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CHAPTER FORTY-THREE

Non-Hodgkin's Lymphoma and Mycosis Fungoides

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INTRODUCTION

Billroth (1871) originally proposed the term "malignant lymphoma" to describe neoplasms of the lymphoreticular system. With the recognition of the Reed-Sternberg cell, Hodgkin's disease was identified as a unique clinicopathologic process that differed from other lymphoreticular malignancies. Plasma cell neoplasms and, more recently, Burkitt's tumor likewise were regarded as distinct diseases. The remaining lymphoreticular cancers have come to be known, albeit clumsily, as the non-Hodgkin's lymphomas (NHL). This heterogeneous group of tumors is reviewed in this chapter, along with a cutaneous variant, mycosis fungoides.

NON-HODGKIN'S LYMPHOMA

Pathology

The classification of NHL has been a source of great confusion over the years. Until rec ntly, there were three major categories: lymphosarcoma (LSA), reticulum cell sarcoma (RCS), and giant follicular lymphoma (GFL). Although pathologists debated the cellular characteristics that defined each entity, this terminology gained general clinical acceptance, and even today is the usual basis for NHL morbidity and mortality statistics. For clarification, various new systems were proposed, with that of Rappaport (1966) gaining widespread acceptance among pathologists, because it is practical and reproducible, and among clinicians, because of its prognostic implications.

Rappaport separates NHL into two groups: the nodular lymphomas, in which the normal follicular pattern of the lymph node is relatively preserved, and the diffuse lymphomas, in which the normal architecture is effaced. Cytologically, each category is further divided into lymphocytic (if the malignant cells are small and resemble normal lymphocytes), *histiocytic* (if the malignant cells are larger, resembling normal histiocytes), and mixed subsets. Lymphocytic lymphomas are further characterized as poorly differentiated or well differentiated. Lymphomas cytologically similar to Burkitt's tumor that fail to meet its strict diagnostic criteria are classified as undifferentiated, pleomorphic NHL. In the natural history of NHL, the tumors tend to evolve from a nodular to a diffuse pattern and from a well differentiated to a poorly differentiated cytology (Berard et al, 1976).

The relationship between the historical nomenclature and the Rappaport classification is summarized in Table 1, as are the frequencies of the Rappaport subtypes and representative survival data. Nodular and diffuse lymphomas occur in equal proportions, with nodular, poorly differentiated lymphocytic lymphoma (NPDL) and diffuse histiocytic lymphoma (DHL) the most common subtypes. When a complete

TABLE 1. Non-Hodgkin's Lymphoma: Selected Pathology and Clinical Data

Historical Nomenclature	*Rappaport Nomenclature*[a]	*Frequency*[b] N	%	*NCI Series*[c] N	% CR[d]	*Median Survival in Months*[e] ALL PATIENTS	CR ONLY	*Cell Surface Markers*[k]
Giant Follicular Lymphoma	Nodular Lymphoma	398	50					
	(1) lymphocytic, poorly differentiated	275	35	49	67	83	95	*B*
	(2) mixed lymphocytic—"histiocytic"	86	11	31	77	NYR[f]	NYR[g]	*B*
	(3) "histiocytic"	37	5	4	75	18	20	*B*
Lymphosarcoma	Diffuse Lymphoma	396	50					
	(1) lymphocytic, well differentiated	23	3	11	64	78	84	*B*
	(2) lymphocytic, poorly differentiated	114	14	25	32	23	NYR[h]	*B*; T; N
Reticulum Cell Sarcoma	(3) mixed lymphocytic—"histiocytic"	25	3	10	10	4	51+	*B*; T
	(4) "histiocytic"	215	27	62	47	11	NYR[i]	*B*; N; rare T, H
	(5) undifferentiated, pleiomorphic	19	2	7	43	6	NYR[j]	B; N

[a]Rappaport (1966).
[b]Combined series cited in Goffinet et al (1977); Chabner et al (1977); Nathwani et al (1978a).
[c]Anderson et al (1977).
[d]Percentage achieving complete response after initial therapy.
[e]NYR: median survival not yet reached.
[f]69 per cent still alive, follow-up 7–101+ months.
[g]91 per cent still alive.
[h]67 per cent still alive; follow-up 28–92+ months.
[i]64 per cent still alive; follow-up 3–116+ months.
[j]67 per cent still alive; follow-up 15–18+ months.
[k]B: B-cell; T: T-cell; N: null cell; H: true histiocyte; *italics* indicate the predominant immunotype (Mann et al, 1979).

remission follows initial therapy, the prognosis is improved for patients with either nodular or diffuse morphology. Among patients who achieve a complete remission, those with DHL are more likely to remain disease-free than are patients with NPDL (Anderson et al, **1977).** However, nodular lymphomas have a more favorable survival overall due to the indolent course of many patients who fail to achieve a complete remission.

Typically, NHL originates in lymph node tissue. However, in **15** to **20** per cent of patients, the tumor develops in an extranodal site (Hande et al, **19771,** such as bone (Boston et al, **1974),** stomach (Stobbe et al, **1966),** thyroid (Burke et al, **19771,** small or large intestine (Henry, **1977),** breast (Wiseman and Liao, **19721,** or brain (Henry et al, **1974).** By definition, primary extranodal NHL develops in the absence of systemic lymphoma and is associated with a more favorable prognosis than nodal NHL, which tends to be widespread at the time of diagnosis (Hande et al, **1977).**

As experience with NHL has accumulated, deficiencies in the Rappaport classification have become apparent. First, its utility is limited in childhood when nodular lymphomas are extremely uncommon and both well-differentiated lymphocytic and mixed lymphomas are virtually unknown (Murphy, **1978).** Second, it does not provide for several recently recognized clinicopathologic subtypes, such as (a) lymphoblastic lymphoma, a variety of NPDL that is cytologically identical to acute lymphoblastic leukemia, predominantly affects adolescent males, has a high rate of leukemic transformation, and (unlike most NHL) seems to be of T-lymphocyte origin (see below) (Jaffe and Berard, 1978) and (b) immunoblastic sarcoma, a variety of DHL, which is frequently associated with prior immune dysfunction in the host (Lichtenstein et al, **1979).** Third, it has become apparent that the malignant cell in the histiocytic lymphomas is derived from lymphocyte precursors, and that NHL of truly histiocytic origin is quite uncommon (Mann et al, **1979).** A possible exception may be found in gastrointestinal NHL, in which one-third of a recent series appeared to be malignancies of histiocytes (Isaacson et al, **1979).**

Finally, and most important, the Rappaport classification scheme does not take into account the immunologic advances that now permit finer classification of lymphoid cells according to their origin and function. As summarized by Jaffe in a recent symposium (Berard et al, **1976)** and discussed in detail by Mann et al **(1979),** there are three classes of immunocompetent cells identifiable by characteristic surface membrane markers: T-lymphocytes (of thymic origin), responsible primarily for cellular immunity; B-lymphocytes (of "bursal-equivalent" origin), which differentiate into antibody-producing plasma cells, effectors of humoral immunity; and mononuclear phagocytic cells, which have many immunoregulatory functions.

These three classes of cells have specific anatomic locations within the normal lymph node and provide a conceptual framework for understanding the distribution and origin of various types of NHL (see Fig. **1).** Thus, nodular lymphomas represent the neoplastic counterpart of the normal lymphoid follicle; well-

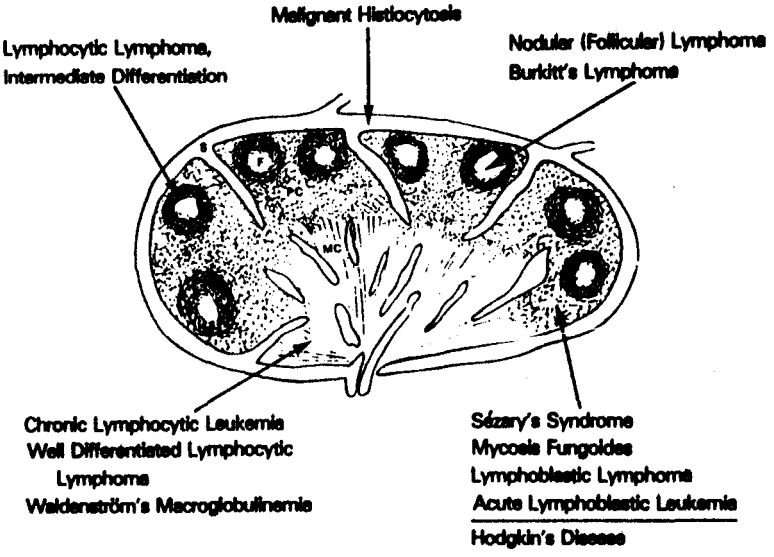

Figure 1. Schematic diagram of a lymph node, illustrating anatomic and functional compartments. The malignancies of the lymphoreticular system are conceptually and functionally related to the above compartments. S. sinuses; *F*, follicles; *PC*, paracortex; *MC*, medullary cords. (From Mann et al, 1979.)

differentiated lymphocytic lymphomas, the counterpart of the medullary cord B-lymphocyte; malignant histiocytosis, the true lymphoma of histiocytes, and so on. Most forms of NHL are B-cell neoplasms (see Table 1). In a recent review of 425 NHL cases, 68 per cent were of B-cell origin, and 19 per cent of T-cell origin; 13 per cent had no surface markers; and 1 case was a true histiocytic lymphoma (Lukes et al, 1978). These observations have led to new classifications (for a summary, see Dorfman et al, 1981), which have not yet gained widespread popularity but which will undoubtedly lead to modification, if not replacement, of the Rappaport system.

It should be noted that all lymphadenopathy is not malignant lymphoma. The differential diagnosis of enlarged lymph nodes is extensive, including nonspecific reactive and inflammatory processes, viral and other infections, drug reactions, and rheumatoid disease (Carr et al, 1978). Even under the microscope, some of these processes can be difficult to distinguish from true neoplasia, as evidenced by the so-called "pseudolymphomas" seen in various organs, particularly the lung (Saltzstein, 1963) and stomach (Faris and Saltzstein, 1964). Thus, histologic verification of NHL by experienced pathologists would add credibility to epidemiologic research into these tumors.

