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PROGNOSIS IN HODGKIN'S DISEASE WITH SPECIAL REFERENCE TO HISTOLOGIC TYPE

Results of treatment predominantly by cytostatics

by

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Hodgkin's disease has been considered by some authors to be of inflammatory or immunologic origin but today it is generally accepted, by clinicians as well as by pathologists, that the disease belongs to the group of malignant lymphomas. It has been widely considered a multifocal systemic disease because of the systemic symptoms but more recent investigations (ROSENBERG & KAPLAN 1966, KAPLAN 1966) have indicated that the disease can just as well be considered of unifocal origin, spreading by continuity.

The results obtained by intensive radiotherapy in various American and British clinics, and presented at the Symposium in Rye, New York, in 1966 (Cancer Res. vol. 26, pp. 1044—1311), seem to accord with the unifocal theory and thereby with curability. The material now presented is therapeutically charac-

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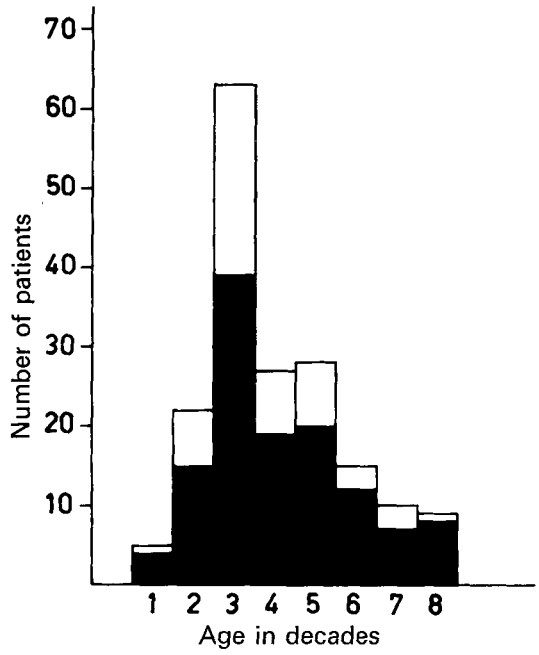

Fig. 1. Distribution of the material according to age and sex: females (55) indicated by white columns and males (124) indicated by black spaces.

terized by previous views holding that Hodgkin's disease is a fatal systemic disease and that the main emphasis must be on chemotherapy. The object of the study has been to report our results and in particular to correlate them to the histologic classifications of the Rye conference.

Material and Method. A total of 195 cases diagnosed as Hodgkin's disease were treated during the period 1st of January 1955 to 31st of December 1964. The histologic preparations in seventeen of these cases could not be procured but in all the others they were reviewed and re-classified by one of the present authors (F. L.) without knowledge of the clinical course.

Ten cases in which the diagnosis could not be maintained were excluded. Of the un-reviewed cases, those in which the histologic report did not mention typical Reed-Sternberg cells were also excluded, i.e. a further six cases. This left 179 cases, and in eleven of these the histologic preparations were not reviewed. The material was analyzed as of 31st December 1967, so that the follow-up period was from 3 to 13 years, the follow-up rate being 100 %. A total of 115 cases were treated primarily in the clinic, while 64 were treated secondarily, the primary treatment having been given elsewhere. All survival times have been calculated from the time at which a definite diagnosis was made.

Clinical staging was made according to the following three groups.

Stage I: Disease restricted to one lymphatic region or to two adjacent lymphatic regions on the same side of the diaphragm.

Stage II: Disease involving more than two lymphatic regions or two lymphatic non-adjacent regions on the same side of the diaphgram.

Stage III: Disease involving the lymphatic system on both sides of the diaphragm or other organs.

All stages were also subdivided into clinical types A or B, indicating the absence or presence of systemic symptoms, i.e. fever, pruritus, or an abnormal tendency to sweating.

The staging thus differs somewhat from that of PETERS (1950), and PETERS & MIDDLEMISS (1958) as well as that of WESTLING (1965). The classification in four stages (ROSENBERG 1966), which by now is internationally recognized, could not be used, inter alia because only a few of the patients had undergone lymphangiography. However, stages I and II are identical with the corresponding stages of the named classification.

Histologic classification. The histologic classification suggested by the Nomenclature Committee (LUKES et coll. 1966) was used in the review of the preparations: lymphocytic predominance, nodular sclerosis, mixed cellularity, and lymphocytic depletion.

A group of ten cases of possible Hodgkin's disease had also to be included. Diagnostic Reed-Sternberg cells could not be demonstrated on review of these cases but in all other respects the histologic appearances were extremely suggestive of Hodgkin's disease, and the cases could not be classified as non-specific reactions or as malignant lymphomas of a different nature.

Remissions. Remission after a given treatment is taken to mean objective improvement with subsidence of pathologic lesions or subsidence of systemic symptoms with or without disappearance of the lesions. No distinction could be made between partial and total remissions.

