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Irradiation Therapy in Hodgkin's Disease

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I. IRRADIATION THERAPY IN HODGKIN'S DISEASE

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The purpose of the present communication is to review the results of irradiation therapy in Hodgkin's disease at the University of Minnesota Hospitals as previously reported[1,2], to review concepts on the nature and therapeutic approach to this condition, and to bring the results of irradiation therapy at the University of Minnesota Hospitals up to date.

Recapitulation

Previous papers of Merner and Stenstrom[1,2] presented many basic principles necessary to the study of Hodgkin's disease. A brief review of these principles is in order.

In 1832, Sir Thomas Hodgkin[3] described gross postmortem observations on seven patients who presented lymphadenopathy, accompanied by anemia and splenomegaly, followed by cachexia and death. In 1856, Sir Samuel Wilks[4] pointed out the frequent involvement of liver, kidney and lungs, and distinguished Hodgkin's disease from the leukemias. In 1878, Greefield[5] referred to the histologic changes of marked increase in fibrous stroma and large number of multinucleated cells. In 1892, Goldman[6] pointed out the importance of eosinophils, and in 1898, Sternberg[7] described the characteristic giant cells and areas of necrosis. In 1902, Reed[8] gave a detailed correlation of pathologic findings with the clinical histories. She gave a more accurate description of the characteristic cells, and strongly upheld the differentiation of Hodgkin's disease from tuberculosis.

Many early workers thought that the tubercle bacillus[9] caused Hodgkin's disease. Bunting and Yates[10] implicated diphtheroid bacilli, naming the organism Bacterium hodgkini. Parsons and Poston[11] and later Wise and Poston[12] thought Brucella organisms responsible. Twort[13], studying leukemia of fowls and pernicious anemia of horses, advocated a viral theory, as did Gordon[14], who produced paralysis and death in animals after injecting material from Hodgkin's glands intracerebrally. Turner, Jackson and Parker[15] thought the Gordon test to be entirely dependent upon the presence of eosinophils. Warthin[16], Mallory[17], Bell[18], and other modern workers incline to the neoplastic theory. The absence of any proved infectious agent, the high fatality rate, and the occurrence of cases with apparent primary lesions with later metastases tend to support the neoplastic theory.

The clinical picture in Hodgkin's disease is variable. Enlargement of single or multiple groups of lymph nodes may be the only complaint. Onset may be heralded by weakness, fever, anorexia, nausea and vomiting, weight loss or pruritus. Cough, dyspnea, cyanosis or dysphagia may indicate mediastinal lymphadenopathy. Pulmonary parenchymal involvement may be accompanied by fever and the lesions may cavitate. Frequent coincident infections include tonsillitis, upper respiratory, otitic and oral infections. Vertebral or extradural involvement may produce monoplegia or paraplegia. Backache is commonly caused by enlarged retroperitoneal nodes. Localized pain usually precedes actual roentgen demonstration of bone lesions, and bone marrow studies may demonstrate multiple granulomas. Jaundice may be due to enlarged nodes about the common duct or to actual hepatic involvement. Enlargement of the spleen, invasion of the stomach and kidneys, as well as involvement of other organs may be accompanied by clinical findings. Specific skin lesions are not infrequently demonstrated and herpes zoster occurs in some cases, responding to roentgen therapy.

Pathologically[18], the lymph nodes grossly are enlarged, pale and firm, discrete, and of fleshy or fibrous consistency. Differentiation from other tumors of lymph nodes may be quite difficult. Microscopically, there is an increase in the number and size of the reticulum cells, often with the formation of mononuclear or polynucleated giant cells of the Reed-Sternberg type, increase of

reticulum fibers with formation of areas of fibrosis, obliteration of sinusoids, variable number of eosinophils, areas of necrosis and increase of lymphoid cells. Invasion of the capsule may be noted. Involvement of other organs or tissues show similar changes. Microscopic differentiation from other tumors of lymph nodes is difficult, and Jackson and Parker[19] would restrict the diagnosis to those cases showing Reed-Sternberg cells. The latter authors also describe three histologic patterns which they consider of prognostic importance: Paragranuloma, the early variety, presenting hyperplasia of adult lymphoid cells, small numbers of Reed-Sternberg cells, and slow progression of disease. This may lead, after a variable period of time to Hodgkin's Granuloma, which presents histologic evidence of eosinophilia, necrosis and fibrosis, a more rapid progression and more serious prognosis. The third type, Hodgkin's sarcoma, presents large tumor cells and Reed-Sternberg cells, with only occasional necrotic areas. This form is rapidly progressive and fatal in a short time. It is most commonly primary in the retroperitoneal lymph nodes and gastro-intestinal tract but rather uncommon in the peripheral nodes. Slaughter and Craver[20] dispute this concept, reporting fourteen cases of Hodgkin's sarcoma, with five patients surviving three years, three patients surviving five years and one seven years. Also, the patients in their general series who survived less than six months presented no consistent histologic picture. This concept is also clouded by the fact that biopsy specimens from different areas may show different histologic characteristics. Obviously, if numerous areas are involved, it is not practical to examine each area histologically.

