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A Reappraisal of Clinical and Biological Signs in Staging of Hodgkin's Disease

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Summary

The current Rye classification no longer appears fully satisfactory for staging of Hodgkin's disease. As a result of a study of clinical, radiological, and biological data taken from the records of 402 patients from 1966 to 1970, we suggest that a new classification should take into account the following factors: the site of onset of the disease which enables a distinction between the high cervical, mediastinal, retroperitoneal, and axillary forms, which all have their specific lymphatic extent; the involvement if any of the spleen; the biological signs as well as clinical symptoms for identification of the systemic syndrome. These changes could bring about significant consequences for therapy, especially in reducing irradiation volumes and in advocating the use of chemotherapy combined with radiotherapy.

Introduction

Progress in treatment and prognosis for Hodgkin's disease is in part related to the efforts made to classify the different stages of its spread. The classification adopted at the Rye (2) and Paris (19) symposia in 1965 has been extremely useful. However, it no longer appears to answer all the problems and several centers have already suggested changes (24).

Several points emphasize the relative inadequacy of this classification. Clinical analysis of spread of the disease differentiates various sites of onset which implicate specific ways of extent (21). The significance of visceral extension is dependent on whether or not there is contiguity with enlarged nodes (21, 24). Biological signs not included in the Rye classification are, however, valid for identification of the "systemic" syndrome and early detection of relapses. Exploratory laparotomy with splenectomy reveals the frequency of unexpected splenic involvement since the very onset of the disease. It also shows the limitations of lymphangiography and of routine liver examination, even including liver biopsies (1, 3–6, 9, 10, 12, 22).

The present study was designed to propose modifications in current staging, by recording data on site of onset and ways of spread and by accounting for biological data which enable a better definition of the systemic syndrome.

Patients and Methods

From January 1, 1966, to December 31, 1970, 402 previously untreated patients with biopsy-proved Hodgkin's disease were examined at this institute.

Chart 1 shows the distribution of patients according to age and sex.

Chart 2 and Table 1 sum up the distribution of the various histopathological types for the 302 cases reviewed according to the Rye classification.

Protocol of study included data as precise as possible on the site and date of appearance of the first anatomical sign as well as on all signs of the "prediagnostic phase" of the disease and staging by routine clinical and radiological examinations (lymphangiography, radiography of the skeleton, tomographies of the mediastinum). Exploratory laparatomy with splenectomy and liver biopsy was not routinely done in this series. It was performed when the disease was thought to have reached the abdominal areas. In these cases, preoperative examinations such as hepatosplenic scanning, arteriography of the celiac trunk, and functional liver tests did not give reliable data. The systemic syndrome was defined according to clinical symptoms [fever, night sweats, generalized pruritus] and biological signs [acceleration of ESR,[2] hyposideremia, hyperfibrinemia, hyper-α-2-globulinemia, neutrocytosis (Table 2)].

The Paris-Rye classification was modified in 2 ways. For finer analytical precision regarding the extent of disease, Stage I was subdivided into 3 groups: I_{10}, disease limited to 1 lymph node group in one anatomic region; I_{11}, disease limited to one anatomic region; I_2, disease in 2 contiguous anatomic regions. Subscript a or b was added to A and B groups depending on the absence or presence of biological anomalies (Table 2).

Results

Extent of Involvement. Table 3 shows the distribution of the 402 patients according to the Rye classification. We focused our investigation on 2 points not accounted for in this classification, the site of onset of the disease and the ways of spread.

Site of onset, was determined in 348 patients (mainly Stages I and II) by comparing the site of the first anatomical sign (anamnestic study) and the extent of lesions at diagnosis. As shown in Table 4, patients were divided into 4 main groups.

Group 1, high cervical localizations (submental, submaxillary, and jugular nodes), includes 101 patients. The outstanding feature here is that we never noticed mediastinum involvement at the time of diagnosis in spite of frequent secondary spread which regularly reached the supraclavicular areas and occasionally axillary areas. A possible source of error

[1] Presented by.