Results

Age and sex distribution. The distribution of the material by age and sex is given in Fig. 1. In both sexes there is, as in other materials, a preponderance of patients in the age group 20 to 29 years. No regard was however paid to the age

Table 1

Distribution by clinical stage, systemic symptoms and sex

Clinical stage	Females			Males			Total females	Total males	Total females +males
	A	B	?*	A	B	?*			
I	9	1	2	35	4	1	12 (22 %)	40 (32 %)	52 (29 %)
II	17	5	5	11	12	4	27 (49 %)	27 (22 %)	54 (30 %)
III	0	9	0	6	32	4	9 (16 %)	42 (34 %)	51 (29 %)
Unknown			7			15	7 (13 %)	15 (12 %)	22 (12 %)
Total	26 (47 %)	15 (27 %)	14 (26 %)	52 (42 %)	48 (39 %)	24 (19 %)	55 (100 %)	124 (100 %)	179 (100 %)

* Unknown whether systemic symptoms were present

Table 2

Distribution by sex and histologic revision of first biopsy

Histologic type	Females		Males		Total	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Lymphocytic predominance	1	2	23	18	24	13
Nodular sclerosis	20	37	26	21	46	26
Mixed cellularity	17	31	31	25	48	27
Lymphocytic depletion	9	16	15	12	24	13
Possible Hodgkin's disease*	3	5	12	10	15	9
Non-specific changes**	1	9	3	14	4	12
No revision***	4		14		18	
Total	55	100	124	100	179	100

* By histologic revision of later biopsy, five cases classified according to LUKES et coll. (See table 4.)

** Histologic revision of later biopsy indicated Hodgkin's disease, and classification was made according to LUKES et coll. (See table 4.)

*** No histologic revision of first biopsy was made, but in seven cases a later biopsy was revised and classified according to LUKES et coll. (See table 4.)

Table 3

Distribution by histologic types compared with the histologic groups of Lukes et coll.

Histologic type	Present material*		Lukes, Butler & Hicks (1966)		
	Number of cases	Per cent	Number of cases	Per cent	Histologic groups
Lymphocytic predominance	24	17	63	17	L. & H. nodular L. & H. diffuse
Nodular sclerosis	46	32	149	40	Nodular sclerosis
Mixed cellularity	48	34	97	25	Mixed
Lymphocytic depletion	24	17	68	18	Diffuse fibrosis Reticular
Total	142	100	377	100	

* The groups possible Hodgkin's disease (15 cases), non-specific changes (at first biopsy) (4 cases), and no revision (18 cases) excluded.

distribution of the general population since a bimodal age-specific distribution would then be expected with an accumulation of cases between 20 to 29 years and over 60 (Meighan & Ramsay 1963).

There were 124 males and 55 females in the material, which gives a male/female ratio of 2.26 : 1. This is somewhat higher than generally reported, i.e. Roos & Videbaek (1959) found 1.06 : 1, Musshoff & Boutis (1968) 1.3 : 1, Westling (1965) 1.58 : 1, while Meighan & Ramsay (1963) found 2.06 : 1, and O'Brien & O'Brien Jr (1954) 3.0 : 1.

Distribution by clinical stage. The distribution by clinical stage at the time of diagnosis is presented in Table 1. In 22 cases it was not possible on the basis of the available data to make any clinical staging, and in a further 16 cases it was not possible to sub-classify the cases into A or B types. While for the material considered as a whole there is a fairly equal distribution within the three clinical stages, there seems to be a female preponderance in stage II and a male preponderance in stages I and III. As might be expected, there is a marked increase of the systemic symptoms in the more advanced clinical stages.

Distribution by histologic type. This is presented in Table 2, based upon the revision of the first biopsy specimen ever taken. As may be seen, nodular sclerosis was more common in females while mixed cellularity occurred more often in males. Moreover, lymphocytic predominance was found to be extremely rare in women.

Table 4

Evolution of the histologic process in the present series

Primary histologic diagnosis	Secondary histologic diagnosis						
	Non-specific changes	Possible Hodgkin's disease	Lymphocytic predominance	Nodular sclerosis	Mixed cellularity	Lymphocytic depletion	No revision
Non-specific changes (4 cases)			1			3	
Possible Hodgkin's disease (15 cases)		2	2			3	8
Lymphocytic predominance (24 cases)	2	1	4	1	1	4	11
Nodular sclerosis (46 cases)				10	2	10	24
Mixed cellularity (48 cases)				1	3	21	23
Lymphocytic depletion (24 cases)						13	11
No revision (18 cases)					1	6	11

It is of interest to compare the histologic distribution in the total series with that given by LUKES, BUTLER & HICKS (1966) in their material of 377 patients. They used a histologic classification which comprised six groups of which (1) lymphocytic and/or histiocytic proliferation, nodular, and (2) lymphocytic and/or histiocytic proliferation, diffuse, are identical with the type 'lymphocytic predominance', while (5) diffuse fibrosis and (6) reticular are identical with 'lymphocytic depletion'. The comparsion is apparent from Table 3, in which cases that could not be classified on revision of the first biopsy are excluded; the percentage distribution has been corrected accordingly. The table indicates good agreement as to the distribution in the two materials.