Hodgkin's disease shows no racial predilection. In America, negroes and whites are affected to about the same extent. From 62 - 70% of the patients are males. All ages are affected with the maximum incidence in the third decade.

The site of onset is in the peripheral nodes, predominantly the cervical, in 75% of the cases. Other less frequent sites of onset include the mediastinal and abdominal lymph nodes, lung, skin and other organs. The peripheral nodes are ultimately involved in about 98% of the patients and endothoracic structures in roughly two-thirds of the patients. Abdominal nodes will be involved in over one-half, and the spleen is involved in about one-third of the patients (as high as 70% in some series). Bone and skin represent moderate frequency of involvement (15-20%).

In the previous reports from this institution[1,2] it was emphasized that treatment of patients should be individualized, bearing in mind certain fundamental principles. It was noted that that most favorable cases are those in which only one chain of nodes is involved and in these patients intensive local irradiation is given after biopsy. In general, 1000 to 2000 tissue roentgens in fourteen treatment days was advised, the larger dose advised where feasible. With mediastinal involvement, initial doses of 50 - 75 r in air were advised to prevent accentuation of symptoms which might follow hyperemia and edema about the bronchial tree. Large masses of long standing were noted to be more resistant to irradiation than smaller masses of more recent origin, and consequently, more intensive therapy was advised in patients with the larger masses. In all cases, however, a certain minimum dosage was advised even though a rapid response was noted before the intended amount was administered. Prophylactic irradiation, based on prediction of future area involvement, was not advised.

Other approaches to therapy were also discussed. Thus, Slaughter and Craver[20] treated five patients with apparent local involvement, with local surgical resection followed by irradiation with survival of five, six, eight, eleven and eleven years respectively. Dessauer[21] in 1907, followed by Chaoul and Lange[22] in 1923 utilized spray or total body irradiation. In the United States this method was utilized by Heublein[23], who, in 1931, introduced what has been called the "Heublein Method" at Memorial Hospital, New York. Heublein, in collaboration with Craver and Failla, devised a method

of treating patients with prolonged continuous irradiation with hard rays of low intensity (17 r per day, 0.86 r per hour), the average total dose being 100 r. Additional local therapy was given to each group of enlarged nodes. In 1942, Medinger and Craver[24] reported ninety-four cases in which this method was used. The five-year survival was 24 per cent, an improvement of 6 per cent over the remaining series of patients treated at that clinic. They further concluded that:

1. Total body irradiation alone is not sufficient to produce lasting results.

2. The greater the amount of previous roentgen therapy, the poorer the response to total irradiation.

3. Terminal cases of Hodgkin's disease were unaffected by the treatment.

4. The first few treatments were most beneficial.

5. Maximum improvement resulted where local disease was first controlled by local therapy.

A modification of the spray method was used at the University of Minnesota Hospitals on a few terminal cases. The irradiation was at a much higher rate per minute, giving two or three treatments at 140 cm. distance for a total of 30 r in air. Most patients were unimproved, but in two, remarkable improvement lasted long enough so that benefit from local therapy was obtained.

Results of irradiation therapy[1,2] in the first 185 proved cases treated here were reported as showing a five-year survival of 21 per cent and a ten-year survival of 8 per cent. The average survival following institution of treatment was 33.1 months.

Ewing[25] gave the average survival of untreated patients as about eighteen months. Craft[26] collected 52 cases of untreated Hodgkin's disease from the autopsy records at the University of Minnesota Hospitals which showed a five-year survival rate of 6 per cent from time of onset, with no ten-year survivals. Slaughter and Craver[20] reported 265 treated cases with five-year survival of 18 per cent and ten-year survival of 3 per cent. The average survival was 33.8 months. This series represented cases followed five years or longer, while the 185 cases reported from this hospital included living patients followed only three years. Thus, it is seen that there is not a great difference in the two series.