[2] The abbreviation used is: ESR, erythrocyte sedimentation rate.

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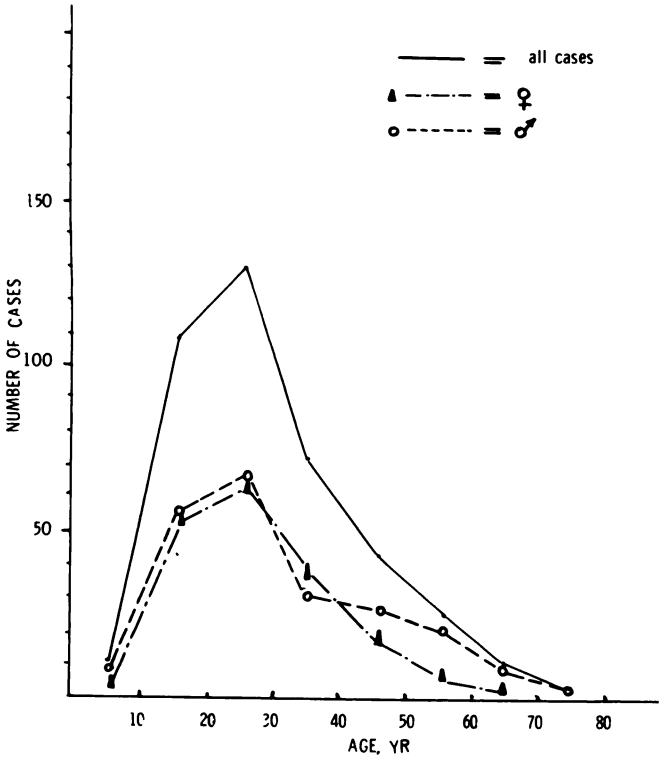

Chart 1. Distribution of 402 patients with Hodgkin's disease according to age and sex.

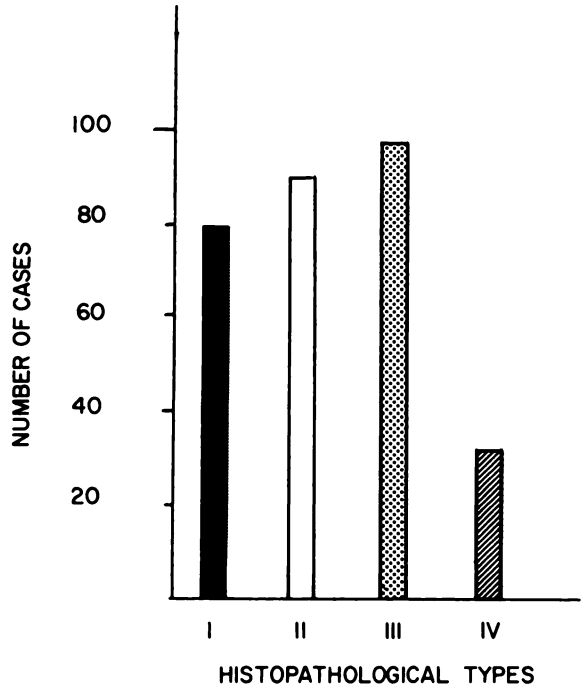

Chart 2. Distribution of histopathological types in 302 cases of Hodgkin's disease.

might have been that diagnosis had taken place prior to mediastinal involvement. This is not the case, however, since high cervical forms are not diagnosed earlier than lower cervical and mediastinal forms (Chart 3).

Group 2, lower cervical and mediastinal localizations, includes, in 181 patients, 126 cases with supraclavicular localizations associated with a mediastinal tumor; 18 cases with apparently isolated supraclavicular nodes (however, after a closer analysis, 10 showed a minimal mediastinal involvement, and 3 others had a suspicious lymphangiography and a retroperitoneal involvement proved by exploratory laparatomy); and 37 cases in which the first anatomical sign was a mediastinal tumor and 26 of these had secondarily one or more supraclavicular nodes at diagnosis.

