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Mycosis Fungoides in Relation to Environmental Exposures and Immune Response: A Case-Control Study

Alice S. Whittemore,* Elizabeth A. Holly, I-Min Lee, Elizabeth A. Abel, Robert M. Adams, Brian J. Nickoloff, Linda Bley, John M. Peters, Connie Gibney

Mycosis fungoides is a cutaneous T-cell lymphoma of unknown etiology, thought to be a rare sequela of chronic antigenic stimulation that may occur, for example, with exposure to contact allergens. To explore this possibility, we interviewed 174 patients with mycosis fungoides and 294 randomly selected control subjects in the San Francisco, Los Angeles, and Seattle areas concerning their lifetime histories of employment, chemical exposures, allergy, atopy, and certain medical conditions. Patients reported higher prevalence of cancers other than the non-Hodgkin's lymphomas and skin cancers (relative risk = 3.3, $P < .001$) and were more likely than controls to burn when exposed to the sun (for nonblacks, relative risk = 1.7, $P = .01$). The latter difference may reflect a manifestation rather than a precursor of the disease. We found no consistent or biologically plausible differences between patients and controls with respect to types of jobs held, or to occupational or avocational exposures to chemicals. These findings do not support the hypothesis that persistent antigenic stimulation by contact allergens is etiologically important in the pathogenesis of mycosis fungoides. [*J Natl Cancer Inst* 81:1560-1567, 1989]

Mycosis fungoides is a cutaneous T-cell lymphoma of unknown etiology. The disease usually manifests itself initially as skin patches or plaques that may progress to nodules and tumors, with eventual involvement of the lymph nodes and internal organs. Alternatively, it may present as generalized erythroderma with lymphadenopathy, hepatosplenomegaly, and leukocytosis with circulating atypical cells in the peripheral blood. This latter variant is called Sezary syndrome. Mycosis fungoides and Sezary syndrome are classified as different clinical manifestations of cutaneous T-cell lymphoma (1,2), and will not be treated separately here.

Incidence of mycosis fungoides has increased more than threefold in the United States between 1970 and 1984 (3,4),

which accounted for an estimated 1,000 new patients in 1984 (3). Few epidemiologic studies have been conducted, and speculation about causal factors has been based largely on case series or ecological comparisons (5-8). These studies have suggested a possible etiologic role for occupational, chemical, and certain host factors (5-7). In particular, it has been hypothesized that persistent exposure to contact allergens induces a chronic inflammatory response, leading to immune imbalances and malignancy (9,10).

Despite the lack of epidemiologic data on mycosis fungoides, clues to the etiology of the disease may be provided by findings on lymphomas in general, particularly non-Hodgkin's lymphoma. Lymphoma risk has been associated with exposures to phenoxy acids, chlorophenols (or contaminants of phenoxy acids and chlorophenols, notably isomers of dioxin), and organic solvents (11-15). Ols-

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A. S. Whittemore, E. A. Holly, I-M. Lee, C. Gibney (Department of Health Research and Policy), E. A. Abel, R. M. Adams (Department of Dermatology), Stanford University School of Medicine, Stanford, CA.

A. S. Whittemore, E. A. Holly, Northern California Cancer Center, Belmont, CA.

B. J. Nickoloff, Departments of Pathology and Dermatology, University of Michigan School of Medicine, Ann Arbor, MI.

L. Bley, Fred Hutchinson Cancer Research Center, Seattle, WA.

J. M. Peters, Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles, CA.

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*Correspondence to: Dr. Alice S. Whittemore, Department of Health Research and Policy, Stanford University School of Medicine, Health Research and Policy Bldg., Stanford, CA 94305-5092.

son and Brandt (14) reported that five of 123 men with non-Hodgkin's lymphoma developed cutaneous lesions as the sole manifestation of their disease, and four of these five had prolonged exposure to phenoxy herbicides. These observations motivated a case-control study of mycosis fungoides to examine the hypothesis that risk increases with certain occupational and chemical exposures, and with certain allergy profiles.