Unfortunately, nearly all epidemiologic studies of NHL to date have used the historic nomenclature. In addition, they have included varying combinations of tumors, not only LSA, RCS, and GFL, but also leukemia, Hodgkin's disease, multiple myeloma, and other lymphoproliferative malignancies. Wherever possible in this review, the specific entities included in each study will be identified. When using the International Classification of Diseases, the term NHL refers to those entities now classified under codes 200 'and 202 of the 8th revision. "Histiocytic" lymphoma is shown with quotation marks as a reminder that the cell of origin is lymphoid, rather than truly histiocytic; "lymphoma" is used when multiple lymphoproliferative tumor types are combined.

Demography

International Patterns'

In view of variations in diagnostic practices, international comparisons should be interpreted with caution. LSA is generally more common than RCS, with males having higher rates than females for both types. The reported age-standardized (world population) incidence rates for RCS in males range from 0.1 per 100,000 in India to 5.9 in New York State, while the rates for LSA in females range from 0.3 per 100,000 in Germany to 5.5 in Nigeria (Waterhouse et al, 1976). There has been an upward trend in incidence since 1960, especially in Western countries (Stukonis, 1978). The increase ranged from one- to twofold in most countries, and primarily affected older age groups. A surprising increase of 250 per cent was noted for Singapore Chinese. A few registries, such as japan and Cali, Colombia, reported decreases in incidence during this time period.

United States Incidence

NHL is relatively uncommon in the United States, with about 15,000 new cases estimated each year (2 per cent of all cancers) (Anonymous, 1979). Based on the Third National Cancer Survey (1969–1971), the average annual age-adjusted incidence rates were 5.8 per 100,000 for white males, 4.1 for white females and black males, and 2.6 for black females. Overall, the male to female ratio is 1.4:1 (Cutler and Young, 1975). Age-specific incidence rates for United States whites reveal a pre-adolescent peak followed by a late teenage nadir; rates then rise logarithmically with increasing age (Fig. 2). Between 1960 and 1972, incidence rates in various United States registries also show an upward trend, with residents of Connecticut (107 per cent increase) and native Hawaiians (120 per cent increase) having the largest increments (Stukonis, 1978).

United States Mortality

Based on United States mortality data (1950–1969), the average annual age-adjusted rates were 4.9 per 100,000 for white males, 3.2 for white females, 3.3 for nonwhite males, and 1.9 for nonwhite females (Mason and McKay, 1974). The rates in all groups increased progressively with age, though a slight decline was seen in the last age group (Fig. 3). In general, the rates for white males were highest at all ages, followed by rates for nonwhite males before age 65 and white females after age 65. Mortality from NHL in childhood differs by cell type. The rates for LSA rise rapidly between ages 0 and 4 years and reach a plateau from 5 to 18 years, while the rates for RCS rise gradually over childhood. LSA occurs three times more frequently than does RCS prior to age 15 (Grundy et al, 1973).

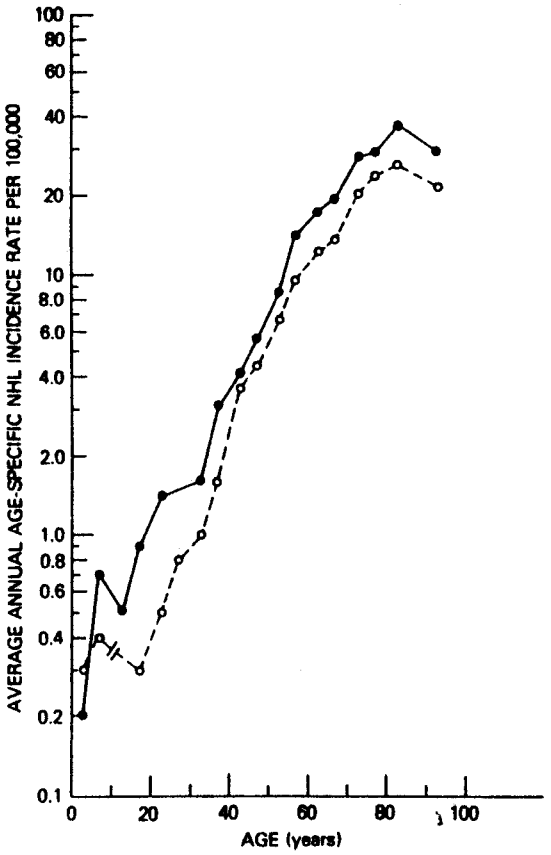

Figure 2. Average annual age-specific incidence rates for NHL per 100,000 population among white males (closed circles) and white females (open circles) in the United States. (From the Third National Cancer Survey [Cutler and Young, 1975].)

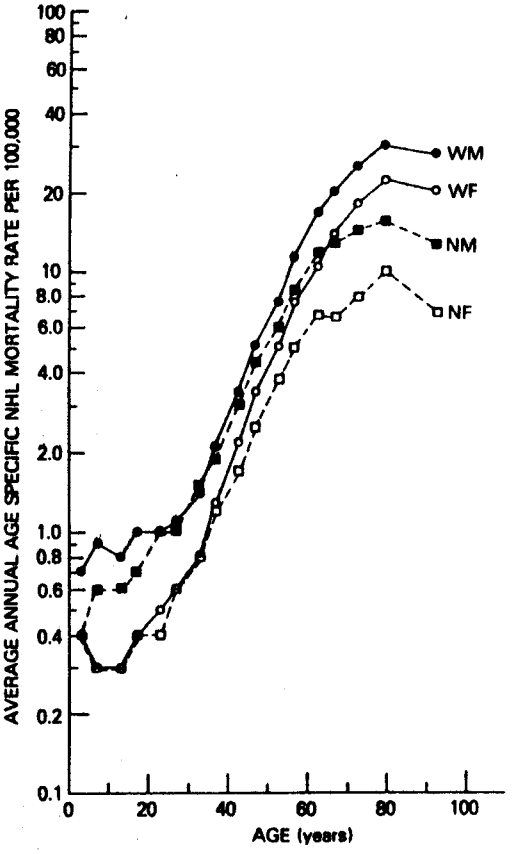

Figure 3. Average annual age-specific mortality rates for NHL per 100,000 population among white males (*WM*, closed circles), white females (*WF*, open circles), nonwhite males (*NM*, closed squares), and nonwhite females (NF, open squares) In the United States: 1950–1975. (From Mason and McKay. 1974.)

TABLE 2. Average Annual Age-Adjusted Mortality Rates for NHL Per 100,000 Population by Age Group, Race, Sex, and Time, for the United States

Age	*Race/Sex*[a]	*1950–1954*	*1955–1959*	*1960–1964*	*1965–1969*	*1970–1975*[b]
0–19	WM	8.2	9.4	9.4	8.1	6.6
	WF	4.6	4.4	4.0	3.6	2.6
	NM	5.3	0.2	6.7	5.4	4.9
	NF	3.2	3.7	3.8	3.4	2.6
20–54	WM	2.6	2.9	3.1	**3.3**	***3.0***
	WF	1.6	**1.8**	2.0	2.1	1.9
	NM	2.3	2.8	2.8	2.6	2.6
	NF	1.3	1.5	1.5	1.7	1.5
55+	WM	13.7	18.7	18.8	21.0	23.2
	WF	9.4	11.5	13.3	15.1	16.3
	NM	7.1	10.8	11.3	13.6	14.8
	NF	4.1	5.9	6.4	7.4	8.6
All ages	WM	3.9	4.6	5.1	5.6	5.7
	WF	2.6	***3.0***	3.4	3.8	3.8
	NM	2.5	**3.9**	3.5	3.8	4.0
	NF	1.4	**1.8**	2.0	2.2	2.3

[a] **WM**: white male; WF: white female; NM: nonwhite male; **NF**: nonwhite female.
[b] **Excluding** 1972 (data not available).

Mortality trends in the United States (1950–1975) are shown in Table 2. Among persons under 20 years of age, mortality peaked in all groups except white females during 1960–1964, and then declined 2 per cent per year through 1975 (Mason, unpubiished data). In contrast, mortality among older adults increased by 2 per cent per year over this 25-year period, with rates rising somewhat faster in nonwhites than whites. The rate of increase in NHL mortality in white females is second only to lung cancer, and in white males it is third, following lung and pancreatic cancers (Cantor and Fraumeni, 1980). Most of the increase seems due to RCS rather than LSA (Burbank, 1971). Similar increases in NHL mortality have been reported in Europe (Stalsberg, 1973), Israel (Abramson and Avitzour, 1975), and the United Kingdom (Smith, 1978a), although the declining rates in young people have not been seen. The upward trend may be partly related to improvements in diagnosis and classification, but parallel increases in incidence data suggest the operation of environmental factors that remain to be identified. The declining mortality among young people in the United States can be traced in part to substantial improvements in therapy and survival for childhood NHL (Murphy, 1978).

Mortality from NHL shows a positive gradient with socioeconomic status and urban residence (Registrar General, 1958; Guralnick, 1963; Hoover et al, 1975). A county by county survey in the United States revealed elevated mortality rates in coastal California and the Midwest and lower than average rates in the Southeast (Cantor and Fraumeni, 1980). This pattern may reflect socioeconomic factors, particularly social class, urbanization, and ethnicity, with higher rates seen in counties with many residents of Russian (mainly Jewish) or Greek ancestry (Cantor and Fraumeni, 1980). It is noteworthy that the risk of NHL is greater among Israelis of Jewish background than other groups in Israel (Waterhouse et al, 1976).