Group 3, retroperitoneal localizations, includes 23 patients with lesions localized below the diaphragm (18 inguinocrural nodes, 5 upper retroperitoneal involvement) and 23 patients presenting in addition extent to the supraclavicular areas (mostly left: 19/23). These patients were classified as Stage III in the Rye classification. None of these 46 patients had mediastinal involvement at diagnosis.

Group 4, axillary localizations, was a group of 18 patients of whom 5 had a mediastinal tumor. In 7 instances the axillary nodes were completely isolated.

In Group 5, in addition, 2 isolated tumors of the spleen were diagnosed by splenectomy.

In lymphatic extension, the first route of spread, two important facts should be pointed out. The mediastinum is not reached by retrograde extension from high cervical

Table 1

Distribution of histopathological types in 302 cases of Hodgkin's disease

Histological types	No. of cases
I. Lymphocytic predominance	80
II. Nodular sclerosis	93
III. Mixed cellularity	98
IV. Lymphocytic depletion	31
Total	302

Table 2

Criteria of the determination of biological systemic syndrome ("b" cases)

ESR	≥	40 mm 1st hr
Sideremia	≤	70 μg/100 ml
Fibrinemia	≥	0.5 g/100 ml
α-2-Globulinemia	≥	1 g/100 ml
Neutrocytosis	≥	9000/cu mm

2 signs = b
0 or 1 sign = a

Table 3

Staging in 402 cases of Hodgkin's disease

Classification			No. of patients
Stage I			
I_{10}	57		
I_{11}	58	190	
I_2	75		325
Stage II		135	
Stages III and IV		77	77
Total			402

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Table 4
Classification of 348 cases of Hodgkin's disease according to site of disease onset

Site of onset		No. of patients	
High cervical nodes		101	101
Supraclavicular nodes			
Mediastinum	+	126	144
	−	18	
Mediastinum			
Supraclavicular nodes	+	26	37
	−	11	
Axillary nodes			
Mediastinum	+	5	18
	−	13	
Retroperitoneal nodes			
Supraclavicular nodes	+	23	46
	−	23	
Tumor of the spleen		2	2
Total			348

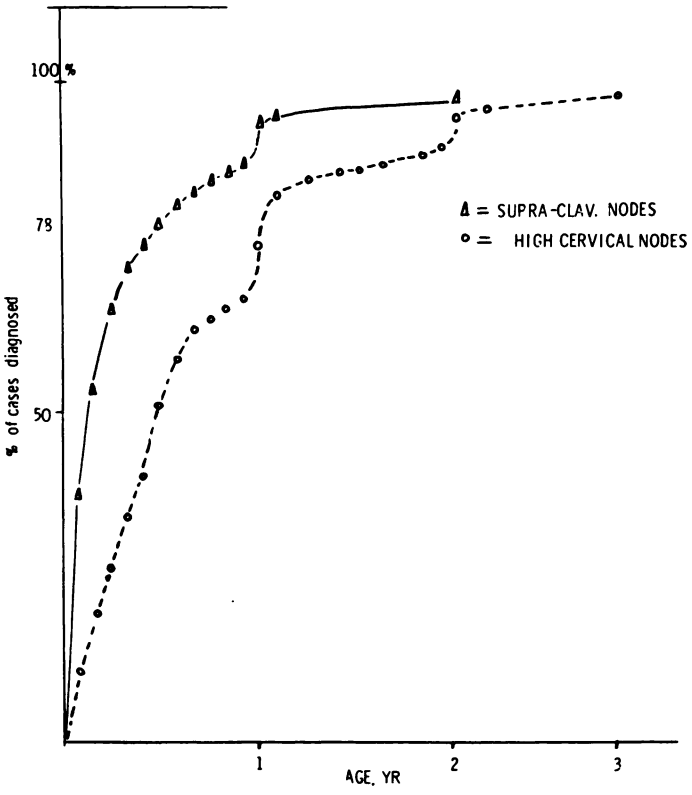

Chart 3. Percentage of diagnosed cases in relation to interval between the first symptom and diagnosis in high cervical and supraclavicular (*supra-clav.*) localizations; 50% high cervical forms *versus* 78% lower cervical forms were diagnosed within the first 6 months of the disease.

