Reprinted from CANCER, Vol. 56, No. 12, December 15, 1985.

Reevaluation of Prognostic Significance of Symptoms in Hodgkin's Disease

PAOLO G. GOBBI, MD,*† CARLA CAVALLI, MD,*† ADELE GENDARINI, MD,*† ANNAMARIA CREMA, MD,*† GIOVANNI RICEVUTI, MD,†‡ MASSIMO FEDERICO, MD,†§ UBALDO DI PRISCO, MD,‖¶ AND EDOARDO ASCARI, MD,*#

The prognostic value—at diagnosis—of fever, sweating and weight loss, which enter the Ann Arbor B category, and of pruritus, whose influence on survival is still debated, were systematically reevaluated in 635 patients with Hodgkin's disease, observed between 1972 and 1982. By means of multivariate analysis an intrinsic, more negative prognostic value was demonstrated for each of the following symptoms: fever over 38°C, weight loss more than 10% of body weight in the 6 months before admission, and severe pruritus, which is defined as being generalized, causing multiple excoriations and resisting local and systemic antipruritics. Patients with the mild counterparts of these symptoms, as well as sweats, were found to have a survival rate quite comparable with that of fully asymptomatic patients. A rearrangement of the Ann Arbor B constitutional symptoms which would replace sweats with severe pruritus might be more correct and more suitable for better selecting the patients who require more aggressive therapy.
***Cancer* 56:2874–2880, 1985.**

A WIDE SPECTRUM of systemic signs and constitutional symptoms can accompany the onset and the course of Hodgkin's disease (HD) or even herald it.[1] Both the clinical variety and the still obscure biology of such manifestations, which are sometimes very helpful indicators of active, otherwise inapparent disease, have often intrigued and stimulated the clinician. Nevertheless, generally it has been believed that only a few of these symptoms may possess a true prognostic significance.

In the first staging systems proposed for clinical use,[2–4] pyrexia, sweats, pruritus, anemia, asthenia, leukocytosis, and leukopenia were considered as equally important. At the Rye Conference[5] in 1965, the following documented symptoms, otherwise unexplained, were indicated as significant: (1) fever over 38°C; (2) sweats, especially nocturnal; and (3) pruritus. Absence or presence of one or more of these should have resulted in classification of the patients as either A or B, respectively. This triad was modified further at the Ann Arbor Conference[6] in 1971, where it was stated that pruritus was no longer to be considered related to a poor prognosis and was replaced by unexplained loss of more than 10% of body weight in the 6 months before admission. These new criteria for A or B classification were accepted nearly all over the world for a long time and contributed largely to therapeutic decisions, as documented by most of the treatment protocols.[7]

Recently, the intrinsic prognostic value of pruritus was reexamined,[8] and some of us[9] pointed out that only the severe form of presentation is *per se* linked to a poorer survival. Considering the practical usefulness of having an accurate definition of those symptoms that are truly unfavorable, we intended to reevaluate systematically the choice of symptoms that enter the Ann Arbor B category and, at the same time, verify the effect of severe pruritus on survival using a series of patients 50% greater than that previously evaluated.[9]

Materials and Methods

The population of the study consisted of 635 patients, with HD, observed between 1972 and 1982 in the Departments of Internal Medicine of Pavia and Modena, Italy. All were staged and histologically evaluated according to the criteria recommended at the Ann Arbor Conference in order to perform a prospective evaluation of therapeutic outcomes and prognostic factors of the disease.[6,10,11] In particular, every patient underwent the evaluation procedures listed as "necessary,"[10] including the specific detailed investigation about presence or absence of any of the possible, otherwise unexplained, constitutional symptoms, their duration and severity. Fever was

From the *Sezione di Patologia Medica e ‡Sezione di Clinica Medica I del Dipartimento di Medicina Interna dell'Università di Pavia, §Cattedra di Clinica Medica e ‖Cattedra di Ematologia dell'Università di Modena, Italy.
† Research Assistant.
¶ Associate Professor.
# Director.
Address for reprints: Paolo G. Gobbi, MD, Sezione di Patologia Medica, Dipartimento di Medicina Interna, Policlinico S. Matteo, 27100 Pavia, Italy.
Accepted for publication March 15, 1985.

recorded as (1) absent, (2) present with temperatures under 38°C, or (3) present above 38°C; sweats were recorded only when they were unexplained and recurrent, regardless of the time of day when they occurred; weight loss was considered as (1) absent, (2) present, less than 10% of body weight in the 6 months before admission, or (3) present, more than 10%; pruritus was recorded as (1) absent, (2) mild, or (3) severe, and the requirements for severity included coexistence of (1) multiple excoriations, generalization of pruritus, and ineffectiveness of local and systemic antipruritics.[9]