More Recent Concepts

In the more recent literature, there seems to be general acceptance of the neoplastic nature of Hodgkin's disease, and no further studies attempting to implicate various infectious agents have been described. Sahyoun and Eisenberg[27] studied twenty-four cases of Hodgkin's disease and described a histopathologic and clinical classification:

(1) A compactly cellular type which progresses slowly and has a range of maximal life expectancy of 48-160 months.

(2) Fibrogranulomatous type with maximal life expectancy of 20-60 months.

(3) A loosely cellular type which is rapidly progressive and has a range of maximal life expectancy of 12-20 months.

Further histologic detail is described in the original article, but it seems that there is at least a gross similarity to the classification of Jackson and Parker, as described above, and that, here again, a relative prognosis is attempted on the basis of the histopathologic picture.

Following the tendency to stage some carcinomas clinically, Peters[28] devised a clinical classification for patients with Hodgkin's disease. She listed the following stages according to the extent of involvement on admission:

I. Involvement of a single lymph node region or a single lesion else-

where in the body.

II. Involvement of two or more proximal lymph node regions of either the upper or lower trunk.

III. Involvement of two or more lymph node regions of both upper and lower trunk.

The survival figures were correlated better with the clinical stage than with any other factor. There was considerable correlation between the histopathologic picture but this correlation was not as good as that obtained with clinical staging. If the presence or absence of constitutional symptoms is added to the classification as further method of delineating stage I patients, an even better correlation is obtained. Peters, therefore, suggested the following clinical classification of Hodgkin's disease:

Stage I. Involvement of only one lymph node region or a single lesion elsewhere, with no constitutional symptoms.

Stage II. Involvement of two or more proximal lymph node regions confined to either upper or lower trunk, with or without constitutional symptoms.

Stage III. Involvement of multiple lymph node regions with or without constitutional symptoms or acute Hodgkin's disease with no obvious lymphatic involvement.

With this type of staging, Peters states that in her series, she would have had 100% five-year survival in stage I.

From time to time, attention is called to the relationship between the various tumors of lymph nodes[29]. Custer and Bernhard[30] analyzed 1300 lymphatic tumors, many sampled several times during their progress. They state that a rigid classification of lymphatic tumors is artificial and confusing and that their series showed a striking fluidity in histologic pattern, with transitions and combinations that could best be interpreted as indicating a single neoplastic entity having a number of variants.

Recent Additions to Therapy

Gilman and Philips[31] introduced the nitrogen mustards into the treatment of Hodgkin's disease and allied disorders in 1946. Since that time, numerous reports[32-37] have indicated distinct temporary palliative effects following use of these agents in patients who were resistant to irradiation, in patients with generalized disease, and as an adjunct to irradiation or other forms of therapy. Gellhorn and Collins[38] studied two series of patients, in one of which radiotherapy alone was used (65 patients) and another in which radiotherapy and nitrogen mustards were administered in alternating courses (67 patients). No significant difference in the four year survival rate was found in the two groups. However, the amount of radiation required was less, asymptomatic periods longer and the economic burden lighter for patients receiving combined therapy.

In 1950, triethylene melamine (TEM) was given to mice in treating leukemia and various tumors[39,40]. Karnofsky et al[41] reported the first group of patients to be treated with TEM. They found palliative results comparable to those obtained by use of nitrogen mustards. However, TEM may be given by mouth, causes less nausea and vomiting, and obviates the difficulties of venous thrombosis encountered in nitrogen mustard therapy. Kravitz et al[42] report successful palliation in 32 of 36 patients with Hodgkin's disease following TEM therapy.

Radioactive phosphorus[43], arsenic[44] and gold[45] and various other agents have failed to show comparable results.

Present Concepts at University of Minnesota Hospitals

The histologic sections of the present study and in previous studies of lymphoid tumors have been reviewed chiefly by Dr.

Robert Hebbel of the Department of Pathology. In his opinion[46], it is difficult to separate the lesions of Hodgkin's disease into sub-groups, certainly to the extent of prognostic implication.

In the clinical appraisal of the patients, a thorough history and physical examination are followed by biopsy of tumor tissue and in some cases, by study of the bone marrow. The latter may be advisable in all patients. In Table I, there is listed the incidence of the sites of onset in various parts of the body in 224 patients, and in Table II, the total incidence is given. It is noteworthy that the disease apparently starts in the peripheral lymph nodes in 70.4 per cent of patients, and sooner or later involvement of one or more groups of superficial nodes occurs in almost all patients. The mediastinal and abdominal lymph nodes, lungs and spleen represent the most frequent internal sites of involvement. It should be emphasized that some patients are still living and some died elsewhere so that a comparable series of postmortem observations would give a much higher incidence in the internal organs.

