

# The New England Journal of Medicine

©Copyright, 1995, by the Massachusetts Medical Society

Volume 332

FEBRUARY 16, 1995

Number 7

## CONCORDANCE FOR HODGKIN'S DISEASE IN IDENTICAL TWINS SUGGESTING GENETIC SUSCEPTIBILITY TO THE YOUNG-ADULT FORM OF THE DISEASE

THOMAS M. MACK, M.D., WENDY COZEN, D.O., DARRYL K. SHIBATA, M.D., LAWRENCE M. WEISS, M.D.,  
BHARAT N. NATHWANI, M.D., ANTONIO M. HERNANDEZ, M.D., CLIVE R. TAYLOR, M.D.,  
ANN S. HAMILTON, PH.D., DENNIS M. DEAPEN, DR.P.H., AND EDWARD B. RAPPAPORT, M.P.H.

**Abstract Background.** Relatives of young adults with Hodgkin's disease are at increased risk of Hodgkin's disease, and lines of evidence implicate both inheritance and environment.

**Methods.** We have identified and followed 432 sets of twins affected by Hodgkin's disease. The number of cases of Hodgkin's disease observed before the age of 50 years in the healthy monozygotic and dizygotic twins of the patients with Hodgkin's disease was compared with the number expected from national age-specific incidence rates.

**Results.** None of the 187 pairs of dizygotic twins became concordant for Hodgkin's disease, whereas 10

of the 179 pairs of monozygotic twins did; in 5 of these pairs, the second case appeared after the original ascertainment. During the observation period, 0.1 (monozygotic) and 0.1 (dizygotic) cases in the unaffected twins were expected. Monozygotic twins of patients with Hodgkin's disease thus had a greatly increased risk (standardized incidence ratio, 99; 95 percent confidence interval, 48 to 182), whereas no increase in the risk for dizygotic twins of patients with Hodgkin's disease was observed.

**Conclusions.** Genetic susceptibility underlies Hodgkin's disease in young adulthood. (N Engl J Med 1995; 332:413-8.)

HODGKIN'S DISEASE is likely to have different causes in young adulthood and old age.<sup>1</sup> The characteristic clinical presentation and histopathological appearance suggest that in young adults the disease is initiated by an environmental exposure, possibly to an infectious agent. The age-specific incidence during young adulthood varies over time and according to place and social class, much like that of infections. Those affected have a small average number of siblings, may not have had the common childhood infections, and are likely to have a history of infectious mononucleosis.<sup>2</sup> These findings have been interpreted to suggest that Hodgkin's disease may occur as a sequela of late infection by a childhood virus, in much the same way that paralytic poliomyelitis does.<sup>3</sup> Although the particular virus cannot be specified, Epstein-Barr virus (EBV) has received special attention because of the link with mononucleosis,<sup>4</sup> the elevated anti-EBV antibody titers that have been shown to precede the onset of the neoplasm,<sup>5</sup> and the presence of EBV in Reed-Sternberg cells.<sup>6,7</sup>

However, Hodgkin's disease occurs preferentially in

certain families,<sup>8,9</sup> and heredity may also have a role. Pairs of twins concordant for the disease have been described,<sup>10</sup> and increases in the risk of Hodgkin's disease in the families of these twins ranging from threefold (first-degree relatives) to sevenfold (siblings) have been reported.<sup>11,12</sup> Links between Hodgkin's disease and HLA-A1, B5, B8, and B18<sup>13</sup> have been invoked to explain the elevated risk.<sup>14</sup> A comparison of the levels of concordance in pairs of monozygotic and dizygotic twins raised together permits an evaluation of the role of heredity. In a general search for twins with chronic disease, we have identified nearly 1000 in whom a lymphoma has been diagnosed; nearly half of these had Hodgkin's disease. The subsequent experience of their healthy twins provides the basis for this report.

### METHODS

#### Ascertainment and Validation

Between 1980 and 1992, weekly advertisements requesting that "twins with cancer" contact one of us by telephone or mail were placed in large newspapers and magazines across the United States and Canada. Each respondent, almost always a twin or the spouse or first-degree relative of a twin, was briefly interviewed by telephone and asked to provide information about the affected pair's birth date, sex, and perceived zygosity; the date and place of any diagnosis of chronic disease; and the date and place of death if either or both twins had died. After receiving permission from the patients or their families, we routinely sought the patients' medical records and coded their diagnoses according to the *International Classification of Diseases for Oncology*.<sup>15</sup> For all patients with lymphoma and for pairs of twins concordant for any type of cancer, histopathological slides

From the Departments of Preventive Medicine (T.M.M., W.C., A.S.H., D.M.D., E.B.R.) and Pathology (T.M.M., D.K.S., B.N.N., A.M.H., C.R.T.), University of Southern California School of Medicine, Los Angeles, and the Department of Pathology (L.M.W.), City of Hope Medical Center, Duarte, Calif. Address reprint requests to Dr. Mack at 1420 San Pablo St., Los Angeles, CA 90033.