Host *Factors*

Familial Aggregation

Although empirical risk studies have not been done, a literature review uncovered 38 multiple-case families with NHL, excluding lymphohistiocytosis (Ladish et al, 1978) ahd its variants (Table 3). There was a total of 111 family members with NHL, an average of 3 cases per family. Nearly 80 per cent were sib pairs, either sibs alone (63 per cent), including one pair of monozygous twins (Zachau-Christiansen and Rasmussen, 1963), or sibs plus other relatives (13 per cent). The male/female ratio for familial cases was 1.8 (versus 1.4 in the general population), while the average age at diagnosis was 23.5 years (versus 42.3 in the general population). About one-half of the familial cases with specified origins were extranodal (44 cases), primarily involving the gastrointestinal tract (26 cases). The distal small bowel and cecum were most often affected. Cell types were difficult to evaluate owing to varying diagnostic criteria. One study of several NHL-prone families classified all cases using the Rappaport system (Greene and Miller, 1978), but found no histologic subtype predominating overall or within particular families. In the 38 high-risk families, 11 were found after testing to have evidence of heritable immune dysfunction, but only 5 could be classified as having a primary immunodeficiency syndrome (ataxia telangiectasia in 2, common variable immunodeficiency in 2, and Bruton type in 1).

Two general types of high-risk families were seen. One group consisted of pre-adolescent male sibships with extra-nodal NHL, primarily of the gastrointestinal tract. These occurrences may be related to the rare X-linked recessive lymphoproliferative syndrome described by Purtilo and coworkers (1975, 1977, 1978). These tumors cover a spectrum of B-lymphocyte disorders, including NHL of the immunoblastic sarcoma type and Burkitt's lymphoma, and mononucleosis-like states. Because of an inborn immunodeficiency state, the affected individuals are unable to regulate lymphoid responses to Epstein-Barr virus (EBV) infection. The second group of families consisted of adult sibs, mainly females, with nodal NHL. The susceptibility of women may be related to changes in hormonal modulation of lymphoid function with increasing age, which has been observed in some animal systems (Raveche et al, 1976).

Primary Immunodeficiency Syndromes

Gatti and Good (1971) surveyed the literature on primary immunodeficiency disorders and estimated that these patients were 10,000 times more likely to develop cancer, especially of the lymphoreticular system, than persons of similar age in the general population. Although reliable risk estimates for lymphoma or other cancers are not available, associations have been clari-

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Potolsky et al	1971	13	F	67	proband	marrow	CLL	relatives had depressed immunoglobulins, cutaneous anergy, and impaired in vitro lymphocyte response to PHA
			F	45	sister	nodal	LL	
			F	70	sister	nodal	LSA	
			F	54	sister	marrow	CLL	
			M	47	brother	marrow	RCS	
			F	50	sister	nodal	RCS	
Barth et al	1972	14	M	0.1	proband	nodal	MH	members of "familial reticuloendotheliosis" kindred previously reported by Omenn (1965)
			F	0.1	?	nodal	MH	
Banishemi et al	1973	15	F	22	proband	small bowel	LSA	distant cousin of proband: leukemia, NOS
			M	28	brother	jejunum	RCS	
		16	M	6	proband	tonsil	LSA	
			M	18	brother	ileum	RCS	
		17	M	10	proband	abdomen	LSA	
			M	6	brother	ileum	RCS	
Brouet et al	1973	18	F	19	proband	?	RCS	both had common variable immunodeficiency
			F	11	sister	?	RCS	
Clemençon	1973	19	M	47	proband	nodal	LLSA	2 patients had sex-linked agammaglobulinemia (Bruton type); 2 others had hemophilia A
			M	2	grandson	brain	LSA	
			M	4	grandson	nodal	LLSA	
			M	21	nephew	brain	RCS	
			M	5	nephew	brain	LLSA	
Hobbs	1973	20	M	?	proband	?	ML	
			M	?	brother	?	ML	
			M	?	brother	?	ML	
Pevzner and Leef	1973	21	M	4	proband	abdomen	NHL	very undifferentiated tumors
			M	4	brother	ileum	NHL	
Buehler et al	1975	22	M	10	proband	?	LSA	large, inbred kindred with 7 cases of Hodgkin's disease, other cancers, and common variable immunodeficiency
			M	47	cousin	?	LSA	
			F	64	cousin	?	LSA	
Camino	1975	23	M	34	proband	jejunum	DHL	
			M	3	son	colon	DHL	
Fraumeni et al	1975	24	M	70	proband	marrow	W	other cancers: Hodgkin's disease (nephew), pulmonary adenocarcinoma (niece), acute lymphocytic leukemia (grand-nephew); relatives had impaired in vitro lymphocyte response to PHA and both polyclonal and monoclonal increases in immunoglobulins
			M	75	brother	nodal	WDLL	
			M	54	brother	nodal	DPDL	
			M	50	brother	nodal	DHL	
			F	68	sister	nodal	DHL	

Table continued on following page

TABLE 3. Families With Multiple Cases of Non-Hodgkin's Lymphoma: Literature Review

Study	Year	No.	Sex	Age	Relation to Proband	Primary Site	Histology[a]	Comments[b]
Maldonado and Levin	1961	1	M	22	proband	mediastinum	LLSA	parents were first cousins
			M	15	brother	mediastinum	LLSA	
Smith	1961	2	[illegible]	3	proband	ileocecum	RCS	
			[illegible]	3	brother	ileocecum	RCS	
Zachau-Christiansen and Rasmussen	1963	3	F	0.9	proband	nodal	RCS	monozygotic twins;
			F	0.9	twin sister	nodal	RCS	brother reported in follow-up paper (Zachau-Christiansen and Christensen, 1966)
			M	0.8	brother	nodal	RCS	
Podgorski and Borowiczowa	1965	4	M	11	proband	mediastinum	LSA	
			F	9	sister	mediastinum	LSA	
Castaigne et al	1966	5	[illegible]	14	proband	?	LSA	both sibs had ataxia telangiectasia
			[illegible]	10	brother	?	RCS	
Rigby and Papenfuss	1966	6	M	3	proband	thymus	WDLL	mother had carcinoma of cervix;
			F	13	sister	thymus	?	cousin had Ewing's sarcoma;
			M.	3	brother	thymus	LLSA	"coeliac syndrome"
Kajii et al	1968	7	M	65	proband	nodal	RCS	previous basal cell carcinoma (skin)
			F	65	mother	nodal	?	
			M	50	brother	nodal	?	
			F	50	niece	?	?	
			M	51	brother	nodal	RCS	
			M	63	brother	nodal	RCS	
			M	64	brother	nodal	LSA	
Amman et al	1969	8	M	4	proband	?	LSA	both sibs had ataxia telangiectasia
			M	6	brother	?	LSA	
Hambleton	1969	9	M	4	proband	ileocecum	LSA	
			M	3	brother	ileocecum	LSA	
Berry	1970	10	M	3	proband	ileocecum	RCS	
			M	4	brother	ileocecum	RCS	
Freeman et al	1970	11	M	12	proband	oropharynx	LSA	low immunoglobulins; marker chromosome
			F	4	sister	abdomen	LSA	aplastic thymus; both sibs dysmorphic
Fisher et al	1971	12	M	13	proband	small bowel	LRCS	
			F	4	sister	small bowel	LRCS	

TABLE 3. Families With Multiple Cases of Non-Hodgkin's Lymphoma: Literature Review (Continued)

Study	Year	No.	Sex	Age	Relation to Proband	Primary Site	Histology[a]	Comments[b]
Purtilo et al	1975	25	M	3	proband	ileocecum	DHL	4 other family members had fatal
				9	*half-brother*	brain	DHL	lymphoproliferative syndromes
Escol a d Bix	1 6	8	F	4	proband	stomach	RCS	
			F	9	sister			*subsequent Hodgkin's disease; p
			F	4	sister	stomach		cancer
			F	8	*sister*	liver	RCS	*antecedent carcinomas of breast
			F	)	niece	esophagus	RCS	*antecedent breast cancer
			M	5	nephew	lung	RCS	*antecedent carcinomas of endom
			F		niece	stomach	RCS	*antecedent *carcinomas of lung. l*
			F		grand-niece	colon	RCS	*antecedent basal cell carcinoma
			M		great-grand-nephew	lung	RCS	*antecedent cervix cancer
Maurer et al						max. sinus	RCS	
			M	7	proband	ileum		
			M	2	nephew	ileocecum	DML	*nephew had multiple small bowel
			M	5	*brother*	*ileocecum*	DML	hypogammaglobulinemia
Law et al			M	3	brother	retroperitoneum	DML	
	8			50	proband	nodal	DPDL	
				?	cousin	nodal	DPDL	
				23	cousin	?	LSA	*subsequently developed colon ca
Mulvihill and McKeen	29			68	proband	jejunum	NHL	cases of colon and endometrial
				58	sister		RCS	*tives; unaffected relatives had bo
Purtilo	30					retroperitoneum	RCS	and cell-mediated immunity abnc
				2	proband	colon	BL	*antecedent carcinomas of colon, r
				?	brother	liver	BL	parotid
				?	?	?	IS	2 sisters with colorectal cancer; mc
				?	?	?	IS	gastric cancer
				?	?	?	IS	
				?	?	?	IS	*pulmonary plasmacytoma
							IS	*acquired hypogammaglobulinemia
								*agranulocytosis and an atrial septal
Stephens et al	1977	31	F	60	proband	marrow	CLL	
			M	58	*husband*	nodal	WDLL	bladder cancer
			M	?	son	?	NHL	
Cushing et al	1978	3	?	?				
			?	?	proband	?		
			?	?	sib	?	LLSA	all 3 were "children" with T-cell NHL;
Freedlander et a	1978	3			sib	?		associated with sti Gar
			F	51	proband		LLSA	syndrome and neu
Greene et a	1978	3	M	54	brother	ileocecum		
			F	4		rectum	DPDL	
			F	6	proband		DML	
			F	6	mother	nodal	NML	
		3	F	3	cousin	nodal	DHL	ante
			F		proband	parotid	NHL	
						nodal		