TABLE I

Site of Initial Involvement in Hodgkin's Disease (224 proved cases)

	No. of Cases	Per Cent
Cervical lymph nodes	134	59.8
Axillary lymph nodes	19	8.5
Supraclavicular lymph nodes	5	2.1
Inguinal lymph nodes	10	4.5
Mediastinal lymph nodes	12	5.3
Mediastinal nodes plus pulmonary infiltration	3	1.3
Abdominal lymph nodes	13	5.8
Skin	11	4.9
Bone (inc. spine)	6	2.6
Generalized	9	4.0
Breast	1	0.4
Thyroid	1	0.4
Tonsil	1	0.4
	224	100%

TABLE II

Sites of Involvement of Hodgkin's Disease (224 proved cases)

	Cases	Per Cent
Peripheral lymph nodes		
Cervical	187	83.5
Axillary	144	64.3
Supraclavicular	39	17.4
Inguinal	101	44.6
Thoracic		
Mediastinal lymph nodes	134	60.0
Parenchymal involvement	65	22.0
Pleural effusion	24	10.7
Pericardial effusion	3	1.3
Heart	1	0.5
Abdominal lymph nodes	111	49.5
Spleen	66	29.2
Skin	35	15.6
Bone	37	16.5
Liver	27	12.0
Muscle	8	3.6
Spine	11	4.9
Kidneys	7	3.1
Face	7	3.1
Breast	6	2.7
Adrenals	6	2.7
Stomach	5	2.2
Thyroid	3	1.3
Nervous System	4	1.8
Parotid Gland	2	0.9
Pancreas	2	0.9
Omentum	1	0.5
Eustachean tube	1	0.5
Skull	1	0.5
Scalp	1	0.5
Bone Marrow	1	0.5
Peritoneum	1	0.5
Gallbladder	1	0.5
Tonsil	1	0.5
Paranasal sinuses	1	0.5

Results of Therapy

In irradiating patients with Hodgkin's disease, as well as in other malignant conditions, it is essential to attempt to utilize an optimum dosage within certain time limits. The treatment of patients

should be individualized. In general, when the disease is localized to one region in two adjacent regions an attempt is made to deliver a minimum of 2000 tissue roentgens to the tumor in 14 days. In the cervical region, this can be accomplished by giving 900 r in air to each of three fields. Factors include 220 K.V.P., filter of 0.5 mm. Cu. plus 1.0 mm. Al., H.V.L. 1.35 mm. Cu., and 60 cm. distance. Added filtration and distance to achieve better depth dose distribution are used in more deep-seated lesions. Large masses of long standing may require heavier dosage, but even in the smaller masses, a minimum dosage of 2000 tissue roentgens is desirable. So-called prophylactic irradiation to adjacent nodal areas is not given, so that adequate dosage may be tolerated in areas where disease appears.

In patients with widespread disease, less intense or palliative therapy is indicated, largely to ameliorate symptoms. When there is involvement of the mediastinal nodes, small doses of 50-75 r in air are used initially, to obviate possible edematous compression of the tracheobronchial tree. A total tumor dose of 2000 tissue roentgens is still given within a period of three weeks. Total body or spray irradiation is occasionally given in very small doses to patients with widespread disease. It is in these patients that nitrogen mustards and TEM may be valuable adjuncts.

Special attention should be paid to patients with spinal cord compression caused by Hodgkin's disease. Laminectomy should be performed without delay if symptoms of paresis develop and the involved area of the cord should then be treated immediately with X-rays. The remarkable palliation which may be obtained from such procedures is exemplified in a report by Marcus Smith and K. W. Stenstrom[47] which refers to eleven of the patients included in the present series.

In Table III, the survival data on 224 proved cases of Hodgkin's disease is given. In each instance, the microscopic diagnosis has been re-evaluated for this study. Of 208 patients followed five years or longer, a survival of 52 patients or 25 per cent is noted. For completeness, a separate survival table (Table IV) is presented in whom the clinical diagnosis seemed quite likely to be Hodgkin's disease. In most of these, a histologic diagnosis has been made but the slides were not available for re-evaluation for this study. The results do not differ remarkably.

For comparison, the five-year survival rates reported from other medical centers are presented. Krumbhaar[47] reported a five-year survival of 15 per cent at the University of Pennsylvania. Slaughter and Craver, mentioned above, in a series of 265 patients at Memorial Hospital, reported a five-year survival of 17.7 per cent with an average survival of 33.8 months after treatment. This series included the 94 patients treated with the Heublein method, in which group there was a 24 per cent five-year survival. In Peters'[28] series of 113 patients, a 51 per cent five-year survival is given, by far the highest reported to this date. Almost all series reported show an improvement in treated as compared to untreated cases.