Supported by grants (CA 42581, CA 09492, and CA 50341) from the National Cancer Institute.

were reviewed to ensure the accuracy of the diagnoses. Each pair of twins has been followed by means of questionnaires mailed approximately every 18 months since the diagnosis was confirmed. For the purposes of this report, follow-up was presumed to end at the time of the diagnosis of Hodgkin's disease in the twin of the proband, death, or last contact; the last contact occurred in 1990 or later in 87 percent of the monozygotic twins and 84 percent of the dizygotic twins.

### Zygoty

Ordinary perceptions of zygoty by adult twins are now usually unambiguous and consistent; such perceptions have repeatedly been found to be over 90 percent accurate,<sup>16</sup> although occasionally young monozygotic twins are erroneously believed to be dizygotic on the basis of reported placentation. We have previously used molecular methods to assess the accuracy of self-assessed zygoty in more than 40 pairs of adult twins with chronic disease<sup>17,18</sup>; all laboratory findings to date have been in agreement with the self-reports.

### Assessment of Pairs Concordant for Hodgkin's Disease

Special efforts were made to assess each pair of twins reported to be concordant for Hodgkin's disease. By contacting one or both twins directly, we reaffirmed the diagnosis and the zygoty and collected additional information about the medical history of the twins and their families. Every effort was made to obtain the pathology report and diagnostic slides in each case. We reviewed these slides blindly, classified them according to a modified Lukes-Butler system,<sup>19</sup> and resolved all differences between reviewers while maintaining the blinding. When adequate samples were available, the phenotype of Reed-Sternberg cells and background lymphocytes was determined with standard immunoperoxidase techniques.<sup>20</sup> Specimens from the pairs of twins concordant for disease were evaluated for evidence of EBV with the polymerase chain reaction to detect viral DNA sequences (with primers SL1 5'GGACCTCAAAGAAGAGGGGG and SL3 GCTCCTGGTCTTCCGCCTCC and a probe specific for EBV nuclear antigen 1, SL2 GGACGAGGACGGGGAAGAGG), or by a method that is at least as sensitive, in situ hybridization (with a 30-base sequence, 5'AGACACCGTCCTCACCACCGGGACTTGT-A3', complementary to a portion of the *EBER-1* gene that is actively transcribed in latently infected cells).<sup>7</sup> In some cases both methods were used. To ensure that all EBV-negative specimens were suitable for use with the polymerase chain reaction, control genomic sequences were amplified.<sup>7</sup> Specimens that were EBV-negative on the basis of in situ hybridization were hybridized with a poly-d(T) probe to verify the presence of adequate RNA.<sup>7</sup>

### Quantification of Concordance

Pairwise concordance is used to measure the proportion of pairs who are concordant, whereas casewise concordance more usefully measures the probability, given a diagnosis in one twin, that the other twin will be affected.<sup>21,22</sup> The interpretation of either measure rests on the assumption that the cumulative incidence has been accurately measured or, when groups are compared on the basis of zygoty, that the age distributions and the environmental exposures of the groups are similar.<sup>23</sup>

Part of the familial risk of Hodgkin's disease involves environmental factors rather than hereditary factors, and both the risk of Hodgkin's disease and the probability of ascertainment are age-dependent. For these reasons, we elected to assess the risk of Hodgkin's disease in groups of monozygotic and dizygotic twins simply by comparing the observed number of secondary cases with the number expected — the standardized incidence ratio. This approach also permits a distinction to be made between all cases and cases that were prospectively ascertained. Accordingly, the number of person-years at risk between the date of initial diagnosis or (when prospectively ascertained cases were analyzed) the date on which the diagnosis was ascertained and the date of last follow-up was analyzed in five-year age increments according to zygoty and sex. With the use of data from the Surveillance, Epidemiology, and End Results study (1985 to 1987)<sup>24</sup> on U.S. national incidence rates according to age and sex, the number of cases expected to occur in the healthy twins of each zygoty group was estimated. When calculated in this man-

ner, the standardized incidence ratio for dizygotic twins should provide a maximal estimate of the familial risk for a non-twin sibling (genetic plus nongenetic risk factors). For practical purposes, the sole difference in risk between a monozygotic and a dizygotic twin results from the effect of sharing the whole genome of the twin with Hodgkin's disease rather than just half of it.