Methods

Case Ascertainment

Cases were patients diagnosed with mycosis fungoides between January 1, 1981, and December 31, 1986, in northern California, Los Angeles County, or the Seattle-Puget Sound Area. These patients were identified through population-based tumor registries in the three areas as well as through a network of 12 hospitals in the Santa Clara County of northern California. Eligible patients were those who at time of diagnosis were 20 years of age or older and residents of the 45-county northern California region, Los Angeles County, or the Seattle-Puget Sound area.

Two hundred ninety eligible patients were identified and of these, 174 (60%) were interviewed. Among the 40% who were not interviewed, 23% were deceased, 8% could not be located, 6% refused to participate in the study, and 1% were too ill to be interviewed. The remaining 2% were not interviewed for other reasons. Patient participation rates differed by geographic area, with $128/186 = 69\%$ eligible patients interviewed in northern California, $25/82 = 30\%$ in Los Angeles County, and $21/22 = 95\%$ in the Seattle-Puget Sound Area. The lower participation rate in Los Angeles was largely due to its greater death rate ($35/82 = 43\%$ in Los Angeles vs. $30/186 = 16\%$ in northern California, and $1/22 = 5\%$ in Seattle). Most patients in northern California were ascertained through the dermatology clinics of the university hospitals in the area. By contrast, patients in Los Angeles were known only through the Los Angeles County tumor registry. Since the lag between diagnosis and registry listing tends to be longer and less complete for the large (169-bed hospital, 7.5 million population) Los Angeles County registry than for the others, this difference may account for the relatively low number of eligible patients per capita and high death rate in Los Angeles.

A centralized review of skin biopsy specimens among 110 patients without Sezary syndrome was conducted by one of us (B. Nickoloff). All of these patients were diagnosed as having mycosis fungoides, according to histologic criteria described elsewhere (16). Virtually all diagnoses for the 64 patients without available slides were based on histopathological examination by pathologists where they were diagnosed.

Control Selection

Control subjects in each of the three geographic areas were selected by random-digit-dial telephone methods (17,18). For each patient, we made an attempt to locate two controls with the same telephone area code and prefix as the patient; the remaining digits were selected from a random number

table. For telephone numbers found to be residential, we took a census by age and sex of each household. We used a second random sampling procedure to select one control from the few households with more than one eligible control. For each geographic area and sex, we selected controls so that their final age distribution (across 5-year age groups) matched that of the patients at the time of the patients' diagnoses.

To locate controls, we made attempts to contact potential subjects at a total of 2,273 telephone numbers. We were unable to contact 1,480 of these potential subjects for the following reasons: 822 were disconnected numbers; 270 were business numbers; 206 respondents refused to divulge information pertaining to eligibility; 166 produced no reply after 10 attempts; and we encountered language problems with 16. We made successful contact with 793 households, which yielded a household response rate of $793/(2,273 - 822 - 270) = 67\%$. Three hundred eighty-six households were found to house eligible controls, of which 92 households refused to participate, leaving a total of 294 controls ($294/386 = 76\%$) who were included in the study. Control response rates were similar in the three geographic areas.

Interviews

Trained professional interviewers administered a pretested computer-assisted questionnaire to each participant by telephone, using the same interview schedule for cases and controls. The average interview was 1 hour and covered demographic factors, medical history, life-style habits, and a detailed occupational history that included all jobs of more than 6 months' duration from the age of 12 years until the date of interview. Jobs were coded according to a coding scheme described elsewhere (19). For each job, participants provided information regarding on-the-job chemical exposures. They also were asked about exposures to a short list of chemicals selected from an occupation-exposure linkage system developed for other epidemiologic studies (19). In addition, participants reported details on any spare-time activities pursued for at least 10 hours per month for 6 months or more, and any exposures to herbicides, rodenticides, or insecticides that occurred more than 10 times a month for at least 6 months. Unless otherwise stated, personal histories and cumulative exposures were evaluated prior to a specific reference date (date of diagnosis for cases, and date of interview for controls).

