HODGKIN'S DISEASE

An Eighteen Year Review at Hartford Hospital (1938-1956)

by

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HISTORICAL REVIEW:

Hodgkin's disease is a complex pathological entity which has a wide variety of clinical manifestations and involves many organs. It has been 130 years since Thomas Hodgkin[34] presented his paper, "On Some Morbid Appearancs of the Absorbent Glands and the Spleen" to the Medico-Chirurgical Society of London in 1832. In 1865, 33 years later, Wilk[67] reviewed the literatures and documented 12 new cases, including those of his own, to a unique entity which he called Hodgkin's disease. Since then, many investigators have reviewed the literatures and it is believed that the first case described which might be classified pathologically as Hodgkin's disease was reported by Malpighi[46] in 1866.

Accurate gross and microscopic description of Hodgkin's disease was first presented by Greenfield[27] in 1878. Goldmann [25] (1892), Sternberg[61] (1898), and Reed [55] (1960) also published very valuable papers concerning the pathological appearances of this disease. The classical microscopic descriptions were an increase of fibrous tissue, multinucleated giant cells of Sternberg and Reed type, infiltration by eosinophils of a varying degree, and an area of necrosis.

Even though it has been more than a century since Hodgkin's first description, the etiology of this pathological entity has not yet been clarified. In 1898 Sternberg[61] thought that Hodgkin's disease was a variety of tuberculosis. Bunting and Yates[8] thought that it might be caused by diphtheroids. Forbus et al.,[21] thought that it might have a relationship to Brucellosis. In 1904 Benda[3] and Yamasaki[70] demonstrated the capsular and venous invasion of Hodgkin's disease and considered this entity as indicating a form of neoplasm. However, in Hodgkin's disease there are many forms and types of cells so that if Hodgkin's is a neoplasm, it should be a kind of mixed tumor. Lately, in 1958, Bostick[7] reports his impression that the cause of Hodgkin's disease may be due to a virus. The etiology of Hodgkin's disease as with other forms of lymphomas and leukemias is not conclusive as yet.

Although the etiology is inconclusive there is, at the present time, general agreement that Hodgkin's disease should be classified in the group of malignant lymphomas. In 1944 Jackson and Parker[37,38,39] published a series of articles and classified Hodgkin's disease into three categories: the paragranuloma, the granuloma and the sarcoma. In their series of 259 cases, they found 90% Hodgkin's granuloma, 10. 8% Hodgkin's paragranuloma, and 19. 7% Hodgkin's sarcoma. There was evidence of transformation of different types of Hodgkin's disease in different areas of the same involved lymph node which accounts for the fact that the total percentages of

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Jackson and Parker's cases were 120.5 instead of 100.

In a group of 618 cases of lymphomas reported by Gall and Mallory,[22] 31.2% was Hodgkin's lymphoma and 5.8% was Hodgkin's sarcoma.

Hodgkin's disease is different from other forms of lymphomas in that it rarely transforms to leukemia. Ackerman and Regato[1] report that they had never seen a single case of Hodgkin's disease changed to leukemia.

CLINICAL CLASSIFICATION :

It is very difficult to correlate the clinical course and survival rate of Hodgkin's disease with the pathological classification of Jackson and Parker.[38] Craver[13] in 1947 and Peters in 1950[52]. suggested a classification based upon clinical evidence which has been widely adopted and frequently used at the present time.

CLINICAL CLASSIFICATION OF HODGKIN'S DISEASE

Stage I The disease is localized in one group of lymph nodes.

Stage II The disease is localized in one anatomical region, either above or below the diaphragm, but involves more than one group of lymph nodes.

A. Without constitutional symptom and sign.

B. With constitutional symptoms and signs.

Stage III The disease is generalized and involves nodes both above and below the diaphragm.

In this report, Stage I and IIA will be considered as localized disease, while Stage IIB and III will be considered as generalized disease.