The striking results reported by Peters bear consideration. As she states, comparison of survival rates from various institutions may vary with the material In recording the survival according to extent of involvement on admission, she notes an 88 per cent five-year survival in 35 stage I cases, 72 per cent in 32 stage II cases and 9 per cent in 46 stage III cases. For the patients followed 10 years or longer, Peters reports a 79 per cent ten-year survival in 19 stage I cases and 21 per cent in 19 stage II cases. None of the 16 stage III cases survived as long as 10 years.

The patients studied here have been accordingly staged and the results tabulated in table V.

From Table V, we note, as did Peters in her series, that the five-year survival rate in Stages I and II differ relatively little, while the ten-year

TABLE III

SURVIVAL RATE IN HODGKIN'S DISEASE AFTER FIRST TREATMENT

(224 Proved Cases)

Year	No. of Cases	Survival																			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	22	Living
1926	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0
1927	3	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1928	5	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1929	8	4	3	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1930	7	4	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0
1931	16	12	7	6	5	3	3	3	3	3	2	2	1	1	1*	0	0	0	0		0
1932	18	13	11	6	6	4	3	3	2	2	1	1	1	1*	0	0	0	0	0		0
1933	15	8	7	7	7	7	5	3	2	2	2	1	1	1	1	1	1	1	1		1
1934	14	11	7	5*	1	1	1	1	1	1	1	1	1	1	1	1	1	1			1
1935	15	9	9	7	6	5	3	3	3	2	2*	0	0	0	0	0	0				0
1936	5	2	2	2	2	2	1	1	1	1*	0	0	0	0	0	0					0
1937	15	9	7	6	6	4	4	4	4**	2	2	2	2	2	1						1
1938	12	10	8	6	4	1	1	1*	0	0	0	0	0	0							0
1939	13	4	3	1	1	0	0	0	0	0	0	0	0								0
1940	14	8	7	7	7	5*	4	4	4	4	4	1									1
1941	10	6	5	5	5	5	5	5	5	3	3										3
1942	18	10	8	7*	3	3	2	2*	1	1*											0
1943	5	5	5	4	3	3	3	3	3												3
1944	4	4	4	3	3	3	3	2													2
1945	6	4	2	2	2	2	0														0
1946	3	3	2	2	2	2															2
1947	9	3	3	1	1																1
1948	7	5	4	2																	
Cases	224	224	224	224	217	208	205	199	195	177	167	153	140	128	113	108	94	79	61	45	18
Survival		140	110	86	69	52	40	37	31	23	19	10	9	8	6	4	3	3	2	1	
Per Cent		65	49	38	32	25	19	19	16	13	11	7	6	6	5	4	3	4	3	2	

* Lost contact with one case

** Lost contact with two cases

TABLE IV

SURVIVAL RATE IN HODGKIN'S DISEASE AFTER FIRST TREATMENT

(78 Clinical Cases)

Year	No. of Cases	Years of Survival																					Living
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	24	
1926	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1927	5	3	3	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2*	1	1
1928	4	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0
1929	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0
1930	7	5	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0
1931	4	2*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0
1932	6	5	4	3	3	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0			0
1933	3	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0				0
1934	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0					0
1935	3	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0						0
1936	2	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0							0
1937	5	3	3	3	1	1	1	1	1	1	1	1	1	1	1								1
1938	4	1	1	1	1	1	1	1	1	1	1	1	1	1									1
1939	0	0	0	0	0	0	0	0	0	0	0	0	0										0
1940	1	1	1	1	1	1	1	1	1	1	1	1											1
1941	5	3	3	3	3*	2	2	1	1	1	1												1
1942	4	3	2	1*	0	0	0	0	0	0													0
1943	1	1	1	1	1	1	1	1	1														1
1944	5	5	5	2	2	2	2																2
1945	5	3	3	3*	2	2	2																2
1946	2	2	2	1	0	0																	0
1947	4	4	3	2	2																		2
1948	3	1*	0	0																			0
Cases	78	78	78	78	75	71	69	64	59	58	54	49	48	48	44	39	37	34	32	29	23	7	13
Survival		50	40	33	22	16	14	9	7	6	6	5	4	4	3	2	2	2	2	2	2	1	
Per Cent		64	51	42	29	23	21	14	12	10	11	10	8	8	7	5	5	6	6	7	9	14	

* Lost contact with one case

TABLE V

Survival According to Clinical Stage

	Five Year Survival			Ten Year Survival		
Stage	No. of cases	No. 5-yr. survival	% 5-yr. survival	No. of cases	No. 10-yr. survival	% 10-yr. survival
I	20	17	85	13	10	77
II	20	18	90	17	6	35
III	168	17	10	143	3	2

survival rate in Stage II is definitely smaller than in Stage I. Although Peters had a 9 per cent five-year survival rate in Stage III, she recorded no ten-year survivals. We note a 10 per cent five-year survival, and 2 per cent (3 of 143 patients) ten-year survival in Stage III.