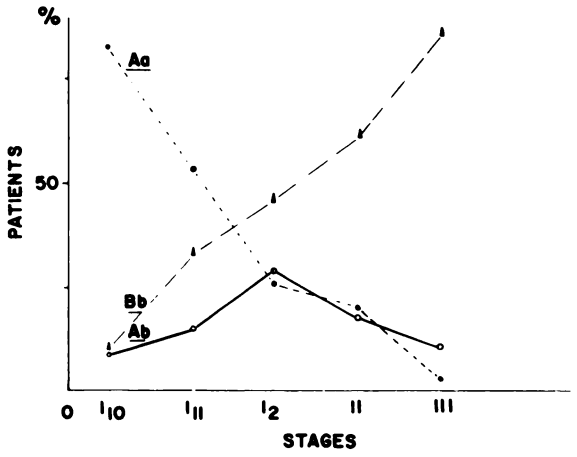

Chart 4. Percentage of Aa, Ab, Bb forms in relation to staging of Hodgkin's disease.

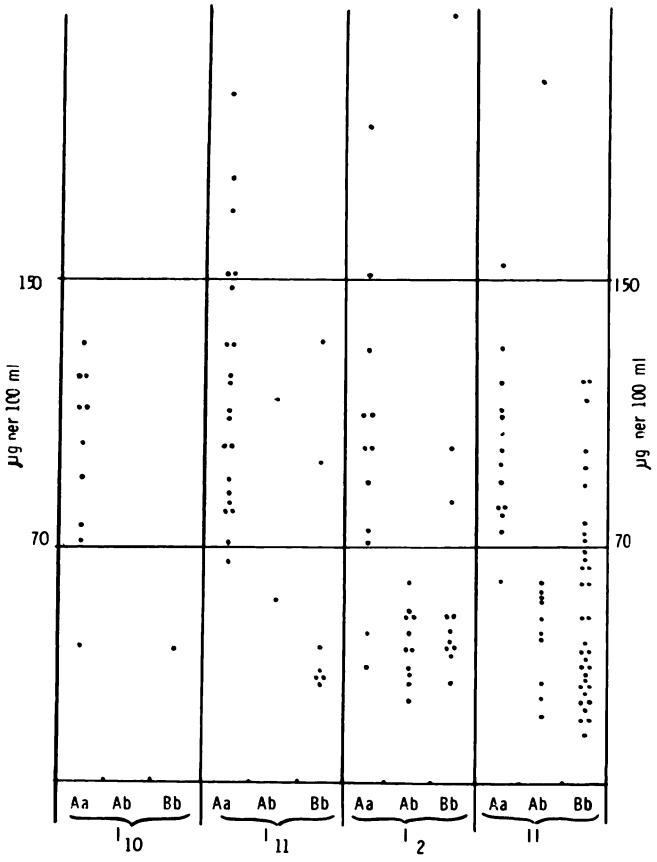

Chart 5. Sideremia in 200 cases of Hodgkin's disease, Stages I and II.

localizations. Supraclavicular areas appear as a "cross-road" region evidencing involvement mostly of the mediastinum and occasionally the retroperitoneal or axillary areas.

Abdominal upper paraaortic node involvement in supradiaphragmatic Hodgkin's disease was studied. Seventeen Stage III patients showed supradiaphragmatic involvement associated with invasion of the abdominal upper paraaortic nodes. Our experience (3) and that of others (5, 6, 12) show that these paraaortic involvements are always concomitant with splenic or more rarely hepatic invasion.