other members of sister

Stephens et al	19?7	∃1	F	60	proband	marrow	CLL	
			M	58	husband	nodal	WDLL	*bladder cancer
			M	?	son	?	NHL	
Cushing et al	19?8	3	?	?	proband	?	LLSA	all 3 were "children" with T-cell NHL;
			?	?	sib	?	LLSA	associated with stigmata of both Gardner's
			?	?	sib	?	LLSA	syndrome and neurofibromatosis
Freedlander et al	1978	∃	F	51	proband	ileocecum	DPDL	
			M	54	brother	rectum	DML	
Greene et al	1978	∞	F	43	proband	nodal	NML	
			F	65	mother	nodal	DHL	nt o de t me in∃ior□
			F	60	cousin	parotid	NHiL	
		%	F	35	proband	nodal	DHL	other cancers: skin (sister); acute
			F	30	sister	nodal	DHL	undifferentiated leukemia (cousin)
			F	67	mother	nodal	WDLL	
		36	F	49	proband	nodal	NPDL	other cancers: skin (sister);
			F	34	niece	lung	DHL	breast (sister)
			M	55	uncle	parotid	NML	*primary hepatocellular carcinoma
		37	F	55	proband	nodal	NHiL	*subsequent rectal cancer;
			F	57	sister	nodal	DML	multiple carcinomas on mother's side of family
			F	61	sister	retroperitoneum	DPDL	
		38	F	16	proband	nodal	DPDL	other cancers: bone (cousin); primary liver
			M	15	brother	nodal	DPDL	(cousin)
			M	60	cousin	nodal	WDLL	

[a]LLSA: lymphoblastic lymphosarcoma
LSA: lymphosarcoma
RCS: reticulum cell sarcoma
ML: malignant lymphoma, NOS (not otherwise spe ified)
MH: malignant histiocytosis
WDLL: well differentiated lymphocytic lymphoma
LRCS: "lymphoreticulosarcoma"
NHL: non-Hodgkin's lymphoma, NOS
DHL: diffuse histiocytic lymphoma
W: Waldenström's macroglobulinemia

CLL: chronic lymphocytic leukemia
LL: lymphocytic lymphoma
DPDL: diffuse poorly differentiated lymphocytic lymphoma
DML: diffuse mixed lymphoma
BL: Burkitt's lymphoma
IS: immunoblastic sarcoma
NML: nodular mixed lymphoma
NHiL: nodular histiocytic lymphoma
NPDL: nodular poorly differentiated lymphoma
?: data not available

[b]An asterisk indicates that comment pertains specifi ally to dj∃ e t individual.

munized populations. For example, an excess of NHL has been reported in some but not all surveys of persons immunized against tuberculosis with BCG vaccine (Skegg, 1978). BCG is considered an "immunostimulant," but its specific effects on various lymphocyte populations in man have not been evaluated. Such data would be useful in understanding possible mechanisms of lymphomagenesis.

Acquired Disorders of *Immunity*

A variety of autoimmune or rheumatoid diseases associated with defective immunity have been related to NHL, although the associations range from controversial to well-established. These diseases are generally characterized by persistent antigenic stimulation and defective regulation of lymphocyte proliferation (Steinberg and Klassen, 1977).

In 1967, Oleinick found no increased risk of NHL in patients with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE), but a more recent review of the literature suggested that untreated patients are prone to NHL (Louie and Schwartz, 1978). A population-based Finnish study indicated a 2.7-fold risk of NHL in patients with rheumatoid arthritis (Isomäki et al, 1978), but the possible effects of immunosuppressive therapy were not considered. It has been suggested that acute nonlymphocytic leukemia (rather than NHL) is the major cancer observed in RA patients treated with immunosuppressive/cytotoxic medications (Louie and Schwartz, 1978). Over 100 patients with SLE and lymphoma have been reported (Wyburn-Mason, 1979), but this relationship has not been quantitatively evaluated. Another literature review suggested a relative excess of NHL among cancer patients with dermatomyositis (Barnes, 1976), but this particular disease may be a complication rather than a precursor of NHL.

A model study of the type required to evaluate these relationships recently quantified the long-standing suspicion of an NHL excess (relative risk = 44) in patients with Sjogren's syndrome (Kassan et al, 1978). The risk was greatest in patients with an unusual degree of lymphoid reactivity, manifested by splenomegaly, lymphadenopathy, and parotid enlargement, suggesting that the NHL is a complication of the autoimmune process rather than of treatment. Immunologic mechanisms also appear responsible for the development of extranodal NHL in the thyroid of patients with Hashimoto's thyroiditis (Burke et al, 1977) and in the stomach of patients with autoimmune gastritis (Dutz, 1978).

Sarcoidosis, a granulomatous disease of unknown etiology, is associated with lymphoid hyper-reactivity, defective cellular immunity, and suppressor cell dysfunction (Goodwin et al, 1979). In a Danish follow-up study, six cases developed lymphoma: two with LSA and four with Hodgkin's disease (Brincker and Wilbek, 1974). More striking is the 100-fold excess of NHL in patients with celiac disease or gluten-sensitive enteropathy (Holmes et al, 1976). Gluten sensitivity may provide chronic antigenic stimulation as a stimulus to the DHL that typically develops in the gastrointestinal tract. A variant of celiac disease is dermatitis herpetiformis, which appears *to* share the increased risk of NHL, although based on smaller numbers (Connon et al, 1975). A number of patients presenting with primary intestinal lymphoma have underlying celiac disease or derrnatitic herpetiformis, but the manifestations are subtle and easily overlooked (Freeman et al, 1977). This suggests that celiac disease/dermatitis herpetiformis may underlie a significant fraction of the so-called "Western" variant of primary intestinal lymphoma, a disease of middle-aged males, with tumors arising in the distal small bowel or proximal large intestine (Lewin et al, 1976).

The "Mediterranean" variant of primary intestinal lymphoma is characterized by an earlier age at onset (20 to 40 years), equal sex risk, inverse correlation with social status, origin in the proximal small intestine, and a pleomorphic cellular pattern, along with diffuse plasma cell infiltration of the bowel wall and often a preneoplastic syndrome known as alpha heavy chain disease (AHCD) (WHO, 1976). In AHCD, the heavy chain proteins normally part of IgA antibody molecules are found free in the serum. The circulating alpha chains are themselves abnormal, while IgA light chains are not synthesized at all, a puzzling observation in view of the independent genetic control of these two proteins (Seligmann, 1975).

The socioeconomic patterns and geographic distribution of AHCD in the Mediterranean region and in southwest Asia have implicated environmental factors, particularly enteric pathogens, and although no one agent has been isolated consistently from these patients, complete remission of AHCD may follow antibiotic therapy (WHO, 1976). When lymphoma complicates AHCD, heavy chains are found on the surface of tumor cells, suggesting a common clonal origin for both diseases (Brouet et al,

TABLE 4. Immunodeficiency Cancer Registry Data: Cancer Cases by Disease Category'

Immunodeficiency Disease	*Total* Cancer Cases	*Lymphoma*"	Hodgkin's Disease	Other Cancer
Ataxia telangiectasia	90	65	9	16
Variable Immunodeficiency	71	34	5	32
Wiskott-Aldrich syndrome	45	39	3	3
IgA deficiency	16	6	1	9
X-linked hypogamrnaglobulinemia	14	11	1	2
Severe combined immunodeficiency	12	11	1	0
IgM deficiency	8	5	1	2
Immunodeficiency/thymoma	4	2	0	2
Immunodeficiency with normal or elevated gammaglobulins	3	3	0	0
X-linked hyper-IgM	1	0	1	0
Episodic lymphopenia	1	1	0	0
Thymic hypoplasia	1	0	0	1
Transient hypogammaglobulinemiaof infancy	1	1	0	0
Total	267	178	22	67

'Modified from Spector et al (1978)
"All lymphomas other than Hodgkin's disease, including unspecified lymphomas

fied by the Immunodeficiency Cancer Registry, as summarized in Table 4 (Spector et al, 1978). Overall, there was a disproportionate number of lymphoid tumors, including NHL, acute lymphocytic leukemia, and Hodgkin's disease. Two-thirds of these NHL cases were male, 60 per cent were below age 15, and DHL was the most frequent form. NHL also has developed in 3 of the 50 known patients with intestinal lymphangiectasia, in which a lymphatic developmental anomaly results in hypogammaglobulinemia from severe enteric protein loss (Waldmann et al, 1972). The susceptibility to lymphoma appears related in some way to defective immunoregulatory processes (Waldmann et al, 1972), although patients with these diseases are prone to recurrent infections, and repeated antigenic challenge may play an etiologic role as well.

Therapeutic Immunosuppression

In two large series of renal transplant recipients, NHL developed 40 to 100 times more often than expected (Fraumeni and Hoover, 1977; Kinlen et al, 1979). These tumors, predominantly RCS, are characterized by a predilection for the central nervous system and an explosive onset following transplantation, with the lymphoma excess clearly evident within the first post-transplant year. This short latent period suggests the involvement of oncogenic viruses, particularly since transplant patients are prone to herpesvirus and other infections. Virus-induced lymphoproliferation may be activated and promoted through graft-versus-host allogeneic stimulation and immunosuppressive agents (Schwartz, *1972;* Matas et al, 1975). The role of viruses is also suggested by the polyclonal proliferations of 6-lymphocytes in NHL following transplantation, rather than the monoclonal pattern usually seen in lymphoma (Hertel et al, 1977), and by a recent case report of a transplant patient developing a fatal lymphoproliferative disorder following an EBV infection (Holahan et al, 1979).