In addition, we estimated the number of pairs of monozygotic twins expected by chance to be concordant for each histologic subtype of Hodgkin's disease and compared it with the observed number, using as a basis for estimation the distribution of disease subtypes among all affected monozygotic twins in the general population.

### RESULTS

More than 13,000 twins with cancer, among them 955 with lymphoma, were identified between 1980 and 1992. The first case of Hodgkin's disease in each of 432 sets of twins had been diagnosed from 1936 to 1993 (median year of diagnosis, 1978; 78 percent of cases were diagnosed from 1970 to 1989). At the time of diagnosis the patients ranged in age from 2 to 82 years (median age, 26 years; 87 percent were 13 to 50 years of age). Eighty-five percent of the patients signed consent forms authorizing the release of their medical records, and records, all confirmatory, were received for 77 percent. We requested permission to review the diagnostic slides for 70 percent of the confirmed cases and received interpretable slides for 76 percent of them. Including the concordant cases, the slides for 159 patients were reviewed; there was frank disagreement about the diagnosis of Hodgkin's disease in 2 patients, who were excluded; disagreements about the histologic subtype were almost entirely confined to cases with the "cellular phase" of nodular sclerosis.<sup>25</sup>

Interpretable histopathological slides were also obtained for 230 twins with non-Hodgkin's lymphoma; 227 of these cases were confirmed, and in no instance did the diagnostic alternatives include Hodgkin's disease.

The risk of Hodgkin's disease in the twins of patients with Hodgkin's disease was evaluated among those who were alive, of known zygoty, and younger than 50 years of age at the time the disease was diagnosed in the affected twin. One hundred seventy-nine monozygotic and 187 dizygotic unaffected twins were observed for an average of 14.1 and 14.3 years, respectively, after the diagnosis in the affected twins. On the basis of national age-specific incidence rates, 0.10 case would have been expected to occur by chance during that period in each zygoty group (Table 1); half would have been expected within seven years of the original diagnosis. In fact, 10 cases were reported among the monozygotic twins (7 male and 3 female), giving a pairwise concordance of 5.6 percent, a casewise concordance of 0.106, and a standardized incidence ratio of 99 (95 percent confidence interval, 48 to 182) — 115 for male twins and 83 for female twins. All but 1 of the 10 cases were reported directly by the twins or their parents. The analysis was then repeated with only the cases ascertained prospectively; 0.04 case was expected in each zygoty group, and 5 cases were observed in the monozygous group, giving a standardized incidence ratio of 128 (95 percent confidence interval, 42 to 299).

Table 1. Occurrence of Hodgkin's Disease and Other Malignant Neoplasms in the Twins of Patients with Hodgkin's Disease or Non-Hodgkin's Lymphoma.\*

MALIGNANT NEOPLASM		ZYGOSITY	NO. AT RISK	CASES EXPECTED†	CASES OBSERVED	SIR (95% CI)	SIR FOR MZ TWINS/ SIR FOR DZ TWINS
PROBAND	TWIN						
HD	HD	MZ	179	0.101	10	99 (48-182)	
HD	HD	DZ	187	0.100	0	—	∞
HD	HD‡	MZ	172	0.039	5	128 (42-299)	∞
HD	HD‡	DZ	181	0.035	0	—	
HD	Any other cancer	MZ	179	5.48	9	1.6 (0.8-3.1)	0.6
HD	Any other cancer	DZ	186	6.05	17	2.8 (1.6-4.5)	
HD	Any other cancer‡	MZ	171	2.64	2	0.8 (0.1-2.7)	0.3
HD	Any other cancer‡	DZ	172	2.46	6	2.4 (0.9-5.3)	
NHL	NHL	MZ	110	0.131	3	23 (4.7-67)	1.7
NHL	NHL	DZ	164	0.293	4	14 (3.8-35)	
Any cancer	Same cancer	MZ	3095	23.0	242	11 (9.2-12)	1.8
Any cancer	Same cancer	DZ	3304	21.9	125	5.7 (4.8-6.8)	
Any cancer	Same cancer‡	MZ	2830	9.27	53	5.7 (4.3-7.5)	2.1
Any cancer	Same cancer‡	DZ	3113	7.94	21	2.7 (1.6-4.1)	

\*SIR denotes standardized incidence ratio, CI confidence interval, MZ monozygotic, DZ dizygotic, HD Hodgkin's disease, and NHL non-Hodgkin's lymphoma.