All patients had bipedal lymphoangiography; intravenous pyelograms were performed in 112 of them when evidence of retroperitoneal mass or signs of kidney, ureter, or bladder displacement or involvement were present. Skeletal roentgenograms were made only in patients with osseous or articular pain. Bone marrow core biopsy, with or without aspiration, was performed in 478 patients; 449 had liver and spleen isotopic scans; and 169 underwent staging laparotomy with splenectomy; 92 had only laparoscopy.

Treatment was related to stage and consisted of extended-field radiotherapy for all Stage IA and for those Stage IIA and Stage IIIA patients with favorable histotypes (lymphocyte predominance and nodular sclerosis) and without bulky disease. Patients in Stage IIA and IIIA disease with unfavorable histotypes or with bulky tumor mass and all those with Stage B or Stage IV disease were admitted to a combined chemoradiotherapy program or to chemotherapy alone. The first-step chemotherapy regimen was mechlorethamine, vincristine, procarbazine, prednisone (MOPP) or COPP (in which cyclophosphamide is substituted for mechlorethamine); the second-step regimen was CcVPP (CCNU, vinblastine, procarbazine, prednisone) or even MOPP again if the first MOPP regimen had ended at least 2 years before; ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine) or, more recently, alternated MOPP–ABVD regimens were used as salvage therapy.

Survival curves were calculated by the life-table method.[12] The Hankey-Myers adjusting procedure[13] was applied to the survival curves to take into account the effects on survival of the main, nonsymptomatic HD prognostic factors. The number of patients studied allowed survival to be evaluated in relation to symptoms, while considering the differences which might be present contemporarily in the distribution of four other major prognostic determinants. The four factors considered were sex, age, stage, and histologic subtypes. According to the methodologic approach of Myers and Axtell when they dealt with HD,[14] the data of age, stage, and histotypes were regrouped in discrete subcategories: <35 or ≥ 35 years for age groups; Stage I and II together or Stage III and IV together for staging groups; lymphocyte predominance and nodular sclerosis together, or mixed cellularity and lymphocyte depletion together for histologic subgrouping.

In any comparison of survival, the crude curve (dotted lines in figures) of one group was systematically adjusted at yearly intervals (continuous lines) for the possible heterogeneous distribution of the four above-mentioned major determinants presented by the second group (dashed lines). Differences in survival remaining after adjustment are independent of the effect of the parameters for which adjustment was made, and have to be considered as more truly related to the factors, *i.e.* symptoms, by which the curves were subdivided and compared.

Differences in survival were statistically evaluated by log-rank analysis,[12] which was applied to adjusted curves only.

Results

The Venn diagrams in Figure 1 and the data in Table 1 illustrate the exact proportions of the 635 HD patients with and without one or more of the evaluated symptoms. Both in A and B patients fever is the most frequent symptom, although with different grades of severity. Severe pruritus, which was not required for B classification according to Ann Arbor Conference and also was found in the A group, is the relatively least common symptom and is present alone in only 25% of those patients who complained of it. Sweats show a high association with fever since nearly 50% of sweating patients experienced temperatures over 38°C in the same period.

The different prognosis of the Ann Arbor A and B patients in this study can be verified in Figure 2. Even after correction for the major prognostic factors that can negatively affect B patients more than A ones (advanced age and stage, unfavorable histotypes, male sex), and despite more aggressive treatment, B patients had a significantly lower survival.

The possible influence on survival of some of the mild symptoms present in A patients can be excluded by Figure 3, which demonstrates that survival of A patients presenting low fever and/or slight weight loss and/or mild pruritus is statistically the same as that of fully asymptomatic ones. The seven patients in group A with severe itching were excluded from this comparison.

To investigate the effect of each B symptom on prognosis, survivals were compared among patients presenting fever, sweats, or weight loss as a single symptom. The survival curves are shown in Figure 4 and, because of the adjustment for the other major prognostic determinants, they can be regarded as reflecting the individual prognostic value of each symptom. Survival of only sweating patients is significantly higher than that of patients with only fever or only weight loss, whereas survivals related to these two symptoms do not differ significantly.

