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Contiguity and Progression in Hodgkin's Disease[1]

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Summary

Analysis of the initial sites of involvement in 340 consecutive, previously untreated cases of Hodgkin's disease revealed that over 90% of cases in Stages II, III, and IV involved lymph node chains that could be considered contiguous by the criterion of direct lymphatic communication. A similar pattern was also seen in cases in which posttreatment extensions occurred. It was found that specific patterns of spread were involved in certain seemingly noncontiguous distributions, and the therapeutic implications of this finding are discussed.

A number of investigators (2, 6, 10, 11) have noted that the lymph nodes in which new manifestations of Hodgkin's disease most often appear after prior treatment are those in direct communication with the originally involved nodes via lymphatic channels. Since late 1961, when we added routine lymphangiography to our diagnostic evaluation regimen, we have made systematic observations of the initial anatomical extent of disease in all patients and of new sites of involvement appearing after the initial course of radiotherapy to accumulate reliable mapping data on the topographic distribution of initial and subsequent sites of involvement.

In a preliminary study (13), Dr. Saul Rosenberg and I found that about 90% of initial distributions, as well as of later extensions of disease, involved lymph node chains that could be considered contiguous by the criterion of direct lymphatic communication. Similar observations have now been reported by others (1, 5). A recent analysis (7) of the frequency with which initial sites of involvement in a series of 340 consecutive, previously untreated cases have been contiguous by the criterion of lymphatic communication is presented in Table 1. By definition, there were no noncontiguous cases among those in Rye Stages I_1 and I_2. In the remainder, 4 of 119 (4%) in Stage II, 11 of 112 (10%) in Stage III, and 2 of 22 (9%) in Stage IV with liver or bone marrow involvement were scored as noncontiguous (8).

We soon became aware of a particular pattern of seemingly noncontiguous distribution ("mediastinal skips") in which the disease was initially present in the lower cervical and/or supraclavicular lymph node chains (with or without axillary node involvement), as well as in the paraaortic lymph node chains, without intervening mediastinal or intrathoracic involvement (13). This distribution pattern was observed in 31 of our series of 340 consecutive cases (7).

There is also an appreciable incidence of primary relapses involving the upper lumbar paraaortic nodes (7). These are usually detected on surveillance films made at intervals after initial lymphangiography or on 2nd lymphangiograms in patients whose disease was initially confined to one or both cervical-supraclavicular lymph node chains, with or without radiographic evidence of mediastinal or hilar lymphadenopathy (Table 2). The interval from treatment of the initial supraclavicular involvement to the detection of paraaortic lymph node involvement has varied from a few months to over 5 years. In one case, a 2nd lymphangiogram performed 3 years after the 1st one was still negative, but the lymph nodes in the upper lumbar chain became demonstrably enlarged on subsequent follow-up radiographs taken approximately 1 year after the 2nd lymphangiogram.

It is difficult to believe that the disease was present in the paraaortic nodes from the beginning in such instances. The long intervals of time before disease becomes apparent below the diaphragm are more consistent with the view that the abdominal involvement is a secondary phenomenon, presumably involving retrograde extension by way of the thoracic duct from the supraclavicular lymph nodes to the paraaortic nodes. This possibility is supported by the roentgenological observation of reversal of flow in the thoracic duct of experimental animals after high ligation (9). We have concluded that extension from the lymph nodes at the base of the neck by way of the thoracic duct to the upper lumbar paraaortic lymph nodes is a major "escape route" for the disease and thus perhaps the single most important cause of failure of localized or regional radiotherapy.

Several other specific patterns of spread have emerged from our data. In our series of 340 consecutive, previously untreated cases, there have been no cases in which Hodgkin's disease has been confined to the parenchyma of the lung without associated hilar and mediastinal lymphadenopathy. Only 20 cases presented evidence of involvement of the lung parenchyma at the time of initial diagnostic evaluation, whereas there were 205 cases with mediastinal lymphadenopathy and 39 with hilar node enlargement. Where hilar lymphadenopathy was unilateral, pulmonary parenchymal involvement, when present, was invariably confined to the ipsilateral lung. We concur, therefore, with Peters' (11) suggestion that the hilar lymph nodes are the gateway for the spread of Hodgkin's disease to the pulmonary parenchyma.

Involvement of the spleen is also of great importance in Hodgkin's disease. In our experience to date, clinical and/or radiographic evidence of splenomegaly has usually been

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Table 1

Hodgkin's disease: contiguity of lymphatic sites of involvement in 340 untreated cases

Site	Total no. of instances involved	Sole site involved	Additional sites involved	Anatomic relationship to other sites		
				Noncontiguous	Contiguous	% contiguous
Right axillary nodes	78	5	73	8	65	89
Left axillary nodes	90	3	87	3	84	97
Right cervical-supraclavicular nodes	199	12	187	1	186	99
Left cervical-supraclavicular nodes	241	23	218	6	212	97
Mediastinal nodes	211	5	206	1	205	99.5
Hilar nodes	39	0	39	0	39	100
Paraaortic nodes	114	1	113	1	112	99
Iliac, inguinal, femoral nodes	54	5	49	1	48	98
Spleen	44	0	44	5	39	88

Table 2

Risk of later spread (extension) to the paraaortic nodes in patients with Stage I and II Hodgkin's disease involving the lower cervical-supraclavicular lymph nodes

	Radiotherapeutic fields			
	Local only	Local + contiguous[a]	Total limited field	Extended "total lymphoid"
No. of cases at risk	23	57	80[b]	74[c]
No. of cases with paraaortic node extension	5	24	29 (36%)	4 (5%)
No. of cases with extension to other sites	3	3	6 (8%)	12 (16%)
Total no. of extensions	8	27	34 (44%)	16 (21%)

[a] Usually, a "mantle" field, encompassing bilateral axillary, cervical, supraclavicular, infraclavicular, hilar, and mediastinal nodes, down to the diaphragm.