†On the basis of data provided by the Surveillance, Epidemiology, and End Results study on age-, sex-, and site-specific incidence.

‡Restricted to cases that were ascertained prospectively.

No such difference between pairs of monozygotic and dizygotic twins was seen with respect to the occurrence of other cancers after the diagnosis of Hodgkin's disease in one twin. In pairs of twins in which one had non-Hodgkin's lymphoma or some other malignant condition, the same type of tumor subsequently occurred in the other twin no more than twice as often in the monozygotic group as in the dizygotic group.

All 20 cases of Hodgkin's disease in concordant twins were diagnosed before the age of 50 years (mean, 25.5), and the interval between diagnoses within pairs ranged from 6 months to 12 years (mean, 4.5 years). Overall, the standardized incidence ratio did not vary according to sex and was relatively constant over a period of 15 years after the diagnosis in the first twin.

After reaffirming each of the 20 diagnoses and the (unambiguous) perception of zygosity by telephone, we received permission to obtain the medical records of all 20 twins and 19 sets of diagnostic slides (for the remaining set, a detailed histologic diagnosis was available from the Roswell Park Cancer Institute, Buffalo, N.Y.).

One concordant pair of dizygotic twins was initially described, well after the death of both twins, by a sibling. Permission to review these medical records could not be obtained, but on both death certificates death was attributed to malignant lymphoma, and we presume these cases not to have been of Hodgkin's disease.

Six pairs of monozygotic twins were concordant for nodular sclerosis, a seventh was concordant for mixed cellularity, and one pair was unambiguously discordant (Table 2). In the ninth pair, the tumor from one twin showed nodular sclerosis, but the original biopsy slides of the other twin's tumor were lost, and the presence of extensive sclerosis in the available slides of splenic

tissue precluded subcategorization. The final pair was originally described as concordant for mixed-cellularity disease; although both tumors had extensive eosinophilic infiltrates, the criteria for that diagnosis were not fully met in our blind review of one case. Thus, no fewer than seven, and no more than nine, of the pairs had the same histologic subtype of Hodgkin's disease.

On the basis of the proportion of each histologic subtype in all discordant pairs of monozygotic twins in whom Hodgkin's disease was diagnosed before the age of 50 years, and including patients with the cellular phase of disease in the group with nodular sclerosis,<sup>25</sup> 4.6 concordant pairs would have been expected by chance. If the patients with the cellular phase of the disease were included in the group with mixed cellularity, as we have advocated on the grounds of epidemiology<sup>26</sup> and as others have advocated on the grounds of molecular biology,<sup>27</sup> 3.8 concordant pairs would have been expected. Either way, a finding of eight or more observed pairs represents an increase unlikely to be due to chance ( $P < 0.05$  for Poisson distribution). The excess concordance is largely attributable to the six sets of twins concordant for nodular sclerosis, although concordance for mixed-cellularity Hodgkin's disease may also be increased.

Immunohistopathological studies were performed on specimens from nine patients (eight with nodular sclerosis), including three pairs of twins. The pattern of cell-membrane antigens expressed was consistent with that of other patients with Hodgkin's disease. Evidence of the EBV genome was detected in 4 of the 19 tumor specimens examined, including 3 of 4 with definite or possible mixed cellularity, but in only 1 of the 15 specimens examined with definite or possible nodular sclerosing Hodgkin's disease.

Relatives of the 10 pairs of concordant twins reported no first-degree relatives with another hematopoietic malignant condition or autoimmune disease and no other relatives with Hodgkin's disease.