COURSE AND CLINICAL MANIFESTATION:

The course of Hodgkin's disease is very complicated. Some of them have a benign course[4,15,30,69], whereas others are very malignant. The clinical symptoms and signs are quite well known. Most patients develop painless enlargement of the peripheral lymph nodes without other subjective symptoms. At the beginning, the nodes are usually discrete and rubbery in consistency, whereas in the late stage they become matted together. Fever is characteristic of the Pel-Ebstein type. Anemia, weight loss, fatigue and anorexia are quite common. Pruritis is not uncommon and in the absence of skin changes usually indicates retroperitoneal or mediastinal nodal involvement. The course of Hodgkin's disease varies, but it eventually becomes generalized and it may involve almost every organ in the body. Almost all of the cases have peripheral lymph node involvement. Splenic involvement is reported clinically and from autopsies to vary from 30-75 per cent.[49,50] Pulmonary involvement is usually observed at autopsy to vary from 22-40 per cent.[18,47,63]. Scott[57] found that 50% of lesions in the neck were associated with mediastinal lesions. Bone involvement is in the range of 10-28%.[24,60,62] The disease has been reported to involve the gastrointestinal tract, genito-urinary tract, heart, and pericardiun, brain, spinal cord, tongue, tonsils, nasopharynx, soft palate, testis and skin. There have been reports of involvement of about every structure, but primary lesions other than in lymph nodes are comparatively rare. Primary pulmonary Hodgkin's disease was reviewed by Kern et al.,[43] in 1961 and they found only 18 cases of primary lung disease in the literatures, including 4 cases of their own. In

1962, Cook and Corbett[10] found only five cases of Hodgkin's disease which primarily involved the gastro-intestinal tract in a series of 425 cases.

MATERIALS:

The purpose of this paper is to evaluate the results of treatment of Hodgkin's disease in the Hartford Hospital for comparison with those of others, hoping to find ways and means of improving our own. From 1938 to 1956, at total of 18 years, there were 182 cases of proven Hodgkin's disease registered in our tumor clinic and the Radiation Therapy Department. The age incidence in the majority of these cases falls between the ages of 20-49. The incidence in the older age group, however, is quite high. The ratio between male and female in 4:3 (Table I and II).

A number of records from a total of 182 cases had to be rejected for various reasons. Fourteen records did not have sufficient data for analysis; 14 cases were not diagnosed until the time of autopsy and 44 cases were those that had been treated somewhere else before being referred to us for some period of time and detailed data concerning treatment were not available. Many of these rejected cases had long survival time, but exclusion was done blindly without any attempt at selection. The remaining 110 cases comprise the material which was analysed.

The details of methods of treatment are in Table V. Ten of the 110 patients were treated by surgery for a period of time before being subjected to other forms of therapy. One of these patients is still alive without evidence of disease at the

Table I: Hodgkin's disease 182 cases registered at Hartford Hospital (1938-1956)
Age Incidence*

Age in Years	Number of Cases	Per Cent
0–9	0	0
10–19	16	8.8
20–29	34	18.8
30–39	29	16.0
40–49	34	18 6
50–59	26	14.4
60–69	24	13.3
70–79	16	8 8
80–over	2	1.1
TOTAL	181*	100

* Age was not registered in one (1) case

end of 12 years without being subjected to any additional treatment. The other nine cases had recurrent disease and four of these follow-up treatment were by irradiation alone, whereas the other five cases were treated by a combination of radiation and chemotherapy.

Four advanced cases in the group of 110 were treated by chemotherapy alone. All of them died within a short period of time after treatment was instituted.

Nitrogen mustard intravenously was used in most of our cases that were treated by comibned radiation and chemotherapy or chemotherapy alone. Usually the dosage was based on 0.4 mg. per kilogram body weight which was given in four divided injections a day apart. This varied somewhat, however, according to each individual physician. Many cases also received oral Triethylene Melamine.

Table II Hodgkin's disease 182 cases registered at Hartford Hospital (1938-1956)

	Sex Incidence	
	Male	**Female**
	104	78
Ratio:	4	3

Table III Hodgkin's disease: 182 cases registered at Hartford Hospital (1938-1956)

Total number of cases registered at Hartford Hospital	182
Data not adequate for analysis	14
Diagnosis determined at autopsy	14
Primary treatment started somewhere else	44
Cases subjected to analysis	110

The uncommon sites of primary lesions are shown in Table IV

Table IV Uncommon sites of primary lesions from 110 cases of Hodgkin's disease (1938-1956)

Determined site of primary lesions	**No. of Cases**
Solely Splenic Involvement	2
Mesenteric Lymph Node Involvement	1
Mesenteric Lymph Nodes and Stomach	2
Periportal Lymph Nodes and Pancreas	1
Stomach alone	1
Small Intestine	2
Large Intestine	2
Urinary Bladder	1
Parotid Gland	1
Lung Parenchyma	1
Bone	3