An increased risk of NHL has also been reported following cardiac transplantation, with tumors occurring in 6 of 95 long-term survivors. The excess was confined to patients under 40 years of age with idiopathic cardiomyopathy (Anderson et al, 1978). The risk of NHL was even higher than in renal transplant recipients, perhaps because primary cardiomyopathy is associated with a defect in mononuclear suppressor cell activity. Suppressor cells play an important role in regulating the proliferation of lymphocytes and may be central to the development of NHL, both in animal models and man (Steinberg and Klassen, 1977).

Kinlen et al (1979) described an excess of NHL in patients receiving immunosuppressive therapy for nonmalignant diseases other than transplantation. The risk observed was substantially below that of transplant recipients, suggesting that allogeneic stimulation from the graft plays a promoting role. Clarification of mechanisms may come from surveys of specially im-

1977). Possible environmental factors include gastrointestinal injury induced by enterotoxins (e.g., Vibrio *cholerae,* which has the same geographic distribution as AHCD) (Al-Saleem, 1978) and persistent thymus-dependent immune dysfunction following early infantile enteritis (Dutz, 1978). Whatever the environmental stimulus, Mediterranean lymphoma appears to evolve from the apparently benign, reversible hyperplastic infiltrate of AHCD (Seligmann, 1977).

Immunoblastic lymphadenopathy (IL) is another apparently benign lymphoproliferative disorder that often progresses to NHL (Frizzera et al, 1974). In the largest series of patients reported, 48 had only immunoblastic lymphadenopathy at initial biopsy; 13 patients had follow-up biopsies, of whom 6 developed frank immunoblastic sarcoma (IS) (Nathwani et al, 1978b). Another 36 patients had focal changes of IS in their initial biopsies, with 10 subsequently evolving into frank IS. A disorder of B-lymphocytes, IL is frequently associated with a history of drug allergy, autoimmune disease, and/or dysproteinemia, and seems to occupy an intermediate position between the benign ("reactive") lymphoid hyperplasias and true immunoblastic sarcoma. It shares many features with graft-versus-host disease (Frizzera et al, 1974), which in animals predisposes to NHL, and niay represent yet another disorder in which suppressor cell regulation of B-cell proliferation is defective (Kosmidis et al, 1978). An excess of NHL has been suggested in other benign lymphoproliferative conditions, which are not well characterized, including nontropical splenomegaly (Dacie et al, 1978) and lymphomatoid granulomatosis (Katzenstein et al, 1979).

Associated Neoplasms

An excess risk of skin cancer has been reported in patients with NHL (Berg, 1967). Immunologic factors may be involved, since melanoma and squamous cell cancers of skin occur excessively, along with NHL, in renal transplant recipients (Hoover and Fraumeni, 1973; Kinlen et al, 1979). An excess of lung cancer was described recently in NHL (Libshitz et al, 1978) and in chronic lymphocytic leukemia (Greene et al, 1978). Case reports have suggested an association with colorectal cancer (Cornes, 1960; Barron and Localio, 1976), particularly in the context of familial aggregation (Law et al, 1977; Mulvihill and McKeen, 1977; Cheng et al, 1979), but risks have not been increased in follow-up studies. Since colorectal cancer is quite common, these double primary neoplasms may represent fortuitous associations.

A leukemic phase has long been recognized in some NHL cases, occurring in over 7 per cent of one large series (Rosenberg, 1961); leukemic transformation is more common in children than adults, and more typical of LSA (12.6 per cent) than RCS (2.4 per cent). This phenomenon was seen in 14 per cent of 214 consecutive patients, with 12 per cent nodular and 7 per cent diffuse NHL so affected (Come et al, 1980). Leukemic transformation of lymphoid cells is considered a part of the natural history of NHL ather than a true second malignancy.

In contrast, a 37-fold excess risk of acute nonlymphocytic leukemia (ANLL) has been reported for NHL (Zarrabi et al, 1979). Most such ANLL cases seem to result from alkylating agents or radiation therapy (Casciato and Scott, 1979), despite some case reports of ANLL in untreated patients with NHL (Lonnqvist and Lockner, 1979). An association once reported between NHL and chronic myelogenous leukemia now seems to be spurious, since the "lymphomas" were actually an extramedullary blast phase of the leukemia (Josephet al, 1968).

Genetic Markers

In contrast to Hodgkin's disease and acute leukemia, there have been limited studies of the HLA phenotype in NHL. Reports based on small numbers of cases have implicated various B-locus antigens, including B5, B7, B12, and B13 (Morris and Forbes, 1971; Jeannetand Magnin, 1972; Rege et al, 1972; Miller, 1974). An excess of the haplotype A9-B5 has also been suggested (Terasaki and Mickey, 1975). Given the evidence for immunologic determinants in NHL, and the possible association of immunoregulatory genes with the major histocompatibility complex in man, this would seem a fruitful area for additional study, particularly if Dr-locus and B-cell alloantigens are determined.

NHL has a diploid modal chromosome number, in contrast to HD, which usually shows hyperploidy (Rowley, 1978). Following the introduction of banding techniques and the discovery that Burkitt's lymphoma involves a specific translocation of a segment from the long arm of chromosome 8 to the long arm of chromosome 14, it was soon recognized that at least half of the patients with NHL also have abnormalities of chromosome 14 (Fukuhara and Rowley, 1978; Mark et al, 1978). Unlike Burkitt's lymphoma, in NHL no single chromosome has been regularly implicated as the donor of

the material found on chromosome 14. The 14q+ abnormality is more common in PDL (poorly differentiated lymphocytic lymphoma) than in DHL, and is found in NHL of T-cell origin as well (Rowley, 1980). It is noteworthy that a report of familial NHL showed a marker chromosome in Group C during the pre-banding era (Kajii et al, 1968) and that chromosome 14 abnormalities have been described in ataxia telangiectasia (AT), which predisposes to NHL (McCaw et al, 1975). The role of viruses was suggested by a recent study of AT lymphoid cells that developed an 8;14 translocation identical to that seen in Burkitt's lymphoma following in vitro infection with EBV (Jeanet al, 1979), a phenomenon not observed following EBV infection of lymphocytes from normal persons. It is clear that there are nonrandom abnormalities of chromosome 14 in various lymphomatous disorders, including NHL, perhaps due to instability in the distal segment of this chromosome. These cytogenetic abnormalities may confer a proliferative advantage on the altered lyniphocytes, thus increasing the likelihood of developing lymphoma (McCaw et al, 1975).

Environmental Factors

Radiation

Although ionizing radiation can induce lymphomas in various animal systems (Loutit and Carr, 1978), the evidence in man is less persuasive. A proportionate mortality survey of radiologists in the United States indicated a nonsignificant excess of lymphoma (Lewis, 1963), while similar surveys in the United Kingdom were entirely negative (Court-Brown and Doll, 1958). Recent follow-up studies of radiologists in North America revealed a "lymphoma" excess that was due to multiple myeloma (Matanoski et al, 1975). However, NHL was among the cancers occurring excessively in patients irradiated for ankylosing spondylitis (Court-Brown and Doll, 1965).

Best documented is the small but significant excess of NHL among Japanese survivors of the atoniic bomb (Nishiyama et al, 1973; Beebe et al, 1978). The elevated risk was found in both sexes and was most pronounced in Hiroshima survivors, persons under 25 years of age at exposure, and persons exposed to more than 100 rads. The excess risk from NHL did not appear until 14 to 16 years after exposure, and was calculated as 0.18 deaths per million person-year-rads of observation. These findings are consistent with preliminary reports of NHL among uranium millers (Archer el al, 1973), among patients therapeutically irradiated for ovarian cancer (Reimer et al, 1978), and perhaps among children given thymic irradiation in childhood (Bisbee and Thoeny, 1975). On the other hand, several irradiated groups have experienced no lymphoma excess (BEIR, 1979). Thus, it would seem that radiation can induce NHL only after relatively heavy exposures, i e., over 100 rads. Immunologic mechanisms niay be involved, in view of the radiation sensitivity of suppressor T-cells (Broder et al, 1978), depletion of which could permit unregulated lymphocyte proliferation to evolve into lymphoma. It is also possible that radiation may activate endogenous oncogenic viruses (Upton, 1976).

Drugs

A variety of medications may produce a lymphadenopathy that histologic ally resembles but fails to meet the diagnostic criteria for lyniphoma (Schen, 1964). Best studied is the so-called "pseudolymphoma" seen in patients taking the anticonvulsant agent phenytoin ([Ii-lantin) (Gams et al, 1968). In the form of a hypersensitivity reaction, the lymphadenopathy typically resolves when the drug is discontinued. This syndrome has some features of immunoblastic lymphadenopathy (Matzner and Polliack, 1978) and sometimes progresses to malignant lymphoma (Harrington et al, 1962). A small excess of phenytoin usage has been reported in surveys of NHL, in which there was no evidence of an intermediate stage (Hyman and Sommers, 1966; Li et al, 1975). However, follow-up of a large Danish series of epilepsy patients indicated no lymphoma excess (Clemmesen, 1974). Although phenytoin is carcinogenic in animals (IARC, 1977) and immunosuppressive in man (Charlesworth, 1977), the available evidence suggests that the risk of lymphoma is increased only slightly, if at all.

Another agent that can produce lymphadenopathy and a hypersensitivity syndrome is dapsone (DeGowin, 1967), a sulfone used in the treatment of leprosy and malaria, and recently found to cause lymphomas and other cancers in laboratory animals (NCI, 1977). Most reports of NHL with the predisposing syndrome dermatitis herpetiformis have been in paticnts receiving dapsone (Freeman et al, 1977). Further studies are needed, particularly since the drug has been widely used by the military for malaria prophylaxis.