Previous surveys of patients with nodular sclerosing Hodgkin's disease have found that roughly 15 percent have a history of infectious mononucleosis,<sup>28</sup> and such a history of exposure was reported by five patients from four of the concordant pairs (Table 2). In one pair of twins concordant for nodular sclerosing Hodgkin's disease, infectious mononucleosis was reported to have occurred in a sibling rather than in the twins themselves. These twins were also concordant for lipoid nephrosis (minimal-change disease), an uncommon and idiopathic complication of Hodgkin's disease.<sup>29</sup> Neither tumor showed evidence of the EBV genome in the Reed-Sternberg cells, even though both twins had highly el-

Table 2. Characteristics of 10 Pairs of Monozygotic Twins Concordant for Hodgkin's Disease.\*

PAIR No.	SEX	YEAR OF BIRTH	AGE AT DIAGNOSIS (YR)		HISTOLOGIC SUBTYPE		EBV GENOME DETECTION				HISTORY OF MONONUCLEOSIS		
			Twin A	Twin B	Twin A	Twin B	PCR		IN SITU HYBRIDIZATION		Twin A	Twin B	Other 1st-degree relative
1	M	1936	37	49	NS	NS	-	-	-	-	-	-	-
2	M	1955	16	21	NS	NOS†	-	-	-	-	-	+	+
3	M	1964	18	19	NS	NS	-	-	-	-	-	-	-
4	F	1960	23	26	NS	NS	NA	+	-	+	-	-	-
					(LD)	(LD)							
5	F	1962	16	23	NS	NS	NA	NA	-	-	+	-	-
6	M	1957	20	28	NS	MC	NA	-	-	-	-	-	-
					(LD)	(LD)							
7‡	M	1949	28	29	NOS	MC	NA	NA	+	+	+	+	-
8§	F	1960	23	30	NS	NS	NA	NA	-	-	-	-	+
9	M	1948	23	24	MC	MC	NA	NA	NA	+	-	-	-
10	M	1953	17	31	NS	NS	-	-	-	-	NA	NA	NA

\*PCR denotes polymerase chain reaction, NS nodular sclerosis, minus sign negative, NOS not otherwise specified, plus sign positive, NA not available, LD lymphocyte-depleted, and MC mixed cellularity.

†There was insufficient tissue for further classification.

‡These twins were concordant for eosinophilic infiltrate in tumor specimens; initial reports indicated concordance for mixed-cellularity Hodgkin's disease.

§These twins were concordant for minimal-change disease (lipoid nephrosis).

evated antibody titers to EBV capsid antigen (1:1280 and 1:10,240). Tumors from the three other twins with nodular sclerosis who were exposed to infectious mononucleosis were similarly negative.

## DISCUSSION

### Genetic Determination of Hodgkin's Disease

Although no pairs of dizygotic twins concordant for Hodgkin's disease were identified, the previously observed level of familial risk suggests that more than the number expected by chance should have occurred. If the highest reported estimate of risk among the siblings of a patient with Hodgkin's disease (a sevenfold increase)<sup>12</sup> is correct, 0.7 case should have occurred among these dizygotic twins in comparison with the 0.1 expected. Had such been observed, the ratio of the standardized incidence ratio for monozygotic twins to the standardized incidence ratio for dizygotic twins would have been 99/7, or 14.

This observed elevation in concordance among monozygotic twins does not appear to be an artifact of ascertainment. A similar disparity between the number of cases observed in monozygotic twins and the number expected was seen when the analysis was restricted to cases identified prospectively. No such disparity was found among monozygotic twins whose status was ascertained and who were observed in the same way (Table 1) for other cancers after Hodgkin's disease, for non-Hodgkin's lymphoma, or for other forms of cancer as a group. In none of these comparisons was the risk more than twice that among dizygotic twins, whether observed prospectively or not. Nor is the elevation likely to be an artifact of differential survival. Because 20 percent of the initial cases of Hodgkin's disease were

diagnosed before 1970, some before the introduction of effective therapy, it could be argued that for some unknown proportion of concordant pairs, neither twin survived long enough to be included in our analysis. However, the results are essentially unchanged if all the twins of patients in whom Hodgkin's disease was diagnosed before 1970 are eliminated (standardized incidence ratio for monozygotic twins, 110).

Given the unremarkable risk of Hodgkin's disease observed in dizygotic twins, the increased risk in monozygotic twins cannot be attributed to any increased risk resulting from twinship itself or to random errors in the assignment of zygosity; it must be assumed to reflect genetically determined susceptibility. The relatively young average age at diagnosis of the twins concordant for Hodgkin's disease and the relatively short average interval between diagnoses in each pair of twins are additional observations consistent with this explanation.

### Genetic Determination of Nodular Sclerosis

Nodular sclerosing Hodgkin's disease accounts for a majority of the diagnoses in the pairs of concordant twins, and although we cannot be sure that the excess of concordance among monozygotic twins is limited to that subtype, such a finding would be consistent with the published findings on familial risk. A large majority of the 53 reported sibships with multiple cases of Hodgkin's disease<sup>10-12,30-41</sup> consisted solely of or included multiple cases of nodular sclerosis. We have previously speculated on the grounds of descriptive epidemiology,<sup>26</sup> as have others on the grounds of pathology and natural history,<sup>42</sup> that nodular sclerosis is particularly distinct from the other histologic subtypes, including mixed cellularity.