Radiation dosage and method of treatment in the early years varisd from a single treatment of approximately 400 roentgens to approximately 1,800 roentgens (tumor dose) over a period of two weeks. Since 1950, the dosage, in general, has been increased to approximately 2,000 roentgens (tumor dose) in two weeks to 2,800 roentgens (tumor dose) in three weeks. Our dosage was in the low range as compared to the Time-Dose Relationship Graph of Scott[58] and other series reported. In earlier years treatment factors were: 200 K.V.P., 1/2 mmcu - 1 mmcu total filtration and 250 K.V.P. with Thoreus filtration (approximately 2.8 mmcu H.V.L.) Cases treated by Cobalt 60 in this series is not sufficient for analysis.

SURVIVAL RATE:

Yearly survivals are shown in Table VI. The five-year survival rate was 30% and the ten-year figure was 15.9%. Approximately 8% lived for 15 to 20 years. Five cases are still alive without any further treatment and 13 cases are alive with disease. One case is alive for 24 years without any treatment subsequent to the first course of radiation therapy.

Comparison of five and ten-year survival rates by staging is shown in Table VII. Of 26 Stage I cases, 57.6% survived five years and 35.2% of 17 cases for ten years. Forty cases of Stage IIA, 42.5% survived five years and 26.7% of 30 cases for ten years. Only 7% of 44 cases, Stage IIB and III survived five years and none for ten years. It is very difficult to differentiate the stages of the disease from the records and if there is any error, the true figure should be higher than shown in this analysis.

Comparison of cases treated by all methods, by radiation therapy alone and by combined irradiation and chemotherapy demonstrates no significant difference as is shown in Table VIII. Combined irradiation and chemotherapy does not seem to increase survival time significantly even though more cases of early stages were subjected to this method as compared to those who were treated by irradiation alone.

Table V Hodgkin's disease (110 cases) 1938-1956
Methods of Treatment

Methods of Treatment	Number of Cases	Remarks
Surgery Alone	1	Alive & cured for 12 yrs.
Surgery followed by irradiation	4	Recurrent after surgery 4, 8, 12 & 38 mos.
Surgery followed by combined irradiation and chemotherapy	5	Recurrent after surgery 1½ 4, 5, 10 & 12 mos.
Radiation Therapy Alone	69	Stage I 17.4%; Stage IIA 37.7% Stage IIB & III 44.9%
Combined radiation and chemotherapy	36	Stage I 22.2%, Stage IIA 41.8% Stage IIB & III 36.0%
Chemotherapy	5	All Stage III

Table VI Hodgkin's Disease 110 Cases (1938-1656)

Total Survival Regardless of Method of Therapy

Survival at the end of the year after first therapy admission

YEAR OF TREATMENT	NO. OF CASES	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1938	6	5	5	4	3	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1+
1939	6	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	
1940	4	4	3	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
1941	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
1942	5	4	4	3	2	2	2	2	1	1	1	1	1	1	1	0	0	0	0	0	0				
1943	8	5	3	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0					
1944	4	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0						
1945	4	4	4	3	3	3	2	2	2	2	1	1	1	1	1	1	1	1+							
1946	3	2	2	1	1	1	1	1	0	0	0	0	0	0	0	0	0								
1947	8	5	4	3	2	2	2	1	1	1	1	1	1	1	1	1*									
1948	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0										
1949	9	7	5	4	4	4	4	4	3	2	2	2	2	2*											
1950	8	7	6	3	2	2	2	2	2	2	2	2	2+												
1951	10	6	5	4	4	4	4	4	4	4	4	4*													
1952	4	2	2	1	1	0	0	0	0	0	0														
1953	8	7	7	6	5	5	5	5	5	4*															
1954	10	5	4	3	1	1	1	1	1+																
1955	6	5	4	4	3	2	2	2*																	
1956	4	1	1	0	9	0	0																		
TOTAL	110	74	62	45	36	33				13 (of 82)				4 (of 49)						2 (of 22)				
PER CENT	100					30				15.9				8.2						9.1				

+Alive Without disease
*Alive with disease

Table VII
Hodgkin's disease (110 cases) 1938-1956
Survival Rate According to the Stage of Disease

Stage	Five-Year Survival		Ten-Year Survival	
	No. of Cases	Per Cent	No. of Cases	Per Cent
I	26	57.6	17	35.2
IIA	40	42.5	30	26.7
IIB and III	44	7.0	–	–