Data Analysis

We used univariate and multivariate logistic regression analyses to estimate odds ratios (hereafter called relative risks) for environmental and host factors. These analyses were adjusted for age and geographic area of residence, using unconditional logistic regression (20,21). Analyses were conducted both with and without adjustment for race (white, nonwhite), years of education, and household income. Results were similar, so these three variables have been omitted from the final regressions. We also conducted analyses both with and without inclusion of Los Angeles participants. Since no important differences emerged, we present only results based on all the data.

Results

Demographic Information

Table 1 summarizes demographic characteristics of participants by sex and case-control status. The mean age within each of the four groups was 56 years. Among women, a significantly higher proportion of cases than controls was Hispanic. This pattern was not, however, observed in men. Among both sexes, blacks were somewhat overrepresented among cases relative to controls, and cases were somewhat less educated and had lower household income. However, these differences were not statistically significant. Cases and controls were similar with respect to marital status and (data not shown) to number of siblings, parents' ages, and parents' education.

Occupational History

The median numbers of distinct prior jobs were six for male cases, six for male controls, four for female cases, and five for female controls. The difference among women was not statistically significant ($P = .13$). Jobs were classified into seven industries and nine major exposure categories. The seven industries were: (1) agriculture, forestry, and fishing; (2) mining; (3) construction; (4) medicine and science; (5) entertainment and recreation; (6) art; and (7) transportation. The nine exposure categories were those processing, producing, or using: (1) paper and wood; (2) glass, clay, and stone; (3) metals; (4) machinery, including electronics; (5) textiles; (6) chemicals, drugs, and paints; (7) rubber, plastics, and synthetics; (8) fuel. The final major exposure category (9) consisted of jobs with little or no chemical exposures. Subsets of these job categories also were analyzed, as were job titles

spanning several categories (for example, mechanics, janitors, etc.).

Within each sex, cases and controls were similar with respect to the proportions reporting employment in each of virtually all the occupational groups analyzed. There were two exceptions to this similarity: (1) fewer patients than controls reported prior employment in the paper and wood industry (relative risk = 0.5, $P = .02$); and (2) among women, fewer patients than controls reported employment in a group of occupations classified as having little or no chemical exposures (relative risk = 0.2, $P < .001$). However, similar proportions of female patients and controls reported employment in the groups of all other occupations.

Chemical Exposures

Based on published reports of suggested associations with mycosis fungoides risk, chemical exposures were grouped into the following categories: all metals and their salts, pesticides, herbicides, solvents (halogenated hydrocarbons, aromatic hydrocarbons), and uncured plastic. We then calculated relative risks corresponding to reported exposure to any chemical in each of these groups.

Table 2 summarizes the findings of these chemical analyses. A significantly lower proportion of cases than controls reported prior exposure to chromium and its salts (relative risk = 0.5 using those with no reported chemical exposure as the referent group; $P = .01$), mercury and its salts (relative risk = 0.4, $P = .01$), halogenated hydrocarbons (relative risk = 0.6, $P = .04$), aromatic hydrocarbons (relative risk = 0.6, $P = .02$), and uncured plastic (relative risk = 0.5, $P = .01$). The results are not independent because participants tended to be exposed to more than one of the latter five chemical

Table 1. Demographic characteristics of cases and controls

Characteristic	Men				Women			
	Cases ($n = 109$)		Controls ($n = 169$)		Cases ($n = 65$)		Controls ($n = 125$)	
	No.	%	No.	%	No.	%	No.	%
Age (mean yr)*	55.9	—	55.6	—	55.9	—	56.5	—
Race								
White	95	87.2	143	84.6	51	78.5	111	88.8
Black	5	4.6	5	3.0	8	12.3	7	5.6
Hispanic	2	1.8	11	6.5	5	7.7	2	1.6
Other	7	6.4	10	5.9	1	1.5	5	4.0
Education								
High school	47	43.1	66	39.0	40	61.5	59	47.2
College	36	33.0	65	38.5	21	32.3	49	39.2
Graduate school	26	23.9	38	22.5	4	6.2	17	13.6
Household income								
<\$20,000	39	35.8	40	23.7	25	38.5	50	40.0
\$20,000-50,000	44	40.4	70	41.4	32	49.2	51	40.8
>\$50,000	24	22.0	54	31.9	6	9.2	16	12.8
Unknown	2	1.8	5	3.0	2	3.1	8	6.4
Marital status								
Single	7	6.4	14	8.3	1	1.5	8	6.4
Married/living together	76	69.7	128	75.7	40	61.6	63	50.4
Separated/divorced	19	17.5	15	8.9	11	16.9	27	21.6
Widowed	7	6.4	12	7.1	13	20.0	27	21.6

* At diagnosis for patients; at interview for controls.