Figure 5 confirms that survival of merely sweating pa-

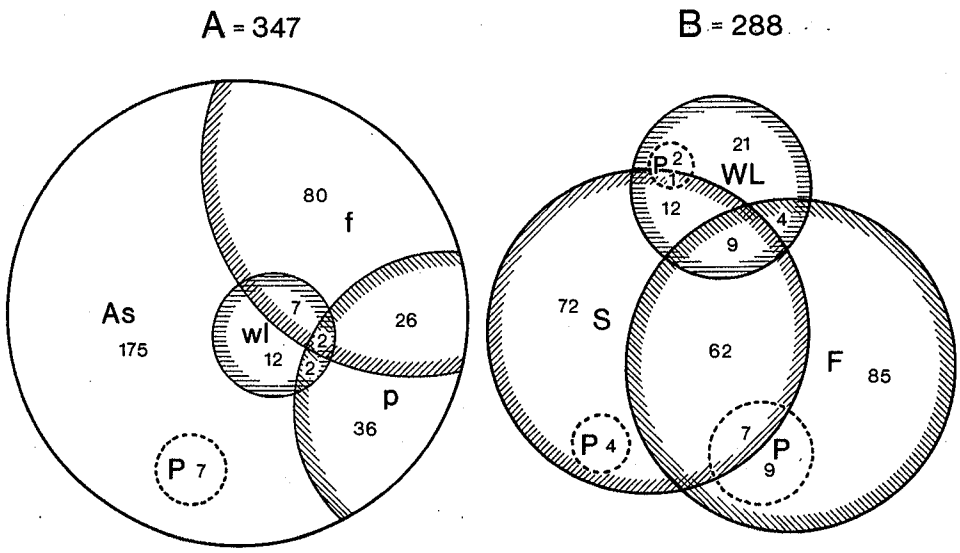

FIG. 1. Venn diagrams of the absolute incidence of fever, weight loss, sweats and pruritus, at different grades of severity in 635 Hodgkin patients: classification as A (left) or B (right) has been made according to Ann Arbor criteria. f: fever < 38°C; F: fever ≥ 38°C; wl: weight loss < 10%; WL: weight loss ≥ 10%; S: sweats; p: mild pruritus; P: severe pruritus; As: asymptomatic cases.

tients is significantly higher than that of all other B patients, *i.e.*, subjects with fever and/or weight loss or with sweating associated with one or both of these symptoms. The same figure also shows that no statistical differences are evident between survival of only sweating patients and that of all A patients.

The study of severe pruritus was made rather complex by the limited number who showed this symptom alone (7 of 30). In order to utilize the 23 patients with other B symptoms, all 30 patients with severe itching were compared as to survival both with all other B patients and with those B patients remaining after exclusion of the ones whose only symptom was sweating. Figure 6 shows that patients with severe pruritus have a significantly poorer survival than other B, nonitching cases, and this is true even after the exclusion of patients with sweats only, who seem to enjoy a less severe prognosis. The essential meaning of this figure is that, sex, age, stage, and histology being equal, an intrinsic pejorative effect seems to be linked to severe pruritus, even when compared with fever and weight loss.

TABLE 1. Percent Frequency, in Decreasing Order, of Each Symptom and Each Combination of Two or More Symptoms in A and B Classes*

A symptom class			B symptom class		
	No.	Percent		No.	Percent
As	175	50.4	F only	85	29.5
f only	80	23.0	S only	72	25.0
p only	36	10.4	(F + S)	62	21.6
(f + p)	26	7.5	WL only	21	7.3
wl only	12	3.5	(S + WL)	12	4.2
P only	7	2.0	(F + P)	9	3.1
(f + wl)	7	2.0	(F + S + WL)	9	3.1
(p + wl)	2	0.6	(F + S + P)	7	2.4
(p + f + wl)	2	0.6	(F + WL)	4	1.4
			(S + P)	4	1.4
			(WL + P)	2	0.7
			(S + WL + P)	1	0.3
Total	347	100.0		288	100.0

* Identified according to the criteria of the Ann Arbor Conference.
f: fever < 38°C; F: fever ≥ 38°C; wl: weight loss < 10%; WL: weight loss ≥ 10%; S: sweats; p: mild pruritus; P: severe pruritus; As: asymptomatic cases.

On the basis of these results, a rearrangement of the symptoms required for classification into the B category seems to be possible. Figure 7 shows the effects on survival curves of the reclassification of our patients as A′ or B′; requirements for B′ category are fever over 38°C and/or weight loss more than 10% and/or severe pruritus, as defined above. Merely sweating patients were included into the A′ group. When compared with the Ann Arbor classification, it is evident that the new A′, B′ categories make a slight enhancement of the differential prognostic value of the two symptomatologic groups possible, but at the same time discrimination of the patient population is much more selective.