An excess of NHL was recently reported in a series of Hodgkin's disease patients, perhaps

TABLE 5. Reported Associations Between Occupation and Lymphomagenesis: General Surveys

Study	Year	Occupation Group[a]	No.	Subsequent Cancer TYPE[b]	OBS.[c]	EXP.[d]	O/E[e]	P[f]	Comments
Guralnick	1963	U.S. Vital Statistics	327,271	lymphoma/leukemia					Analysis of death certificate occupational statements and cause of death for all U.S. males ages 20–64 in 1950.
		salesman/clerk	9,796	lymphoma/leukemia	135	93.8	1.4	<0.05*	
		machinist	5,935	lymphoma/leukemia	65	43.0	1.5	<0.05*	
		mine operative	8,207	lymphoma/leukemia	65	41.9	1.6	<0.05*	
		transportation/communications operator	2,107	lymphoma/leukemia	29	13.0	2.2	<0.01*	
		compositor	1,483	lymphoma/leukemia	22	12.0	1.8	<0.05*	
		electrician	2,799	lymphoma/leukemia	28	23.0	1.2	NS*	
		stationary engineer	2,549	lymphoma/leukemia	30	19.0	1.6	<0.05*	
		meat cutter	1,571	lymphoma/leukemia	20	12.0	1.7	<0.05*	
		police	2,332	lymphoma/leukemia	26	16.0	1.6	<0.05*	
		rubber worker	1,190	lymphoma/leukemia	20	13.0	1.5	= 0.05*	
		apparel worker	3,110	lymphoma/leukemia	46	22.3	2.0	<0.01*	
		insurance/real estate	7,533	lymphoma/leukemia	98	64.1	1.5	<0.01*	
		postal service	2,875	lymphoma/leukemia	39	32.0	1.2	NS*	
		construction	35,837	lymphoma/leukemia	320	278.3	1.2	<0.05*	
		shipbuilding	1,787	lymphoma/leukemia	22	13.0	1.7	<0.05*	
		trucking	7,100	lymphoma/leukemia	58	41.1	1.4	<0.05*	
		entertainment	3,770	lymphoma/leukemia	37	26.1	1.4	NS*	
		medical/health	4,629	lymphoma/leukemia	56	45.2	1.2	NS*	
Anonymous	1967	SSA Disability Claims	691,028	lymphoma/leukemia					Proportionate incidence analysis of occupations of U.S. males filing disability claims with the Social Security Administration 1959–1962
		engineer	2,748	lymphoma/leukemia	56	27.6	2.0	<0.01*	
		professional/technical worker	8,898	lymphoma/leukemia	176	90.7	1.9	<0.01*	
		barber/beautician	3,058	lymphoma/leukemia	52	28.9	1.8	<0.01*	
		compositor	1,480	lymphoma/leukemia	30	14.7	2.0	<0.01*	
		tool/die-maker	2,618	lymphoma/leukemia	42	25.3	1.7	<0.01*	
		carpenter	18,222	lymphoma/leukemia	260	174.5	1.5	<0.01*	
		mechanic	17,390	lymphoma/leukemia	258	170.9	1.5	<0.01*	
		farmer	26,206	lymphoma/leukemia	414	245.0	1.7	<0.01*	
		stationary engineer	3,566	lymphoma/leukemia	46	33.3	1.4	<0.01*	
Milham	1976	Washington State, 1950–1971	300,000						Proportionate mortality analysis of death certificate occupation statement and cause of death for males above age 20 in Washington State, 1950–1971
		accountant	2,649	LSA; RCS	20	11.8	1.7	<0.05	
		professor/instructor	383	LSA; RCS	7	1.8	3.9	<0.05	
		aluminum worker	583	LSA; RCS	7	3.2	2.2	<0.05	
		mechanic	4,263	LSA; RCS	28	21.5	1.3	NS	
		guard	1,489	LSA; RCS	12	6.0	2.0	<0.05	
		police	1,586	RCS	4	1.7	2.3	NS	
		locomotive engineer	1,535	RCS	4	1.2	3.2	NS	

		all engineers	7,343	LSA	28	19.4	1.4	<0.05	
		misc. engineers	5,955	LSA	23	15.3	1.5	<0.05	
		all electrically exposed	4,788	LSA	28	17.4	1.6	<0.05	
		elec. engineer	487	LSA	4	1.1	3.5	NS	
		electrician	3,190	LSA	13	9.2	1.4	NS	
		elec. lineman	1,111	LSA	6	3.1	1.9	NS	
		paper/pulp worker	2,077	LSA	10	5.5	1.8	<0.05	
		bookkeeper	969	LSA	6	2.4	2.6	<0.05	
		mail carrier	880	LSA	6	2.0	3.0	<0.05	
		postal clerk	835	LSA	6	2.1	2.8	<0.05	
		real estate agent	2,501	LSA	11	5.7	1.9	<0.05	
		building contractor	2,936	LSA	12	6.6	1.8	<0.05	
Goldsmith and Guidotti	1977	California, 1959–1961	?	LSA					
		civil engineer	?	LSA	7	2.7	2.6	<0.05*	
		food delivery	?	LSA	6	1.7	3.6	<0.05*	
		postal clerk	?	LSA	2	1.4	1.4	NS	
		real estate agent	?	LSA	11	7.0	1.6	NS	
		California, 1971–1972	?	LSA					
		engineer	?	LSA	28	18.7	1.5	<0.05	
		craftsman	?	LSA	131	96.0	1.4	<0.001	
		farmer	?	LSA	36	14.6	2.5	<0.05	
Williams et al	1977	TNCS, 1969–1971	7,518						Based on interviews from a sample of individuals identified in the Third National Cancer Survey; problems: (a) poor response rate (57%), (b) relatively small numbers in many occupation groups
		transportation worker (M)	267	LSA	7	1.1	6.5	<0.01	
		agriculture worker (M)	198	LSA	3	0.2	14.4	<0.05	
		manufacturing worker (M)	905	NHL	12	5.7	2.1	<0.01	
		entertainment/personal service (M)	121	OL	2	0.2	8.5	<0.05	
		entertainment/personal service (F)	529	OL	4	1.6	2.5	NS	The lymphoma excess in health workers cited in this report is due to Hodgkin's disease, not NHL
		health worker (F)	260	LSA	5	3.1	1.6	NS	
		food manufacturing (F)	87	OL	3	0.7	4.4	NS	
		insurance/finance (F)	69	NHL	3	0.9	3.3	NS	
Decouflé and Stanislawezyk	1977	Hospitalized Cancer Patients	13,949	NHL; HD					P
		locomotive engineer (M)	50	NHL; HD	8	3.8	2.1	NS	
		machinist (M)	79	NHL; HD	8	5.7	1.4	NS	
		primary metal operator (M)	77	NHL; HD	8	5.0	1.6	NS	
		hairdresser/cosmetologist (F)	41	[illegible]	5	2.2	2.3	NS	years

[a]M: male; F: female.
[b]LSA: lymphosarcoma; NHL: non-Hodgkin's lymphoma; OL: NHL other than LSA; HD: Hodgkin's disease; RCS: reticulum cell sarcoma.
[c]Obs.: observed number of lymphoma cases.
[d]Exp.: expected number of lymphoma cases.
[e]O/E: ratio of observed/expected deaths.
[f]NS: not statistically significant (i.e., $p > .05$);* indicates the calculation was made based on data provided.

resulting from the immunosuppressive properties of combination cheniotherapy and radiotherapy (Krikorian et al, 1979). The diagnostic difficulties inherent in such a study make this a controversial observation, but one that merits further investigation.

Occupational Exposures

It is difficult to evaluate occupational factors because in most studies NHL has been combined with other lymphatic and hematopoietic neoplasms. Nevertheless, six surveys of occupation and cancer were reviewed for clues (Table 5). An excess of lymphoma was reported among sales anti clerical personnel, postal workers, insurance and real estate brokers, engineers, stationary engineers, several types of electrical workers, niechanics, machinists, primary metal workers, and farmers. Some of these groups niay reflect socioeconomic or general environmental fat tors, while others may involve chemical or physical exposures in the work place. The association with electrical occupations may be relevant to the recent report that childhood lymphoma arid other cancers rnay occur excessively near high-current flow electrical fields (Wertheimer and Leper, 1979).

The findings for several occupational groups have been inconsistent. An excess of lymphomas has been reported for anesthesiologists in sonic, but not all studies (Vessey, 1978). A small excess of lymphomas has been observed among vinyl chloride workers in the United States, but not in the United Kingdom (Chiazze et al, 1977; fox and Collier, 1977). Mortality from lymphoma is excessive in chemists from three countries (Li et al, 1969; Olin, 1980; Searle, 1978), although specific exposures have not been identified. Rubber workers are prone to lymphoma, particularly in the tire building processes (Monson and Nakano, 1976). An excess has also been suggested in workers involved in petroleum refining (Tabershaw and Cooper, 1974), in the processing of arsenic-containing ore (Axelson et al, 1978), and in herbicide exposure to phenoxyacetic acid or chlorophenol (Hardell, 1979). Thus, there are preliminary indications that various occupational chemical exposures may induce NHL, but more definitive analytic studies are needed.

Infectious Agents

In various mammalian and avian species, lymphomas have been induced by C-type RNA viruses or by DNA viruses of the herpes class (Kaplan, 1974). Similar viruses can cause leukemias or sarcomas in laboratory animals (Hehlmann et al, 1973). Seroepideniiologic studies in man have shown no evidence of infection by feline and bovine leukemia viruses (Donham et al, 1977; Krakower and Aaronson, 1978), and there is no convincing evidence relating human lymphoma or other canters to pets or domestic animals (Essex and Francis, 1976). tiowever, a suggestive excess of lymphomas has been reported in mortality surveys of veterinarians (Matanoski and Lilienfeld, 1976; Blair and Hayes, 1980).

The association between EBV and Burkitt's lymphoma has stimulated efforts to link this virus with other lymphoproliferative malignanties. With the exception of the X-linked lymphoproliferative syndrome (Purtilo et al, 1978), there has been no Convincing evidence that EBV induces NHL (Carter et al, 1977) A recent report suggesting that persons who have had childhood varicella are at increased NHL risk as adults remains unconfirmed (Paffenhargcr, 1978). The role of RNA viruses was suggested by the finding that in tumor tissue 70 per cent of human NtIL cases had RNA sequentes that were honiologous to the Rauscher leukemia virus (Hehlmann et al, 1973). In addition, 6 of 13 permanent human NHL cell lines showed spontaneous C-virus particle production; one cell line contained a reverse transcriptase apparently related to those seen in viruses from subhuman prifnate and feline hosts (Kaplan et al, 1979).