Several authors assume that the paraaortic nodes are reached by retrograde invasion from supradiaphragmatic areas coming through the thoracic duct; in the same way, the liver and spleen would be reached by retrograde lymphatic extension from the paraaortic nodes (8). On the other hand, we do not reject the hypothesis that the spleen could be

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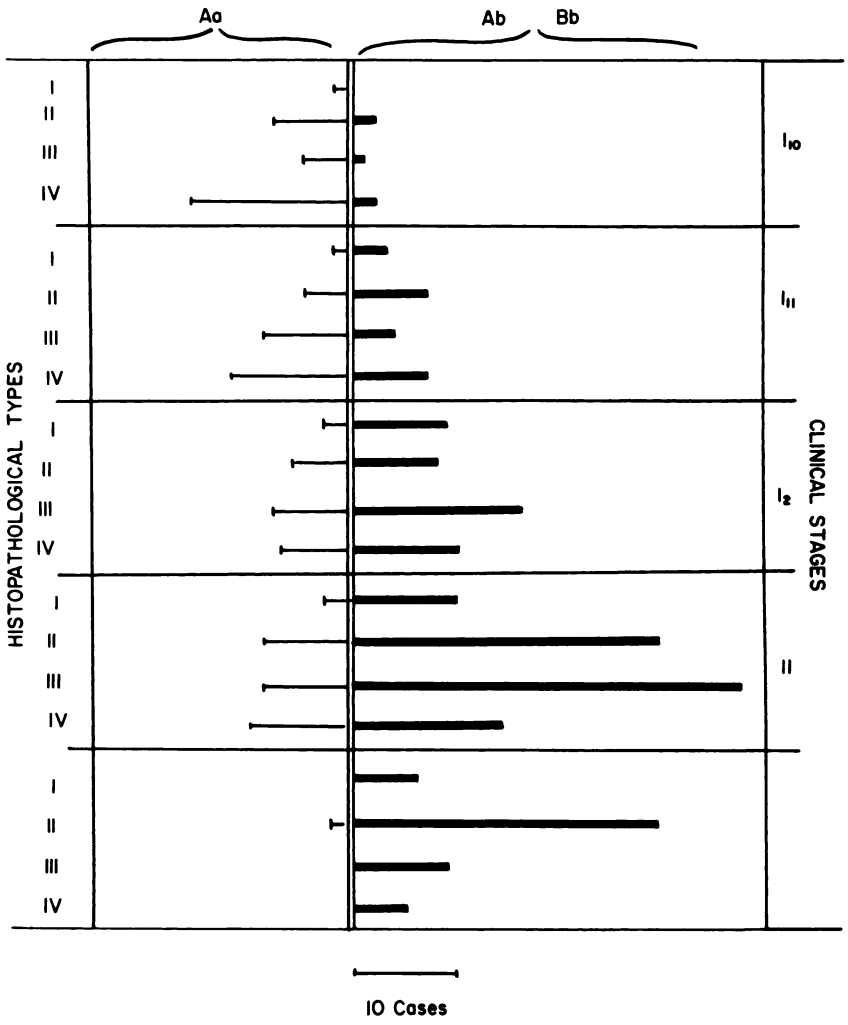

Chart 6. Correlation between histopathological types, clinical staging, and presence or not of systemic signs.

reached by the blood stream (13, 14) and that upper paraaortic nodes could be invaded secondarily through the normal efferent lymph flow of the spleen (Refs. 7, 11, 15, and 16; J. L. Binet, personal communication).

At least, in a group of 16 Stage IV patients[3] there were 9 diffused forms with subacute evolution and 7 patients with limited nodal involvement but with several visceral localizations, mostly bone, distributed at random. In such cases, extension via the blood stream was supported by the diffusion of the disease (17, 18, 21).