Discussion

The basic concept that constitutional symptoms of HD may reflect a more severe and complete engagement of the host organism by the tumor is strengthened by the poorer prognosis that is generally recorded in symptomatic patients. In most treatment protocols the presence or absence of general symptoms is regarded as one of the primary parameters by which therapeutic decisions have to be guided. Nevertheless, the choice of the individual symptoms to consider as having greater prognostic value has been made on merely empirical grounds without comparable studies, and has been changed several times in last decades. Moreover, very few efforts have been made

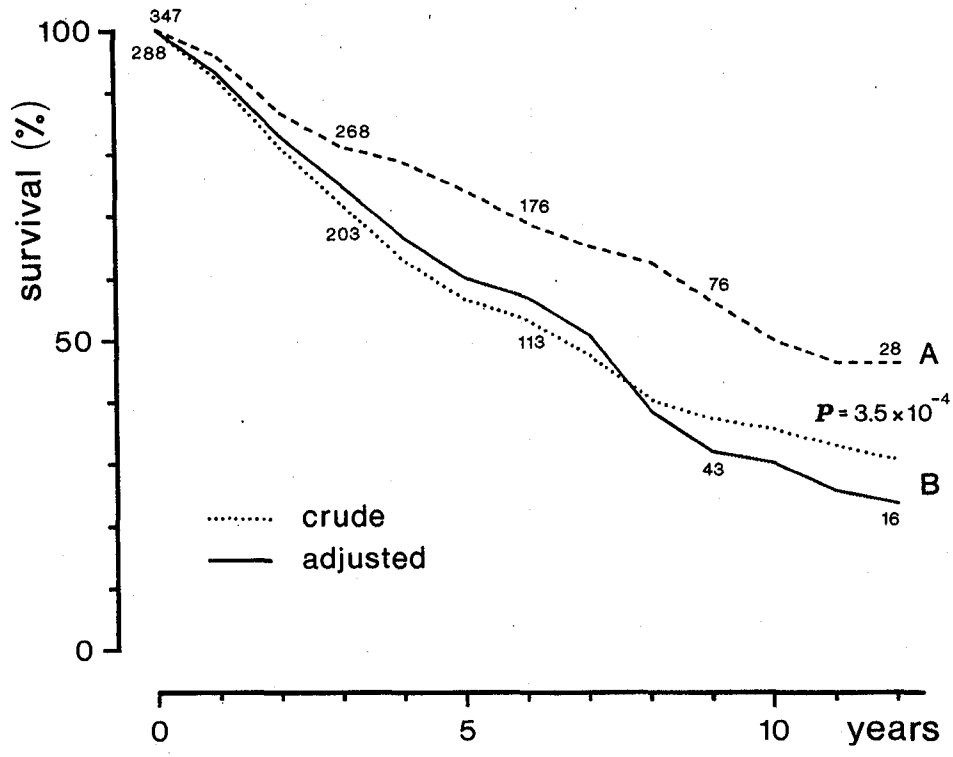

FIG. 2. Survival of A and B patients classified according to Ann Arbor criteria: Adjustment is made for the unbalanced distribution of sex, age, stage, and histotypes in the two groups.

to delineate the effect of each symptom on survival, although there is some doubt, as Aisenberg already observed 20 years ago[15] that all constitutional symptoms bear the same clinical and prognostic significance.

An additional obstacle is represented by the very limited knowledge that is still available regarding the pathogenesis and intrinsic biologic meaning of most symptoms in HD.[16-19] An essential review of the possible mechanism underlying HD symptoms has been made by Kaplan;[20] however, the significant scarcity of our knowledge about this topic does not help us to interpret our results at this time.