In some instances, parasites may be a risk factor. Among 863 patients in Brazil undergoing splenectomy because of infestation with *Schistosoma mansoni,* 8 were found to have giant follicular lymphoma of the spleen (Andrade and Abreu, 1971). In an autopsy study from Africa, NHL was found in 6 per cent of patients with schistosomiasis, compared to 1 per cent of controls (Edington et al, 1970). As with the relationship between malaria and Burkitt's lymphoma, it has been claimed that the chronic lymphoid stimulation from Schistosoma *mansoni* may predispose to NHL. This mechanism may also apply to the excess risk of NHL reported in patients with leprosy (Rodriguez et al, 1968), although this association has not been confirmed (Kolonel and Hirohata, 1977).

The case clustering found in some studies of Hodgkin's disease and Burkitt's lymphoma has prompted similar investigations of NHL, but the evidence is insufficient to implicate person-to-person transmission (Smith, 1978b). The risk of NHL in spouse pairs does not appear to exceed the limits of chance (Stephens et al, 1977), and

no lymphomas were identified in a follow-up of persons receiving blood transfusions from donors who later developed NHL (Greenwald, 1976)

Diet

Evidence for dietary variables is scarce, although the positive gradient of NHL mortality by socioeconomic class suggests the influence of over-nutrition. An excess of lymphoma was reported in rats fed sodium nitrite (Newberne, 1979) or a diet rich in protein (Ross and Bras, 1965), and international surveys have shown a correlation between NHL mortalitv and per capita animal (bovine) protein consumption (Cunningham, 1976). It was proposed that ctironic antigenic stimulation from ingested foreign protein might explain this latter relationship

Drinking water contaminated by organic halomethane conipounds has been linked with NHL mortality, particularly in males, in several correlation studies (Cantor et al, 1978). A positive correlation has been reported with the concentration of lead and cadmium in drinking water (Berg and Burbank, 1972) and a negative correlation with the selenium content of forage crops (Shamberger et al, 1976). A role for magnesium deficiency in NHL has been suggested in laboratory studies (Bois et al, 1969).

MYCOSIS FUNGOIDES

Pathology

Mycosis fungoides (MF) is a primary cutaneous lymphoma with unique clinical and histologic features. Its onset is heralded by a nonspecific scaling dermatitis lasting months to years, which evolves into plaques and ulcerated tumors. These patients frequently develop diffuse lymphadenopathy and visceral lymphoma, with 50 per cent dying within four years of initial diagnosis (Lutzner et al, 1975). The median survival is 2.5 years from onset of skin tumors or adenopathy, and 1.5 to 2.0 years from onset of visceral disease (Safai, 1977). A leukemic variant is called Sézary's syndrome (SS), arid it is accompanied by an acute erythroderma. The malignant cells in the peripheral blood have a characteristic lobular, cerebriform morphology that resembles MF tumor cells (Mann et al, 1979). These neoplasms appear to be of T-cell origin, involving the thymus-dependent portions of the spleen and lymph nodes (see Fig. 1). Recent studies suggest that patients with MF and SS lack a population of suppressor T-cells, which normally regulate the proliferation of helper T-cells (Kermani-Arab et al, 1978), and that both MF and SS represent neoplastic proliferations of helper T-cells (Broder et al, 1976; Berger at al, 1979).

Demography

International incidence statistics for M i are unavailable because this neoplasm is generally combined with other lymphoproliferative tumors. Unpublished data from the 11 SEFR cancer registries (1973–1976) in the United States reveal the following average annual age-adjusted incidence rates: white males, 0.2×10^{5}; white females, 0.1×10^{5}; black males, 0.3×10^{5}; and black females, 0.1×10^{5} In general, MF rarely occurs before age 40, but the incidence then rises with age to reach a plateau of 0.7 cases per 100,000 in white males above age 60.

During the 25-year period 1950–1975 (excluding 1972), there were 1,948 deaths attributed to MF in the United States — 1,034 in white males, 631 in white females, 162 in nonwhite males, and 121 in nonwhite females. The rates were generally higher among males than females and among nonwhites than whites (Fig 4). Mortality rose sharply with age, peaking at ages 65 to 69 for nonwhite males and at ages 75 to 84 for white males. The average annual age-adjusted mortality rates for the total United States population during this 25-year period were as follows: white males, 0.53×10^{6}; white females, 0.28×10^{6}; nonwhite males, 0.84×10^{6}; and nonwhite females, 0.54×10^{6} (Greene et al, 1979).

Mortality rates showed an upward trend over time. For whites of both sexes and nonwhite females, the rates rose 10 to 20 per cent between 1950–1954 and 1970–1975, while for nonwhite males the rate doubled. The rates in white males were highest in the Northeast (0.61×10^{6}), in association with a strong urban gradient but no socioeconomic differential (Greene et al, 1979). Geographic clustering of MF has also been reported in Swedish men (Gip and Nilsson, 1977), a finding of uncertain significance given that multiple comparisons were made in a small number of patients.

Host Factors

Familial Tendency

Five multiple-case families with MF have been reported (Greene et al, 1979), but etiolog-

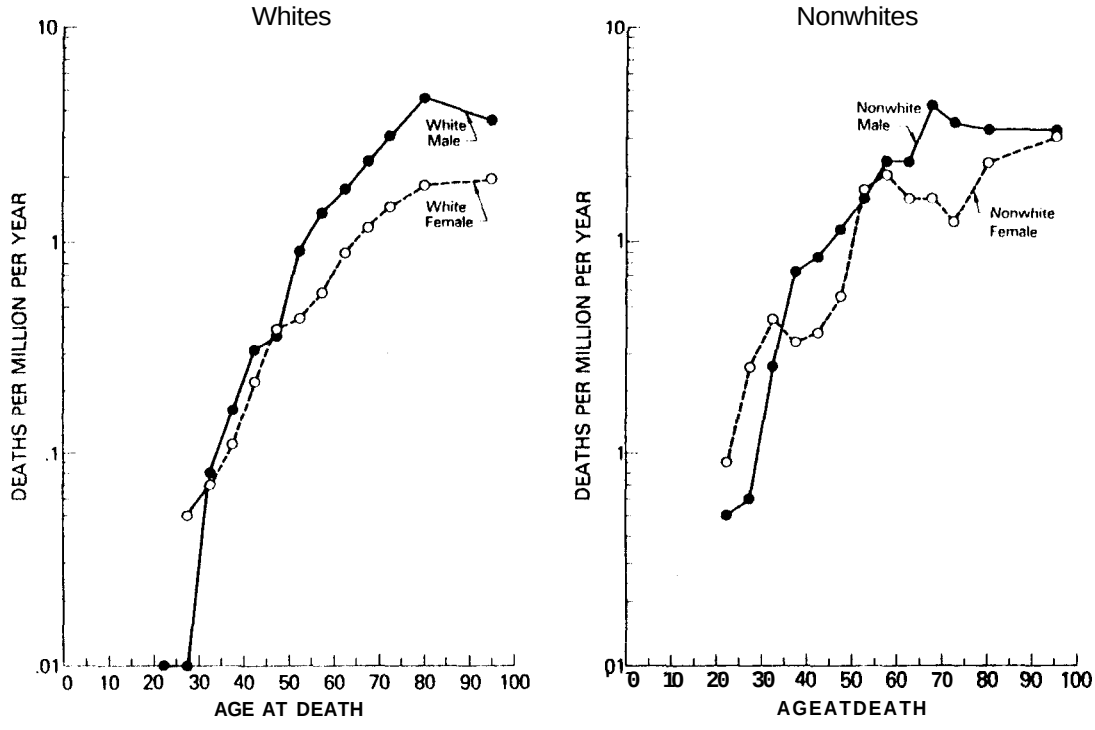


Figure 4. Average annual age-specific mortality rates for mycosis fungoides per 100,000 population by race and sex, United States, 1950–1975.

ic details are sparse. Of the four instances in which the relationship was specified, two were sib pairs and two involved a parent and child. Leukemia or lymphoma was reported in a first-degree relative of 9 of 211 MF patients (4.3 per cent) in the MF Cooperative Study Group series (Greene et al, 1979), compared to 15 of 315 patients (4.8 per cent) from Temple University (E. C. Vonderheid, E. J. VanScott, personal communication) and 3 of 59 patients (5.1 per cent) from Yale (Cohen et al, 1980). Hodgkin's disease seemed to be especially common. These data suggest that some cases of MF are part of a familial predisposition to lymphoproliferative tumors. A recent study supports this notion; the occurrence of Hodgkin's disease among the relatives of patients with MF was particularly striking (Greene et al, 1981). Genetic factors are suggested also by the excessive frequency of HLA antigens B8, Aw31, and Aw32 in MF patients (Dick et al, 1976).

Cytogenetic studies of MF and SS are rare, arid most antedate the introduction of chromosome banding. One well-studied MF patient had chromosomally normal bone marrow cells, hut abnormal lymph node cells, including a translocation to the long arm of chromosome 14 (Fukuhara et al, 1978). The finding resembles that described for other lymphoproliferative tumors (Rowley, 1978).

Associated Conditions

In the analysis of the MF Cooperative Study Group data, a number of antecedent host conditions were reported by patients with surprising frequency (Greene et al, 1979). These included histories of allergic conditions (56 per cent), fungal and viral skin infections (64 per cent), sun sensitivity (43 per cent), and possible MF precursor states (e.g., parapsoriasis, poikiloderma, and alopecia mucinosa) (16 per cent). In the absence of a control group, it is difficult to interpret these descriptive data other than as leads for future studies.