[b] The paraaortic and pelvic nodes, and usually also the spleen, were irradiated in addition to the "mantle" field.

[c] Mediastinal adenopathy was also present initially in 26 of the 80 cases treated with limited fields and in 62 of the 74 cases treated with extended fields.

Table 3

Results of laparotomy in 100 consecutive untreated patients with Hodgkin's disease[a]

Site	Preoperative assessment	A. Systemic symptoms absent	B. Systemic symptoms present	Total
Liver	Clinically positive	0/4[b]	1/11	1/15
	Clinically negative	1/53	1/32	2/85
Spleen	Clinically positive	2/6	6/10	8/16
	Clinically negative	11/51	9/33	20/84
Abdominal nodes	Positive lymphangiogram	8/11 (1)[c]	10/12	18/23 (1)
	Negative lymphangiogram	5/33 (4)	2/24 (1)	7/57 (5)
	Equivocal lymphangiogram	3/13 (1)	1/ 7	4/20 (1)

[a] Adapted from "Hodgkin's Disease and Other Malignant Lymphomas" by Saul A. Rosenberg and Henry S. Kaplan (Calif. Med., *113:* 23–38, 1970).

[b] No. with histological evidence of Hodgkin's disease of number examined.

[c] Figures in parentheses are numbers with positive splenic hilar nodes but negative paraaortic node biopsy.

accompanied or preceded in time by lymphangiographic evidence of involvement of the upper lumbar paraaortic lymph nodes. In several instances, we have observed the secondary development of splenic involvement after apparently successful radiotherapy directed locally to involved paraaortic lymph node chains. These observations have suggested that the disease tends to spread from the upper lumbar paraaortic lymph nodes, presumably again by way of lymphatic channels, to the spleen.

Clinical and radiographic evidence of splenomegaly are

relatively insensitive indicators of splenic involvement by Hodgkin's disease. This has become apparent during the past few years in an increasing number of cases subjected to laparotomy and splenectomy (3, 4). In 40 to 50% of instances, enlarged spleens have been removed which, on histological examination, were found to be uninvolved by Hodgkin's disease. Conversely, small spleens, in some instances weighing less than 100 g, contained focal or diffuse involvement in about one-third of all cases. Data on the first 100 consecutive, unselected cases (14) are presented in Table 3.

The laparotomy data have also provided important new insights into the relationship between hepatic and splenic involvement in Hodgkin's disease. In our series of 340 cases of previously untreated Hodgkin's disease, involvement of the spleen was documented during the initial diagnostic evaluation in 44 instances, whereas the liver was involved initially in only 9 (7). The spleen was involved in every instance in which the liver was involved. Our recent laparotomy studies indicate that massive enlargement of the spleen is accompanied by biopsy evidence of liver involvement in over 50% of instances, whereas small spleens, with minimal or moderate degrees of involvement, are much less often associated with hepatic involvement (3). Collectively, these observations strongly suggest that Hodgkin's disease usually reaches the liver only after prior involvement of the spleen.

Hepatic involvement which was not initially demonstrable became clinically manifest after radiotherapy or surgical removal of an involved spleen. Hepatic spread was observed in 15 of 34 cases (45%) in which prior splenic involvement had been documented; it is likely that the true cumulative risk exceeds 50%. For this reason, and taking into consideration the known large sampling error of liver biopsy in Hodgkin's disease, we now consider that surgically documented involvement of the spleen constitutes presumptive evidence of concomitant microscopic involvement of the liver. even in patients with an apparently normal liver at laparotomy and a negative liver biopsy.

Although the available data are still sparse, the probability of spread to the bone marrow appears to be strongly correlated with prior or concomitant involvement of the paraaortic lymph nodes and spleen. Positive marrow biopsies were obtained during initial diagnostic study in only 7 of 340 of our consecutive, previously untreated cases; the spleen was involved in at least 5 of these, and the paraaortic nodes were involved in all 7 (7). Of 16 patients in whom later extension of disease to the marrow was documented, all but 1 (a patient who developed marrow involvement while on chemotherapy) had prior or concomitant disease in the paraaortic nodes and spleen. Although Hodgkin's disease may occasionally gain access to the vertebral marrow by direct extension from the paraaortic nodes, it is probable that in most instances it reaches the bone marrow in many areas simultaneously by hematogenous dissemination.

In summary, these clinical investigations, which entail a meticulous search for initial sites of involvement and subsequently the persistent and painstaking follow-up of patients for the detection and mapping of initial sites of spread of disease, have yielded much valuable data concerning the natural history of Hodgkin's disease. Contiguity of sites of initial and subsequent involvement, explicable until relatively late in the course of the disease in terms of spread via lymphatic channels, occurs in such a high proportion of cases as to be predictable and therapeutically exploitable. The small proportion of cases in which sites of initial involvement or subsequent spread appear to be noncontiguous may well be attributable to sampling error, to residual inadequacies of our diagnostic methods, and to vascular invasion (12).

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