Histologic re-classification on biopsies taken later in the course (33 cases) or on autopsy specimens (58 cases) in a total of 91 cases are listed in Table 4. In only four cases were the changes in the secondary histologic preparations less 'advanced' than in the primary biopsies, while in forty-four the histologic type was more 'advanced' in the secondary specimens. Lymphocytic depletion was present in 54 out of the 58 autopsy specimens reviewed. The findings thus indicate that a change in the histologic appearances may occur in the course of Hodgkin's disease.

Table 5

Relationship between histologic types and clinical stage

Histologic types	Number of cases	Per cent of cases in the different clinical stages		
		I	II	III
Lymphocytic predominance	21	52	29	19**
Nodular sclerosis	44	36	43	21
Mixed cellularity	44	32	34	34
Lymphocytic depletion	21	19**	29	52
Possible Hodgkin's disease	11	36**	36**	28*

* This group contains only 3 cases
** This group contains only 4 cases

Relation between clinical stage and histologic type. The clinical stage and the histologic type on the first biopsy are compared in Table 5. Only cases in which the clinical stage could be assessed have been included in this comparison. It is seen that there is a preponderance of the type 'lymphocytic predominance' in stage I, decreasing towards clinical stage III. Lymphocytic depletion correspondingly showed a preponderance of cases in clinical stage III, decreasing towards clinical stage I. Nodular sclerosis and mixed cellularity, the intermediate histologic types, and the group of possible Hodgkin's disease exhibit a more even distribution between the three clinical stages.

The material of LUKES, BUTLER & HICKS had exactly the same tendency as regards the distribution within the clinical stages. However, these authors reported a somewhat greater preponderance of the histologic groups 'lymphocytic or histiocytic proliferation', nodular + diffuse, within clinical stage I (70 %), but the clinical stages used were not entirely identical. The groups 'diffuse fibrosis' and 'reticular' were together most common in stage III (56 %), while 'nodular sclerosis' and 'mixed cellularity' were approximately equally represented in the three clinical stages.

Survival in the entire material. Fig. 2 gives the percentage survival in the entire material, a 5-year survival of 33.1 % and a 10-year survival of 13 %. These findings agree with those of others in similar series in which radiotherapy and cytostatic treatment has been employed (SHIMKIN et coll. 1955, TRÜBESTEIN 1956, ROOS & VIDEBAEK 1959, and COOK et coll. 1959). However, these results do not appear to be up to those obtained by PETERS et coll. (1966) by intensive radiotherapy, at least not as regards the 10-year survival.

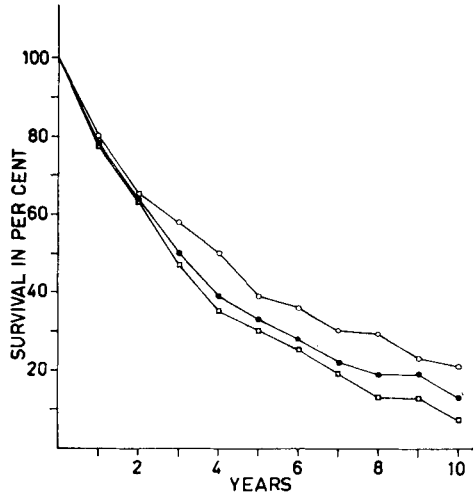

Fig. 2. Survival (crude) rate in relation to sex: females (55 ○—○), males (124 □—□), entire material (179 patients ●—●).

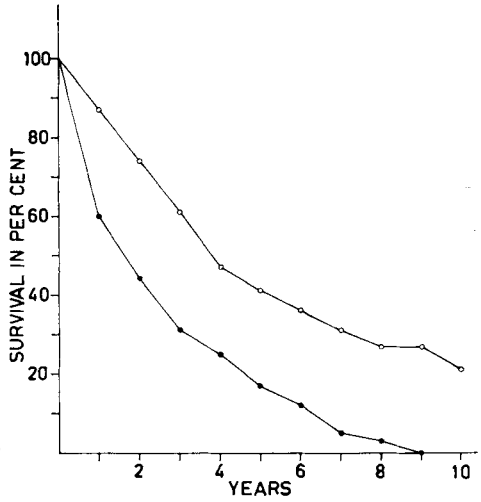

Fig. 3. Survival (crude) rate in relation to age: under 40 years of age (117 patients ○—○), and over 40 years (62 patients ●—●).

Survival in relation to sex and age. Fig. 2 also gives the percentage survival for women and men separately. Like numerous other workers, the present authors found a somewhat better prognosis in women than in men, 39 % of the female patients living for 5 years, as compared with only 30 % of the males; furthermore, 21 % of the female patients lived for 10 years, as compared with 7 % of the males.

The prognosis in relation to age is given in Fig. 3. The material was divided into two age groups, patients over 40 and under 40. In the older age group the prognosis is distinctly poorer (5-year survival, 17 %) than in the younger (5-year survival, 41 %). This graph does not, however, take into account the higher normal mortality in the older age groups.