In Table VI, average and median survival data for separate stages and the total group is given. Here again is noted a relatively small difference between stages I and II, with definite decrease, both in survival after treatment and total survival, in the Stage III

TABLE VI

Average and Median Survival Data

	Stage I Years	Stage II Years	Stage III Years	Total Years
Average duration before treatment	1.7	0.6	1.3	1.4
Median duration before treatment	0.6	0.5	0.7	0.7
Average survival after first treatment	9.9	8.6	2.2	3.5
Median survival after first treatment	9.9	8.1	1.0	1.6
Average total survival	11.6	9.2	3.5	4.9
Median total survival	11.8	9.5	2.3	3.3

group. The relatively little difference in duration of disease before treatment between Stages I and III would seem to indicate a biologic difference in tumor-host relationship, i.e., the tumor is less invasive and spreads less rapidly. This should, in turn, make the patients in Stage I more amenable to intensive therapy.

DISCUSSION

The evidence presented would seem to corroborate the clinical opinions so well demonstrated by the previous publication of Peters, viz., that clinical staging is the most accurate method by which we can predict survival in patients with Hodgkin's disease, and that comparison of large series from different medical centers has more meaning if grouping into clinical stages is presented. It has been our experience that patients with malignant lymphoid tumors, regardless of histopathologic diagnosis or grading, may present with localized or dissemi-

nated disease. Holmes and Schulz[49] reviewed 500 lymphoma records and selected 15 who were alive and apparently free of disease five years or longer in whom the lesion at the time of treatment was localized and who were treated by irradiation only, biopsy excepted. When the histologic sections were reviewed, they found examples of all lymphoid tumors. Only one of these was a follicular lymphoma (giant follicle tumor, Brill-Symmers disease), and there were no examples of the so-called Hodgkin's paragranuloma. The latter fact is mentioned because proponents of histopathologic prognosis consider these two tumors the least malignant of the group. Additional evidence of unifocal origin of lymphoid tumors is cited by Hellwig[50] who reports approximately 10 per cent of 135 lymphoma necropsies revealing only localized disease, and by Gall[51] who found 29 of 33 lymphomas of the gastrointestinal tract free of metastases.

Gall and Hellwig state a preference of surgery over irradiation in localized lymphoid tumors. Very few of our patients have been subjected to surgery, but we have noticed a tendency to recurrence which leads us to believe that if surgery is undertaken as the primary procedure, it should be followed immediately by intensive irradiation. This view is shared by Craver[52].

Baker and Mann[53] reported two patients with localized Hodgkin's disease who were treated by surgical excision followed by irradiation. These patients had lived ten and twelve years respectively at the time of the report. Rhoads[54] prefers the combination of surgical excision followed by immediate irradiation in localized lymphosarcoma, a closely allied disease.

In most of the literature reviewed, the opinion seems to be that primary surgical excision alone is not the procedure of choice in localized lymphoid tumors. Whether a combination of surgery plus irradiation is superior to irradiation alone is still a debatable point in lesions of the peripheral lymph node areas. Surgical excision of primary foci in the gastrointestinal tract and lungs seems quite logical, since the definite diagnosis is made quite often during exploratory operation, and laminectomy seems mandatory in the cases in which compression of the spinal cord is present.

SUMMARY AND CONCLUSIONS

A series of 208 patients with proved Hodgkin's disease showed a five-year survival rate of 25 per cent; of 167 patients followed ten years or longer, the ten-year survival rate is 11 per cent.

Clinical staging is the most accurate aid in prognosis and is necessary in comparing series from various medical centers. For twenty patients in stage I, the five-year survival rate is 85 per cent; for thirteen of these, followed ten years or longer, the ten-year survival is 77 per cent.

In Stage II, there is a 90 per cent survival in twenty patients followed five years, and a 35 per cent survival in seventeen patients followed ten years. Thus, the difference between Stages I and II is shown in the ten year period.