Table 2. Mycosis fungoides risk versus reported exposure to selected chemical groups

Reported exposure	Cases (n = 174)		Controls (n = 294)		RR*	95% Confidence interval
	No.	%	No.	%		
No chemicals	57	32.8	79	26.9	1.0	—
Chromium and chromium salts	27	15.5	71	24.1	0.5	0.3-0.8
Mercury and mercury salts	31	17.8	83	28.2	0.4	0.3-0.8
Halogenated hydrocarbons	78	44.8	154	52.4	0.6	0.4-1.0
Aromatic hydrocarbons	70	40.2	149	50.7	0.6	0.3-0.9
Uncured plastic	54	31.0	126	42.9	0.5	0.3-0.9

*RR = relative risk, adjusted for age, sex, and area of residence.

groups. Indeed, 25 cases and 66 controls had been exposed to all five of them. Among those exposed, there was no evidence of trend in risk with duration of exposure to any of these five chemical groups.

Overrepresentation of controls among those reporting chemical exposures might arise if more controls than cases had been employed in chemistry-related occupations, because such persons might be more aware of chemical exposures and, thus, report them more fully. However, we found equal proportions of cases and controls ($3/174 = 1.7\%$ cases vs. $5/294 = 1.7\%$ controls) who reported having worked in such occupations.

Because organic solvents have been implicated in lymphoma risk in previous studies, we classified each occupation as having highly probable, probable, possible, or no potential exposure to solvents. Using this linkage system, we found no relationships between mycosis fungoides risk and occupational exposure to solvents.

History of Allergy and Atopy

Table 3 shows that somewhat fewer cases than controls reported skin allergy to a broad class of antigens (relative

risk = 0.7 using those with no reported skin allergy as the referent group; $P = .08$). In particular, cases were less likely than controls to report skin allergy to plants (relative risk = 0.07, $P = .08$), metals (relative risk = 0.3, $P = .01$), cosmetics (relative risk = 0.7, $P = .17$), drugs other than skin medications (relative risk = 0.9, $P = .62$); and among women, skin medications (relative risk = 0.5, $P = .24$), food (relative risk = 0.3, $P = .02$), and insect bites (relative risk = 0.3, $P = .07$). In contrast, among men, a significantly higher proportion of cases than controls reported skin allergy to medications applied to the skin (relative risk = 5.9, $P = .03$). No men reported skin allergy to hair dyes. Among women, a higher fraction of cases than controls reported hair dye allergy, although the difference was not statistically significant (relative risk = 1.2, $P = .83$). Relative risks associated with exposures to metals and their salts did not differ between those with and without histories of skin allergy to metals or to any of the above contact allergens.

Table 4 shows that among the 69 participants tested, fewer cases than controls reported a positive outcome to scratch or needle allergy tests for inhalants or ingestants (relative risk = 0.2 using those with negative outcome as the referent group;