Systemic Symptoms. There is no agreement yet as to the definition of the systemic syndrome. Several investigators (2) have taken into consideration only clinical symptoms (fever, night sweats, generalized pruritus). These symptoms are usually linked with the exception of pruritus, which is not seen in children (20, 23) and is present in only one-third of the adult cases. In addition to these, we point out the value of biological symptoms: increase of ESR; hyposideremia without noticeable lowering of transferin; hyperfibrinemia; hyper-α-2-globulinemia; neutrocytosis.

[3] Of this series, 37 cases were originally classed Stage IV. However, because of limited visceral involvement in contiguity with enlarged nodes, 21 of these cases were not considered to be real Stage IV.

Table 5
Histological features of the spleen in 27 previously untreated patients

	Spleen +[a]	Spleen −	Total
Presence or absence of systemic signs			
Aa	2	6	8
Ab	1	1	2
Bb	8	9	17
Staging			
I_{10}	3	3	6
I_{11}	0	2	2
I_2	1	5	6
II	7	6	13

[a] +, specific involvement of the spleen; −, normal spleen or nonspecific involvement.

In 80% of cases, clinical and biological symptoms are both present or absent. However, there can be dissociation.

Presence of clinical signs, absence of biological signs (Ba). This type of dissociation is rare (4% of cases). Of 392 cases (Ten were excluded because of the lack of reliable data or corticotherapy before diagnosis.), 18 were Ba. Mofeover, in all these cases, minor biological anomalies were present.

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Presence of biological signs, absence of clinical signs (Ab). This dissociation is not rare; 68 patients in the present series, that is 17%, were Ab. The study of the frequency of these forms in relation to staging is shown in Chart 4. The percentage of distribution of Ab cases is not very different from Bb cases ($p < 0.05$) in Stage I, whereas the difference with Aa cases is statistically significant ($p < 0.0001$).

On the other hand, frequency of Ab cases in Stages II and III becomes rarer than that of Bb. This could mean that, in a certain number of cases, biological anomalies preceded the appearance of clinical symptoms.

Hyposideremia seems to be the best test to identify the systemic syndrome (Chart 5) and its combination with increased ESR is particularly meaningful.

The significance of the systemic syndrome is not really confirmed yet. We have looked for correlations which may exist between the systemic syndrome and factors such as age and sex, histopathological type, extent of disease, and splenic involvement with these findings. There is no correlation with age and sex or with the histopathological type (Chart 6). There is a clear correlation between the systemic syndrome and the extent of disease (Chart 6). Preliminary data taken from 27 early splenectomies did not show a relationship between spleen involvement and the systemic syndrome (Table 5).

Table 6

Rate of relapses in Aa, Ab, and Bb groups, for 144 Stage I and II Hodgkin's disease patients treated by combined chemotherapy (HN2 and vinblastine) plus extended fields cobalt therapy and followed up for 2.5 years or more

		RELAPSES	COMPLETE REMISSION
I_{10}	Aa		(10)
	Ab		
	Bb	(1)	(1)
I_{11}	Aa		(20)
	Ab	(1)	(2)
	Bb	(5)	(3)
I_2	Aa		(10)
	Ab	(3)	(6)
	Bb	(6)	(15)
II	Aa	(6)	(6)
	Ab	(4)	(8)
	Bb	(21)	(15)

No. in parentheses, no. of cases available to study.

Table 7

Preoperative clinical and biological findings in 22 splenic relapses observed in the series of 144 patients recorded in Table 6

Preoperative findings	No. of patients
Clinical symptoms	
A	17
B	5
Biological signs	
a	2
b	20

