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Relationship of Histological Findings to Survival in Hodgkin's Disease

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Summary

In five of eight series of cases of Hodgkin's disease classified as to histological type according to the Rye classification, patients with the lymphocytic predominance type of the disease had the best prognosis, those with the nodular sclerosis type had the 2nd best, those with the mixed cellularity type had the 3rd best, and those with the lymphocytic depletion type had the poorest prognosis. In two of the remaining three series, the 5-year survival rate was the same for the mixed cellularity and lymphocytic depletion groups; otherwise, the ranking was identical. In the eighth series, the ranking was the same, except for the fact that patients with the nodular sclerosing type had a slightly better survival rate than those with the lymphocytic predominance type. In all eight studies, there was a clear-cut difference in the survival rates between the nodular sclerosis and mixed cellularity groups. In spite of differences in the types of institutions, and therefore possibly of the patients included and therapy given, and questionable errors in histological classification in four of the series, there were only four variations from the ranking as to prognosis of the four histological types in the eight series. A comparison of the series as to the percentage of patients, sex distribution, clinical stage, and survival rates in each histological group suggests that, in some series, the histological type of Hodgkin's disease given in a significant number of patients was erroneous. This finding is believed to indicate that the histological material in all reports on Hodgkin's disease should be reviewed by more than one pathologist.

Introduction

Since tissues are studied histologically for determining the nature of a pathological process, such a study provides, roughly, the prognosis associated with that disease. Histological classifications of neoplasms of the various tissues and organs are attempts to define more accurately and systematize this relationship between histological findings and prognosis.

Rosenthal (19), in 1936, was the first pathologist to attempt to relate the histological features of Hodgkin's disease to prognosis. Although the histological types which he suggested did not gain wide acceptance, his findings were precursors of the generally accepted classification of Jackson and Parker (9), proposed in 1944. Their classification was prognostically significant, in that the paragranuloma type carried a good prognosis, whereas that of the sarcoma type was poor. Its value was limited, however, since both these groups were small; each comprised only about 10% of the cases of most reported series (1). The granuloma group consisted of the remaining 80%. Approximately 20% of those patients who lived 5 years or longer had the paragranuloma type of Hodgkin's disease, while the remaining 80% were in the large granuloma group, and could not be identified histologically (1). Following Peter's (15) report of the relationship of the clinical stage of the disease to its prognosis, the value of this classification was further questioned, since it was found that the prognosis could be more accurately predicted by the clinical stage of the disease at the time the patient was first observed (1).

In 1966, Lukes and Butler (12) published a detailed study of a series of cases of Hodgkin's disease in servicemen from World War II. They used 6 histological types, based upon the ratio of lymphocytes to Reed-Sternberg cells and upon the presence of characteristic types of fibrosis. This study demonstrated a relationship between the histological features and the clinical stage of the disease, as well as the prognosis. The findings were believed to be evidence that the described histological types reflected the reaction of the patient to his disease.

The classification used in this study was based upon the above-mentioned 6 histological types described by Lukes and Butler at the conference on Hodgkin's disease held in Rye, N. Y., in 1965. The Rye classification (13) consists of 4 types and represents a combination of prognostically similar groups. The lymphocytic predominance group includes the lymphocytic and/or histiocytic (nodular and diffuse) types of Lukes and Butler, as well as the paragranuloma type of Jackson and Parker. The nodular sclerosis and mixed cellularity types are those described by Lukes and Butler. The lymphocytic depletion type includes the diffuse fibrosis and reticular types of Lukes and Butler and the sarcoma type of Jackson and Parker. The relationship between the 3 classifications is presented in Table 1.