The older literature is replete with reports describing the "transformation" of MF into other malignant lymphomas. The vast majority of such cases now appear to represent the extracutaneous dissemination of MF, as part of its natural history (Rappaport and Thomas, 1974). An exception to this general rule is the recent description of three MF patients who developed clear-cut Hodgkin's disease (Chan et al, 1979). An association with nonlymphoid tumors is limited to case reports, such as those

linking MF to fibrosarcoma (Presbury et al, 1974) and acute myelomonocytic leukemia (Lofgren et al, 1978). The leukemias may have been induced by ionizing radiation and/or alkylating agents used to treat the primary disease. An excess of skin carcinomas in MF patients also seems related to therapeutic measures, including arsenicals (Edgcomb et al, 1963), radiation (Volden and Larsen, 1977), and topical nitrogen mustard (DuVivier et al, 1978).

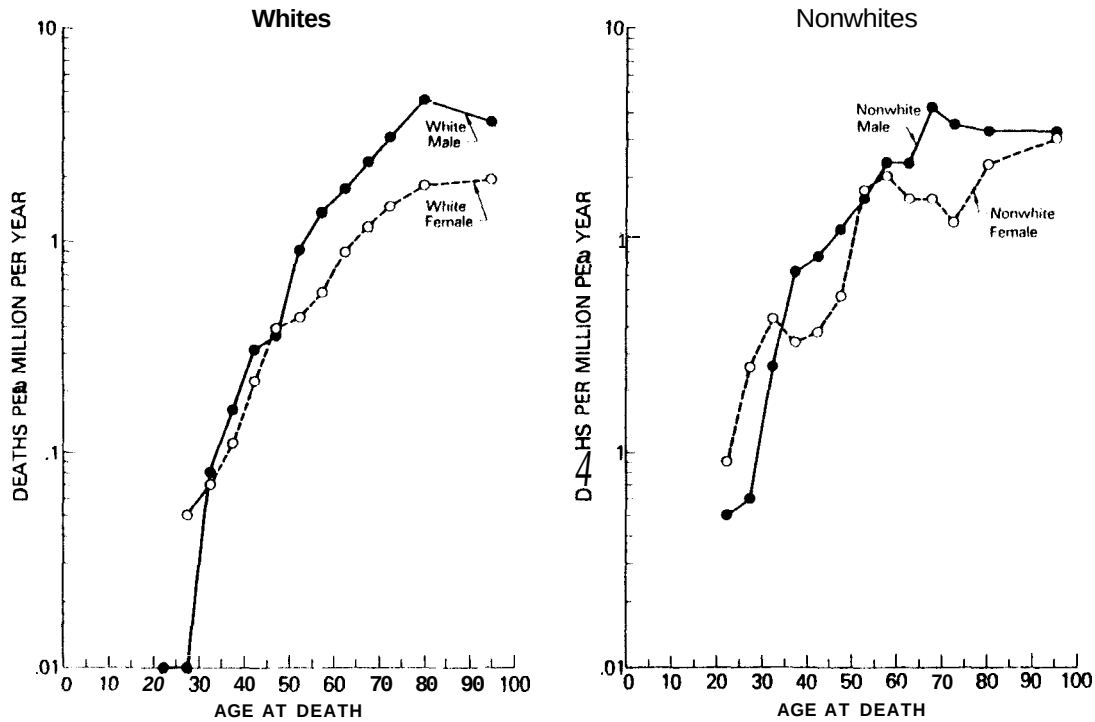
Environmental Factors

Some case reports have linked MF with exposure to arsenic, bismuth, and tar ointments, but the evidence is inconclusive (Bluefarb, 1959). Detailed interviews of the 44 patients in the NCI series revealed a history of multiple, potentially toxic environmental exposures in 43, the most frequent exposures being to chemicals (91 per cent) and drugs (86 per cent) (Fischmann et al, 1979). Exposure to hazardous chemicals was reported by 30 per cent of the patients evaluated by the MF Cooperative Study Group, with petrochemicals, metals, and solvents most frequently cited (Greene et al, 1979). Analysis of the occupational histories of these patients, and a correlation study of occupation and MF mortality in the United States suggested that the petrochemical, rubber, metals, machinery, printing, and textile industries might be associated with elevated MF mortality (Greene et al, 1979). Preliminary results from a case-control study of MF indicated a fourfold relative risk for manufacturing and construction workers (Cohen et al, 1980). Ultraviolet radiation is the major risk factcr for skin cancer, but the absence of a latitudinal gradient in MF suggests that any sunlight effect differs from that observed in skin carcinoma and melanoma (Greene et al, 1979). Of special interest is the recent isolation of a unique retrovirus from several patients with MF and SS (Poiesz et al, 1980). Further assessment of a viral etiology for this disorder will be needed to clarify this observation.

BIOLOGIC MECHANISMS

Since lymphomas arise from cells of the immune system, etiologic insights should result from a better understanding of the normal dynamics of the immune response. Like other complex biologic systems, the immune response is controlled by a network of delicately balanced positive and negative regulatory processes. For example, cells that aid the conversion of 6-lymphocytes into immunoglobulin-secreting plasma cells are classified as helper cells, while those that inhibit this transition are called suppressor cells (Broder and Waldmann, 1978). Special subsets of B-cells, T-cells, and monocyte/macrophages may mediate eittier a helper or a suppressor function for different aspects of the immune response. Lymphocytes seem to be genetically committed to mediating only one of these two regulatory functions. It is normal for lymphocytes to proliferate in response to various stimuli (e.g., antigen exposure), and suppressor cells play an important role in terminating this normal proliferative response (Steinberg and Klassen, 1977). Immune regulation may be impaired by genetic or environmental factors, leading to excessive proliferation of that subset of cells normally controlled by the injured component. A critical role may be played by immunoregulatory genes that are found partly within or near the major histocompatibility complex determining the HLA phenotype.

With this background, the various lymphoma-prone states begin to form a pattern. NHL tends to develop after prolonged antigenic stimulus to lymphoproliferation, after loss of normal regulation (inhibition) of lymphocyte proliferation, or especially after both processes. Experimental data in mice support this formulation (Krueger et al, 1971). In the organ transplant setting, the host is simultaneously subjected *to* persistent antigenic challenge from the allograft and to therapeutic immunosuppression to prevent graft rejection. In cardiomyopathy patients, who have an antecedent suppressor cell abnormality, the risk of NHL after cardiac transplantation appears to be even greater than in renal transplant recipients, who have no primary immune defect. The presence of a graft is clearly not required for NHL development, since nontransplant patients with connective tissue diseases treated with immunosuppressive drugs are at increased risk, although not nearly as high a risk as in transplant recipients (Kinlen et al, 1979). A source for chronic antigenic stimulation exists in the primary immunodeficiency disorders (e.g., recurrent infection), rheumatoid disease (autoimmunity), celiac disease (gluten sensitivity), immunohlastic lymphadenopathy (drug allergy, autoimmunity), chronic infections (schistosomiasis, leprosy), and possibly certain occupational exposures. Suppressor cell abnormalities have been reported in primary cardiomyopathy, certain rheumatoid diseases,



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and sarcoidosis and may exist in therapeutic immunosuppression as well.

Viruses can be incorporated into this model, since latent oncogenic viruses in mammals may be activated by various types of immune dysfunction, particularly graft-versus-host disease. Schwartz (1972) suggested that viral information present in lymphocytes, expression of which is normally inhibited, may be triggered as lymphocytes proliferate in response to an antigenic challenge or to a loss of regulatory control. Another mechanism for viral induction is radiation exposure, although more recent data suggest that the viruses seen in that experimental setting are not of etiologic significance (Ihle, 1978). Nonetheless, the animal models for viral lymphoma, the various types of viral information in human lymphoma tissue, and the possible role of viruses in transplant-related lymphomas (Holahan et al, 1979) underscore the importance of this hypothesis.

Immunogenetic factors in NHL are illustrated by the primary immunodeficiency disorders and lymphoma-prone families, including the X-linked lymphoproliferative syndrome. The abnormalities in chromosome 14 that characterize various lymphoproliferative neoplasms may confer a proliferative advantage on affected lymphocytes. Ionizing radiation and chemicals may produce a selective injury to suppressor cells. Thus, the proposed mechanisms for inducing NHL intertwine, and sharp distinctions are difficult to draw.

Mycosis fungoides may also fit into this model, since its pathogenesis has been linked to epidermal Langerhans' cells (Rowden and Lewis, 1976), which play a role in the primary immune response to external contact allergens (Silberberg-Sinakin et al, 1976). Langerhans' cells modulate the response of specific T-lymphocytes to various foreign antigens; persistence of these antigens in the skin may be a source of chronic antigenic stimulation. The influence of environmental agents in MF is supported by the affinity of Langerhans' cells for such contact sensitizers as heavy metals, various aldehydes, and amines (Shelley and Juhlin, 1976).

RECOMMENDATIONS

It remains to be seen whether or not the clinical and pathologic diversity of NHL reflects major etiologic heterogeneity. In the meantime, whenever possible, epidemiologic studies should employ a contemporary pathology scheme to relate etiologic hypotheses to specific morphologic entities. At a minimum, NHL must be considered separately from the other lymphoproliferative malignancies. There are now many etiologic leads to NHL that can be tested by analytic studies with sufficient sample size.

NHL accounts for only a small fraction of all cancers, but is important beyond its frequency as a model for new therapeutic regimens and for improved understanding of the immune response and carcinogenic mechanisms. Recent advances in immunology should lead to rapid progress in the delineation of pathogenic mechanisms in lymphoma. The immunologist and epidemiologist should join forces to clarify the risk of NHL and other cancers in various disorders with defective immunity and to determine the immunoregulatory abnormalities found in these high-risk states. As specific host factors and environmental exposures are linked to NHL, it will be important to study their effects on the immune response, since the evidence to date points to disturbances in immune regulation as precursors to lymphoma.

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