Table 3. Mycosis fungoides risk versus reported allergy history

Allergic skin reaction	Cases (n = 174)		Controls (n = 294)		RR*	95% Confidence interval
	No.	%	No.	%		
None	66	37.0	91	31.0	1.0	—
Any†	100	57.5	203	69.0	0.7	0.5-1.0
Plants	64	36.8	132	44.9	0.7	0.4-1.1
Metals	10	5.7	36	12.2	0.3	0.1-0.8
Cosmetics	30	17.2	63	21.4	0.7	0.4-1.2
Skin medications						
Men‡	8	7.3	2	1.2	5.9	1.2-29.9
Women‡	6	9.2	12	9.6	0.5	0.1-1.6
Other drugs	30	17.2	44	15.0	0.9	0.5-1.6
Hair dyes						
Women§	7	10.8	6	4.8	1.2	0.3-4.4
Food						
Men‡	12	11.0	12	7.1	1.5	0.6-3.8
Women‡	6	9.2	22	17.6	0.3	0.1-0.8
Insect bites						
Men‡	8	7.3	6	3.6	1.8	0.6-5.6
Women†	5	7.7	17	13.6	0.3	0.1-1.1

*RR = relative risk, adjusted for age, sex, and area of residence.

†Includes plants, metals, cosmetics, skin medications, other drugs, hair dyes, food, and insect bites.

‡Relative risks differed significantly ($P \leq .05$) between men and women.

§No men reported hair dye allergy.

Table 4. Mycosis fungoides risk versus skin test outcome and cancer history

	Cases (n = 174)		Controls (n = 294)		RR*	95% Confidence interval
	No.	%	No.	%		
Scratch or needle allergy test	22	100.0	47	100.0	—	—
Negative	10	45.5	8	17.0	1.0	—
Positive	12	54.5	39	83.0	0.2	0.1-0.7
Patch skin test	39	100.0	40	100.0	—	—
Negative	15	38.5	11	27.5	1.0	—
Positive	24	61.5	29	72.5	0.5	0.2-1.4
Tuberculin or PPD test	92	100.0	169	100.0	—	—
Negative	77	83.7	142	84.0	1.0	—
Positive	15	16.3	27	16.0	1.2	0.6-2.3
Cancer history†						
None	125	71.8	268	91.2	1.0	—
Any	24	13.8	18	6.1	3.3	1.7-6.5
Breast cancer	5	2.9	3	1.0	4.5	1.0-19.8
Leukemia	1	0.6	0	0.0	Infinite	—
Hodgkin's disease	4	2.3	0	0.0	Infinite	—
Other cancer	16	9.2	16	5.4	2.3	1.2-5.1

*RR = relative risk, adjusted for age, sex, and area of residence.

†Excluding mycosis fungoides, other non-Hodgkin's lymphoma, and skin cancer.

$P = .01$). However, the two groups were similar with respect to reported positive patch tests for contact allergies (relative risk = 0.5, $P = .20$ among 79 tested), and positive tuberculin tests (relative risk = 1.2, $P = .69$ among 261 tested).

Cases and controls also did not differ significantly with respect to reported history of atopy, regardless of whether the atopy was manifested as asthma (24 cases vs. 29 controls), hay fever (52 cases vs. 109 controls), hives (45 cases vs. 88 controls), or eczema (14 cases vs. 22 controls).

Medical History

Patients were significantly more likely than controls to report a history of cancer at any time in the past. This association might reflect a tendency for patients with mycosis fungoides to report their disease as non-Hodgkin's lymphoma or skin cancer, since fewer than half of them reported it as mycosis fungoides. However, the association persisted after exclusion of non-Hodgkin's lymphoma and skin cancer. Table 4 gives the numbers and types of cancers reported by study participants. Overall, the relative risk was 3.3 ($P < .001$) for any malignancy other than skin cancer and non-Hodgkin's lymphoma. Five patients reported breast cancer (relative risk = 4.5, $P = .05$). One patient reported leukemia and four patients reported Hodgkin's disease, compared to no such reports among the controls, giving infinite relative risks. The other cancers reported by patients were cancers of the thyroid, lung, colon, kidney, bladder, prostate, fallopian tube, uterus, and cervix. Most of these cancers preceded or coincided with the diagnosis of mycosis fungoides (four of five patients for breast cancer, one of one for leukemia, three of four for Hodgkin's disease, and 12 of 16 for other cancers). The prevalence of site-specific cancers among controls is in good agreement with population estimates based on Connecticut Tumor Registry data (22).