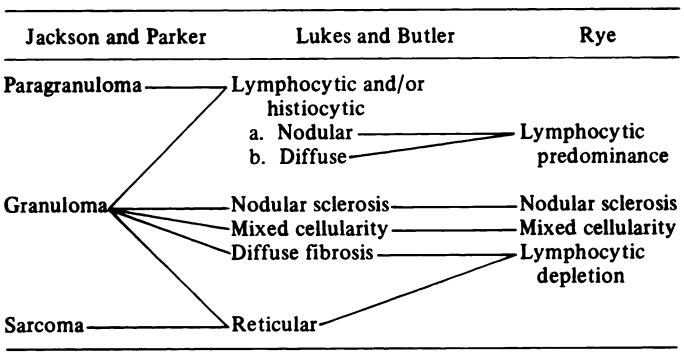
More recently, Rappaport and Strum (18) and Strum *et al.* (20) have presented evidence of the importance of vascular invasion in Hodgkin's disease. Their findings suggest that this additional histological parameter will be most useful in identifying those patients with the nodular sclerosis and mixed cellularity types of the disease who have the poorest prognosis.

Materials and Methods

A review of the medical literature revealed 7 series of patients with Hodgkin's disease in which pretreatment biopsies were classified according to the previously mentioned Rye

Table 1

Comparison of Jackson and Parker (9), Lukes and Butler (12), and Rye (13) classifications of Hodgkin's disease



classification. The number of patients with each histological type was given, together with the 5-year survival of those with each type. In 2 of the 7 series, the 10-year survival rate also was reported.

The hazards of comparing personal series to those reported in the literature, wherein the basis for the selection of cases is an element to be considered, is recognized. Particularly is this true in a condition such as Hodgkin's disease, in which the clinical stage, age, and sex of the patient all seem to have a bearing upon the prognosis (1). This seems, however, to be the only means of evaluating efforts being made in many institutions to relate histological findings in the pretreatment biopsy to survival.

A brief description follows of the type of hospital or the population involved in the 7 studies. The study of Lukes and Butler (12) was largely concerned with young, adult males, in the United States Army between 1942 and 1945, who apparently had been in sufficiently good health to pass the army physical examination prior to the diagnosis of Hodgkin's disease. The study of Hamann *et al.* (8) in Germany and that of Gough (7) in England were from general hospitals. Since the studies of Keller *et al.* (10) in this country, Landberg and Larsson (11) in Sweden, and Franssila *et al.* (5) in Finland are from radiotherapy institutes, the elements of selection natural to such institutions are involved. The study of Fuller *et al.* (6), which was made in a cancer hospital in this country, includes only patients with Stage I or II disease, as determined prior to the routine use of lymphangiography. Presented herein also are the results of a study of 235 cases taken from the group of 395 cases collected from many of the major radiotherapy centers, classified according to the Jackson and Parker classification and reported by Lukes *et al.* (14) at the meeting on Hodgkin's disease held in Paris in February 1965. The 235 cases from this group were reclassified according to the Rye classification by the same pathologists[1] after the Paris meeting. The material on the remaining 160 cases had been returned to their contributors before this review was initiated. The original 395 cases were contributed by many of the major radiotherapy centers; each center submitted material on all their patients who had lived 10 years or longer and on an equal number of patients who had lived less than 10 years following the diagnosis of the disease.

[1] R. J. Lukes, personal communication.

Results

The 7 series taken from the medical literature were compared with respect to the number of patients with each histological type of Hodgkin's disease, the percentages of the entire series that these numbers represent, and the percentage of patients who survived 5 years or longer (Table 2). The total number of patients in each series and the percentage of those patients who survived 5 years or longer are also included in this table.

There is a significant difference ($p < 0.01$) in the 5-year survival rates of the total number of patients in each of the 7 series, as well as of the patients in any single histological group in the 7 series. In all except 1 series, that of Landberg and Larsson, the lymphocytic predominance group had the most favorable 5-year survival rate and the nodular sclerosis group had the second most favorable. In the study of Landberg and Larsson, the nodular sclerosing group had a slightly better survival rate than the lymphocytic predominance group. In 5 of the 7 series, patients with the mixed cellularity type had the 3rd best survival rate, and those with the lymphocytic depletion type the poorest rate. In the studies of Hamann *et al.* and Keller *et al.*, the survival rate of the latter 2 groups of patients was essentially the same. The latter group is, however, a small one.