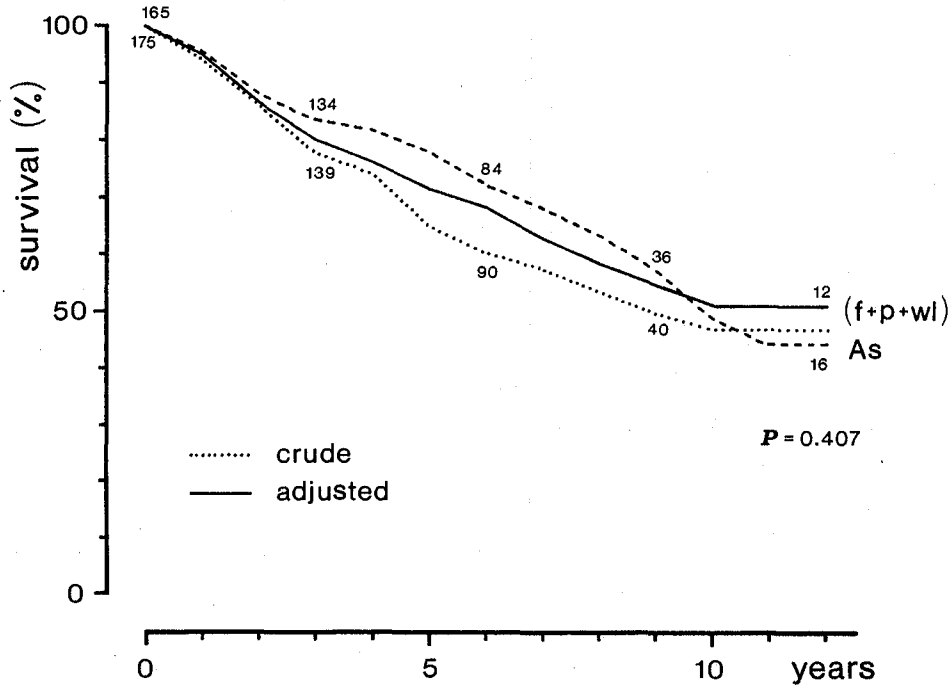

FIG. 3. Comparison, within A patients, between survival of fully asymptomatic cases and that of cases presenting fever under 38°C and/or weight loss of less than 10% of body weight and/or mild pruritus. Adjustment is made for the unbalanced distribution of sex, age, stage, and histotypes in the two groups.

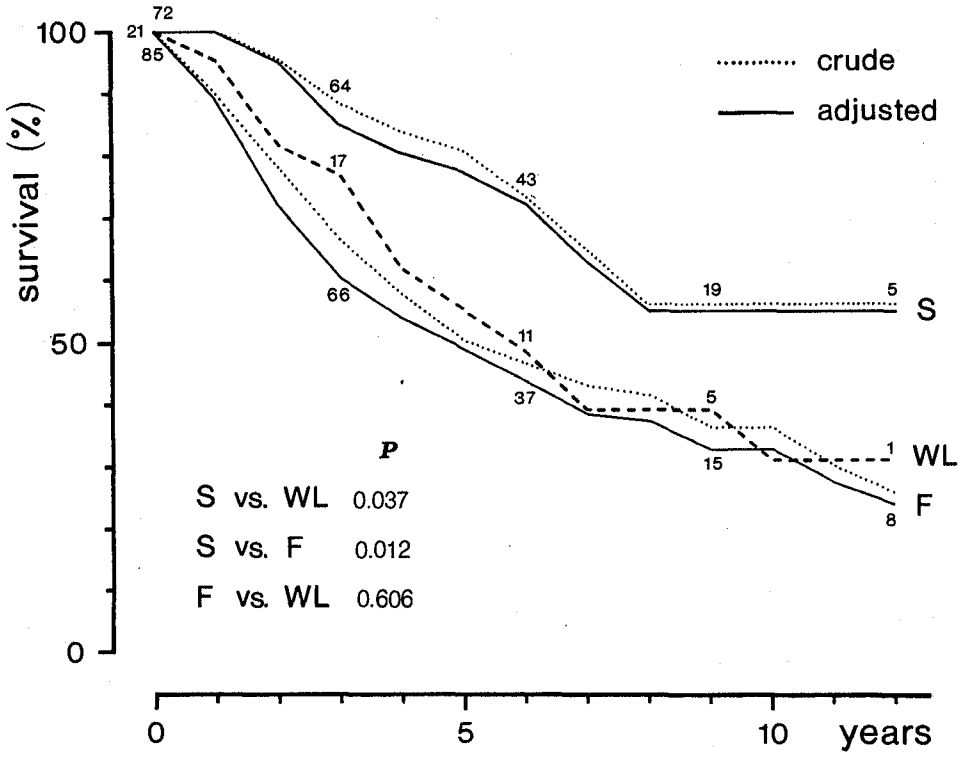

FIG. 4. Comparison, within B patients, of survival in those presenting only fever over 38°C, or only weight loss of more than 10% or only sweats, respectively. Adjustment is made for the unbalanced distribution of sex, age, stage, and histotypes in the two groups.