None of the participants reported a prior thymectomy or

splenectomy. Similar proportions of cases and controls reported past tonsillectomies. Cases and controls also were similar with respect to reported history of psoriasis and prior viral infections (mumps, chicken pox, shingles, mononucleosis, viral pneumonia, and hepatitis). However, among women, a lower proportion of cases than controls (26 cases vs. 71 controls) reported herpes simplex 1 infection (relative risk = 0.5, $P = .03$). Cases and controls did not differ with respect to prior fungal infections.

One hundred twenty-three cases and 109 controls reported ever having used topical cortisone creams (relative risk = 4.6, $P < .001$). Cases and controls were similar with respect to reported systemic cortisone administration.

Other Factors

Among nonblacks, 77 patients and 103 controls reported burning rather than tanning when exposed to the sun (relative risk = 1.7, $P = .01$). Among blacks with all degrees of skin pigmentation, three patients reported burning in the sun, compared to none of the black controls. Six patients who were black and three controls who were black reported having skin that neither burned nor tanned in the sun (relative risk = 6.3, $P = .13$).

Relationships between radiation exposures and risk for mycosis fungoides were equivocal. Patients were somewhat more likely than controls to report ultraviolet light therapy for conditions other than mycosis fungoides (33 cases vs. 40 controls; relative risk = 1.5, $P = .09$). Among men, eight cases versus two controls reported x-ray treatment for conditions other than mycosis fungoides (relative risk = 6.6, $P = .02$). Among women, however, only two cases reported having had such treatment, compared to seven controls (relative risk = 0.5, $P = .45$). Cases and controls did not differ with respect to reported occupational exposures to ultraviolet light (17 cases vs. 22 controls, relative risk = 1.2, $P =$

.71) or x rays (13 cases vs. 19 controls, relative risk = 1.4, $P = .30$).

Tobacco and alcohol consumption was evaluated at a reference date 5 years prior to the date of diagnosis for cases, and 5 years prior to the date of interview for controls. One hundred nine cases versus 170 controls reported ever smoking cigarettes (relative risk = 1.2, $P = .29$). Seventy-two cases versus 77 controls reported current cigarette smoking (relative risk = 2.0, $P < .001$). However, there were no consistent trends of increased risk with total number of packs smoked. A decreasing trend was noted for women, in contrast to an absence of trend in either direction for men. We found no relationships between risk for mycosis fungoides and alcohol consumption or parental history of the following: eczema, psoriasis, other skin diseases, or cancer.

Discussion

The demographic features of the 174 patients with mycosis fungoides in this study are consistent with those observed elsewhere. The male:female ratio of 1.7 noted here agrees with other reported sex ratios, which range from 1.4 to 2.2 (3,5-8). For women, we found a significantly higher proportion of Hispanics among cases than among controls, and for both sexes, we found a somewhat higher proportion of blacks among cases than among controls. These observations are consistent with higher mycosis fungoides mortality rates among nonwhites found in a retrospective analysis of U.S. cancer deaths (6), and with higher incidence of mycosis fungoides among blacks noted in another study using data from the National Cancer Institute (3).

Several limitations of the study must be considered. First, occupational and environmental exposures of eligible cases who participated may differ from those who died prior to contact. If certain exposures were associated with increased mortality, then our failure to interview deceased cases could lead to underestimation of the corresponding relative risk. Yet, risk estimates did not change when we excluded data from Los Angeles, where most of the deaths occurred.

Second, the completeness and accuracy of self-reported chemical exposures may be influenced by the socioeconomic status of the participant. Since controls in this study were somewhat more educated and affluent than cases, this potential bias might explain the lack of positive association of chemical exposures with the mycosis fungoides risks seen in table 2. However, relative risk estimates were unchanged when household income and years of education were added to the regressions. Moreover, risk also showed no positive relationship to employment in any of the 16 major job categories, whose reporting completeness and accuracy is less apt to be influenced by socioeconomic factors.

Third, although this is the largest case-control study of mycosis fungoides reported to date, sample size constraints limit its power to detect associations of small or moderate magnitude for infrequently occurring exposures or host characteristics. Nevertheless, the lack of positive associations noted here provides some upper bounds for the potential roles of environmental exposures in the etiology of the disease.