The 10-year survival figures in the series of Lukes and Butler and Fuller *et al.* are shown in Table 3. As is true of the 5-year survival figures for the majority of the 7 series, the 10-year survival rate was the best in the lymphocytic predominance group, next best in the nodular sclerosis group, the third best in the mixed cellularity group, and poorest in the lymphocytic depletion group. Table 3 also shows comparable 10-year survival rates in the 235 cases collected at the 1965 meeting on Hodgkin's disease held in Paris and classified by the Rye classification after this meeting.

The 5-year survival rates of the series of Gough, Landberg and Larsson, and Franssila *et al.* were similar and much lower than those of the other 4 series, which suggests that the former contain more far-advanced cases or differences in the population. While the percentages of males and females (Table 4) are similar in all the series except that of Lukes and Butler, the series differ significantly ($p < 0.01$) with respect to the percentage of patients in any one histological group (Table 2) and to the sex distribution in the different histological groups (Table 5). The series of Gough and of Landberg and Larsson contained a significantly smaller percentage of patients with the nodular sclerosing type and are the only 2 in which less than 50% of females had this type. Gough's series also shows a difference in the clinical stages (Table 6) of the disease in patients with this histological type. In the series of Landberg and Larsson, the percentage of both patients and females with the mixed cellularity type was notably higher: further, theirs is the only series in which this histological type was found in the majority of both sexes and in which a considerably larger number of patients with this histological type had Stage III or IV disease. Gough's series contains a larger percentage of patients and of females with the lymphocytic depletion type; it is the only series in which the majority of patients with this type were female and in which the percentage of females with this histological type was higher than those with any other

Table 2
Five-year survivals by histological types

	Lymphocytic predominance		Nodular sclerosis		Mixed cellularity		Lymphocytic depletion		Total series	
	No. of cases	Survival 5+ yr (%)	No. of cases	Survival 5+ yr (%)	No. of cases	Survival 5+ yr (%)	No. of cases	Survival 5+ yr (%)	No. of cases	Survival 5+ yr (%)
Lukes and Butler (12)	63 (17%)	73	149 (40%)	44	97 (26%)	31	68 (18%)	13	377	40
Hamann *et al.* (8)	24 (12%)	60	88 (46%)	56	40 (21%)	37	41 (21%)	38	193	49
Gough (7)	19 (20%)	59	14 (15%)	45	28 (29%)	18	35 (36%)	8	96	26
Keller *et al.* (10)	9 (5%)	88	92 (52%)	72	65 (37%)	37	10 (6%)	38	176	57
Landberg and Larsson (11)	18 (12%)	50	31 (21%)	55	80 (54%)	21	20 (13%)	5	149	30
Franssila *et al.* (5)	9 (9%)	55	45 (47%)	47	32 (33%)	3	11 (11%)	0	97	28
Fuller *et al.* (6)	13 (10%)	77	71 (53%)	72	43 (33%)	58	5 (4%)	20	132	67

Table 3
Ten-year survivals by histological types

	Lukes and Butler (12)		Fuller *et al.* (6)		Lukes[1]	
	No. of cases	Survival 10+ yr (%)	No. of cases	Survival 10+ yr (%)	No. of cases	Survival 10+ yr (%)
Lymphocytic predominance	63 (17%)	44	13 (10%)	69	35 (15%)	66
Nodular sclerosis	149 (40%)	25	71 (53%)	52	103 (44%)	53
Mixed cellularity	97 (26%)	14	43 (33%)	37	67 (28%)	28
Lymphocytic depletion	68 (18%)	4	5 (4%)	≤20	30 (13%)	20
Total	377 (100%)	22	132 (100%)	51	235 (100%)	44

Table 4
Sex distribution by series

	Males (%)	Females (%)
Lukes and Butler (12)	98	2
Hamann *et al.* (8)[a]	57	43
Gough (7)	56	44
Keller *et al.* (10)	61	39
Landberg and Larsson (11)	62	38
Franssila *et al.* (5)	62	38
Fuller *et al.* (6)	61	39

[a] The percentages are for the entire series of 508 patients rather than for the 193 patients who were followed for 5 years.

type of the disease. His is also the only series in which the majority of patients with the lymphocytic depletion type did not have Stage III or IV disease (Table 6).