### Etiologic Heterogeneity of Hodgkin's Disease

Despite the unexpected level of concordance in monozygotic twins, 90 percent of the monozygotic twins of patients with Hodgkin's disease can be expected to remain unaffected, and no other cases are known to have occurred in the families of these concordant twins. Thus, either the overall penetrance for the susceptible genotype is rather low or only a subgroup is genetically susceptible. Either way, the difference in risk between monozygotic and dizygotic twins is larger than that expected if a major dominant gene were responsible.

The particularly low prevalence of EBV genome in the Reed-Sternberg cells of the tumors of twins concordant for nodular sclerosing Hodgkin's disease, especially in the face of clear evidence of past infection, is

of interest and may also indicate etiologic heterogeneity. It is true that the average titer against EBV capsid antigen after diagnosis is no lower in nodular sclerosis than in other subtypes of Hodgkin's disease,<sup>43</sup> and a history of infectious mononucleosis is as common in nodular sclerosis as it is in other histologic subtypes.<sup>4</sup> However, whereas evidence of intracellular viral genome appears in the large majority of cases of mixed-cellularity Hodgkin's disease, it is present in only a minority of nodular sclerosing tumors<sup>6,7,27,44,45</sup> and was nearly absent among the twins concordant for nodular sclerosis, even among those who had been infected with mononucleosis. Other familial cases of Hodgkin's disease with a low prevalence of the EBV genome in the tumor despite serologic evidence of past infection have been reported.<sup>46</sup>

### Phenotypic Mechanism

The evidence of an inherited susceptibility to Hodgkin's disease is completely consistent with the evidence of an environmental determinant. If the disease does represent a genetically determined response to infection with a common childhood virus, it will be important to characterize the susceptibility phenotype. Although genetically determined physical and behavioral characteristics can determine the frequency of environmental exposures (i.e., unattractive or withdrawn children may have less interpersonal contact and thus less exposure to fomites), the magnitude of the effect found here suggests a much more fundamental genetic influence on pathophysiology. An underlying immune abnormality is suggested not only by the hypothesis that this disease represents an unusual response to a common infection, but also by the reported association with certain HLA haplotypes and the evidence of abnormal cytokine production in affected patients<sup>47</sup> and of immune abnormalities in the close relatives of some patients.<sup>48</sup> Moreover, lipid nephrosis, which rarely accompanies Hodgkin's disease,<sup>49</sup> occurred in both members of one concordant pair. This condition has been found in association with HLA-B8<sup>50</sup> and is characterized by altered cytokine levels<sup>51</sup> and other derangements of immunity,<sup>52,53</sup> including altered expression of the C3 complex, which includes the receptor for EBV.<sup>54</sup> Although it is unlikely that any single HLA allele or haplotype is responsible for susceptibility to Hodgkin's disease, susceptibility might result from a particular DNA base sequence common to several alleles.

We are indebted to the subjects and the International Twin Study staff, to the health care providers and pathologists of 18 medical centers in 13 states for their cooperation, and to Drs. P. Scheerer (Phoenix), P.H.H. Anderson (Pittsburgh), J.A. Benda (Ames, Iowa), P. Marshall (Sheboygan, Wis.), M. Orjuela and B. Jamieson (New York), P. Gregersen and V. Vinceguerra (Manhasset, N.Y.), and D. Inwards, J.G. Strickler, and L.E. Wold (Rochester, Minn.).