Finally, the many associations tested for statistical signif-

icance increase the likelihood that some of the findings are due to chance. Yet we found few positive associations between occupational exposures and mycosis fungoides risk. Men and women with a history of employment in the paper and wood industry were at decreased risk for mycosis fungoides. Since chlorophenols are widely used in the paper and wood industry, this association is not consistent with other findings relating chlorophenols or their contaminants to increased risk for lymphoma (11-13,15,23). Women who had ever worked in occupations with few chemical exposures also were at decreased risk for mycosis fungoides. A decreased risk was not observed among men working in the same occupations. It is unlikely that the decreased risk among women is due to confounding of case-control differences in education or income, because adding these variables to the regression did not alter the finding. In view of the many comparisons made, chance is a more likely explanation for the relationship among women between mycosis fungoides risk and employment in jobs with few chemical exposures.

Similarly, we found no positive associations between chemical exposures and mycosis fungoides risk. On the contrary, risk was reduced among those exposed to chromium and its salts, mercury and its salts, halogenated hydrocarbons, aromatic hydrocarbons, and uncured plastic. The biological implausibility that these chemicals are protective, and the large extent of overlap among study subjects exposed to them, suggest that these associations are due to chance. We found no relationships between mycosis fungoides risk and exposure to solvents, whether self-reported or determined by ranking jobs with respect to possible solvent exposures.

Thus, the present observations do not support the relationships between occupational or chemical exposures and mycosis fungoides risk suggested by previous case series or ecological comparisons (5-7). This lack of relationship also was found in a study of 53 case-control pairs in Scotland (8). The present larger study supports the Scottish one, and reduces the likelihood that an important risk factor has been missed because of small sample size.

Patients in this study were somewhat less likely than controls to report skin reactions to certain irritants and allergens. However, among those tested, cases and controls were similar with respect to positive patch tests for contact allergies, a more accurate indication of allergic response. Therefore, these data provide no evidence for altered delayed cutaneous hypersensitivity among patients with mycosis fungoides. The data also provide no evidence of interaction between metal exposures and skin allergy either to metals or to a broad class of antigens. We conclude that the present study does not support the hypothesis that chronic antigenic stimulation leads to mycosis fungoides.

The present data show no increase in prevalence of self-reported atopy among cases relative to controls, in contrast to a positive relationship suggested in a case series (6). Self-reported atopy provides only limited evidence of altered immunologic response as measured by elevated serum IgE levels. For example, elevated serum IgE levels have been found in 10 of 19 patients with mycosis fungoides, yet only two of these patients reported a history of atopy (9). Among subjects in this study who had been tested, fewer patients

than controls had positive outcome to scratch or needle allergy tests for inhalants or ingestants. This difference fails to support a positive association between atopy prevalence and mycosis fungoides risk.

Patients were significantly more likely than controls to report a history of any other cancer. This association persisted after exclusion of skin cancer and non-Hodgkin's lymphoma, and thus it cannot be explained by a possible tendency for patients to report their mycosis fungoides as skin cancer or non-Hodgkin's lymphoma. The excess of other cancers is unlikely to be related to treatment for mycosis fungoides, because 18 of 24 other cancers among patients with mycosis fungoides occurred prior to or concurrent with the mycosis fungoides diagnosis. Chan et al. (24) have described three patients with mycosis fungoides prior to the diagnosis of Hodgkin's disease. These authors postulate that treatment for mycosis fungoides may have caused the Hodgkin's disease. We conjecture instead that those predisposed to mycosis fungoides are also at elevated risk for Hodgkin's disease. This interpretation is consistent with the present finding of four diagnoses of Hodgkin's disease among patients with mycosis fungoides, three of whom reported that their diagnosis of Hodgkin's disease preceded that of mycosis fungoides.