Although not reflected in the relative distribution of patients with each histological type, the series of Hamann *et al.* contains a lower percentage of females in the nodular sclerosis group; moreover, with the exception of that of Gough, the percentage of both patients and females in the lymphocytic depletion group were higher in this series than in the others. The relatively good survival for the lymphocytic depletion type in this series may be the result of including patients with the nodular sclerosis type in the lymphocytic depletion type.

Another important variable, aside from the type of therapy given, is the ages of the patients in the series, since survival is generally poor in older patients (1). The median age in Lukes and Butler's series was 25 years; in that of Franssila *et al.*, it was 34 years; in that of Fuller *et al.*, it was 29 years; and in that of Hamann *et al.*, it was 43 years. Landberg and Larsson reported a median age of 50 for females and 43 for males. From the information given, the median age of the series of Keller *et al.* has been estimated as just above 30 years, and it is approximately 40 years for that of Gough. The series of Landberg and Larsson had patients of the oldest median age as well as the largest number of patients with clinical Stage III or IV disease. From the information given, no other association between median age and any other feature of the disease was apparent in this or any other series.

Discussion

The study of Keller *et al.* is one of the most important for assaying the Rye classification of Hodgkin's disease, because of the factors and relationships evaluated and because of the experience in hematopathology of the pathologists. Their confirmation of the relationship between clinical stage and histological type, found by Lukes and Butler, is evidence of the value of this relationship as a rough means of determining the distribution of histological types in other series, as are their findings regarding sex distribution according to histological type. Further, their finding that the decreased survival of males and of all patients over 30 years of age is largely attributable to unfavorable histological types and advanced clinical stages suggests that the direct comparison of series is meaningful, particularly if the clinical stages are given in addition to the histological types. It will be of interest to observe whether these findings change materially in future

studies wherein all cases are staged by lymphangiography and, in selected cases, by laparotomy.

In this presentation, no attempt is made to evaluate the part which differences in therapy may have played in explaining the variation in survivals in the series reviewed, since details of therapy are given in only 2 of the series. However, it is surprising that the results in the series of Lukes and Butler, comprising cases in which therapy was given in many different institutions, should be better than those of 3 of the 7 series described above, in which all the patients were treated in a single institution.

In comparing the survival rates according to the histological type of pretherapy biopsies of the various series, 3 considerations related to histology must be kept in mind. In the first place, the original classification of Lukes and Butler was based upon 5 groups with definite criteria, *i.e.*, lymphocytic and/or histiocytic (nodular), lymphocytic and/or histiocytic (diffuse), nodular sclerosis, diffuse fibrosis, and reticular. A 6th group, mixed cellularity, encompassed all the cases which did not fit into the other 5 (Chart 1). The Rye classification has the same basis as is illustrated in Chart 2. When dealing with an individual case in either classification, one should attempt to place it in one of the 3 or 5 groups, depending upon the classification used, for which criteria are well defined; if the case does not fulfill the criteria for any of these, it should be placed in the mixed cellularity group. In any study, a small number of cases remain which one may have difficulty in determining whether they belong in the mixed cellularity group or one of the others. As a result, reports of different series would be expected to show

Table 5

Sex distribution by histological types

	Lymphocytic predominance (%)		Nodular sclerosis (%)		Mixed cellularity (%)		Lymphocytic depletion (%)		Total series (%)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Hamann *et al.* (8)[a]	20	9	33	51	26	14	21	26	=100	100
Gough (7)	24 (13)[b]	14 (6)	9 (5)	21 (9)	37 (20)	19 (8)	30 (16)	45 (19)	=100 (54)	100 (42)
Keller *et al.* (10)	8 (9)	0	39 (42)	72 (50)	46 (49)	23 (16)	7 (7)	4 (3)	=100 (107)	100 (69)
Landberg and Larsson (11)	12 (11)	13 (7)	16 (15)	29 (16)	59 (55)	44 (25)	13 (12)	14 (8)	=100 (93)	100 (56)
Franssila *et al.* (5)	10 (6)	8 (3)	34 (21)	67 (24)	41 (25)	19 (7)	15 (9)	6 (2)	=100 (61)	100 (36)
Fuller *et al.* (6)	13 (11)	4 (2)	41 (33)	75 (38)	41 (33)	20 (10)	5 (4)	2 (1)	=100 (81)	100 (51)

[a] The percentages are for the entire series of 508 patients rather than for the 193 patients who were followed for 5 years.
[b] No. in parentheses, no. of patients.

