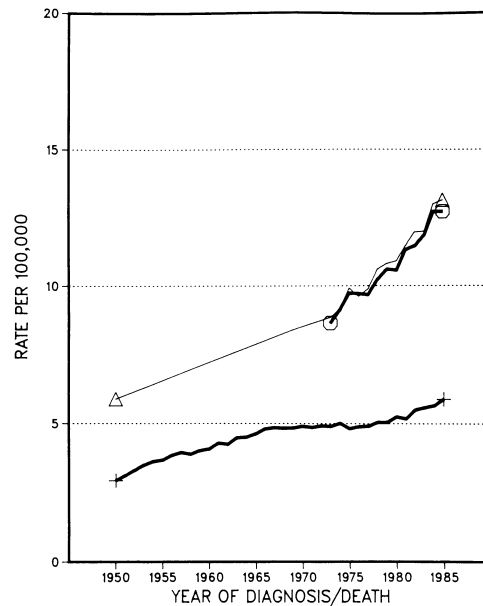


Fig 6. Non-Hodgkin's lymphoma incidence and mortality in white males and females in the United States from 1950 to 1985. The upper curves represent incidence figures from the SEER programme (octagons) and from four selected areas (triangles), and the lower curve represents mortality. (From the National Cancer Institute Division of Cancer Control, 1988).

improving survival figures initially suggested an advantage of the third generation programmes, randomized investigation unfortunately revealed no improvement over the CHOP results (Fisher *et al*, 1993).

High dose therapy, in association with autologous haematopoietic cell transplantation (Horning & Nademanee, 1999; Bierman & Armitage, 1999), has emerged as the only potentially curative treatment available to patients with relapsed intermediate and high grade non-Hodgkin's lymphomas. Stem cell transplantation is currently employed earlier in the course of relapsed aggressive non-Hodgkin's lymphoma than in Hodgkin's disease. It is of historical interest that lethal doses of nitrogen mustard, with attempted bone marrow salvage, were first employed in end-stage Hodgkin's disease more than 40 years ago and discarded because of unacceptable mortality (Thomas, 1999).

Mortality from non-Hodgkin's lymphoma (Fig 6) has not undergone the salutary improvement observed in Hodgkin's disease; (Reis *et al*, 1997; National Cancer Institute Division of Cancer Control, 1987). Though five-year survival at the national level has risen from 28% (1950 to 1964) to 52% (1983-89), overall non-Hodgkin's lymphoma mortality continues to climb, though less rapidly than the increase in disease incidence. The impressive gains achieved with diffuse large cell and paediatric lymphomas are submerged by the increased disease incidence, the many indolent but incurable follicular lymphomas, and the poor results in the aged.

The dramatic improvement in paediatric non-Hodgkin's lymphoma survival contrasts with the modest gains in adults. While less than 10% of children and adolescents

with *localized* or *regional* non-Hodgkin's lymphoma survived 5 years prior to 1967 (Aur *et al.*, 1970), recent series report 80% disease-free survival in all stages combined (Reiter *et al.*, 1995; Sandlund *et al.*, 1996). This progress was achieved first, through recognition that paediatric non-Hodgkin's lymphoma is almost always a disseminated process requiring acute lymphoblastic leukaemia-like treatment regimens (Aur *et al.*, 1970; Wollner *et al.*, 1976), and second, that optimal results require treatment intensity stratified by stage and immunophenotypically-determined biologic subtype (Burkitt's, lymphoblastic of T- or B-cell lineage, and large cell lymphoma variants) (Reiter *et al.*, 1995; Sandlund *et al.*, 1996; Link *et al.*, 1997).

There has been a striking increase of AIDS (acquired immunodeficiency syndrome)-related lymphomas noted in sexually active males in certain geographical regions over the past several years. These are usually intermediate- or high-grade neoplasms of undifferentiated or immunoblastic subtypes, advanced in stage with extranodal spread at the time of presentation, and with short survival times (Ziegler *et al.*, 1984). The underlying immunodeficiency made lymphoma chemotherapy difficult until the introduction of effective HIV treatment with protease inhibitors. Based on the projected AIDS incidence, the increased mortality from AIDS-related lymphomas may soon overwhelm any treatment-related improvement in non-AIDS lymphoma survival.