Survival in relation to clinical stage. The percentage survivals in three clinical stages (22 cases excluded because of deficient data) are given in Fig. 4. It is evident that the staging places the cases into threee entirely different prognostic groups. The results are in keeping with those of WESTLING (1965) but for stages I and II there is a striking difference in relation to materials treated by more intensive irradiation, especially in respect to survivals beyond 5 years. Thus, PETERS et coll. (1966) reported 5- and 10-year survivals for stage I of 73 % and 52 %, respectively, for stage II-A 90 % and 67 %, and for stage II-B only 23 % and 13 %.

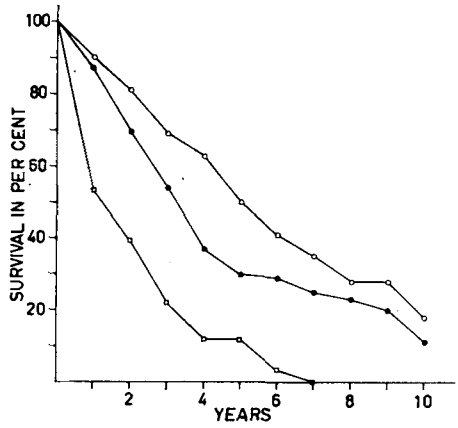

Fig. 4. Survival (crude) rate in relation to the clinical stages: I (52 patients ○—○), II (54 patients ●—●), III (51 patients □—□). (The stage was unknown for 22 patients.)

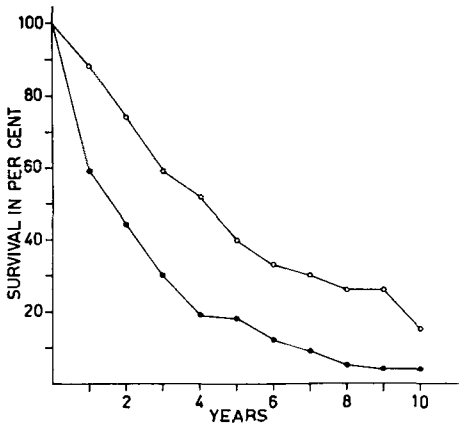

Fig. 5. Survival (crude) rate in relation to systemic symptoms: no symptoms (78 patients ○—○), systemic symptoms (63 patients ●—●). (It was unknown for 38 patients whether systemic symptoms were present.)

After using intensive irradiation in the treatment of cases that he called 'localized lymphadenopathy' EASSON (1966) reported a 5-year survival of 55 % and a 10-year survival of 43 % (age-corrected survival rates). KAPLAN (1966), in a series treated by megavoltage irradiation, gave a 5-year survival of 82.4 % for stages I and II, a rate that remained unchanged until the 9th year (actuarial value).

A prognostic comparison of clinical types A and B is presented in Fig. 5, which per se of course bear relation to the clinical stage (cf. Table 1). Systemic symptoms constitute a serious prognostic sign (cf. the above-mentioned results of PETERS et coll. for stage II-A compared with stage II-B). LUKES et coll. (1966) even recorded poorer 5-year results for stage II-B than for stage III-A, and KELLER et coll. (1968) consider systemic symptoms in localized disease to be equally poor prognostically as lymphadenopathy and the dissemination in stage III.

Survival in relation to histologic type. Table 6 gives the percentage survival within the histologic types and for the group possible Hodgkin's disease at 1, 3, and 5 years. At 3 years there is a satisfactory correlation with a decreasing number of survivors in the more 'advanced' histologic type. At 5 years, on the other hand, there is a striking fall in the number of survivors within the histologic type 'lymphocytic predominance', as compared with the results of LUKES et coll. (1966). This phenomenon will be discussed later.

Table 6

Survival according to histologic types, compared with the histologic groups of Lukes et coll.

Histologic type	Present material*			
	1 year		3 years	
	Number at risk	Survival per cent	Number at risk	Survival per cent
Lymphocytic predominance	24	83	24	63
Nodular sclerosis	46	93	46	61
Mixed cellularity	48	71	48	38
Lymphocytic depletion	24	54	24	21
Possible Hodgkin's disease	15	93	15	80

Survival in relation to duration of symptoms before diagnosis. In Fig. 6, the material is divided into three groups by duration of symptoms. Sufficient data were however not available in 31 of the cases. There does not seem to be any definite difference between the three groups, so that in the present material it is not possible to assess the prognostic significance of the duration of symptoms.

Treatment

It is only natural that the treatment varied a good deal seeing that the material comprises a period of ten years. A number of cytostatic substances have been launched on the market during this period and used for such a short time on so few cases that it is impossible to draw conclusions. Most cases were treated several times by irradiation, cytostatics or steroids, and frequently these types of treatment have been used in varying combinations. Numerous factors are accordingly difficult to assess but an attempt will be made to point out a few features.

Irradiation. About 160 to 250 kV radiation was used during the greater part of the period. Telecobalt was employed for only a few cases in the last years of the study period. The dosage varied a good deal but with a tendency to higher dosage in recent years. Cases of localized disease treated primarily by irradiation received a dosage generally in the range 1 500 to 2 500 R over two to three weeks

Table 6 *(cont.)*

		Lukes, Butler & Hicks (1966)		
5 years		5 years		
Number at risk	Survival per cent	Number at risk	Survival per cent	Histologic groups
22	27	63	73	L. & H. nodular L. & H. diffuse
36	44	149	44	Nodular sclerosis
40	15	97	32	Mixed
17	24	68	13	Diffuse fibrosis Reticular
13	69			

* The groups non-specific changes (at first biopsy) and no revision excluded.