Moreover, it is rather perplexing that, although fever over 38°C, weight loss of more than 10%, and severe pruritus showed a very poor prognostic significance, their less severe counterparts were found to have none at all, not even an intermediate one; really there should be no reason to suspect different mechanisms for severe and mild symptoms.

However, the most important results of this study concerns sweats, which do not seem to influence survival. Indeed, our data do not indicate clearly whether sweats

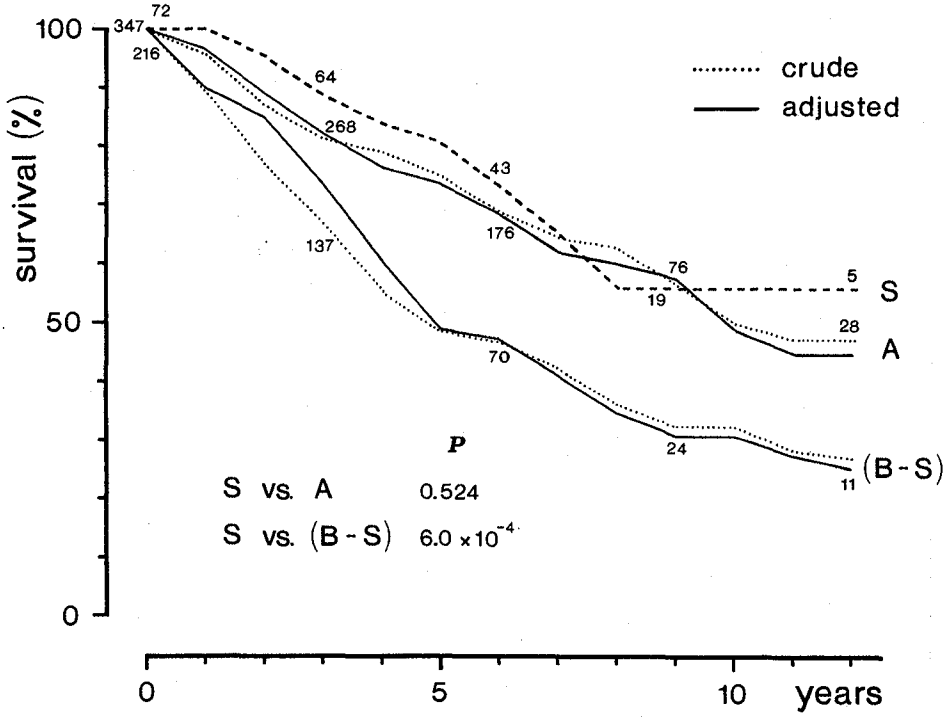

FIG. 5. Survival of sweating only patients compared with that of all other B patients (*i.e.*, those presenting fever and/or weight loss associated or not with sweats) and with that of all A patients. Adjustment is made for the unbalanced distribution of sex, age, stage, and histotypes in the two groups.