Some differences noted in tables 3 and 4 suggest that patients with mycosis fungoides may be immunosuppressed. Individuals who are immunosuppressed because of organ transplantation or immunosuppressive therapy have an excess of squamous cell carcinomas, non-Hodgkin's lymphoma, and mesenchymal tumors (25). We also found excess reports of skin cancer and non-Hodgkin's lymphoma (excluding reports of mycosis fungoides) among cases. However, we were unable to determine how many of these reports referred to the patients' mycosis fungoides rather than second primary cancers.

The present finding that 16% of cases reported a history of other malignancies disagrees with the case-control study conducted in Scotland (8), which found no increased prevalence of other malignancies (one of 53 cases compared to three of 53 controls), but agrees with other reports that have noted second malignancies in 5%-16% of patients with mycosis fungoides (5-7). Genetic susceptibility may play a role in the development of these cancers, a possibility suggested by increased levels of the HLA antigen DR5 found among 34 patients in a case-control study of mycosis fungoides (26). The authors postulate that individuals with the DR5 antigen might be at higher risk for neoplastic diseases, possibly through an HLA-linked defect in the immune system. A genetic component for mycosis fungoides would suggest that such patients tend to have a family history of cancer. We found no excess of parental cancer history among cases relative to controls. This finding agrees with some studies (7,8), but disagrees with other findings that first degree relatives of patients with mycosis fungoides have a high frequency of cancer, especially leukemia and lymphoma (6,27). The inconsistencies may be due, in part, to errors in reporting family cancer history.

Patients were more likely to burn in the sun than were controls. The difference may not be etiologically relevant, but may instead reflect increased photosensitivity due to the dis-

ease (28). We found no evidence to support other suggested relationships between mycosis fungoides risk and thymectomy, splenectomy, tonsillectomy, herpes simplex infection, or fungal infection of the skin (6). Patients in this study were more likely than controls to report use of topical glucocorticosteroids, and (among men) x-ray treatment for conditions other than mycosis fungoides. However, these associations probably reflect the effects of treatment for early clinical manifestations of the disease. Similarly, although we found increased mycosis fungoides risk among current smokers, male smokers showed no trend of increased risk with increased smoking, and female smokers showed decreased risk with increased smoking. These inconsistencies argue against a plausible biologic relationship between smoking and mycosis fungoides risk.

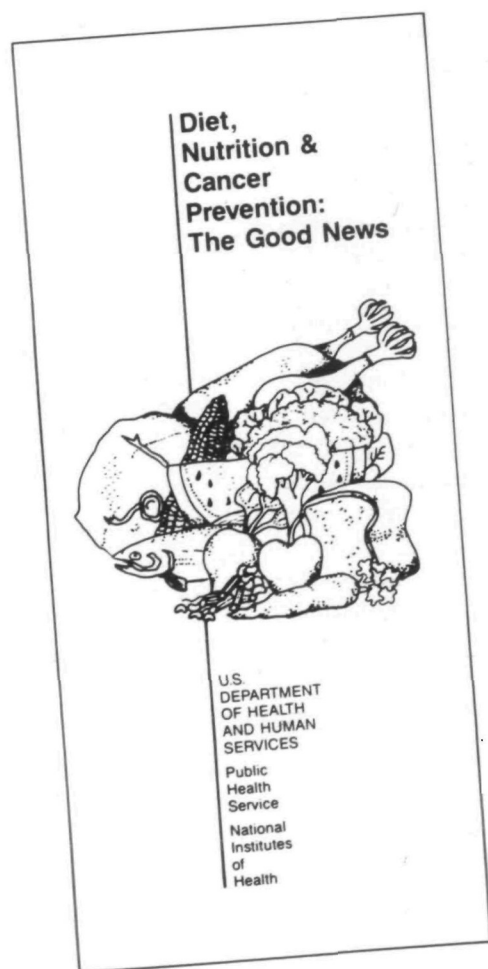
In summary, we found no biologically plausible or consistent relationships between occupational or chemical exposures and risk for mycosis fungoides. Risk was positively associated with a history of other malignancies, and with a tendency to sunburn. The latter association may be a symptom rather than a precursor of the disease. We found no evidence to support the hypothesis that mycosis fungoides is an abnormal response to chronic antigenic stimulation.

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