(tumour dose), but the fields were generally rather small. Secondary radiotherapy was given with a purely palliative object, directed at local lesions causing symptoms.

Table 7 presents the primary treatment in relation to clinical stage. As might be expected, irradiation was most often used in clinically localized stages. If chemotherapy was used in localized stages, this was mainly in cases where the condition was characterized by systemic symptoms. However, chemotherapy, without concomitant radiotherapy, in these stages is not in keeping with present views concerning the treatment of Hodgkin's disease (Karnofsky et coll. 1963, Aisenberg 1964, Karnofsky 1966, Perry et coll. 1967).

Chemotherapy. From the total of 179 cases, 152 received at some stage between one to twelve courses of one or more out of a total of 15 cytostatic substances. Chemotherapy alone as the primary treatment (Table 8) was given to 56, while the others had the courses at later stages when the disease was more or less clinically advanced or generalized. A total of 468 courses were administered, but in some cases the cytostatic medication was combined with irradiation or with steroid agents so it was not possible to assess the cytostatic effect per se. Several cases moreover received two cytostatics in combination, but those used for this treatment varied, so that for numerical reasons the combined treatment with cytostatics cannot be assessed. Lastly, several single courses were excluded because data for estimating the length of the remission were absent. This leaves 307 single courses that could be evaluated.

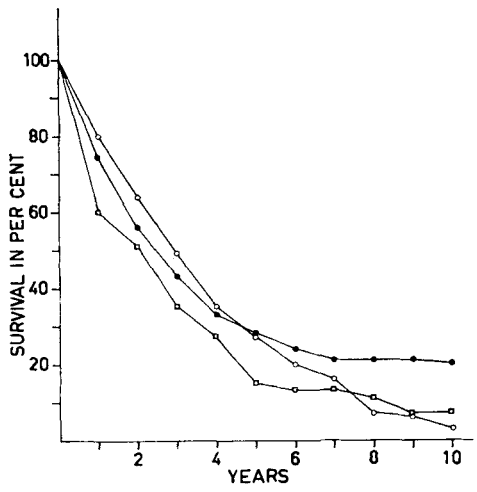

Fig. 6. Survival (crude) rate in relation to duration of symptoms: 0 to 5 months (88 patients ○—○), 6 to 11 months (37 patients □—□), over 12 months (23 patients ●—●). (Data missing for 31 patients.)

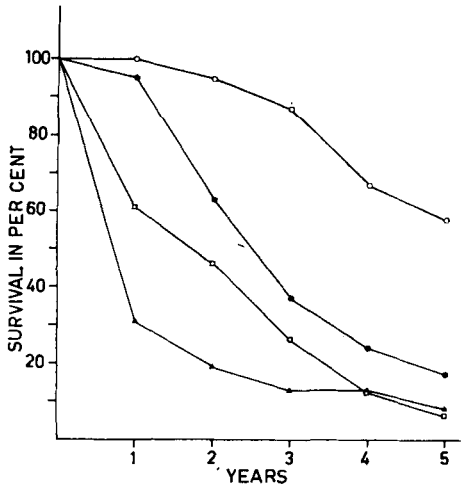

Fig. 7. Survival (crude) rate in relation to duration of initial remission: no remission (△—△), remission 1 to 6 months (□—□), remission 7 to 12 months (●—●), remission over 12 months (○—○).

The dependence of the prognosis upon the duration of the remission obtained by the primary treatment was analyzed regardless of whether it consisted of irradiation, chemotherapy, or a combination of both.

The result is presented in Fig. 7. In the cases that obtained no remission at all after the initial treatment, the prognosis appeared to be serious, even at short sight, only 31 % surviving for a year. In the group of cases that obtained initial remission of from 1 to 6 months, only 6 % survived for 5 years, while the 5-year survival among the group having an initial remission exceeding 12 months was 58 %. The investigation thus indicates that the longer the initial remission the better the prognosis. A long initial remission may be a sign of slower progression of the disease, a factor that has been pointed out by Cook et coll. (1959) and Karnofsky et coll. (1963). Musshoff et coll. (1966), on the other hand, considered the remission rate and the duration of the first remission to be indications of therapeutic effectiveness.

In Table 8 are listed the six most common cytostatics, representing 234 single courses without maintenance therapy. The remaining 73 courses are distributed over a total of nine additional cytostatics, so that these numerical values are too small for comparison. The table also gives the average duration of the remissions with the drugs used. It will be seen that Natulan induced the longest

Table 7

Primary treatment according to clinical stage

Primary treatment	Clinical stage			Unknown	Total
	I	II	III		
Irradiation	38	28	12	14	92
Chemotherapy	6	18	29	3	56
Irradiation + chemotherapy	1	5	4	2	12
Miscellaneous types of treatment	7	3	6	3	19

remissions. The table also indicates the number of cases in which no remission was obtained. More than one course of the same drug was given in a number of cases. The duration of the remissions after the second and third courses was always shorter than after the first in all the cases in which more than two courses were available as a basis for the calculations. This indicates that secondary cytostatic therapy is less effective than primary therapy, a certain form of resistance developing on continued use of the same chemotherapeutic agent.