Table VIII
Hodgkin's disease 1937-1956
Comparison of Survival Rate according to various methods of therapy

Method of Treatment	No. of Cases	Survival Rate			
		5 year	10 year	15 year	20 year
Treated by all methods	110	30.0%	15.9%	8.2%	9.1%
Radation therapy and combined radiation and chemotherapy	105	29.5%	15.4%	6.0%	7.1%
Radiation therapy alone	69	20.0%	16.7%	8.1%	9.5%
Combined radiation and chemo-therapy	36	30.7%	12.5%	–	–

Comparison of the survival rate of our series with those reported previously by others is tabulated in Table IX, and the survival rates of localized early stages of disease (Stage I and IIA) are compared and tabulated in Table X.

DISCUSSION:

It would appear from the review of the cases of Hodgkin's disease at the Hartford Hospital that some of the patients who suffered from this disease can be cured. Even though the course of many cases of Hodgkin's disease is very benign, our own studies and those of others indicate without much doubt that treatment pro longs the patient's life. This is supported by figures of Minot et al.,[48] who report that the mean survival time of untreated cases is about 22 months as compared to approximately 44 months[54] for treated cases.

It is important to decide whether the disease is unifocal or multifocal because of the influence this may have on planning the course of therapy. Many investigators, for instance, advocate radical treatment either by means of surgery or irradiation when the disease is localized. Smith and Klopp,[59] Hellwig,[32] Sugarbaker and

Table IX Hodgkin's Disease (110 cases) (1938-1956)
Comparison of Total Survival Rate with Others

Authors	Date of Publication	No. of Cases	Per Cent Survivals			
			5 Yr.	10 Yr.	15 Yr.	20 Yr.
Hare et al.[29] (1950-1952)	1958 Lahey Clinic & M.I.T.	28	37.5+ 10.7 *	–	–	–
Healy et al.[31]	1955 Walter Reed Hosp.	216	37.0	6.0	–	–
Peters[54] (1924-1954)	1960 Ontario Cancer Institute Canada	285	36.1	22.8	18.5	15.7
Cook et al.[9] (1922-1952)	1958 Harper Hosp. (Detroit)	347	34.6	18.5	13.0	10.2
Hilton et al.[33]	1962 Univ. College Hosp. (London, Eng.)	107	31.0	–	–	–
Levinson et al.[45]	1957 Univ. of Utah	58	31.0	–	–	–
Worwick et al.[68] (1932-1951)	1959 All clinics in Ontario Canada	411	30.0	–	–	–
Author's Series	1962 Hartford Hospital	110	30.0	15.9	8.2	9.1
Boden[6]	1951	112	26.0			
Nice et al.[49]	1954 Univ. of Minnesota	208	25.0	11.0	4.0	–
Elkin[19]	1956 Univ. of Iowa	–	25.0	–	–	–
Paterson et al.[51]	1954 Christie Hosp. (Eng.)	256	25.0	–	–	–
Craver[12]	1952 Memorial Hosp., N.Y.	471	23.6	–	–	–
Hall et al.[28] (1940-1950)	1956 Albany Medical College	64	20.0	–	–	–
Diamond[17] (1918-1953)	1958 Memorial Hosp., N.Y.	713	19.5	7.2	–	–
Bethel et al.[5]	1950	119	19.3	–	–	–
Krumbhaar	1939 Univ. of Pennsylvania	–	15.0	6 0	–	–

\+ Alive without disease
* Alive with disease

Table X Hodgkin's Disease 1938-1956

Comparison of Survival Rate in Localized Cases (Stage I & IIA) with others

Authors	Per Cent 5-Yr. Survival	Per Cent 10-Yr. Survival
Nice & Stenstrom(49) (1954)	Stage I 85 Stage II 90	Stage I 77 Stage II 35
Peters(52) (1950)	Stage I 88 Stage II 72	
Peters(54) (1961)	Stage I 66.6 Stage IIA 73.2	Stage I 48.2 Stage IIA 47.8
Hilton et al.(33) (1962)	Stage I 79 Stage IIA 55	
Peters & Middlemiss (1958)	Stage I) 64 Stage IIA)	Stage I) 60 Stage IIA)
Jelliffe et al.(40) (1955)	Stage I 59 Stage IIA 60	
Holme & Kunkler(35) (1961)	Localized disease 53	—
Author's Series (1962)	Stage I 57.6 Stage IIA 42.5	Stage I 35.2 Stage IIA 26.7
Healy et al.(31) (1955)	Stage I 50.0 Stage II 43.0	Stage I 12 Stage II 9
O'Brien et al.(50)	Localized disease 45	—