However, the AIDS-associated lymphomas do not account for the 3–4% annual increase in non-Hodgkin's lymphoma incidence observed in the United States and Europe since the early 1970s (Reis *et al.*, 1997).

Aetiology and pathogenesis

The nature of Hodgkin's disease. With the exception of the earliest description of follicular lymphoma, the neoplastic nature of the non-Hodgkin's lymphomas was never in doubt.

However, because neoplastic-appearing cells form only a minor population of the Hodgkin's disease infiltrate, the malignant nature of Hodgkin's disease was disputed. The majority of investigators, Virchow, Wilks, and most modern students of the disorder, considered it a neoplasm of the lymphoid system, but some distinguished observers, including both Reed and Sternberg, held a contrary opinion. Indeed, until recently, the Reed–Sternberg cell resisted attempts to define its lineage because of its sparsity. Its immunophenotypic characteristics were not those of garden-variety B lymphocytes, T lymphocytes, macrophage/monocytes, or dendritic cells.

The pathogenesis of Hodgkin's disease is at last being resolved. Recent evidence of clonally rearranged immunoglobulin genes obtained from polymerase chain reaction study of single Reed–Sternberg cells, and from immunophenotype study, strongly supports their neoplastic and aberrant ('crippled') B-cell lineage in nodular sclerosis, mixed cellularity and lymphocyte-depletion Hodgkin's disease (Küppers & Rajewsky, 1998; Küppers *et al.*, 1999). These cells lack CD45 (leucocyte common antigen), surface Ig, and most common B-cell antigens, but are usually reactive with antibodies to CD15 and the activation antigen

CD30 (Ki-1) (Schwab *et al.*, 1982). The Reed–Sternberg cells in nodular lymphocyte-predominant Hodgkin's disease more closely resemble conventional neoplastic B lymphocytes.

The multitude of failed aetiologic agents proposed as the cause of Hodgkin's disease will not be catalogued here (Hooster *et al.*, 1948).

Epstein–Barr virus (EBV) is demonstrable in clonal form in Reed–Sternberg cells in one-third to one-half of Hodgkin's disease biopsies, and in a frequency that is dependent on disease subtype, but its causal role remains to be documented (Niedobitek, 1996). The defect in cell-mediated immunity which accompanies active Hodgkin's disease (Twomey & Rice, 1980) will probably be elucidated with further clarification of the cytokine network (Gruss *et al.*, 1997).

Viruses and the aetiology of lymphoma. Despite the central aetiologic role of viruses in a variety of naturally-occurring lymphomas and leukaemias of animals (including avian leukosis, lymphomas of wild and laboratory mice, feline lymphoma/leukaemia, bovine lymphoma/leukaemia, and lymphoma/leukaemia of the gibbon ape) (Gallo & Wong-Staal, 1982), progress in establishing a viral causation of human lymphomas has been slow and elusive.

The regular isolation of Epstein–Barr virus (EBV) from African Burkitt's lymphoma in 1964 and since that time (Epstein *et al.*, 1964), together with extensive epidemiologic (serologic) evidence, established an aetiologic role of this DNA herpes-type virus in the endemic disorder. However, while EBV was isolated from almost all African cases, it was identified in only a small fraction (20%) of non-endemic cases, which share the same cytogenetic translocations, but differ slightly in clinical behaviour and molecular genotype (Lenoir, 1986). More recently, EBV has been identified in lymphomas which complicate a variety of acquired and inherited immune deficiency states (Niedobitek & Young, 1997): ataxia-telangiectasia, Wiskott–Aldrich syndrome, severe combined and common variable immunodeficiencies, the X-linked immunodeficiency syndrome (Harrington *et al.*, 1987), organ transplantation (Penn, 1993), and AIDS (particularly those cases with immunoblastic histology or primary central nervous system presentations). In all the above conditions the virus is clonal, but its relationship to causation remains to be elucidated.

Gallo and Wong-Staal (1982) isolated a novel retrovirus (HTLV-I) from a patient with an atypical cutaneous T-cell lymphoma. Subsequently, the same virus was regularly recovered from the tumour cells of Japanese and Caribbean patients with adult T-cell leukaemia/lymphoma (ATL), and antibody to the virus was demonstrated in almost all individuals with that disorder.