A comparison of the drugs triethylene melamine, cyclophosphamide, Natulan and vinblastine is presented in Fig. 8. The most striking feature is that Natulan and vinblastine give a larger number of remissions than the alkylating substances triethylene melamine and cyclophosphamide. In addition, it may be seen that with Natulan a larger number of long-lasting remissions was obtained than with the other drugs. On the other hand, no remission lasted beyond 6 months on vinblastine. The alkylating agents triethylene melamine and cyclophosphamide possessed approximately the same effectiveness. With triethylene melamine especially there were only a few remissions longer than 6 months.

Discussion

Definite information concerning the spontaneous course of Hodgkin's disease is lacking, as only very few series of untreated cases have been published. EWING in an early paper (1940) reported an average duration of 18 months. SHIMKIN et coll. (1955), collecting a total of 433 cases from the literature prior to 1936, reported a 5-year survival of less than 15 % from the time of diagnosis. They compared this result with 1 109 cases collected from the period after 1940, among which the 5-year survival was 26.6 %. This difference is statistically significant. They mentioned that factors other than the treatment may have contributed to this difference but avoided drawing further conclusions.

Table 8

The six most frequently used drugs; number of courses, average duration of remission, and number with no remission

Drug	One course	Two courses	Three courses	Four courses
Diepoxybutan	14	2	0	0
Triethylene melamine	85	26	7	1
Cyclophosphamide	26	5	1	0
Vinblastine	21	2	0	0
Vincristine	6	3	0	0
Natulan	29	6	0	0

At all events, the prognosis of Hodgkin's disease has improved in recent years, particularly in series where intensive radiotherapy has been used. The present results are in keeping with this trend.

Various factors influence the prognosis, inter alia the age. The prognosis is poorer in the older group of cases (Fig. 3), a factor explained by JACKSON & PARKER (1947) as a higher incidence of a sarcomatous histologic appearance, while UDDSTRÖMER (1934) believed that elderly patients had a greater tendency to generalization of the disease.

Sex is undoubtedly another prognostic factor (Fig. 2). However, doubts have been raised as to whether the apparently better prognosis in women is real. EPSTEIN (1939), PETERS et coll. (1966) and WESTLING (1965) found the same sex difference but without a statistical significance, and SHIMKIN et coll. (1955) reported a significant sex difference only for stage I. MEIGHAN & RAMSAY (1963) recorded a better prognosis only in women of fertile age, a phenomenon also pointed out by BICHEL (1955). VIDEBAEK (1950) could not demonstrate any sex difference, and MUSSHOFF & BOUTIS (1968) believed that the better prognosis in women was due to a lower incidence of the more advanced clinical stages. The better prognosis in women in the present material may have been due to the lower incidence of clinically more advanced stages.

The clinical stage at diagnosis is an important prognostic factor (Fig. 4), and this seems to be generally accepted. Since the clinical stage no doubt bears some relation to the histologic appearance (Table 5), the latter must also be considered of importance, although, unlike LUKES et coll. (1966), we failed to notice so benign a course of the histologic type known as 'lymphocytic predominance'. Incidentally, it has been stated by HILTON & SUTTON (1962) that Hodg-

Table 8 *(cont.)*

Total number of courses	Average duration of remission in months				No remission	
	Total courses	First course	Second course	Third course	Number of courses	Per cent
16	1.4	1.1	(3.5)		8	50.0
119	2.2	2.5	1.5	1.6	41	34.4
32	2.9	3.4	0.8	(2.0)	11	34.4
23	3.0	3.0	(4.0)		3	13.0
9	3.4	4.3	1.7		1	11.1
35	5.0	5.7	2.0		2	5.7

kin's disease is the only group of malignant lymphomas in which clinical staging is of any value from the prognostic point of view.

The duration of the disease before diagnosis (Fig. 6) has by some authors also been related to the prognosis. PETERS & MIDDLEMISS (1958), for instance, regarded the 5-year survival to be the better the longer the disease had lasted before treatment. Later, PETERS et coll. (1966) noted a considerable preponderance of 10-year survivors with symptoms for more than one year. WESTLING (1965), on the other hand, reported the best 5- and 10-year survivals in cases with symptoms for only 0 to 6 months, but the difference as compared to the other groups was not significant.

Finally, the duration and the completeness of the remission on initial treatment is obviously of prognostic importance, as is also apparent from Fig. 7.

During the past 50 years, several attempts have been made to correlate the histologic appearances in Hodgkin's disease partly to the prognosis and partly to the anatomical spread of the disease. JACKSON & PARKER (1944) used a classification into three groups: paragranuloma, granuloma, and Hodgkin's sarcoma. The first group represented a benign and slow course, the third group a malignant and short course. The main objection to this classification was that the group of paragranulomas made up only 7 to 8 % of the cases and the group of Hodgkin's sarcoma only 2 to 3 %, while the intermediate group of granulomas represented about 90 %. In this group therefore there was a wide histologic and thus also prognostic variation.