In the much larger group in Stage III, representing those patients with disseminated disease, the five and ten-year survival rates are 10 and 3 per cent respectively.

In Stage I, the treatment of choice is either intensive irradiation or possibly surgical excision followed immediately by intensive irradiation. In Stage II, intensive irradiation is the treatment of choice. In Stage III, palliative irradiation to reduce tumor masses or relieve symptoms is indicated. It is in the latter group that the nitrogen mustards and triethylene melamine may serve as useful adjuncts.

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II. MEDICAL SCHOOL NEWS

Coming Events

March 17	Minnesota Pathological Society Lecture; "Renal Vascular Disease in Diabetes Mellitus"; Dr. E. T. Bell; Owre Amphitheater; 8:00 p.m.
March 26	Special Lecture; "Trace Elements in Biochemistry and Medicine"; Dr. Burt L. Vallee, Associate in Medicine, Harvard Medical School, and Research Associate, Department of Biology, Massachusetts Institute of Technology; Owre Amphitheater; 4:00 p.m.
March 27	Tape-Recorded Symposium: Is the Concept of Science Different in Biology than it is in the Physical Sciences? Owre Amphitheater; 3:00 p.m. (This is a tape recording of a discussion which was held on December 8, 1952, at the meeting of the Boston Society of Biologists. The participants were Dr. James B. Conant, Harvard; Dr. Phillip G. Frank, Harvard; and Dr. Paul Weiss, University of Chicago.)
April 6-11	Continuation Course in Proctology for General Physicians
April 16-18	Continuation Course in Gynecology for Specialists

* * *

Faculty News

Dr. Reynold A. Jensen, Professor of Psychiatry and Pediatrics and Director of the Division of Child Psychiatry, attended the meeting of the American Orthopsychiatric Association in Cleveland on February 23-25 where he discussed two papers and served as chairman of one of the sessions. In addition he participated in two workshops; one on the subject, "Encopresis," and the other on "The Teaching of Medical Psychology and Child Psychiatry in Pediatrics". Dr. Jensen was also a member of the organization committee for the American Academy of Child Psychiatry which was formally organized on February 22.

Dr. David Glick, Professor, Department of Physiological Chemistry, has been certified by the American Board of Clinical Chemistry.

* * *

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III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

March 16 - 21, 1953

Monday, March 16

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; W-612, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom; Todd Amphitheater, U. H.

12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:30 Physiology Seminar; 214 Millard Hall.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Pediatric Seminar; Youth Program and Delinquency; Jack Wallinga; Sixth Floor West, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

4:30 - Public Health Seminar; 15 Owre Hall.

4:30 - 6:00 Physiology 114A and Cancer Biology 140 -- Research Conference on Cancer, Nutrition, and Endocrinology; Drs. Visscher, Bittner, and King; 129 Millard Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Ancker Hospital

8:30 - 10:00 Tuberculosis and Chest Conference; Auditorium.

2:00 - 3:00 Surgery Journal Club; Classroom.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Eldon Berglund; Newborn Nursery, Station C.

10:30 - 12:00 Tuberculosis and Contagion Rounds; Thomas Lowry; Station M.

11:00 - Pediatric Rounds; Erling Platou; Station K.

Monday, March 16 (Cont.)

Minneapolis General Hospital (Cont.)

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. A.

1:00 - X-ray Conference; Classroom, 4th Floor.

2:00 - Pediatric Rounds; Robert A. Ulstrom; Stations I and J.

Veterans Administration Hospital

8:00 - 9:00 Neuroradiology Conference; J. Jorgens, R. C. Gray; 2nd Floor Annex.

9:00 - G. I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; J. Jorgens; Conference Room, Bldg. I.

2:00 - Psychosomatic Rounds; Bldg. 5.

Tuesday, March 17

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

12:30 - 1:30 Physiology 114D -- Current Literature Seminar; 129 Millard Hall.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 6:00 X-ray Conference; Presentation of Cases by Veterans Hospital Staff; Eustis Amphitheater, U. H.

*8:00 p.m. Minnesota Pathological Society Lecture; Renal Vascular Disease in Diabetes Mellitus; E. T. Bell; Owre Amphitheater.

Ancker Hospital

8:00 - 9:00 Fracture Conference; Auditorium.

9:00 - 10:00 Medical X-ray Conference; Auditorium.

Minneapolis General Hospital

10:00 - Pediatric Rounds; Spencer F. Brown; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station F.

12:30 - Grand Rounds; Fractures; Sta. A.; Willard White, et al.

12:30 - Neuroroentgenology Conference; O. Lipschultz, J. C. Michael and Staff.