Cytogenetics. The identification by Manolov & Manolova (1972) of extra chromosomal material on chromosome 14 (14q+) in Burkitt's lymphoma is another landmark event in lymphoma history. Several years later, Zech *et al.* (1976) proved this finding to be the result of an unbalanced translocation between chromosomes 8 and 14 [t(8;14)(q24;q32)]. Subsequent investigation demonstrated the same translocation in approximately 80% of Burkitt's

lymphoma cell lines; the remaining 20% revealed one of two variant translocations, between chromosome 8 and either chromosome 2 [t(2;8)(p12;q24)] or chromosome 22 [t(8;22)(q24;q11)] (Lenoir, 1986).

With improvement in cytogenetic techniques, additional chromosomal abnormalities specific to particular lymphoma subtypes were identified with increasing frequency (Rowley, 1982). Thus, Fukuhara *et al* (1979) identified a translocation between chromosomes 14 and 18 [t(14;18)(q32;q21)] in follicular (nodular) lymphomas, trisomy of chromosome 11 was frequently found in small lymphocytic lymphomas and chronic lymphocytic leukaemia (Yunis, 1983), and abnormalities of the long arm of chromosome 14 (14q11–13) and trisomy 3 were detected in ATL (Fifth International Workshop on Chromosomes in Leukaemia-Lymphoma, 1987). Indeed, recent results employing high-resolution chromosomal analysis suggest that characteristic cytogenetic defects can be identified in most, if not all, subtypes of non-Hodgkin's lymphoma.

Molecular genetics and oncogenes. The chromosomal localization of the human immunoglobulin genes between 1979 and 1981 provided the basis for breathtaking insight into the pathogenesis of Burkitt's lymphoma. The immunoglobulin heavy chain, and kappa and lambda light chain, genes were localized, respectively, to specific bands on chromosomes 14, 2 and 22 (at bands 14q32, 2p12 and 22q11), the three sites involved as one partner of essentially all common and variant Burkitt translocations. In 1982, both the Leder (Taub *et al*, 1982) and the Croce laboratories (Dalla-Favera *et al*, 1982) cloned the translocation breakpoint, and identified the *c-myc* oncogene on the chromosome 8 fragment (8q24). Since the *c-myc* oncogene was already known to virologists from its role in fowl leukosis, the circle was closed. Transgenic injection (introduction into the germline by addition to the murine egg nucleus) of *c-myc* coupled to the IgM heavy chain or kappa light chain genes regularly produced aggressive B-cell lymphomas, but complete or truncated *c-myc* alone was inactive (Adams *et al*, 1985). Active work continues on the detailed mechanism by which dysregulation of *c-myc* by immunoglobulin-gene segments leads to Burkitt's lymphoma.

Within two years of the elucidation of the role of *c-myc* in Burkitt's lymphoma, Tsujimoto *et al* (1984) cloned the breakpoint of the 14;18 translocation of follicular lymphoma. This breakpoint involved the junction of a joining region segment of the IgM gene at chromosome 14q32, and the *bcl-2* oncogene (at 18q21), whose protein product suspends apoptosis or programmed cell death (Hockenberry *et al*, 1990). Similarly, the 11;14 translocation of mantle cell lymphoma juxtaposed the *bcl-1* gene (whose product is a mitosis-regulating cyclin) on chromosome 11q13 to the same IgM gene (Rosenberg *et al*, 1991). *Bcl-3*, an oncogene at 19q13 whose product regulates gene transcription, is similarly joined in a small fraction of cases of chronic lymphocytic leukaemia (Wulczyn *et al*, 1992). *Bcl-6* is a putative oncogene at chromosome 3q27 translocated to a variety of chromosomal sites in a fraction of large cell lymphomas (Offit *et al*, 1994; Gaidano & Dalla-Favera, 1997). In T-cell lymphomas, one breakpoint site is at

chromosome 14q11, the site where the gene for the delta chain of the T-cell receptor is embedded in the T-cell receptor alpha chain gene (Reis *et al*, 1989).

Thus, a catastrophe in the generation of antigen receptor genes, immunoglobulin genes (in the case of B-cells) and T-cell receptor genes (in the case of T-cells) is a major cause of human lymphoma. Available evidence suggests that more than a single genetic misadventure is required for tumour induction (Land *et al*, 1983). The remarkable progress in understanding the molecular events in lymphomagenesis achieved in the past several years suggests that comprehensive understanding of the process is not far off.

Lymphoma subtypes are increasingly being defined at the molecular level by their causal oncogene defects.

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