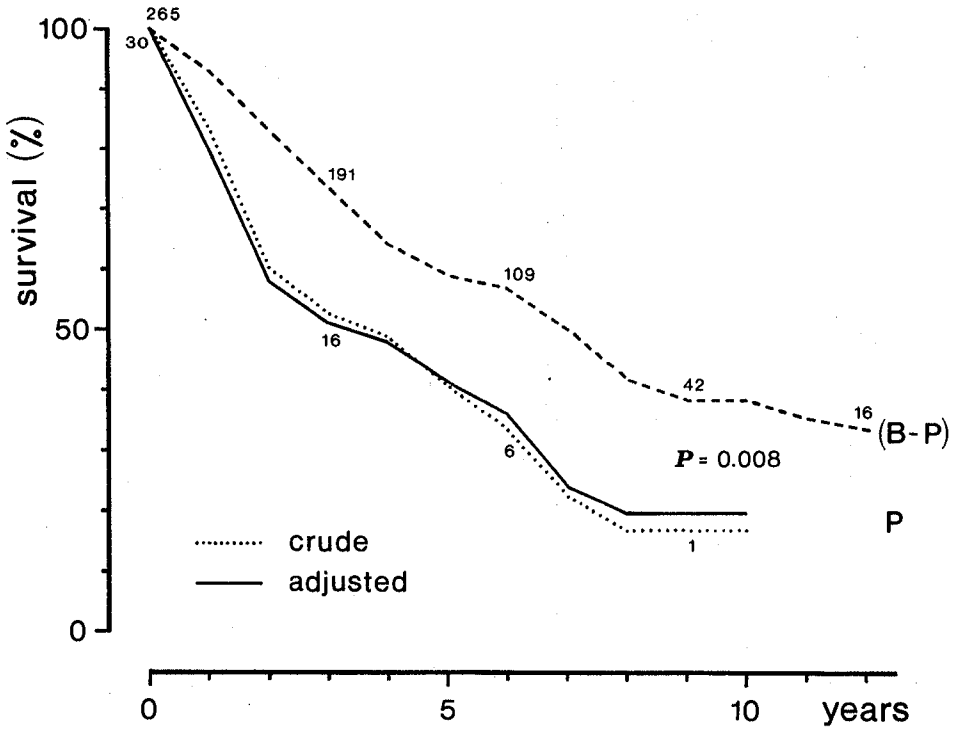

FIG. 6. Survival of patients with severe pruritus (7 as unique symptom, 23 with other B symptoms) compared with that of all other non-severely itching B patients. Adjustment is made for the unbalanced distribution of sex, age, stage, and histotypes in the two groups.

should be considered as having no prognostic importance at all or only a minor one, but some considerations lead us to think that the first hypothesis should be favored. As a matter of fact, when dealing with patients who underwent more aggressive therapy, a higher survival in a subgroup of them also could mean that the therapy itself might have been more effective just on that subgroup. So, only under the same treatment policy as that for asymptomatic patients can the lack of prognostic importance for sweats be demonstrated definitively. Nevertheless, we

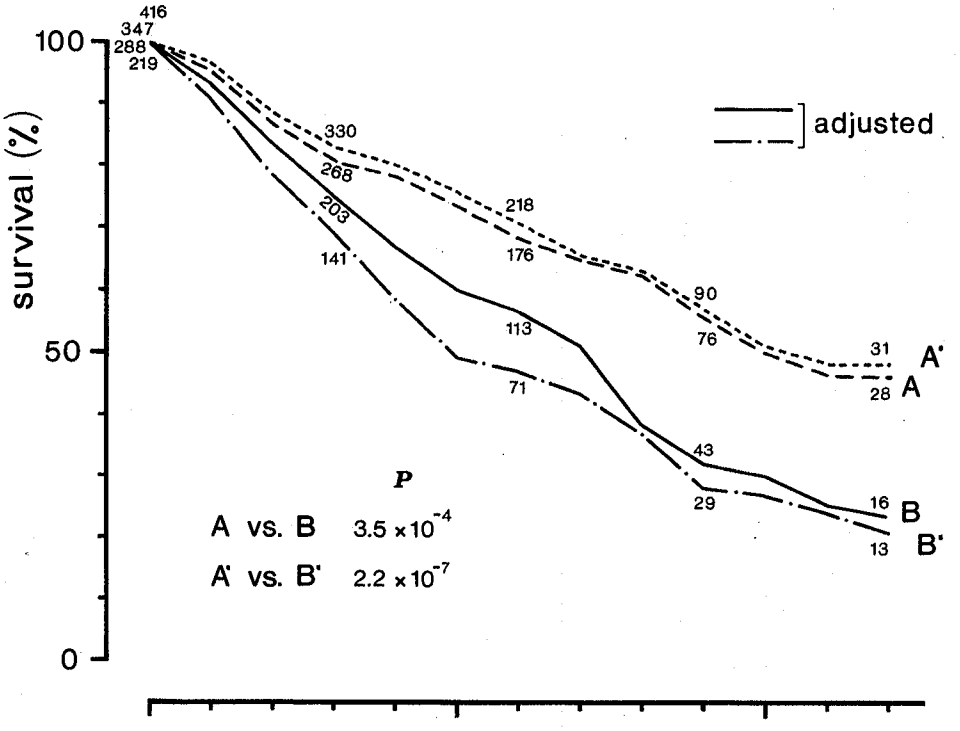

FIG. 7. Prognostic value of the Ann Arbor classification of constitutional symptoms compared with that of a new proposed reclassification: in B' category sweating was replaced by severe pruritus.

feel that Kaplan's hypothesis about unawareness of fever in patients apparently complaining of sweats only[20] seems to be simple and substantially convincing, and it could explain a number of sweats "without" prior fever, especially those recurring at night, when it is more probable that a febrile pulse may be unperceived.

Furthermore, it is well known that some febrile conditions can produce a functional instability in the sweat-regulating hypothalamic center, so that sweating may recur for days or months after the fever has subsided. This was skillfully and succinctly noted by Davison[21] who, after reviewing reports on the historical epidemics of influenza, bubonic plague and typhus, as well as his personal experience with Asian influenza, suggested the term of "sweating sickness." In HD a similar mechanism might be triggered by some initial pulses of fever, either unperceived or even well perceived at the time but later not related by the patient to his subsequent sweats.