12:30 - EKG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

Tuesday, March 17 (Cont.)

Minneapolis General Hospital (Cont.)

1:00 - Tumor Clinic; Drs. Eder, Cal, and Lipschultz.

1:00 - Neurology Grand Rounds; J. C. Michael and Staff.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:30 - Infectious Disease Rounds; Dr. Hall.

8:30 - Surgery Staff Seminar; Carotid Body Tumors; Harry Burich; Medical Conference Room, Bldg. I.

9:00 - Liver Rounds; Drs. Nesbitt and MacDonald.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery Tumor Conference; L. J. Hay, J. Jorgens; Conference Room, Bldg. I.

1:00 - Review of Pathology, Pulmonary Tuberculosis; Conference Room, Bldg. I.

1:30 - Combined Medical-Surgical Chest Conference; Conference Room, Bldg. I.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Autopsy Conference; E. T. Bell and Donald Gleason; Conference Room, Bldg. I.

Wednesday, March 18

Medical School and University Hospitals

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Paul Lober and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

12:30 - 1:30 Radioisotope Seminar; Subject to be announced; James F. Marvin; 12 Owre Hall.

1:30 - 3:00 Physiology 114B -- Circulatory and Renal System Problems Seminar; Dr. M. B. Visscher, et al; 214 Millard Hall.

4:00 - 5:30 Physiology 114C -- Permeability and Metabolism Seminar; Nathan Lifson; 214 Millard Hall.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Wednesday, March 18 (Cont.)

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

12:30 - 1:30 Medical Journal Club; Library

Minneapolis General Hospital

9:30 - Pediatric Rounds; Max Seham; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Seminar; Arnold Anderson; Classroom, Station I.

11:00 - Pediatric Rounds; Erling S. Platou; Station K.

12:00 - Surgery-Physiology Conference; Drs. Zierold and E. B. Brown; Classroom.

12:15 - Pediatrics Staff Meeting; Classroom, Station I.

1:30 - Visiting Pediatric Staff Case Presentation; Station I, Classroom.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Conference Room; Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

2:30 - 4:00 Psychosomatic Rounds; C. K. Aldrich. Conference Room, Bldg. I.

4:00 - Combined Medical-Surgical Conference; Conference Room, Bldg. I.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, March 19

Medical School and University Hospitals

8:00 - 9:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Heart Hospital Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 6:00 Radiology Seminar; Fanconi's Syndrome; Howard Worthen; Eustis Amphitheater, U. H.

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Ancker Hospital

8:00 - 10:00 Medical Grand Rounds; Auditorium.

Thursday, March 19 (Cont.)

Minneapolis General Hospital

9:30 - Neurology Rounds; Heinz Bruhl; Station I.

10:00 - Pediatric Rounds; Spencer F. Brown; Station K.

10:00 - Psychiatry Grand Rounds; J. C. Michael and Staff; Sta. H.

1:00 - Fracture - X-ray Conference; Dr. Zierold; Classroom.

1:00 - House Staff Conference; Station I.

2:00 - 4:00 Infectious Disease Rounds; Classroom.

4:00 - 5:00 Infectious Disease Conference; Wesley W. Spink; Classroom.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

8:00 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.

Friday, March 20

Medical School and University Hospitals

8:00 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Hypotensive Anesthesia; Frederick H. Van Bergen; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Physiology 124 -- Seminar in Neurophysiology; Ernst Gelhorn; 113 Owre Hall.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Wallace Lueck; Station J.

10:30 - Pediatric Surgery Conference; Oswald Wyatt; Tague Chisholm; Station I. Classroom.

Friday, March 20 (Cont.)

Minneapolis General Hospital (Cont.)

12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.

1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.

1:15 - X-ray Conference; Oscar Lipschultz; Classroom, Main Bldg.

2:00 - Pediatric Rounds; Robert Ulstrom; Stations I and J.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Pathology Slide Conference; E. T. Bell; Conference Room, Bldg. I.

Saturday, March 21

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

9:00 - 10:00 Infertility Conference; Louis L. Friedman, David I. Seibel, and Obstetrics Staff; Station 54.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

9:15 - 10:00 Surgery-Roentgenology Conference; L. G. Rigler, J. Friedman, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

11:00 - 12:00 Medical - X-ray Conference; O. Lipschultz, Thomas Lowry, and Staff; Main Classroom.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - 11:15 Hematology Rounds; Drs. Hagen, Goldish, and Aufderheide.
11:15 - 12:00 Morphology . . . . . Dr. Aufderheide.

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* Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.