LUKES et coll. (1966) originally used a classification comprising six groups which however was reduced to four types by the Nomenclature Committee. We felt that it might be of interest to test this classification by review and re-classification of the histologic preparations. This revealed conformity as regards the distri-

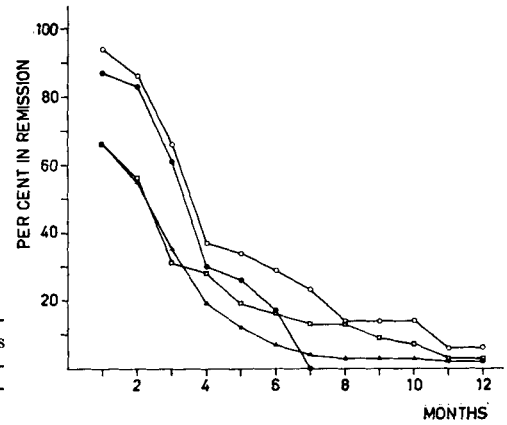

Fig. 8. Duration of remission following treatment with different drugs: Natulan (35 courses ○—○), vinblastine (23 courses ●—●), cyclophosphamide (32 courses □—□), triethylene melamine (119 courses △—△).

bution of the material within the histologic types (Table 3) and the distribution in relation to clinical stage (Table 5), with due consideration of the fact that our material was less than half as large as that submitted by LUKES et coll. The main disagreement was, as already mentioned, the 5-year survival in the group 'lymphocytic predominance' (Table 6). We cannot explain this disagreement. As emphasized by KELLER et coll. (1968), one of the difficulties with Lukes' classification is to distinguish between the types 'mixed cellularity' and 'lymphocytic predominance'. We may have placed some of the former group into the latter, and this would account for the discrepancy. This does not seem particularly likely, however, as the type 'lymphocytic predominance' in our material makes up exactly the same proportion (17 %) of the total series as in that of LUKES et coll. On the other hand KELLER et coll. found this proportion to be only 5 %. Another contributory cause of the poor prognosis with this histologic type in the present series may be that while only 52 % of the cases in this group were in clinical stage I, LUKES et coll. had 70 % in this stage. Furthermore, there was only one woman in the group, so that it is predominated entirely by the prognostically more unfavourable male patients. The favourable prognosis in lymphocytic predominance may be due to immunologic defence mechanisms, suppressed by the extensive use of chemotherapy so that the 5-year survival is poorer than that obtained by others who have used irradiation to a greater extent. This is of course mere hypothesis which cannot even be supported by the present findings. The histologic type nodular sclerosis has been emphasized by some workers (PERRY et coll. 1967) as the most difficult group to classify according to Lukes' system. Nevertheless, we found conformity with the material of LUKES et coll. for this group as well as in respect to the 5-year survival.

We found that in a large number of the cases in which two biopsies had been performed in the course of the disease the histologic appearances had altered (see Table 4). This alteration was in a more malignant direction in the majority of the cases. However, it is well known that different histologic Hodgkin changes within different groups of lymph nodes may be present in the same subject. Such differences may even occur within the same group of nodes or in the same histologic section (CUSTER & BERNHARD 1948, RÜTTNER 1953). This may be the explanation of the change towards a more benign appearance that was noted in a few cases, a phenomenon also reported by CUSTER & BERNHARD. However, the predominant number of cases with changes in the histologic appearances undergo a transformation in a more malignant direction. It may thus be expected that in a certain proportion of cases, at least, the clinical and histologic progression is concurrent. Histologic progression has also been demonstrated by CUSTER & BERNHARD (1948), JELLIFFE & THOMSON (1955), TRÜBESTEIN (1956), and WESTLING (1965). It may be that other factors, e.g. bacterial, viral, or fungal infections that often affect these patients in the terminal stages (CASAZZA et coll. 1966) may also be contributory. The same applies to a possible effect of irradiation and chemotherapy. However, CUSTER & BERNHARD failed to demonstrate that irradiation alone could induce transformations in the histologic process, either into a more malignant or a more benign direction (presupposing that the lesion had not healed during the treatment). Let it be emphasized that among the twenty-two cases of nodular sclerosis in which new biopsies were performed later in their course, twelve presented evidence of conversion to more malignant histologic types, viz. two to mixed cellularity and ten to lymphocytic depletion. LUKES et coll. (1966) were unable to demonstrate with certainty any histologic evolution in nodular sclerosis but felt that it presumably existed.

It would appear that according to the view prevailing to-day isolated chemotherapy is not the treatment of choice for Hodgkin's disease in localized clinical stages I and II. Intensive radiotherapy is indicated in such cases. We must admit that the treatment of our material does not accord with these principles. However, chemotherapy still remains of value for certain groups of cases in Hodgkin's disease. Although it is accepted that clinically less advanced stages of Hodgkin's disease may be cured by irradiation, a number of these cases will later become generalized, and a not inconsiderable proportion have primarily been disseminated. In such instances, chemotherapy is still of great value.