Table 6

Relationship of clinical stages and histological types

	Lymphocytic predominance		Nodular sclerosis		Mixed cellularity		Lymphocytic depletion		Total series	
	I and II	III and IV	I and II	III and IV	I and II	III and IV	I and II	III and IV	I and II	III and IV
Gough (7)	16 (84%)	3 (16%)	12 (86%)	2 (14%)	16 (57%)	12 (43%)	18 (51%)	17 (49%)	=62 (61%)	34 (39%)
Keller *et al.* (10)	8 (89%)	1 (11%)	63 (68%)	29 (32%)	37 (57%)	28 (43%)	3 (30%)	7 (70%)	=111 (63%)	65 (37%)
Landberg and Larsson (11)	15 (93%)	1 (7%)	20 (65%)	11 (35%)	30 (37%)	50 (63%)	4 (20%)	16 (80%)	=71 (48%)	78 (52%)

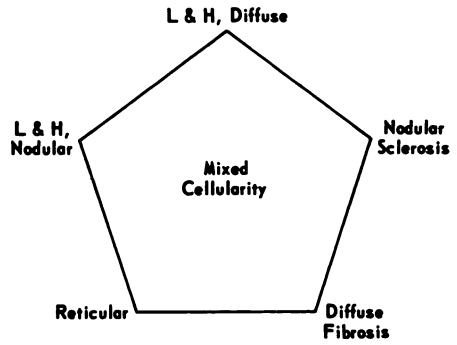


Chart 1. Schematic representation of the classification of Lukes and Butler (12) showing the relationship between the 5 histologically distinct groups and the less well-defined mixed cellularity group. *L & H*, lymphocytic and histiocytic type.

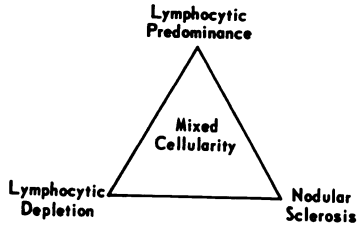


Chart 2. Schematic representation of the Rye classification (13) of Hodgkin's disease showing the relationship between the 3 histologically distinct groups and the less well-defined mixed cellularity group.

differences in the incidence of the various histological types, even if the population in all were similar. In the study of Coppleson *et al.* (4), in which the Rye classification was used, 3 pathologists, 1 particularly experienced in the diagnosis of lymphomatous diseases, failed to agree with the consensus diagnosis of the 3 in 20.7% of the cases. This study and that of Keller *et al.* show that the nodular sclerosis type is most easily classified, whereas the lymphocytic depletion type presents the most difficulty. The majority of pathologists in both these studies, however, had extensive experience and interest in diseases of the reticuloendothelial system. It remains to be proven whether these results would be at all similar for pathologists who do not have this experience. In the 7 series of this presentation, the significant differences ($p < 0.01$) in the incidence of the various histological types and the distribution according to sex within these histological types suggest that the histological types of Hodgkin's disease in a considerably larger number of patients have been incorrectly interpreted. In only one of these series, that of Franssila *et al.*, is it stated that cases which appeared to belong in one group, *i.e.*, nodular sclerosis, were placed in another, *i.e.*, the lymphocytic depletion group. The variations found in the present review support the contention of Coppleson *et al.*, that histological material in all studies on Hodgkin's disease should be reviewed by more than 1 pathologist.