It must be pointed out, however, that for a fever to be unperceived it probably will not be very high, and in this case, it seems quite likely that sweating, because it is preceded by low fever, would have the same prognostic significance as fever under 38°C, *i.e.* substantially none.

Further investigation is certainly needed on the mechanism of general symptoms in HD, but a redefinition of the Ann Arbor clinical categories also seems to be necessary for practical purposes. The major clinical consequence of the actual classification might not be so much undertreatment of patients with severe itching only, who constitute about 2% of all A patients and can be easily rescued by salvage regimens, as possible overtreatment of those with sweats only, who comprise about 25% of the B group, because of the well-known risk of the late effects of more aggressive therapies.[22,23]

REFERENCES

1. Ultmann JE, Cunningham JK, Gellhorn A. The clinical picture of Hodgkin's disease. *Cancer Res* 1966; 26:1047–1060.
2. Peters MV. A study of survivals in Hodgkin's disease treated radiologically. *Am J Roentgenol* 1950; 63:299–311.
3. Jelliffe AM, Thomson AD. Prognosis in Hodgkin's disease. *Br J Cancer* 1955; 9:21–36.
4. Peters MV, Middlemiss KCH. A study of Hodgkin's disease treated by irradiation. *Am J Roentgenol* 1958; 79:114–121.
5. Rosenberg SA. Report of the Committee on the Staging of Hodgkin's Disease. *Cancer Res* 1966; 26:1310.
6. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1971; 31:1860–1861.
7. Canellos PG, Came SE, Skarin HT. Chemotherapy in the Treatment of Hodgkin's Disease. *Semin Hematol* 1983; 20:1–24.
8. Feiner AS, Mahmood T, Wallner SF. Prognostic importance of pruritus in Hodgkin's Disease. *JAMA* 1978; 240:2738–2740.
9. Gobbi PG, Attardo-Parrinello G, Lattanzio G, Rizzo SC, Ascari E. Severe pruritus should be a B-symptom in Hodgkin's disease. *Cancer* 1983; 51:1934–1936.
10. Rosenberg SA, Boiron M, De Vita VT Jr *et al.* Report of the Committee on Hodgkin's Disease Staging Procedures. *Cancer Res* 1971; 31:1862–1863.
11. Rappaport H, Berard CW, Butler JJ, Dorfman RF, Lukes RJ, Thomas LB. Report of the Committee on Histopathological Criteria Contributing to Staging of Hodgkin's Disease. *Cancer Res* 1971; 31: 1864–1865.
12. Peto R, Pike MC, Armitage P *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. *Br J Cancer* 1977; 35:1–39.
13. Hankey BF, Myers MH. Evaluating differences in survival between two groups of patients. *J Chron Dis* 1971; 24:523–532.
14. Myers MH, Axtell LM. Statistical procedures for evaluating survival in Hodgkin's disease. *Natl Cancer Inst Monogr* 1973; 36:555–559.
15. Aisenberg AC. Hodgkin's disease: Prognosis, treatment and etiologic considerations. *N Engl J Med* 1964; 270:508–514.
16. Bodel P, Ralph P, Wene K, Long JC. Endogenous pyrogen production by Hodgkin's disease and human histiocytic lymphoma cell lines *in vitro*. *J Clin Invest* 1980; 65:514–518.
17. Braverman IM. Skin Signs of Systemic Diseases. Philadelphia: WB Saunders, 1981; 118–121.
18. Costa G, Bewley P, Aragon M, Siebold J. Anorexia and weight loss in cancer patients. *Cancer Treat Rep* 1981; (Suppl) 65:3–7.
19. Demis DJ, Robson RL, McGuire J. Pruritus. In: Clinical Dermatology, ed. 10. Philadelphia: Harper and Row, 1983; 29/2, 1–21.
20. Kaplan HS. Hodgkin's Disease, ed. 2. Cambridge, Massachusetts: Harvard University Press, 1980; 120–125.
21. Davison WC. Sweating sickness. *Am J Dis Child* 1960; 100:934.
22. Perry MC. Chemotherapy, toxicity and the clinician. *Semin Oncol* 1982; 9:1–4.
23. Kyle RA. Second malignancies associated with chemotherapeutic agents. *Semin Oncol* 1982; 9:131–141.