Craver[64] and Warren[66] have reported that surgery in selected localized groups of nodes has proven to be of value in obtaining cures or long-term survivals. It would be wise, however, to estimate carefully whether radical surgery is the treatment of choice since tissue previously operated upon will tolerate less irradiation if this form of treatment becomes necessary later. There are many chemotherapeutic agents used in the treatment of Hodgkin's disease. Fowler's solution was used as early as the late 19th century but proved not to be beneficial. Nitrogen mustard was first introduced by Goodman et al.,[26] at Yale University in 1941 and their results were published in 1946, which proved that this agent had a beneficial effect on Hodgkin's disease. Since then many more chemotherapeutic agents have been introduced, but so far there are none which are considered curative. Craver,[11] in his Janeway Lecture, mentioned that P-32 has not been beneficial in the treatment of Hodgkin's disease and that so far nitrogen mustard and its related compound are the most effective chemotherapeutic agents. He advised a single dose intra venous injection. Dameshek et al.,[14] in 1949 reported that the remission from introgen mustard ranged from 50-331 days. Gellhorn and Collins[23] evaluated 67 cases of combined treatment by nitrogen mustard and irradiation and compared them with 65 cases treated by irradiation alone. They found that the addition of nitrogen mustard did not seem to improve the overall five-year survival significantly, but that it did seem to lengthen the time interval between courses of irradiation. This also is in agreement with report of Cook et al.,[9] Peters[52,53,54] Hall et al.,[28] and our own statistics. Nitrogen mustard, however, is very useful for palliation in late or advanced stages of the disease as well as in special situations, such as spinal cord compression and superior vena cava obstruction because of its decongestant-effect as mentioned by Craver.[11] Triethylene Melamine is effective but less so than nitrogen mustard. It can, however, be given orally and it is for less toxic. There are many other ankylating agents as well as antimetabolites, antibiotics and hormones used as palliative agents in the treatment of this disease[16,42,56,65] Farber[20] summarizes the case for these agents when he says that they must continue to be used in the field of cancer research. Combined chemotherapy of different substances has been reviewed extensively by Sampley.[56]

Cortizone and ACTH seem to have no direct effect on Hodgkin's disease but they are very useful as supportive therapy, especially for anemia, which is commonly found in Hodgkin's disease and which is often the result of irradiation treatment.

Radiation therapy still seems to give longer remission than other forms of therapy and this has been true since the first application of Roentgen Rays for this diseass by such men as Pusey, Coley, Williams, Childs, Steiwan and Heinke[47] in 1902-1905. There has, however, been considerable progress in the knowledge of dosage and modality of treatment. Peters,[52] Hynes and Frelick,[36] Healy, Armory and Friedman[31] were among the first to advocate segmental therapy with high dosage in localized bisease. Soon thereafter Hare, Dahle and Trump[29] reported on the use of 2 million volt machine and Kaplan,[41] on the use of the linear accelerator. The results are quite interesting

because there seems to have been better survival rates and longer periods of remissions with the higher voltage. However, the number of cases reported and long-term follow-up are not yet sufficient for comparison with lower voltages at this date, especially since the survival rate in early stages of the disease of patients treated conservatively by orthovoltage radiation as reported by Nice and Stenstrom is also high as well as those in our series treated with lower dosages.

SUMMARY:

1. A review of cases at Hartford Hospital from 1938 to 1956 revealed a five-year survival rate of 30% from a total of 110 cases with a ten-year survival rate of 15.9% in 82 cases.

2. A comparison of survival rates from all methods of treatment, radiation therapy alone and combined rediation and chemotherapy revealed no significant difference in five-year and ten-year survivals.

3. Combined radiation and chemotherapy does not seem to improve the long-term survival rate in our series which is in agreement with previous reports by other investigators.

4. Even though our dosage range is somewhat low, the statistics show very interesting results of long-term survival.

5. The literature which was reviewed suggested that the planned treatment is moving towards radical treatment. However, up-to-date data is not as yet sufficient and should be evaluated further.

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