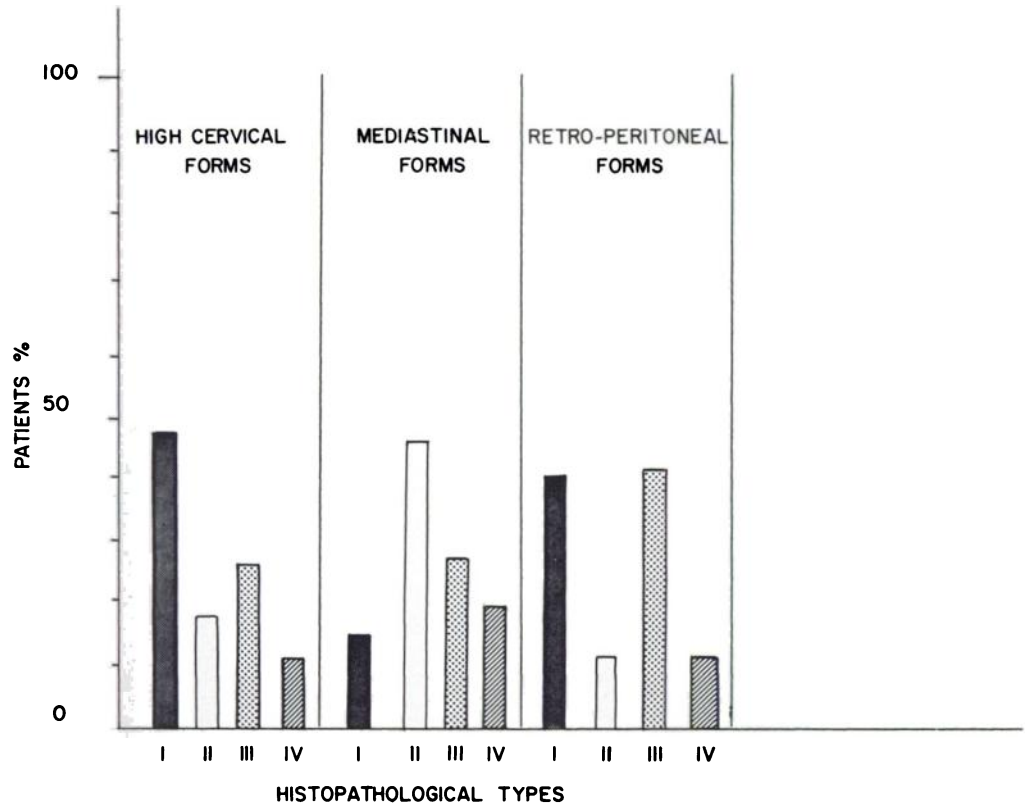

Chart 7. Distribution of histopathological types according to site of disease onset.

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The prognostic value of the systemic syndrome has been studied. The frequency of relapses was not significantly different between Groups II Aa, II Ab, and II Bb in a series of 144 Stage I and II patients who were treated in the same way for 2.5 years or more (Table 6). However, there was a strong difference in Stage I cases in which 3 facts must be pointed out: Group Ab is close to Group Bb; none of the 40 Aa patients has relapsed so far; there have been relapses in Group Bb. Consequently the systemic syndrome seems to have a definite value for prognosis. Moreover, biological symptoms are of the utmost importance in the early detection of relapses prior to the advent of clinical symptoms, especially in splenic relapses (Table 7).

Discussion

In relation to the site of onset, the data recorded in this study show that supraclavicular localizations represent a secondary dissemination of the disease from various primary sites (mostly mediastinum and retroperitoneal areas).

Therefore, in relation to the real site of disease onset, it seems that only 4 major forms should be distinguished: high cervical forms, without mediastinal involvement; mediastinal forms, with dissemination to supraclavicular and/or axillary areas; retroperitoneal forms, with frequent supraclavicular dissemination (especially on the left side) but where the mediastinum usually remains free of disease; axillary forms.

The first 3 forms can also be characterized by the 2 following facts. Of the histopathological types, (Chart 7), Type I is frequent in high cervical forms, Type II in mediastinal forms, and Types I and III in retroperitoneal forms. High cervical forms are more frequent in the male and children, mediastinal forms are more frequent in the female, and retroperitoneal forms are seen most often in older patients (Chart 8).

It therefore seems important for staging to take into account the real site of disease onset. Prognosis and modalities of treatment may depend on these data.