Chemotherapy may be administered in various ways, with or without irradiation, as courses of one drug with or without maintenance therapy, or as combination of two or more drugs.

The results obtained by chemotherapeutic management in our series (Table 8 and Fig. 8) cannot be compared directly with the results of others. In part,

our results are based upon a retrospective study, not upon a controlled clinical series, and in part the definition of remission may vary. Within our own series, however, the various drugs may be compared, but for numerical reasons a relative assessment is permitted only for the invidual drugs, not for combined medication.

Three factors must be stressed in evaluating the effectiveness of a cytostatic. In the first place the ability to induce remission and in the second place the duration of the induced remission must be considered. The third factor is the influence upon the patient's survival.

There is little doubt, on the basis of such a comparative evaluation of the cytostatics in the present series, that Natulan was the most effective, both in respect to the duration and the frequency of remissions (Table 8). Moreover, Natulan induced a relatively larger number of long-lasting remissions, i.e. remissions sustained for up to one year (Fig. 8). Other authors (MATHÉ et coll. 1963, DEVITA et coll. 1956, SAMUEL et coll. 1967) have also experienced encouraging results in clinical experiments with Natulan in Hodgkin's disease. Vinblastine and vincristine produced only a slight increase in the average duration of remissions, compared with the alkylating substances, but there was a marked increase in the incidence of remissions. Long-lasting remissions were not common with vinblastine (Fig. 8).

As may be seen from Table 8, when the same drug was used there was a decrease in the average duration of remission in courses administered after the primary one and, as has been demonstrated repeatedly, resistance develops in the event of continued treatment with the same substance or group of substances. However, this need not entail cross resistance to other groups, which is often a difficult problem to assess, the secondary treatment usually being administered at a time when the disease is more advanced, clinically as well as histologically, and when the patient's general condition is poorer, partly because of the disease and partly because of previous treatment which may have compromised the normal biologic defence mechanisms.

It is difficult to say whether cytostatic treatment, administered alone, prolongs survival in Hodgkin's disease, and the present material does not allow of any conclusions. SHIMKIN et coll. (1955) failed to demonstrate that HN_2 (nitrogen mustard) was able to prolong life. Others (ROOS & VIDEBAEK 1959, KARNOFSKY et coll. 1963, KARNOFSKY 1966) felt that life may be extended secondarily by improving the general condition through cytostatic therapy. However, it must be borne in mind that during the very period that cytostatics have been used a number of other therapeutic measures, such as modern antibiotics and corticosteroids, have been introduced, and these too may constitute contributory aids. PERRY et coll. (1967) have expressed the most optimistic view in relation

to this problem, stating that proper manipulation of the available chemotherapeutic substances may produce such destruction of the malignant cells that this per se prolongs the life of the patient.

Conclusions

A 10-year material (1955—1964) comprising 179 cases of Hodgkin's disease is reported. Chemotherapy was used to a great extent but irradiation was employed as well, mainly for palliative purposes. The total 5-year survival rate was 33.1 % and the 10-year survival rate 13 %. The poorest prognosis was in (1) cases in an advanced clinical stage, (2) cases with systemic symptoms, (3) elderly patients, (4) male patients, and (5) patients with short and incomplete remission after the primary treatment. The duration of symptoms before the diagnosis did not appear to play any prognostic role.

All histologic preparations but eleven were reviewed, and re-classification was made into the histologic types suggested by the Nomenclature Committee (LUKES et coll. 1966). There was agreement with the material of LUKES, BUTLER & HICKS (1966) in respect to distribution within the histologic type, relation to clinical stage, and prognosis within the histologic types save the lymphocytic predominance type in which the prognosis was considerably poorer than reported by LUKES et coll. This finding is discussed in more detail. Signs of evolution in a more malignant direction of the histologic types with clinically progressing disease, also within the type nodular sclerosis were apparent.

Natulan was the most effective of the various cytostatic drugs, both in respect to the length of remission and the ability to induce remission.

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SUMMARY

A total of 179 cases of Hodgkin's disease, treated predominantly by chemotherapy during the period 1955—1964, were reviewed histologically and reclassified into the histologic types recommended by the Nomenclature Committee (LUKES et coll. 1966). The 5-year survival rate was 33.1 per cent. Natulan® proved to be the most effective of the cytostatic drugs.

ZUSAMMENFASSUNG

In 179 Fällen der Hodgkin'schen Erkrankung, die hauptsächlich mit Chemotherapie während der Periode 1955—1964 behandelt wurden, wurden die Befunde histologisch überprüft und in den von der Nomenclature Committee (LUKES et coll. 1966) empfohlenen histologischen Typen reklassifiziert. Die 5-Jahre-Überlebenszeit war 33,1 %. Natulan® erwies sich als das beste der cytostatischen Mittel.

RÉSUMÉ

Les auteurs ont revu histologiquement et reclassifié d'après les types histologiques recommandés par le Comité de Nomenclature (LUKES et coll. 1966) un total de 179 cas de maladie de Hodgkin traités principalement par chémothérapie au cours de la période 1955—1964. Le taux de survie à 5 ans était de 33,1 pour cent. La Natulan® était le plus efficace des médicaments cytostatiques.

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