### REFERENCES

- MacMahon B. Epidemiology of Hodgkin's disease. *Cancer Res* 1966;26:1189-201.
- Gutensohn N, Cole P. Epidemiology of Hodgkin's disease in the young. *Int J Cancer* 1977;19:595-604.
- Mack TM. Epidemiology of Hodgkin's disease in young adults: compatibility with various infectious-disease models. In: Essex M, Todaro G, zur Hausen H, eds. *Viruses in naturally occurring cancers*. Vol. 7 of Cold Spring Harbor Conferences on Cell Proliferation. Book B. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1980:1221-30.
- Kvale G, Hoiby EA, Pedersen E. Hodgkin's disease in patients with previous infectious mononucleosis. *Int J Cancer* 1979;23:593-7.
- Mueller N, Evans A, Harris NL, et al. Hodgkin's disease and Epstein-Barr virus: altered antibody pattern before diagnosis. *N Engl J Med* 1989;320:689-95.
- Jarrett R, Onions D. Viruses and Hodgkin's disease. *Leukemia* 1992;6:Suppl 1:14-7.
- Weiss LM, Chen Y-Y, Liu X-F, Shibata D. Epstein-Barr virus and Hodgkin's disease: a correlative in situ hybridization and polymerase chain reaction study. *Am J Pathol* 1991;139:1259-65.
- Kerzin-Storarr L, Faed MJ, MacGillivray JB, Smith PG. Incidence of familial Hodgkin's disease. *Br J Cancer* 1983;47:707-12.
- Halazun JF, Kerr SE, Lukens JN. Hodgkin's disease in three children from an Amish kindred. *J Pediatr* 1972;80:289-91.
- Shibuya H, Tsukada K, Takagi M, Horiuchi JI, Suzuki S, Kamiyama RI. Synchronous Hodgkin's disease in monozygotic twins. *Acta Radiol Oncol* 1984;23:425-8.
- Robertson SJ, Lowman JT, Grufferman S, et al. Familial Hodgkin's disease: a clinical and laboratory investigation. *Cancer* 1987;59:1314-9.
- Grufferman S, Cole P, Smith PG, Lukes RJ. Hodgkin's disease in siblings. *N Engl J Med* 1977;296:248-50.
- Chakravarti A, Halloran SL, Bale SJ, Tucker MA. Etiological heterogeneity in Hodgkin's disease: HLA linked and unlinked determinants of susceptibility independent of histological concordance. *Genet Epidemiol* 1986;3:407-15.
- Risch N. Assessing the role of HLA-linked and unlinked determinants of disease. *Am J Hum Genet* 1987;40:1-14.
- Percy C, Van Holten V, Muir C, eds. *International classification of diseases for oncology*. 2nd ed. Geneva: World Health Organization, 1990.
- Kasriel J, Eaves L. The zygosity of twins: further evidence on the agreement between diagnosis by blood groups and written questionnaires. *J Biosoc Sci* 1976;8:263-6.
- Kumar D, Gemayel NS, Deapen D, et al. North-American twins with IDDM: genetic, etiological, and clinical significance of disease concordance according to age, zygosity, and the interval after diagnosis in first twin. *Diabetes* 1993;42:1351-63.
- Deapen D, Escalante A, Weinrib L, et al. A revised estimate of twin concordance in systemic lupus erythematosus. *Arthritis Rheum* 1992;35:311-8.
- Lukes RJ, Butler JJ. The pathology and nomenclature of Hodgkin's disease. *Cancer Res* 1966;26:1063-83.
- Sherrod AE, Felder B, Levy N, et al. Immunohistologic identification of phenotypic antigens associated with Hodgkin and Reed-Sternberg cells: a paraffin section study. *Cancer* 1986;57:2135-40.
- Allen G, Hrubec Z. Twin concordance: a more general model. *Acta Genet* 1979;28:3-13.
- McGue M. When assessing twin concordance, use the probandwise not the pairwise rate. *Schizophr Bull* 1992;18:171-6.
- Kendler KS. Limitations of the ratio of concordance rates in monozygotic and dizygotic twins. *Arch Gen Psychiatry* 1989;46:477-8.
- Miller BA, Reis LAG, Hankey BA, et al., eds. *SEER cancer statistics review, 1973-1990*. Bethesda, Md.: National Institutes of Health, 1993. (Report no. NIH-NCI-03-2789.)
- Lukes RJ. Criteria for involvement of lymph node, bone marrow, spleen, and liver in Hodgkin's disease. *Cancer Res* 1971;31:1755-67.
- Cozen W, Katz J, Mack TM. Risk patterns of Hodgkin's disease in Los Angeles vary by cell type. *Cancer Epidemiol Biomarkers Prev* 1992;1:261-8.
- Delsol G, Brousset P, Chittal S, Rigal-Huguet F. Correlation of the expression of Epstein-Barr virus latent membrane protein and in situ hybridization with biotinylated BamHI-W probes in Hodgkin's disease. *Am J Pathol* 1992;140:247-53.
- Gutensohn N, Cole P. Childhood social environment and Hodgkin's disease. *N Engl J Med* 1981;304:135-40.
- Peces R, Sanchez L, Gorostidi M, Alvarez J. Minimal change nephrotic syndrome associated with Hodgkin's lymphoma. *Nephrol Dial Transplant* 1991;6:155-8.
- Armata J, Balwierz W, Tacik J. Hodgkin's disease in siblings. *Lancet* 1991;337:502.
- Thorling K. Familial Hodgkin's disease. *Dan Med Bull* 1973;20:61-3.
- Martin BJ, Lennox IM, McGowan A. Familial Hodgkins disease. *Scott Med J* 1985;30:239-40.
- Gracz K, Kofman S, Economou SG. Hodgkin disease in monozygotic twins: a case report. *J Surg Oncol* 1979;12:221-6.
- Olisa EG, Kovi J, Onuora CA. Familial Hodgkin disease. *JAMA* 1974;230:536.