For example, the absence of mediastinal involvement in high cervical forms could lead to selective irradiation which would exclude the mediastinum. On the other hand, supraclavicular areas which are the elective extension sites of retroperitoneal forms could be, in these forms,

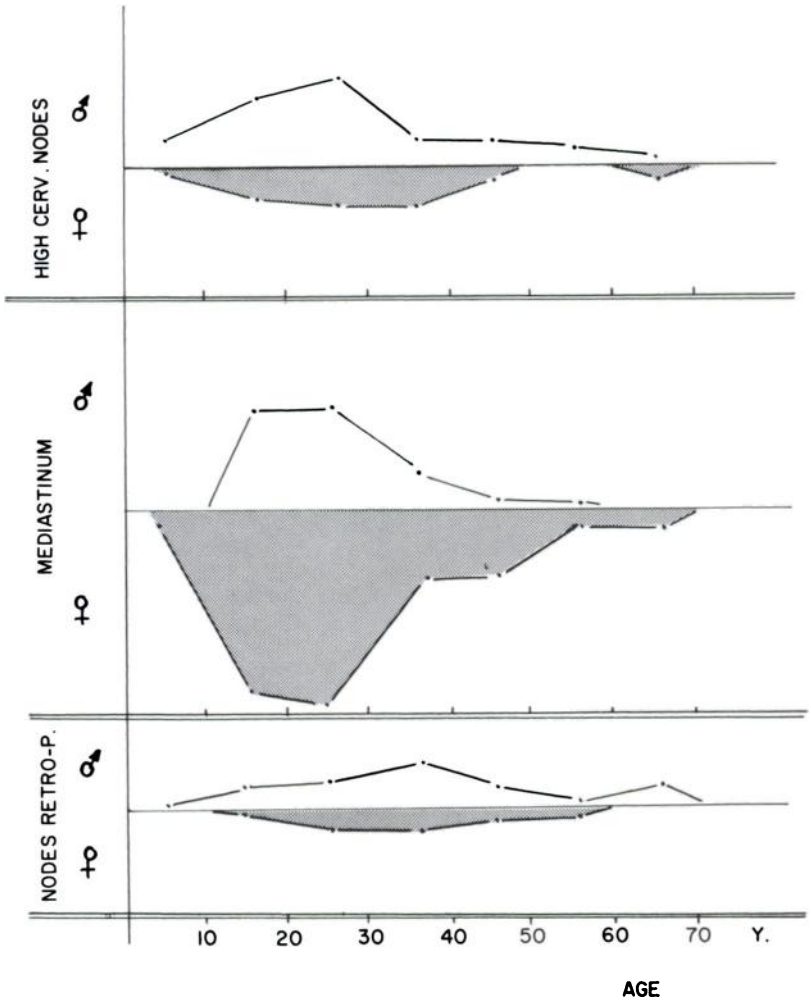

Chart 8. Distribution of age and sex according to site of disease onset.

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prophylactically irradiated in addition to abdominopelvic fields.

Regarding ways of extent, the key problem is the distinction between forms extended to lymphoid tissues which should be treated by selective radiotherapy depending on the real site of disease onset and forms with blood dissemination requiring a combination of chemotherapy and radiotherapy. We must, however, admit that criteria proving blood dissemination are still not reliable enough to include this distinction in a new classification.

The main problem in this field is to determine the significance of splenic involvement which may be present since the very onset of the disease (3, 6, 9, 12.)

We have developed elsewhere (14, 21) reasons leading us to believe that spleen involvement could be good evidence for blood dissemination. On the other hand, most investigators think that the spleen is reached by the lymphatic route (8). Further studies on this point are needed.

Whatever the mechanism of spleen invasion may be, it is difficult to escape the conclusion that the involvement of the spleen, routinely checked by splenectomy, is a preeminent factor of staging and should be taken into account in the building of any new classification.

Biological systemic signs should be included in the classification, thereby enabling an improved definition of the systemic syndrome and the early detection of relapses.

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