The 2nd problem in comparing the series is the inclusion of cases of other than Hodgkin's disease. If one depends upon the presence of Reed-Sternberg-like cells without consideration of the cellular background or architectural features, benign conditions, such as infectious mononucleosis (21), postvaccination lymphadenitis, or viral lymphadenitis (2), may be erroneously included, as well as malignant conditions, such as histiocytic lymphoma (17), nodular lymphomas of all types, and an occasional nonhematopoietic neoplasm (21). Since the inclusion of a material number of benign conditions in any one series would be reflected in a much better survival period, this seems unlikely; in this discussion, the problem is to attempt to explain the poor survival in 3 series: those of Gough, Landberg and Larsson, and Franssila *et al.* The inclusion of malignant conditions other than Hodgkin's disease cannot be so easily dismissed although any statements in this regard admittedly reflect mere suspicions: they cannot be substantiated. In the series of Franssila *et al.*, the total incidence of any one histological type, as well as the sex distribution of the patients with any one type is within the range of that shown in the series of Lukes and Butler, Hamann *et al.*, Keller *et al.*, and Fuller *et al.* The 5-year survival rate of the mixed cellularity group is much lower, however, than that of the same histological group in all the other series. Also, the combined 5-year survival rate of the mixed cellularity and lymphocytic depletion groups, together containing 44% of the patients in this series, is only 3%. In view of these facts, one may question whether malignant conditions other than Hodgkin's disease were included by Fransilla *et al.* This is particularly true since the 5-year survival rate in the other 2 histological groups in this series are at the lower limit of the range of survival in the same groups in all other series. The series of Gough contains a notably large number of patients and of females with the lymphocytic depletion type and a lower percentage of patients and females with the nodular sclerosing type. The survival rates in this series do not suggest that patients with a histological type which carries a better prognosis have been included in one of the histological types with an expected poorer prognosis. The survivals of those patients with the lymphocytic predominance and nodular sclerosis types are, in fact, at the lower limits of the range for all the series; the survival for the mixed cellularity group is significantly lower than for the series of Lukes and Butler, Hamann *et al.*, Keller *et al.*, and Fuller *et al.*, and the survival of the large lymphocytic depletion group is as low as that in all except the series of Fransilla *et al.* and Landberg and Larsson. In view of the size of the lymphocytic depletion group, the abnormal sex distribution, and the low 5-year survival rate, even though one-half these patients had Stage I or II disease, one might also question whether this group contains malignant conditions other than Hodgkin's disease.

A 3rd possible problem is the exclusion of cases of Hodgkin's disease from the 8 series under discussion. Such cases are usually interpreted as lymphocytic lymphoma. In my study of Hodgkin's disease in children (3), a review of histological material from all cases of lymphoma and Hodgkin's disease in the selected age group revealed 3 cases of Hodgkin's disease in a series of 58 which initially had been regarded as cases of lymphocytic lymphoma; 2 of these were of the lymphocytic predominance type, and one was of the mixed cellularity type. Pitcock *et al.* (16), in a review of all lymph node biopsies from children at their institution, found 7 cases among 46 which initially had not been recognized as Hodgkin's disease; 6 had been considered to be lymphocytic lymphoma, and 1 to be reactive hyperplasia. Although this problem was undoubtedly present in all 8 series under discussion, it cannot be determined whether it was of more import in one series than in another.

It is unfortunate that the clinical stages of Hodgkin's disease in all the series were not reported. Certainly, the significantly higher percentage of patients with Stage III disease in the series of Landberg and Larsson could explain the poor overall 5-year survival rate. It would be of interest to know whether the poor survival rate in the series of Franssila *et al.* could be similarly explained. The poor 5-year survival in Gough's series can hardly be attributed to advanced disease, since the distribution according to clinical stage was almost identical to that reported by Keller *et al.*, in whose series the survival rate was more than twice that reported by Gough.

In view of the differences already discussed in the 8 studies, it is significant that in 5 [Lukes and Butler (12), Gough (7), Franssila *et al.* (5), Fuller *et al.* (6), and Lukes[1]] of the 8, the ranking as to prognosis was the same, that of lymphocytic predominance being most favorable, nodular sclerosis being second, mixed cellularity next, and lymphocytic depletion poorest. In 2 others [Hamann *et al.* (8) and Keller *et al.* (10)], the order was the same, although the 5-year survival rates for the mixed cellularity and lymphocytic depletion groups were similar. In the final study [Landberg and Larsson (11)], the order of the first 2 groups was reversed. In all 8 studies, the difference in survival between the nodular sclerosis and mixed cellularity groups was clear-cut.

Acknowledgments

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