35. Maldonado JE, Taswell HF, Kiely JM. Familial Hodgkin's disease. *Lancet* 1972;2:1259.
36. Vianna NJ, Davies JN, Polan AK, Wolfgang P. Familial Hodgkin's disease: an environmental and genetic disorder. *Lancet* 1974;2:854-7.
37. Creagan ET, Fraumeni JF Jr. Familial Hodgkin's disease. *Lancet* 1972;2:547.
38. Donhuijsen-Ant R, Abken H, Bornkamm G, et al. Fatal Hodgkin and non-Hodgkin lymphoma associated with persistent Epstein-Barr virus in four brothers. *Ann Intern Med* 1988;109:946-52.
39. Lynch HT, Saldivar VA, Guirgis HA, et al. Familial Hodgkin's disease and associated cancer: a clinical-pathologic study. *Cancer* 1976;38:2033-41.
40. Perlin E, Levine PH, McCoy J, Dean J, Herberman R. Hodgkin's disease in siblings: a family study. *Oncology* 1976;33:116-8.
41. Lin A, Whitehouse J, Shaw G, Tucker M. Familial aggregation of Hodgkin's disease in a cohort of 48 families. *Prog Proc Am Soc Clin Oncol* 1993;12:184. abstract.
42. Smithers DW. Hodgkin's disease: one entity or two? *Lancet* 1970;2:1285-7.
43. Evans AS, Gutensohn NM. A population-based case-control study of EBV and other viral antibodies among persons with Hodgkin's disease and their siblings. *Int J Cancer* 1984;34:149-57.
44. Gledhill S, Gallagher A, Jones DB, et al. Viral involvement in Hodgkin's disease: detection of clonal type A Epstein-Barr virus genomes in tumour samples. *Br J Cancer* 1991;64:227-32.
45. Weiss LM, Movahed LA, Warnke RA, Sklar J. Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin's disease. *N Engl J Med* 1989;320:502-6.
46. Lin A, Kingma D, Lennette E, et al. Epstein-Barr virus (EBV) is not associated with familial Hodgkin's disease (FHD). *Prog Proc Am Soc Clin Oncol* 1994;13:185. abstract.
47. Gause A, Keymis S, Scholz R, et al. Increased levels of circulating cytokines in patients with untreated Hodgkin's disease. *Lymphokine Cytokine Res* 1992;11:109-13.
48. Merk K, Bjorkholm M, Tullgren O, Mellstedt H, Holm G. Immune deficiency in family members of patients with Hodgkin's disease. *Cancer* 1990;66:1938-43.
49. Dabbs DJ, Striker LM, Mignon F, Striker G. Glomerular lesions in lymphomas and leukemias. *Am J Med* 1986;80:63-70.
50. Zwolinska D, Morawski Z, Makulska I, Dmochowska D, Jasniak K, Morawski A. Histocompatibility antigens (HLA) in children with lipid nephrosis. *Pol Tyg Lek* 1992;47:671-2.
51. Schnaper HW, Aune TM. Identification of the lymphokine soluble immune response suppressor in urine of nephrotic children. *J Clin Invest* 1985;76:341-9.
52. Kelly CJ, Haverty T, Neilson EG. Control of the nephritogenic immune response. In: Wilson CB, Brenner BM, Stein JH, eds. *Disease: immunopathology of renal disease*. New York: Churchill Livingstone, 1988:35-56.
53. Shalhoub RJ. Pathogenesis of lipid nephrosis: a disorder of T-cell function. *Lancet* 1974;2:556-60.
54. Cybulsky AV, Quigg RJ, Salant DJ. Role of the complement membrane attack complex in glomerular injury. In: Wilson CB, Brenner BM, Stein JH, eds. *Disease: immunopathology of renal disease*. New York: Churchill Livingstone, 1988:57-63.